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

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ABSTRACT

Background: Recombinant trivalent influenza vaccine (RIV3, Flublok®, Sanofi Pasteur) 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 the rates of pre-specified diagnoses of interest (Guillain-Barré Syndrome, pericarditis, pleural effusion, narcolepsy/cataplexy, asthma, acute hypersensitivity reactions and fever) during various post-vaccination risk intervals, as well as all-cause hospitalization and mortality 0-180 days following 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 pre-specified diagnoses of interest between the 2 groups. Specifically, RIV3 vaccination was associated with fewer fever diagnoses during the 0-41 days post-vaccination (OR 0.38, 95% CI 0.14–0.86). RIV3 was also associated with fewer all-cause hospitalizations during the 0-180 day post-vaccination (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; vaccine; safety; recombinant
INTRODUCTION

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 (e.g., 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 (RIV), and the addition of new adjuvants to increase immune response.

In January 2013, on the basis of two 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.
METHODS

Study Setting

This observational safety study was conducted as a post marketing commitment to the United States Food and Drug Administration. The study was conducted at KPNC, an integrated healthcare organization that provides comprehensive medical care to nearly 4 million members. KPNC 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 one type of influenza vaccine, or who were recorded as receiving influenza vaccines on more than one date.
**Study Design**

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

*Pre-Specified Diagnoses of Interest (PSDI)*

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/CBER to satisfy a post-marketing commitment of evaluating safety. We considered post-vaccination 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 prior to vaccination. We considered a narcolepsy/cataplexy episode as new if an individual had not had a narcolepsy/cataplexy diagnosis within 12 months prior to 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 post-vaccination interval. We mapped ICD-9 codes to ICD-10 codes using the Centers for Medicare and Medicaid Services (CMS) General Equivalence Mappings (GEMS) 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 prior to RIV3 being 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.

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 condition codes (e.g., chronic obstructive pulmonary disease, asthma, diabetes mellitus) in the year prior to 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.

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.

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 which 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 1) conducting supplemental analyses stratified on pregnancy status; 2) performing analyses which more finely adjusted for calendar time and for health-care 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 prior to 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.

ClinicalTrials.gov Identifier is NCT02600585.

RESULTS

The study period was November 5, 2015 (first dose of RIV3 in KPNC) to March 11, 2016 (last dose of RIV3). The 6-month post vaccination 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 percent of RIV3 subjects were vaccinated in November 2015 (59.26% vs 53.12%), while smaller percents were vaccinated in December (18.20% vs 24.39%) and...
January 2016 (10.97% vs 12.93%). There were small differences between the groups in the percent with high risk conditions in the year prior to vaccination (34.04% vs 31.30%; Table 3).

There were statistically significant differences between the groups in the primary analyses (Table 4). RIV3 was associated with significantly decreased incidence of fever (OR 0.38, 95% CI 0.14–0.86, combined emergency department 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 0.79–1.0) (Table 6). More finely adjusting the model for vaccination timing and facility among non-pregnant vaccinees did not substantially alter the results (data not shown), however the model was unstable due to its complexity.

Hospitalizations among non-pregnant RIV3 and IIV3 vaccinees did not differ with regard to influenza disease-related hospital discharge codes (i.e., 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 ICD10 category “Z00-Z99: Factors influencing health status and contact with health services”, which consist of diagnoses related to chemotherapy, ileostomy, and colostomy, was significantly reduced among RIV3 recipients (OR 0.19, 95% CI 0.01–0.98).

Hospitalization rates prior to vaccination were lower among RIV3 vaccinees during the 90 and 365 days prior to vaccination, though not significantly different (90 days: 13.65 per 10,000 RIV3
vaccinees and 17.84 per 10,000 IIIV3 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 IIIV3 vaccinees, OR 0.83, 95% CI 0.67–1.02). Hospitalization rates during the 730-days prior to vaccination were significantly less among RIV3 vaccinees (68.26 per 10,000 RIV3 vaccinees and 91.19 per 10,000 IIIV3 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 IIIV3. 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 though 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 IIIV3 vaccinees, which one might expect if RIV3 prevented more influenza-related hospitalizations. In addition, RIV3 recipients had significantly fewer hospitalizations related to chemotherapy, ileostomy, and colostomies, suggesting that RIV3 vaccinees may have been healthier at the time of immunization. Finally, the fewer number of prior hospitalizations among RIV vaccinees further implies that there were differences in baseline health status between RIV3 and IIIV3 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 18-49 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 18-49 year olds comparing quadrivalent versions of RIV with IIV found similar rates of local and systemic reactions and SAEs [11], as did trials compared RIV3 with IIV3 among 50+ year olds [12,13,14]. One of these studies noted more hypersensitivity reactions after RIV3 [14], while another determined that a vasovagal syncope SAE was related to RIV3 [13].

This study had several limitations. RIV3 was not available at KPNC until November 2015 and therefore, unlike IIV3 which began administration in September 2015, was not given early in the 2015-16 influenza season. Our comparisons were therefore 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 post-vaccination diagnoses that were coded in the electronic medical record and did not conduct medical record review, however it is unlikely that diagnostic coding would be differential between study groups. Similarly, we required that a subset of diagnoses be new onset (e.g., Guillain-Barré Syndrome) based on the absence of a code for a time interval prior to 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

This observational study evaluating the safety of RIV3 compared with IIV3 did not detect any concerns. Understanding the observed reduction in all-cause hospitalization following 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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| Pre-specified 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.*         | 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 |
| Pre-specified diagnoses        | ICD-9 code(s) | ICD-10 code(s) | Setting       |
|-------------------------------|--------------|---------------|---------------|
| 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: OP = Outpatient. ED = Emergency Department, IP = Inpatient.

† The dagger symbol indicates that the diagnosis code appears in more than one category.
Table 2. Primary and Secondary Study Outcomes

| Analysis   | Days following 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: OP = Outpatient. ED = Emergency Department. IP = Inpatient. PSDI = Pre-specified diagnoses of interest.
|                                | RIV3               | IIV3               |
|--------------------------------|--------------------|--------------------|
|                               | N (%)              | N (%)              |
| **Gender**                    |                    |                    |
| Female                         | 11,588 (52.73)     | 156,986 (55.34)    |
| Male                           | 10,388 (47.27)     | 126,697 (44.66)    |
| **Age Categories**             |                    |                    |
| 18 to 49*                      | 10,164 (46.25)     | 148,374 (52.30)    |
| 50 to 64*                      | 7,742 (35.23)      | 89,886 (31.69)     |
| 65 to 79*                      | 3,459 (15.74)      | 38,329 (13.51)     |
| Over 80*                       | 611 (2.78)         | 7,094 (2.50)       |
| **Race**                       |                    |                    |
| White*                         | 9,831 (44.74)      | 135,427 (47.74)    |
| Hispanic*                      | 4,749 (21.61)      | 56,606 (19.95)     |
| Asian*                         | 4,735 (21.55)      | 55,228 (19.47)     |
| Black*                         | 1,208 (5.50)       | 16,924 (5.97)      |
| Unknown                        | 614 (2.79)         | 8,537 (3.01)       |
| Multiracial                    | 591 (2.69)         | 7,672 (2.70)       |
| Pacific Islander               | 157 (0.71)         | 2,094 (0.74)       |
| Native                         | 91 (0.41)          | 1,195 (0.42)       |
| American                       |                    |                    |
| **Injection month**            |                    |                    |
| November*                      | 13,024 (59.26)     | 150,697 (53.12)    |
| December*                      | 3,999 (18.20)      | 69,202 (24.39)     |
| January*                       | 2,410 (10.97)      | 36,682 (12.93)     |
| February*                      | 1,785 (8.12)       | 21,782 (7.68)      |
| March*                         | 758 (3.45)         | 5,320 (1.88)       |
| **Concomitant vaccination**    |                    |                    |
| No                             | 18,477 (84.08)     | 238,435 (84.05)    |
|                  | Yes  | 3,499 (15.92) | 45,248 (15.95) |
|------------------|------|---------------|----------------|
| High risk*       | No   | 14,496 (65.96)| 194,879 (68.70)|
|                  | Yes  | 7,480 (34.04) | 88,804 (31.30) |

* Differences were statistically significant using a Chi square test.

Abbreviations: RIV3 = Recombinant Trivalent Influenza Vaccine. IIV3 = Trivalent Standard-Dose Inactivated Influenza Vaccine.

There were 66 subjects vaccinated with RIV3 at less than 18 years of age and they were not included in any analyses.
| Setting        | Risk Window | Diagnosis                          | RIV3 N (Rate*) | IIV3 N (Rate*) | 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              | 0.0776  |
| OP, ED, IP    | 0-2         | Fever                              | 2 (0.91)       | 70 (2.47)      | 0.392      | 0.064              | 1.340              | 0.1655  |
| ED, IP        | 0-13        | Acute noninfectious pericarditis   | 0 (0.00)       | 2 (0.07)       | 0.000      | 0.000              | 33.684             | 0.8826  |
| ED, IP        | 0-13        | Allergic conditions, nonspecific   | 15 (6.83)      | 309 (10.89)    | 0.619      | 0.368              | 1.041              | 0.0703  |
| ED, IP        | 0-13        | Asthma                             | 22 (10.01)     | 419 (14.77)    | 0.664      | 0.432              | 1.021              | 0.0623  |
| ED, IP        | 0-13        | Fever                              | 3 (1.37)       | 70 (2.47)      | 0.548      | 0.136              | 1.553              | 0.3114  |
| ED, IP        | 0-13        | Guillain-Barré syndrome (GBS)      | 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             | 0.8436  |
| OP            | 1-13        | Acute noninfectious                | 0 (0.00)       | 3 (0.11)       | 0.000      | 0.000              | 15.179             | 0.8023  |
| Setting | Risk Window | Diagnosis                        | RIV3 N (Rate*) | IIV3 N (Rate*) | Odds Ratio | 95% CI Lower Bound | 95% CI Upper Bound | P Value |
|---------|-------------|----------------------------------|----------------|----------------|------------|---------------------|---------------------|---------|
| OP      | 1-13        | pericarditis                      | 113 (51.42)    | 1,370 (48.29)  | 1.057      | 0.871               | 1.283               | 0.573   |
| OP      | 1-13        | Allergic conditions, nonspecific  |                |                |            |                     |                     |         |
| OP      | 1-13        | Asthma                            | 133 (60.52)    | 1,643 (57.92)  | 1.023      | 0.856               | 1.223               | 0.8034  |
| OP      | 1-13        | Fever                             | 6 (2.73)       | 57 (2.01)      | 1.262      | 0.490               | 2.794               | 0.5695  |
| OP      | 1-13        | Guillain-Barré syndrome (GBS)     | 0 (0.00)       | 0 (0.00)       |            |                     |                     |         |
| OP      | 1-13        | Narcolepsy/catatpexy              | 0 (0.00)       | 1 (0.04)       | 0.000      | 0.000               | 78.000              | 0.8966  |
| 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               | 0.7374  |
| ED, IP  | 0-41        | Allergic conditions, nonspecific  | 58 (26.39)     | 813 (28.66)    | 0.910      | 0.696               | 1.189               | 0.4875  |
| ED, IP  | 0-41        | Asthma                            | 82 (37.31)     | 1,157 (40.78)  | 0.891      | 0.712               | 1.117               | 0.3175  |
| ED, IP  | 0-41        | Fever                             | 5 (2.28)       | 166 (5.85)     | 0.379      | 0.137               | 0.857               | 0.0159  |
| Setting | Risk Window | Diagnosis                                      | RIV3 N (Rate*) | IIV3 N (Rate*) | Odds Ratio | 95% CI Lower Bound | 95% CI Upper Bound | P Value |
|---------|-------------|------------------------------------------------|----------------|----------------|-------------|---------------------|---------------------|---------|
| ED, IP  | 0-41        | Guillain-Barré syndrome (GBS)                    | 0 (0.00)       | 3 (0.11)       | 0.000       | 0.000               | 16.066              | 0.8093  |
| ED, IP  | 0-41        | Narcolepsy/catataplexy                          | 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               | 0.5718  |
| OP      | 1-41        | Acute noninfectious pericarditis                | 0 (0.00)       | 4 (0.14)       | 0.000       | 0.000               | 10.376              | 0.7486  |
| OP      | 1-41        | Allergic conditions, nonspecific                | 317 (144.25)   | 3,932 (138.61) | 1.040       | 0.926               | 1.168               | 0.5076  |
| OP      | 1-41        | Asthma                                          | 378 (172.01)   | 4,843 (170.72) | 0.990       | 0.889               | 1.101               | 0.8485  |
| OP      | 1-41        | Fever                                           | 15 (6.83)      | 183 (6.45)     | 1.024       | 0.603               | 1.737               | 0.9303  |
| OP      | 1-41        | Guillain-Barré syndrome (GBS)                    | 0 (0.00)       | 1 (0.04)       | 0.000       | 0.000               | 112.600             | 0.9260  |
| OP      | 1-41        | Narcolepsy/catataplexy                          | 0 (0.00)       | 6 (0.21)       | 0           | 0                   | 5.896               | 0.6286  |
| OP      | 1-41        | Noninfectious pleural effusion                  | 0 (0.00)       | 0 (0.00)       | -           | -                   | -                   | -       |
| Setting | Risk Window | Diagnosis | RIV3 N (Rate*) | IIV3 N (Rate*) | Odds Ratio | 95% CI Lower Bound | 95% CI Upper Bound | P Value |
|---------|-------------|-----------|--------------|---------------|------------|-------------------|-------------------|---------|
| IP      | 0-180       | All-cause hospitalization | 527 (257.69) | 10,224 (385.90) | 0.663 | 0.606 | 0.725 | <0.0001 |
| -       | 0-180       | All-cause mortality | 48 (21.84) | 748 (26.37) | 0.760 | 0.566 | 1.020 | 0.0679 |

Abbreviations: RIV3 = Recombinant Trivalent Influenza Vaccine. IIV3 = Trivalent Standard-Dose Inactivated Influenza Vaccine. OP = Outpatient. ED = Emergency Department. IP = Inpatient. CI = Confidence Interval.

* Rate per 10,000 doses
| Setting | Risk Window | Diagnosis                                      | RIV3 N (Rate*) | IIV3 N (Rate*) | Odds Ratio | 95% CI Lower | 95% CI Upper | P Value |
|---------|-------------|-----------------------------------------------|----------------|----------------|-------------|--------------|--------------|---------|
| OP      | 1-2         | Acute hypersensitivity reactions               | 3 (1.37)       | 49 (1.73)      | 0.855       | 0.210        | 2.460        | 0.8545  |
| OP      | 1-2         | Fever                                         | 0 (0.00)       | 12 (0.42)      | 0.000       | 0.000        | 2.873        | 0.4246  |
| OP, ED, IP | 0-13   | Acute noninfectious pericarditis               | 0 (0.00)       | 3 (0.11)       | 0.000       | 0.000        | 16.125       | 0.8119  |
| OP, ED, IP | 0-13   | Allergic conditions, nonspecific               | 540 (245.72)   | 6,882 (242.59) | 1.028       | 0.938        | 1.127        | 0.5493  |
| OP, ED, IP | 0-13   | Asthma                                        | 701 (318.98)   | 8,847 (311.86) | 1.030       | 0.948        | 1.120        | 0.4818  |
| OP, ED, IP | 0-13   | Fever                                         | 10 (4.55)      | 147 (5.18)     | 0.860       | 0.452        | 1.638        | 0.6468  |
| OP, ED, IP | 0-13   | Guillain-Barré syndrome (GBS)                | 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        | 0.6813  |
| Setting    | Risk Window | Diagnosis                      | RIV3 N (Rate*) | IIV3 N (Rate*) | Odds Ratio | 95% CI Lower | 95% CI Upper | P Value  |
|------------|-------------|--------------------------------|----------------|----------------|------------|--------------|--------------|----------|
| OP, ED, IP | 0-13        | Noninfectious pleural effusion | 0 (0.00)       | 2 (0.07)       | 0.000      | 0.000        | 26.952       | 0.8570   |
| OP, ED, IP | 0-41        | Acute noninfectious pericarditis | 0 (0.00)       | 5 (0.18)       | 0.000      | 0.000        | 7.194        | 0.6739   |
| OP, ED, IP | 0-41        | Allergic conditions, nonspecific | 744 (338.55)   | 9,483 (334.28) | 1.023     | 0.946        | 1.106        | 0.5761   |
| OP, ED, IP | 0-41        | Asthma                         | 941 (428.19)   | 11,936 (420.75) | 1.017     | 0.947        | 1.093        | 0.6435   |
| OP, ED, IP | 0-41        | Fever                          | 20 (9.10)      | 357 (12.58)    | 0.710     | 0.451        | 1.115        | 0.1368   |
| OP, ED, IP | 0-41        | Guillain-Barré syndrome (GBS)  | 0 (0.00)       | 3 (0.11)       | 0.000     | 0.000        | 16.160       | 0.8094   |
| OP, ED, IP | 0-41        | Narcolepsy/catatpexy           | 0 (0.00)       | 10 (0.35)      | 0.000     | 0.000        | 3.396        | 0.4776   |
| OP, ED, IP | 0-41        | Noninfectious pleural effusion | 0 (0.00)       | 6 (0.21)       | 0.000     | 0.000        | 4.813        | 0.5722   |
Abbreviations: RIV3 = Recombinant Trivalent Influenza Vaccine. IIV3 = Trivalent Standard-Dose Inactivated Influenza Vaccine. OP = Outpatient. ED = Emergency Department. IP = Inpatient. CI = Confidence Interval.

* Rate per 10,000 doses
Table 6. All-cause Hospitalization Finding by Pregnancy Status

| Prespecified Outcome                  | RIV3     | IIV3     | Odds Ratio | 95% CI Lower | 95% CI Upper | P     |
|--------------------------------------|----------|----------|------------|--------------|--------------|-------|
| All-cause hospitalization, pregnant  | 56 (4590.16) | 3,644 (5647.86) | 0.677     | 0.467        | 0.983        | 0.0401 |
| subjects                             |          |          |            |              |              |       |
| All-cause hospitalization, non-pregnant | 471 (231.69) | 6,580 (254.56) | 0.866     | 0.787        | 0.953        | 0.0032 |

Abbreviations: RIV3 = Recombinant Trivalent Influenza Vaccine. IIV3 = Trivalent Standard-Dose Inactivated Influenza Vaccine. CI = Confidence Interval.

* Rate per 10,000 doses