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Relative Effectiveness of Cell-based Versus Egg-based Quadrivalent Influenza Vaccines in Children and Adolescents in the United States During the 2019–2020 Influenza Season

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Background: Egg-based influenza vaccine production can lead to the accumulation of mutations that affect antigenicity. The mammalian cell-based inactivated quadrivalent influenza vaccine (IIV4c) may improve effectiveness compared with egg-based vaccines. This study estimated the relative vaccine effectiveness (rVE) of IIV4c versus egg-based inactivated quadrivalent influenza vaccine (IIV4e) in preventing influenza-related medical encounters (IRME) among children and adolescents during the 2019–2020 US influenza season.

Methods: This retrospective cohort study used a dataset linking primary and specialty care electronic medical records with medical and pharmacy claims data from US residents 4 through 17 years of age vaccinated with IIV4c or IIV4e during the 2019–2020 influenza season. Odds ratios (ORs) were derived from a doubly robust inverse probability of treatment-weighted approach adjusting for age, sex, race, ethnicity, region, index week, health status and two proxy variables for healthcare accessibility and use. Adjusted rVE was estimated by $(1\text{-}OR_{adjusted})*100$, and an exploratory analysis evaluated IRMEs separately for outpatient and inpatient settings.

Results: The final study cohort included 60,480 (IIV4c) and 1,240,990 (IIV4e) vaccine recipients. Fewer IRMEs were reported in subjects vaccinated with IIV4c than IIV4e. The rVE for IIV4c versus IIV4e was 12.2% [95% confidence interval (CI): 7.5–16.6] for any IRME and 14.3% (9.3–19.0) for outpatient IRMEs. Inpatient IRMEs were much less frequent, and effectiveness estimates were around the null.

Conclusions: Fewer IRMEs occurred in pediatric subjects vaccinated with IIV4c versus IIV4e. These results support the greater effectiveness of IIV4c over IIV4e in this population during the 2019–2020 US influenza season.

Key Words: influenza, cell-based influenza vaccine, egg-based influenza vaccine, quadrivalent inactivated influenza vaccine, relative vaccine effectiveness, pediatric

(*Pediatr Infect Dis J* 2022;41:769–774)

Influenza is a major cause of morbidity and mortality worldwide, resulting in up to a billion infections, 3–5 million cases of severe disease, and 290,000–650,000 deaths annually.[1] Influenza vaccination reduces both pediatric outpatient visits and hospitalizations.[2,3] In addition, although the rates of hospitalization and death from influenza are lower in the pediatric population compared with older adult age groups, children and adolescents play an important role in the transmission of influenza.[4] Pediatric influenza virus infections are associated with increased viral transmission through prolonged shedding, which could put family members more vulnerable to influenza complications at risk.[5,6] Vaccinating children and adolescents to interrupt community-wide transmission of influenza may be a strategy to mitigate the spread of influenza in the larger population, including those at high risk of influenza complications.[4,7–9]

The US Advisory Committee on Immunization Practices recommends annual vaccination for children and adults to reduce the impact of influenza on public health.[6] In younger individuals, influenza vaccine effectiveness varies from season to season due to multiple factors including vaccine mismatch due to antigenic drift of circulating viruses as well as egg adaptive mutations which can occur when vaccine viruses are propagated in chicken eggs.[10,11] As such, mutations in the viral hemagglutinin protein can accrue during egg-based manufacturing due to selection pressures within the embryonic egg, which can lead to vaccine mismatch.[10,12,13] In contrast, when vaccine viruses are propagated by other means, such as in mammalian cell culture, the possibility of egg-adaptive mutations is eliminated.

Propagation of vaccine viruses in cell culture can, therefore, lead to vaccine strains that are more antigenically faithful to the recommended virus by eliminating the possibility of egg adaptation.[14–16] The first cell-based, inactivated quadrivalent influenza vaccine (IIV4c) (Flucelvax Quadrivalent, Seqirus USA Inc., Summit, NJ) received initial approval in the US in May 2016.[17] Observational studies have subsequently provided evidence that cell-based vaccines may have greater effectiveness than traditional egg-based vaccines, particularly in seasons during which egg-adaptation may have affected egg-based vaccines.[18–22]

In previous retrospective cohort studies conducted during the 2017–2018 and 2018–2019 seasons, we compared IIV4c to standard dose egg-based inactivated quadrivalent influenza vaccine (IIV4e) in a cohort of subjects at least 4 years of age and found

Accepted for publication May 24, 2022

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M.I., C.B. are employees of Seqirus Inc. J.A.M. was an employee of Seqirus during study conduct. J.R.O. reports receiving grants to his institution from NIH for influenza vaccine research, grants to his institution from GSK, Pfizer, and PATH for vaccine (non-influenza) research, honoraria from Seqirus to serve on Real World Evidence Scientific Advisory Board and from Pfizer to serve on the Immunization for All Ages Advisory Board. The other authors have no conflicts of interest to disclose.

This work was supported by Seqirus.

M.I., C.B., and J.A.M. were involved in study conception, design and conceptual frameworks. L.F., D.O., and M.B. were involved in the analysis. H.Q.M., and J.R.O. provided regular feedback on each of these steps. All authors were involved in the interpretation of data. M.I. and C.B. were involved in drafting the article and L.F., D.B., M.B, J.A.M, H.Q.M., and J.R.O revised the article critically. All authors made substantive intellectual contributions to the development of this article and approved the final version.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/22/4109-0769
DOI: 10.1097/INF.0000000000003620

increased vaccine effectiveness of cell-based vaccines.[21,22] The 2017–2018 influenza season in the US was predominated by circulating A(H3N2) influenza viruses, whereas in the 2018–2019 season, A(H1N1)pdm09 viruses were predominant from October 2018 to mid-February 2019, and A(H3N2) viruses dominated from February 2019. The 2019–2020 season was characterized by the early onset of influenza B/Victoria viruses followed by A(H1N1)pdm09 viruses. Due to the seasonal variability of the influenza epidemiology, it is important to generate annual evidence of relative effectiveness (rVE) of influenza vaccines. In this study, conducted during the 2019–2020 US influenza season, we estimated the effectiveness of IIV4c relative to IIV4e in preventing influenza-related medical encounters (IRME) specifically for children and adolescents 4 through 17 years of age.

METHODS

The study concerned a noninterventional, retrospective cohort study based on an analysis of electronic medical records and claims data. This study was designed, implemented and reported in accordance with Good Pharmacoepidemiological Practice, applicable local regulations, and the ethical principles laid down in the Declaration of Helsinki. Study findings are reported in accordance with the Reporting of Studies Conducted using Observational Routinely Collected Health Data recommendations.[23] Because this study was a noninterventional, retrospective study using a certified Health Insurance Portability and Accountability Act (HIPAA)-compliant database, approval for this analysis by an institutional review board was not necessary.

Study Period

This retrospective cohort study was conducted in the US during the 2019–2020 influenza season. The main study period was from August 1, 2019 through March 7, 2020. This aligns with the Centers for Disease Control and Prevention (CDC) influenza surveillance season defined as epidemiologic weeks 40 through 20 of the subsequent year, however, to avoid potential bias arising from outcome misclassification due to overlap with serious acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the influenza season was truncated at March 7, 2020.

Data Sources and Linkage

The dataset used in the analysis was an integrated dataset of patient-level electronic medical records (EMRs) from primary care and specialty clinics, linked with pharmacy and medical claims data for approximately 123 million individuals from all 50 US states. The integrated dataset provides comprehensive pharmaceutical, demographic, diagnostic and healthcare utilization information. Data from 3 national EMR systems form the basis of the integrated dataset (ie, Veradigm Health Insights Ambulatory database): Allscripts Professional and Allscripts Touchworks (Chicago, IL) and Practice Fusion (San Francisco, CA). These datasets include medical practices of a range of sizes: small practices (1–3 physicians), medium-sized practices (5–40 physicians) and integrated delivery networks. The Komodo Healthcare Map (Komodo Health Inc., New York City, NY) consists of anonymized patient-level US pharmacy and medical claims. Both open and closed claims were utilized in this analysis. Data from open claims are sourced from practice management systems, billing systems and claims clearinghouses and provide a view of the patient journey over a longer period of time, whereas closed claims are sourced from insurance providers and payers and encompass a more complete view of a patient's interactions with the health care system within a set time frame for which patient enrollment/eligibility information in the health plan is available. Before linkage, each individual dataset underwent de-identification and privacy certification to confirm it met the minimum Protected Health Information (PHI) data requirements. The dataset was also evaluated and certified for HIPAA compliance by a third-party statistician (see Supplementary Data for de-identification and linkage details, Supplemental Digital Content 1, http://links.lww.com/INF/E764).

Exposure Ascertainment

Current procedural terminology codes, codes for vaccines administered and national drug codes (Table 1, Supplemental Digital Content 1, http://links.lww.com/INF/E764) were used to identify vaccinated subjects from both EMRs and claims data within the vaccination intake period. The date of recorded vaccination was considered the index date. The exposure of interest was IIV4c and was compared to individuals with a record of receiving standard-dose, egg-based inactivated influenza vaccines (IIV4e).

Study Population

The study population for the current analysis included children and adolescents 4 through 17 years old who were residing in the US and who had received either IIV4c or IIV4e between August 1, 2019 and January 31, 2020 (vaccination intake period) with at least 1 year of primary care medical history in the EMR and claims components of the integrated dataset. Subjects were excluded if they had a record of influenza vaccination outside the vaccination intake period or had an IRME during the 2019–2020 season before being fully vaccinated. Subjects were excluded if they were at least 9 years of age with a record of more than 1 influenza vaccination during the study period, and those younger than 9 years were excluded if they had received more than 2 influenza vaccinations. Subjects with missing sex or geographic region information were also excluded from the analysis.

Outcome Ascertainment

The outcome of interest was the occurrence of an IRME in any setting (outpatient or inpatient) and ascertained using International Classification of Diseases (ICD) codes specific for the diagnosis of influenza disease (Table 2, Supplemental Digital Content 1, http://links.lww.com/INF/E764).[24] IRMEs were identified from both patient EMRs and claims and were considered valid for study purposes only if they occurred ≥14 days after the index date to allow for the development of vaccine-specific immunity. Inpatient IRME results are presented separately for an influenza diagnosis as the admitting diagnosis and an influenza diagnosis in any diagnosis position within the medical claim. IRMEs recorded during an emergency room (ER) visit were classified as inpatient. The follow-up period lasted either until a record of an IRME or the end of the observation period (March 7, 2020).

Covariates

Covariates were identified in the 12 months before the recorded date of IIV4c or IIV4e vaccination and included age, sex (male and female), race (Black, White, not reported and other), ethnicity (Hispanic, non-Hispanic and not reported), US census geographic region (Northeast, Midwest, South, West, other), index week, individual comorbidities included in the Charlson comorbidity index[25,26] (Table 4, Supplemental Digital Content 1, http://links.lww.com/INF/E764), number of outpatient visits in the 12 months before the recorded vaccination date and number of inpatient admissions in the 12 months before the recorded vaccination date.

Statistical Methods

Between-group differences in baseline covariates were assessed using standardized mean differences, with a value of ≤0.1 indicating a negligible difference. Categorical variables with missing or null values were classified as 'not reported/unknown'; missing or out-of-range values were not imputed.

TABLE 1. Subject Selection in the 2019–2020 Influenza Season

Selection Criterion	No. Subjects (%)
1. Patient received an influenza vaccine between August 1, 2019 and January 31, 2020	10,087,998 (100.0)
2. Patient is 4 through 17 years of age at time of vaccination	1,850,442 (18.3)
3. Patient is at least 9 years of age and does not have ≥1 influenza vaccination during the influenza season or patient is younger than 9 years and does not have ≥2 influenza vaccinations	1,828,043 (18.1)
4. Patient does not have an IRME prior to becoming fully vaccinated or before the influenza season	1,807,279 (17.9)
5. Patient has a transcript record in the Veradigm EMR ≥1 year prior to vaccination date	1,535,248 (15.2)
6. Patient has activity in Komodo claims ≥1 year prior to vaccination date	1,305,504 (12.9)
7. Patient does not have missing or conflicting data for age, gender or geographic region	1,301,470 (12.9)
IIV4c recipients	60,480 (0.6)
IIV4e recipients	1,240,990 (12.3)

IIV4c, cell-based inactivated quadrivalent influenza vaccine; IIV4e egg-based inactivated quadrivalent influenza vaccine; EMR, electronic medical record

Inverse probability of treatment weighting (IPTW) was implemented to adjust for covariate imbalance between vaccine cohorts.[27] In the IPTW method, weights are assigned to individuals based on the inverse of their probability of receiving the vaccine, as estimated by propensity scores. Propensity scores were first calculated for each exposure cohort using a multivariable logit model adjusted for all covariates listed above. Next, propensity scores were used to create stabilized IPTWs. Weights were truncated at the 99th percentile to mitigate any extreme variability due to outlier patients. Final adjusted ORs were estimated for the IPTW-weighted cohort using a multivariable logistic regression model (including all variables in the propensity score model).[28] rVE was calculated as 100* $(1 - OR_{adjusted})$ and is reported with 95% confidence intervals (CI). The main outcome concerned IRME in any setting. In an exploratory analysis, outpatient and inpatient IRMEs were analyzed separately. Analyses were conducted using SQL and SAS (Version 9.4).

Sensitivity analyses were conducted to assess the robustness of study assumptions. Using the moving epidemic method (MEM), we restricted the rVE analysis to the period of the highest incidence of laboratory-confirmed influenza (ie, December 8, 2019 through March 7, 2020) with the goal of improving the specificity of case definitions. To assess the impact of the SARS-CoV-2 (COVID-19) pandemic, we conducted an analysis restricting to an earlier study period cutoff (September 29, 2019 through February 15, 2020) before widespread SARS-CoV-2 circulation and another that extended through the full influenza season (September 29, 2019 through May 16, 2020). Finally, a negative control outcome analysis with urinary tract infections (UTI; defined by ICD-10 N39.0 codes) was conducted to evaluate the balance between the 2 cohorts after weighting.

RESULTS

Study Subjects

The total study population included 1,301,470 children and adolescents, 4.6% (n = 60,480) of whom received IIV4c and 95.4% (n = 1,240,990) received IIV4e (Table 1). Demographic characteristics are listed in Table 2. The IIV4c cohort was approximately a year older than IIV4e recipients on average (11.9±3.7 vs. 10.3±4.0 years). A little less than half of the subjects in each group were female; the plurality was White and non-Hispanic and resided in the southern US. A larger proportion of the IIV4c than the IIV4e group had claims data originating from pharmacy settings. The most common comorbidities in both cohorts were chronic pulmonary disease and diabetes. Other comorbidities affected <0.5% of the population (Table 3, Supplemental Digital Content 1, http://links.lww.com/INF/E764).

Main Results

As shown in Fig. 1, 4.9% (n = 2936) of IIV4c and 6.2% (n = 76,618) of IIV4e recipients experienced an IRME of any kind. The associated rVE was 12.2% (95% CI: 7.5–16.6). Outpatient IRMEs were reported by 3.9% (n = 2335) of IIV4c and 5.0% (n = 61,748) of IIVe recipients, with an rVE of 14.3% (9.3–19.0).

Inpatient IRMEs were far more infrequent. In the IIV4c cohort, 0.8% (n = 502) had an IRME in an inpatient setting as the admitting diagnosis and 1.0% (n = 601) had an IRME in an inpatient setting with a diagnosis in any position on the claim. Corresponding event rates in the IIV4e group were 1.0% (n = 12,377) and 1.2% (n = 14,870), respectively. rVE estimates for inpatient IRMEs were close to the null with much wider CI (Fig. 1). Unadjusted rVEs for all analyses are shown in Figure 1, Supplemental Digital Content 1, http://links.lww.com/INF/E764.

Sensitivity Analyses

As shown in Fig. 2, between December 8, 2019, and March 7, 2020 (peak influenza season; Figure 2, Supplemental Digital Content 1, http://links.lww.com/INF/E764), the rVE was 12.5% (95% CI: 7.7–17.1) in any setting (outpatient and inpatient). Applying an

TABLE 2. Subject Demographics at Baseline

Characteristic	IIV4c (n = 60,480)	IIV4e (n = 1,240,990)	SMD
Mean age, years ± SD	11.9±3.7	10.3±4.0	0.48
Female sex, n (%)	29,914 (49.5)	598,557 (48.2)	0.03
Race and ethnicity, n (%)			
Black or African American	2,169 (3.6)	74,575 (6.0)	−0.08
White	28,328 (46.8)	517,198 (41.7)	0.11
Other	8,090 (13.4)	187,785 (15.1)	−0.05
Not reported	21,893 (36.2)	461,432 (37.2)	0.00
Hispanic	5,304 (8.8)	174,833 (14.1)	−0.18
Non-Hispanic	49,163 (81.3)	1,050,096 (84.6)	
Not reported	6,013 (9.9)	16,061 (1.3)	
Geographic region, n (%)			
Northeast	7,931 (13.1)	236,245 (19.0)	−0.13
Midwest	11,177 (18.5)	280,388 (22.6)	−0.07
South	29,927 (49.5)	495,492 (39.9)	0.20
West	11,410 (18.9)	228,374 (18.4)	−0.01
Other	35 (0.1)	491 (0.0)	0.00
CCI ± SD	0.1±0.4	0.2±0.4	−0.16
Outpatient visits, mean ± SD	0.7±1.5	1.1±2.0	−0.35
All-cause hospitalizations, n (%)			
0	44,838 (74.1)	844,978 (68.1)	−0.19
1	9,409 (15.6)	227,727 (18.4)	
≥2	6,233 (10.3)	168,285 (13.6)	
Place of service (data source), n (%)			
Pharmacy only claims	22,574 (37.3)	54,528 (4.4)	0.76
Medical claims	35,095 (58.0)	1,095,911 (88.3)	-0.64
EMR-only claims	2,811 (4.6)	90,551 (7.3)	-0.08

ADL indicates activities of daily living; CCI, Charlson comorbidity index; EMR, electronic medical record; IIV4c, cell-based inactivated quadrivalent influenza vaccine; IIV4e, egg-based inactivated quadrivalent influenza vaccine; SD, standard deviation; SMD, standardized mean difference.

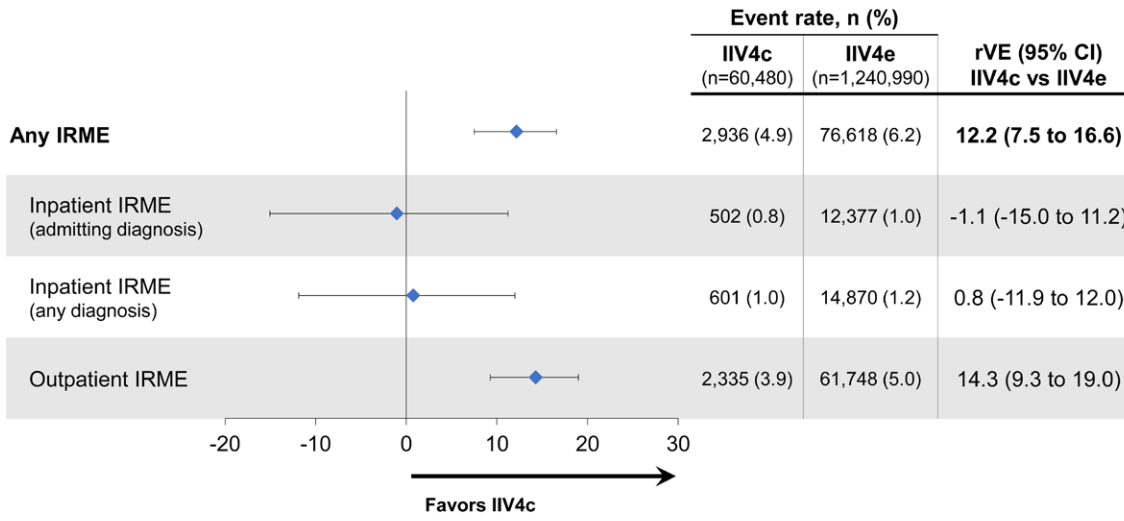

FIGURE 1. Adjusted relative vaccine effectiveness (rVE) of cell-based inactivated quadrivalent influenza vaccine (IIV4c) compared with egg-based inactivated quadrivalent influenza vaccine (IIV4e) among individuals 4 through 17 years in the 2019–2020 influenza season in any setting (primary analysis) and by inpatient and outpatient separately (exploratory analysis). CI, confidence interval; IRME, influenza-related medical encounter. full color online

earlier cutoff before the widespread circulation of the SARS-CoV-2 virus gave an rVE of 12.1% (6.8–17.0), and over the full influenza season, the rVE was 12.0% (7.3–16.4) and hence did not materially change the results. After weighting, UTI rates were 0.6% and 0.9% in the IIV4c and IIV4e cohorts, respectively.

DISCUSSION

In our study, IIV4c provided a 12% greater reduction in IRMEs relative to IIV4e in children and adolescents 4 through 17 years of age. Specifically, rVE against outpatient IRMEs was significantly lower among recipients of IIV4c versus IIV4e. The far less frequent occurrence of inpatient IRME resulted in wide CIs around the null.

The CDC estimated the absolute vaccine effectiveness against all influenza strains during the 2019–2020 US season in young children (age 6 months through 8 years) as 34% (95% CI: 19–46) and in children and adolescents 9 through 17 years as 40% (22–53).[29] Cumulative hospitalization rates and deaths among the pediatric population were the highest reported for the preceding 10 influenza seasons.[30,31] The season was characterized by the early onset of influenza B/Victoria viruses followed by A(H1N1)pdm09 viruses.[32] Against B/Victoria viruses, which were predominantly detected among children and youth, CDC estimated the absolute vaccine effectiveness during the 2019–2020 season of 39% (95% CI: 20–54) and 43% (23–58) for the younger and older pediatric cohorts, respectively.[29] Among B/Victoria viruses, clade V1A.3 viruses predominated (97%), but the vaccine virus belonged to the V1A.1 clade.[32] Fewer circulating B/Victoria viruses were antigenically similar to the egg-propagated vaccine reference virus compared to the cell-propagated vaccine reference virus (60% vs. 8%).[33] For A(H1N1)pdm09 viruses, 6B.1A subclades 5A, 5B and 7 predominated globally whereas the vaccine virus was clade 6B.1A1, indicating genetic drift.[34] While the CDC found that circulating and vaccine A(H1N1) viruses were antigenically similar based on antigenic characterization with ferret antisera, the World Health Organization (WHO) stated that based on human serology studies, circulating A(H1N1) viruses had decreased antigenic similarity to cell-propagated reference virus and even more pronounced differences when compared to an egg propagated reference virus, indicating potential egg-adaptation.[32,34,35] Although we were unable to determine influenza strains from our dataset, our findings nevertheless support the use of a cell-based vaccine, which eliminates the potential for adaptive viral mutations that may occur during the propagation of influenza vaccine viruses in embryonated chicken eggs.[12]

We used a large integrated dataset linking EMRs with medical and pharmacy claims data for the estimation of rVE with robust statistical power in real-world settings.[22,36] By retrospectively ascertaining covariate information from the integrated database in the same manner for both vaccine cohorts, we limited the possibility of differential misclassification. Integration of EMRs and claims data improves the likelihood of capturing all medical encounters and diagnoses, and the variety of the data permitted for adjustment of confounders using a doubly-robust IPTW methodology. Consistent results were demonstrated across sensitivity analyses. Results were similar during the period of peak influenza activity and the SARS-CoV-2 pandemic did not appear to have an effect on these findings, with rVEs similar to the main study during periods ending before the widespread circulation of the virus and extending through May 2020. There is still a possibility of misclassification of SARS-CoV-2 as influenza because SARS-CoV-2 may have been circulating earlier in the season when coding practices for COVID-19 had not yet been established. UTI rates, although uncommon in this age group, were balanced between cohorts after adjustment.

Limitations apply to our study. First, our study design, based on IRMEs, lacked a laboratory-confirmed study outcome. However, results were consistent when limited to the period of a high incidence of laboratory-confirmed influenza as per public health surveillance (Fig. 2).[37] Moreover, incidence rates of laboratory-confirmed influenza reported by the CDC showed a similar trend when compared to the frequency of influenza-related medical encounters in the study cohort (Figure 2, Supplemental Digital Content 1, http://links.lww.com/INF/E764).[37] Second, because of the small number of inpatient events in the pediatric cohort, estimation of rVE in inpatient settings was not feasible. Third, our study population was limited to insured individuals for whom pharmacy and medical claims data were available, and we could not assess outcomes in uninsured individuals. Finally, unmeasured confounding is a potential source of bias in all observational research,

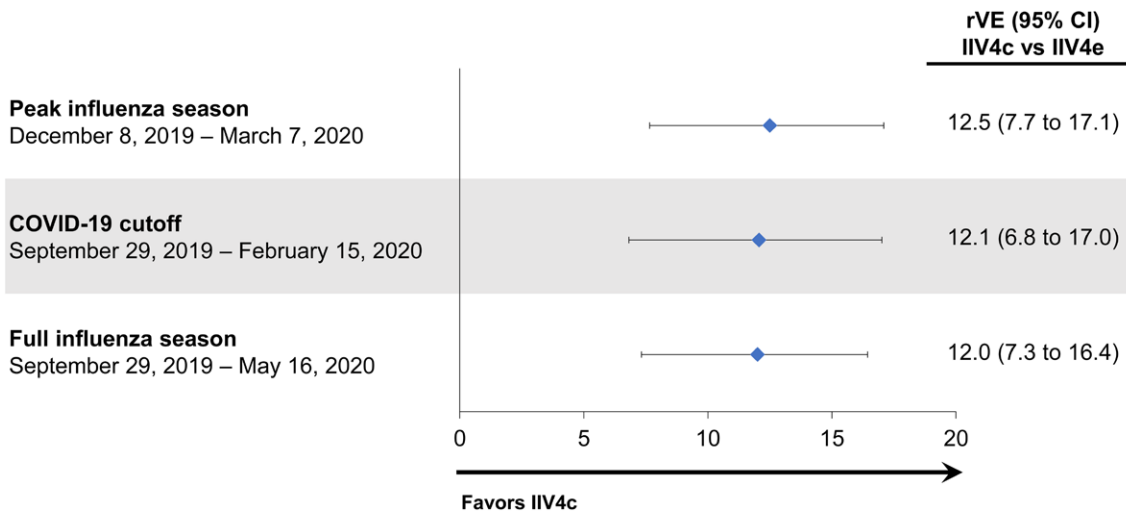

FIGURE 2. Sensitivity analyses determining adjusted relative vaccine effectiveness (rVE) of cell-based inactivated quadrivalent influenza vaccine (IIV4c) compared with egg-based inactivated quadrivalent influenza vaccine (IIV4e) in preventing influenza-related medical encounters (IRME) in any setting (outpatient and inpatient) among individuals 4 through 17 years in the 2019–2020 influenza season. CI, confidence interval. full color online

particularly prominent in studies using routinely collected data, as these data are not specifically collected for research purposes.

CONCLUSION

In this analysis of a large integrated EMR and claims database, IIV4c was associated with statistically significantly fewer IRME versus IIV4e in children and adolescents during the 2019–2020 US influenza season. These findings lend support to the use of IIV4c as a potentially more effective public health measure against influenza than an egg-based equivalent, as demonstrated previously.[21,22,38,39]

ACKNOWLEDGMENTS

Medical consultants C. Gordon Beck and Amanda M. Justice provided editorial support in the preparation of this manuscript, which was funded by Seqirus Inc.

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