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MAJOR ARTICLE

Effectiveness of the Cell-Derived Inactivated Quadrivalent Influenza Vaccine in Individuals at High Risk of Influenza Complications in the 2018–2019 United States Influenza Season

Constantina Boikos,[1] Mahrukh Imran,[1] Van Hung Nguyen,[2] Thierry Ducruet,[2] Gregg C. Sylvester,[3] and James A. Mansi[1]

[1]Seqirus Inc., Kirkland, Quebec, Canada, [2]VHN Consulting, Montreal, Quebec, Canada, [3]Seqirus USA Inc., Summit, New Jersey, USA

Background. Higher rates of influenza-related morbidity and mortality occur in individuals with underlying medical conditions. To improve vaccine effectiveness, cell-based technology for influenza vaccine manufacturing has been developed. Cell-derived inactivated quadrivalent influenza vaccines (cIIV4) may improve protection in seasons in which egg-propagated influenza viruses undergo mutations that affect antigenicity. This study aimed to estimate the relative vaccine effectiveness (rVE) of cIIV4 versus egg-derived inactivated quadrivalent influenza vaccines (eIIV4) in preventing influenza-related medical encounters in individuals with underlying medical conditions putting them at high risk of influenza complications during the 2018–2019 US influenza season.

Methods. An integrated dataset, linking primary care electronic medical records with claims data, was used to conduct a retrospective cohort study among individuals aged ≥4 years, with ≥1 health condition, vaccinated with cIIV4 or eIIV4 during the 2018–2019 season. Adjusted odds ratios (ORs) were derived using a doubly robust inverse probability of treatment-weighting (IPTW) model, adjusting for age, sex, race, ethnicity, geographic region, vaccination week, and health status. Relative vaccine effectiveness was estimated by (1 − OR) × 100 and presented with 95% confidence intervals (CIs).

Results. The study cohort included 471 301 cIIV4 and 1 641 915 eIIV4 recipients. Compared with eIIV4, cIIV4 prevented significantly more influenza-related medical encounters among individuals with ≥1 health condition (rVE, 13.4% [95% CI, 11.4%–15.4%]), chronic pulmonary disease (rVE, 18.7% [95% CI, 16.0%–21.3%]), and rheumatic disease (rVE, 11.8% [95% CI, 3.6%–19.3%]).

Conclusions. Our findings support the use of cIIV4 in individuals ≥4 years of age at high risk of influenza complications and provide further evidence supporting improved effectiveness of cIIV4 compared with eIIV4.

Keywords. cIIV4; eIIV4; influenza; quadrivalent influenza vaccine; relative vaccine effectiveness.

Seasonal influenza causes substantial morbidity and mortality each year in the United States. The Centers for Disease Control and Prevention (CDC) estimates that influenza has resulted in 9 million to 45 million illnesses, 140 000–810 000 hospitalizations, and 12 000–61 000 deaths annually since 2010 [1]. Influenza infections are characterized by the sudden onset of high fever as well as myalgia, headache, severe fatigue, nonproductive cough, sore throat, and runny nose [2]. Most healthy infected individuals recover within 7–14 days without requiring medical treatment; however, individuals with underlying medical conditions, including chronic pulmonary diseases, cardiovascular, renal, hepatic, neurologic, hematologic, and metabolic disorders such as diabetes, are more likely than healthy persons to suffer from influenza complications [3]. In these high-risk populations, influenza infection can lead to exacerbations of chronic illnesses as well as neurological complications, pneumonia, and death [4–7]. For these reasons, the US Advisory Committee on Immunization Practices (ACIP) has designated individuals with the above-listed underlying medical conditions a priority group for annual influenza vaccination [8]. More importantly, however, high-risk individuals are often excluded from randomized trials evaluating vaccine efficacy, and influenza vaccine coverage among US adults with high-risk chronic medical conditions continues to be suboptimal [9].

Standard, egg-derived influenza vaccines have demonstrated suboptimal effectiveness, likely due to the isolation and propagation steps of vaccine production in eggs [10–13]. Egg-based manufacture of influenza vaccines is prone to antigen mismatch due to amino acid substitutions in the influenza hemagglutinin glycoprotein. These substitutions can affect receptor-binding and alter antigenicity [14]. Such antigenic changes are associated with reduced vaccine

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Correspondence: Constantina Boikos, MScPH, PhD, Suite 504, 16766 TransCanada Highway, Kirkland, Quebec, H9H 4M7, Canada (constantina.boikos@seqirus.com).

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performance, particularly in years when A(H3N2) virus strains predominate, and could potentially also reduce effectiveness of influenza pandemic vaccines [12]. These mutations can alter antigenicity and can contribute to reduced effectiveness of egg-derived influenza vaccines [10–13]. In the US 2018–2019 season, influenza vaccines were 29% (95% confidence interval [CI], 21%–35%) effective against influenza-associated illness. Vaccine effectiveness was 44% (95% CI, 37%–51%) against A(H1N1)pdm09-related illnesses but provided limited protection against A(H3N2)-related illnesses (9%; 95% CI, −4% to 20%) [15]. Emerging evidence suggests that egg-adapted mutations in influenza viruses have affected antigenicity against A(H3N2) viruses, which may explain the potential for lower vaccine effectiveness against A(H3N2) observed in the 2018–2019 season in the United States [16].

Alternatively, replication of influenza viruses in cell-based manufacturing avoids adaptive genetic mutations, resulting in a vaccine that includes influenza strains that are more antigenically faithful to the starting candidate virus compared with egg-derived influenza vaccine viruses [16–18]. A cell-based quadrivalent, inactivated influenza vaccine ([cIIV4] Flucelvax Quadrivalent; Seqirus USA Inc., Summit, NJ) was approved in the United States in May 2016. Recent studies have demonstrated significantly improved effectiveness of cIIV4 compared with egg-derived quadrivalent-inactivated influenza vaccine (eIIV4), which has been attributed to a better match between vaccine strains and circulating virus [19–21]. The effectiveness of cell-based vaccines has not been evaluated in persons with underlying medical conditions who are at increased risk of influenza complications. This retrospective cohort study aimed to estimate the real-world effectiveness of cIIV4 relative to eIIV4 in individuals ≥4 years of age with underlying medical conditions who are at high risk of influenza complications during the US 2018–2019 influenza season.

METHODS

Study Design

A retrospective cohort study was conducted among a subset of patients who had underlying health conditions from a larger retrospective cohort study evaluating the rVE of cIIV4 versus eIIV4 in US individuals during the 2018–2019 influenza season [22]. 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 (RECORD) recommendations.

Data Sources and Linkage

An integrated dataset was created by linking primary care and specialty clinic patient-level electronic medical records (EMRs) from Veradigm Health Insights (Allscripts Touchworks & Allscripts PRO, Chicago, IL, as well as Practice Fusion, Inc., San Francisco, CA) with pharmacy and medical claims data, where available (Komodo Health Inc., New York, NY). A third party (Datavant, San Francisco, CA) performed deidentification and linkage. Tokens from the identifiable information (last name, first name, sex, birth date) were created separately for each patient in both data sources. For patients in both sources with matches on both tokens, 1 unique patient identifier was created and the 2 data sources were linked using the patient identifier. The dataset was checked to verify that it contained no Protected Health Information (PHI) and was evaluated and certified for Health Insurance Portability and Accountability Act (HIPAA) compliance. Research staff were not involved in preparation of datasets containing PHI or the running of the linkage algorithm.

Study Population

The study population included US residents ≥4 years of age with ≥1 health condition who had a record of receiving either eIIV4 or cIIV4 between August 1, 2018 and February 28, 2019 and had at least 1 record in the primary care EMR platform 12 months before the recorded vaccination date. Subjects were considered "fully vaccinated" 14 days after vaccination to allow for the development of vaccine-specific immunity. Subjects were excluded from the cohort if they (1) were ≥9 years of age and had received >1 influenza vaccination during the 2018–2019 influenza season, (2) were <9 years of age and had received >2 influenza vaccinations during the 2018–2019 influenza season, or (3) had an influenza-related medical encounter during the 2018–2019 season but before the vaccination date.

Health conditions of subjects identified from the integrated dataset were defined using the Charlson Comorbidity Index (CCI) categories and coded according to an adaptation of Deyo-Charlson comorbidity score (Supplementary Table 1) [23]: chronic pulmonary disease (including chronic lower respiratory diseases, respiratory conditions due to external agents, pulmonary heart diseases, and lung diseases), asthma (a subcategory of chronic pulmonary disease that was identified a priori for separate evaluation given its prevalence in the United States [24]), myocardial infarction and/or congestive heart failure, cerebrovascular disease and/or peripheral vascular disease, renal disease, diabetes with chronic complication and/or diabetes without chronic complication, any malignancy and/or metastatic solid tumors, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), rheumatic disease, mild liver disease and/or moderate or severe liver disease. Individuals with these underlying conditions have been identified by the CDC as being at higher risk for complications due to influenza [8]. High-risk categories were not mutually exclusive, and individual patients could be included in more than 1 category.

Patient Consent

This study was a noninterventional, retrospective database study using a certified HIPAA-compliant deidentified research database. Approval for this analysis by an institutional review board was not necessary.

Exposure Ascertainment

Potential study subjects were identified if they had a record of an influenza immunization between August 1, 2018 and February 28, 2019. The date of recorded immunization was considered the index date. Eligible study participants were classified into 2 exposure cohorts based on the type of influenza vaccine (cIIV4 or eIIV4) recorded in either the EMR or the claims components of the integrated dataset. Current Procedural Terminology (CPT) codes, codes for vaccines administered (CVX), and national drug codes (NDCs) (Supplementary Table 2) were used to ascertain exposure status.

Outcome Ascertainment

The primary outcome of interest was the occurrence of influenza-related medical encounters in both hospital and primary care, defined by *International Classification of Diseases* (ICD) codes specific to influenza (ICD-10 J09*-J11*), ascertained from both the EMR and claims components of the integrated dataset. The diagnostic codes used correspond to the US Armed Forces Health Surveillance Center (AFHSC) Code Set B, which includes only influenza-specific ICD codes (Supplementary Table 3) [25]. Code Set B was identified a priori as the primary outcome of interest because it corresponded to a higher positive predictive value for influenza in a validation study conducted within a population of Armed Forces members and their dependents [26]. In addition, a secondary, broader case-definition for "influenza-like illness (ILI)" defined by AFHSC Code Set A was also evaluated (Supplementary Table 3).

Covariates

Covariates of interest were identified in the 12 months before the recorded date of immunization with cIIV4 or eIIV4 (termed the "pre-index period"). Data were ascertained from each subject's EMR on age (categorical: ≥4 years, ≥4 to ≤17 years, ≥18 to ≤49 years, ≥18 to ≤64 years, ≥50 to ≤64 years, and ≥65 years), sex (male, female), race and ethnicity (black, white, Hispanic, other), US geographic region (South, West, Northeast, Midwest, Other), and health status (quantified using binary variables for categories in the CCI) [23, 27]. Covariate balance between the exposure groups before and after weighting was assessed using Austin's standardized mean difference before and after inverse probability of treatment weighting (IPTW), with a value ≤0.1 indicating a negligible difference in proportions between exposure groups [28, 29].

Observation Period

Ascertainment of exposure and outcome spanned between August 1, 2018 and May 18, 2019.

Statistical Methods

Per Protocol

A descriptive analysis was conducted for both vaccine cohorts. Continuous and categorical variables were reported as mean ± standard deviation and proportional values, respectively. Unadjusted odd ratios (ORs) of influenza-related medical encounters were estimated from a univariable model with vaccine type as the only predictor variable. Adjusted ORs were derived from a weighted sample using IPTW. First, a multivariable logit model adjusted for age, sex, race, ethnicity, geographic region, week of influenza vaccination, and health status was used to generate propensity scores (PSs) to estimate the probability of receiving ccIIV4 versus eIIV4. An individual's health status was quantified using binary variables that corresponded to health categories in the CCI (ie, presence or absence of high-risk condition). All binary variables were included in the model with the exception of the medical condition under evaluation. Propensity scores were regenerated for each cohort defined by a high-risk condition and used to create stabilized IPTW weights. Weights were truncated at the 3rd and 97th percentile weight to attenuate any extreme variability from outlier patients. Adjusted ORs were then estimated for the full study sample and for each individual high-risk category using a logistic regression model (record of influenza-related medical encounter versus no influenza-related medical encounter as outcome) in the IPTW-weighted cohort with vaccine type as the predictor. The rVE was calculated as $100 \times (1 - \mathrm{OR}_{\mathrm{adjusted}})$ and reported with 95% CIs. Categorical variables with missing or null values in the EMR were classified as "not reported" or "unknown." Missing or out-of-range values were not imputed. All analyses were conducted using SQL and SAS version 9.4.

Post hoc

A doubly robust IPTW analysis was conducted post hoc to account for any residual confounding of adjusted rVE estimates from measured covariates [30]. Adjusted ORs for the overall study population and for each high-risk category were re-estimated in an IPTW-weighted sample using a multivariable model that included vaccination status as a predictor as well as all variables from the PS-generation model.

RESULTS

In total, 2 113 216 individuals with at least 1 health condition were included in the study, 471 301 (22.3%) of whom had a record of immunization with cIIV4 and 1 641 915 (77.7%) had a record of immunization with eIIV4 (Table 1). Among cIIV4 recipients, 25.8% reported an influenza-related medical encounter compared with 27.1% in the eIIV4 high-risk

Table 1. Patient Selection Process

Criteria	Patients (No.) Overall	Patients (%) Overall	Stepwise Change (%)
1) Patient received influenza vaccine between August 1, 2018 and February 28, 2019	14 734 352	100.0%	-
2) Patient is ≥4 at time of immunization	14 211 914	96.5%	96.5%
3) Patient does not have more than 1 influenza immunization during the influenza season unless they are <9 years of age	13 848 844	94.0%	97.4%
4) Patient does not have an influenza-related medical encounter in the influenza season before immunization	13 808 250	93.7%	99.7%
5) Patient has a transcript record in the Veradigm EMR at least 1 year before immunization date	10 126 333	68.7%	73.3%
6) Patient has ≥1 selected health condition	2 113 216	14.3%	20.9%
Total number of cIIV4	471 301	3.2%	22.3%
Total number of eIIV4	1 641 915	11.1%	77.7%

Abbreviations: ccIIV4, cell-based quadrivalent inactivated influenza virus; eIIV3, egg-derived quadrivalent inactivated influenza virus; EMR, electronic medical record.

cohort. Table 2 lists baseline demographics for the 2 cohorts. Subjects receiving cIIV4 were approximately 8 years older, on average, than eIIV4 recipients. In the cIIV4 and eIIV4 groups, the majority of subjects were female (58% and 57%, respectively), white (53% and 57%), and not Hispanic (>75% in both groups). The largest proportions in each group resided in southern United States (52% of cIIV4 and 39% of eIIV4 recipients). Diabetes (43% and 36% of cIIV4 and eIIV4 recipients, respectively) and chronic pulmonary disease (37% and 46%) were the most common high-risk comorbidities in

Table 2. Subject Demographics at Baseline

Characteristic	cIIV4 (n = 471 301)	eIIV4 (n = 1 641 915)
Mean age, years ± SD	60.2 ± 16.1	51.6 ± 20.7
Female sex, n (%)	275 499 (58.5)	933 021 (56.8)
Race, n (%)		
White	249 394 (52.9)	931 869 (56.8)
Black or African American	43 635 (9.3)	142 964 (8.7)
Other	52 368 (11.1)	176 525 (10.8)
Not reported	125 904 (26.7)	390 557 (23.8)
Ethnicity, N (%)		
Non-Hispanic	371 805 (78.9)	1 260 730 (76.8)
Hispanic	39 748 (8.4)	146 497 (8.9)
Not reported	59 748 (12.7)	234 688 (14.3)
Geographic region, n (%)		
Northeast	79 837 (16.9)	302 342 (18.4)
Midwest	60 221 (12.8)	372 724 (22.7)
South	246 374 (52.3)	638 307 (38.9)
West	76 899 (16.3)	305 741 (18.6)
Unknown	7970 (1.7)	22 801 (1.4)
High-Risk Health Condition, n (%)		
Chronic pulmonary disease	173 301 (36.8)	758 446 (46.2)
Asthma*	107 423 (22.8)	543 648 (33.1)
Myocardial infarction or congestive heart failure	41 348 (8.8)	117 924 (7.2)
Cerebrovascular disease or peripheral vascular disease	39 786 (8.4)	110 586 (6.7)
Renal disease	50 329 (10.7)	121 517 (7.4)
Diabetes with or without chronic complications	200 617 (42.6)	589 941 (35.9)
Any malignancy or metastatic tumor	54 646 (11.6)	168 565 (10.3)
AIDS/HIV	5035 (1.1)	16 357 (1.0)
Rheumatic disease	33 979 (7.2)	104 278 (6.4)
Mild, moderate, or severe liver disease	33 005 (7.0)	126 382 (7.7)
Charlson Comorbidity Index, mean ± SD	2.1 ± 1.4	1.9 ± 1.3

Abbreviations: AIDS, acquired immune deficiency syndrome; cIIV4, cell-based quadrivalent inactivated influenza virus; eIIV4, egg-derived quadrivalent inactivated influenza virus; HIV, human immunodeficiency virus; SD, standard deviation.
*Subcategory of chronic pulmonary disease.

both groups. Of individuals with chronic pulmonary disease, asthma was the most common condition. The Charlson comorbidity scores were 2.1 ± 1.4 in the cIIV4 and 1.9 ± 1.3 in the eIIV4 cohorts (Table 2). Although several imbalances between the exposure groups were observed before IPTW, after IPTW the majority of covariates had a standardized mean difference of <0.1 (Supplementary Figure 1).

As shown in Figure 1, the unadjusted rVE for cIIV4 versus eIIV4 in the overall study population of individuals with at least 1 underlying medical condition was 29.4% (95% CI, 27.7% to 31.0%), and the PS-IPTW adjusted rVE was 18.9% (95% CI, 17.0% to 20.8%). The PS-IPTW adjusted rVE for subjects with chronic pulmonary disease, asthma, and diabetes (the most common underlying medical conditions) were 26.3% (95% CI, 23.8% to 28.6%), 30.0% (95% CI, 27.4% to 32.6%), and 0.4% (95% CI, −3.5% to 4.3%), respectively. After post hoc doubly robust IPTW adjustment, the rVE for cIIV4 versus eIIV4 in the overall population was 13.4% (95% CI, 11.4% to 15.4%), and among those with chronic pulmonary disease, asthma, and diabetes it was 18.7% (95% CI, 16.0% to 21.3%), 21.4% (95% CI, 18.4% to 24.3%), and 1.1% (95% CI, −2.9% to 4.9%), respectively (Figure 1C). Unadjusted and adjusted results using broadly defined ILI (Code Set A) are shown in Supplementary Figure 2.

DISCUSSION

During the 2018–2019 US influenza season, standard influenza vaccines provided limited protection against A(H3N2)-related illnesses [15]. Although the flu season began with A(H1N1) pdm09 viruses predominating in most US regions, the proportion of illness caused by antigenically distinct A(H3N2) viruses increased during the season, ultimately predominating throughout the United States after February 2019 [15]. Antigenic differences between egg-passaged vaccine viruses and circulating A(H3N2) viruses may have contributed to the observed reduced vaccine effectiveness, along with other factors [15, 31, 32]. Overall, the 2018–2019 US influenza experience highlights recent challenges with the effectiveness of egg-derived vaccines against influenza A(H3N2) viruses and the need for alternative production platforms that prevent egg-adaptive mutations [15]. The production of vaccines using cell-based influenza viruses eliminates opportunities for viral mutations to occur during the

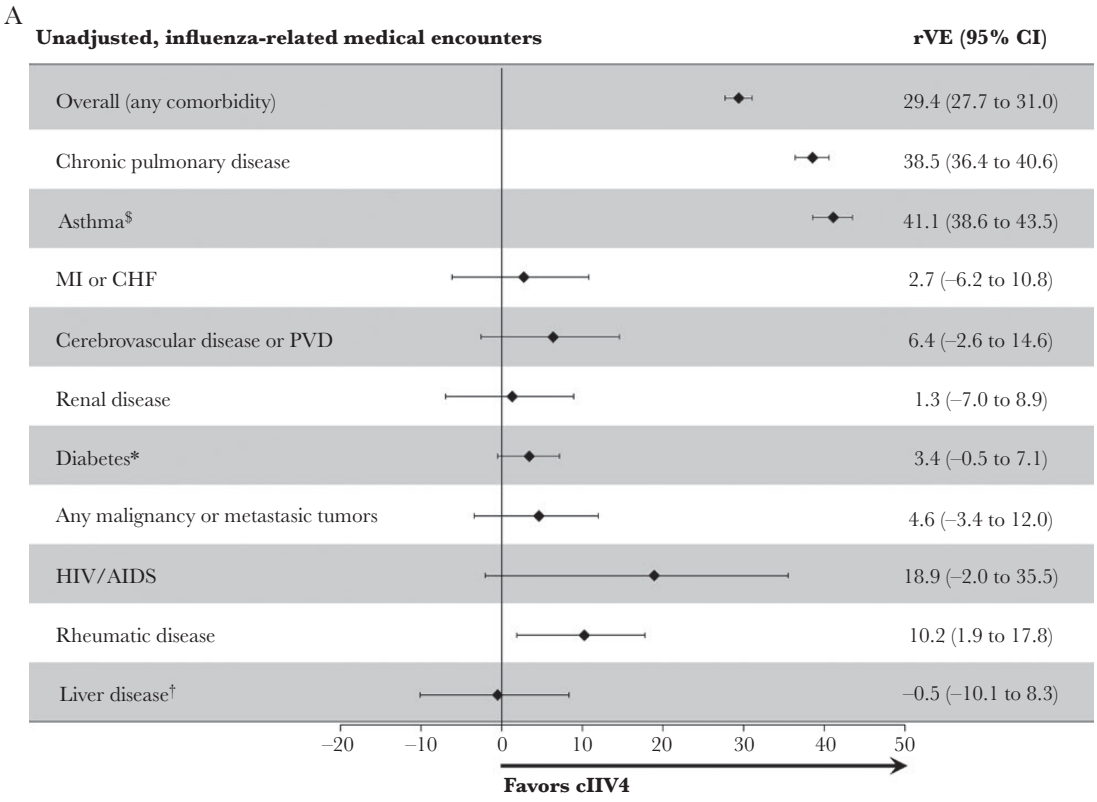
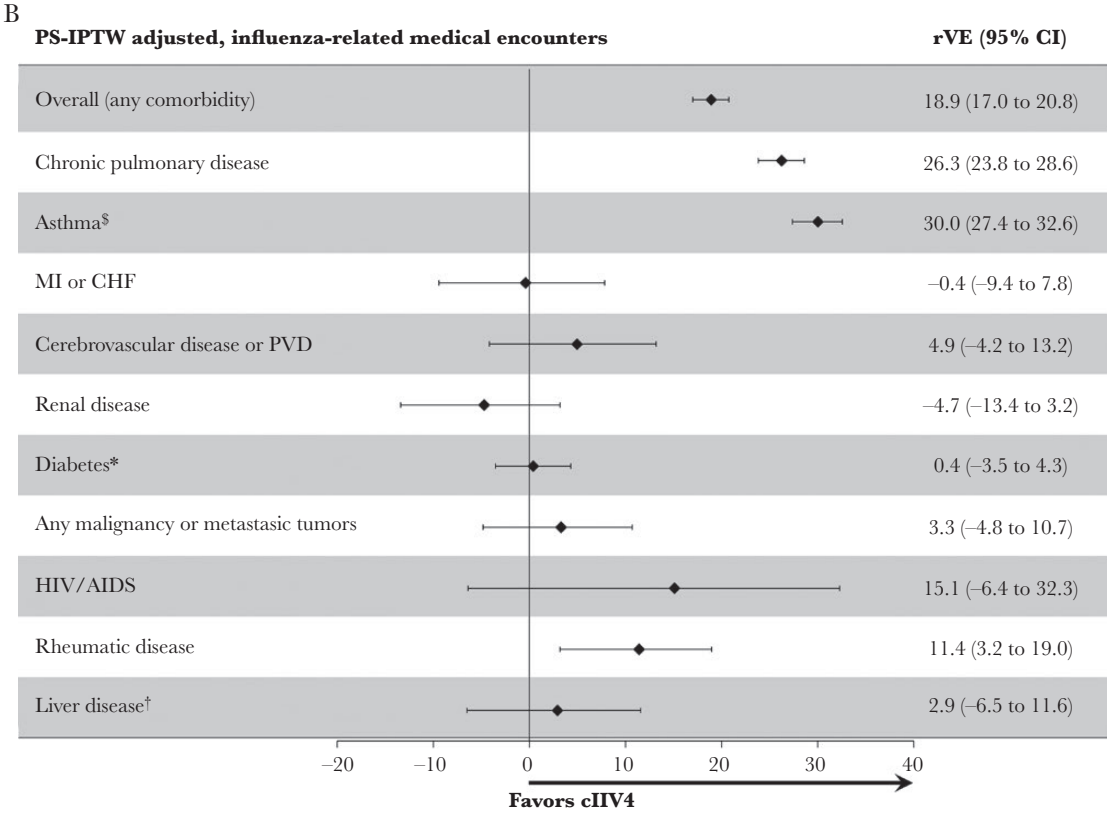


Figure 1. Relative vaccine effectiveness (rVE) of cell-based quadrivalent inactivated influenza virus (cIIV4) compared with egg-derived quadrivalent inactivated influenza virus (eIIV4) in preventing influenza-related medical encounters (Armed Forces Health Surveillance Center [AFHSC] Code Set B) among high-risk individuals ≥4 years in the 2018–2019 influenza season. (A) Unadjusted rVE. (B) Adjusted using propensity score (PS)-inverse probability of treatment weighting (IPTW) for age, sex, race, ethnicity, geographic region, week of influenza vaccination, and health status. (C) Doubly robust adjustment using a multivariable model that included an IPTW-weighted sample and all variables from the PS-IPTW model as covariates. *With or without chronic complications. †Mild, moderate, or severe. $Subcategory of chronic pulmonary disease. AIDS, acquired immune deficiency syndrome; CHF, congestive heart failure; CI, confidence interval; HIV, human immunodeficiency virus; MI, *myocardial infarction; PVD,* peripheral vascular disease.



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virus propagation step and maintains viral antigenicity, which supports the improved effectiveness of cIIV4 observed in this study [33].

In this analysis of more than 2 million vaccinated individuals at high risk of influenza disease and sequelae, cIIV4 was statistically significantly more effective in preventing influenza-related medical encounters than eIIV4 in the overall cohort with ≥1 health condition. The trend was consistent among those with chronic pulmonary disease, including asthma, and for those with rheumatic disease. Nonstatistically significant estimates preclude definitive conclusions for the other high-risk groups; however, trends in point estimates suggested benefit of vaccination with cIIV4 in most high-risk categories. Although the relative effectiveness of cIIV4 compared with egg-derived vaccines has been studied in the general population [19–21, 34–37], this is one of the first large-scale cohort studies assessing the effectiveness of cIIV4 versus eIIV4 in individuals with health conditions who are at high risk of developing influenza complications. These results are consistent with the larger retrospective cohort study evaluating more than 10 million vaccinated individuals ≥4 years wherein cIIV4 was statistically significantly more effective than egg-derived eIIV4 [22]. Findings from this study provide further evidence supporting the improved effectiveness of cIIV4 against influenza compared with eIIV4 and are particularly important because chronic health conditions increase an individual's risk of influenza infection, complications, and death [3]. For this reason, most national recommendations regarding influenza vaccination are primarily focused on protection of individuals at higher risk of influenza complications and include those with chronic health conditions [8, 38–42].

Results from this study must be interpreted considering several limitations that are inherent to retrospective cohort studies conducted using routinely collected data. The study was limited by the lack of a laboratory-confirmed influenza outcome. However, a descriptive evaluation of the overlap between the incidence of CDC-reported, laboratory-confirmed influenza and the incidence of influenza-related medical encounters (AFHSC Code Set B) in the integrated dataset was conducted in the larger retrospective cohort study [22]. Concordance between trends was observed, supporting the use of the diagnostic AFHSC Code Set B in evaluations of influenza. Although a large proportion of individuals with health conditions were identified for inclusion in the study, stratification by specific medical condition resulted in small subgroup sample sizes, limiting statistical power to detect differences in vaccine effectiveness in some comparisons. Moreover, identification of high-risk conditions from diagnostic codes does not differentiate by the level of severity or immunosuppression within each specific condition. For instance, the current coding scheme did not differentiate

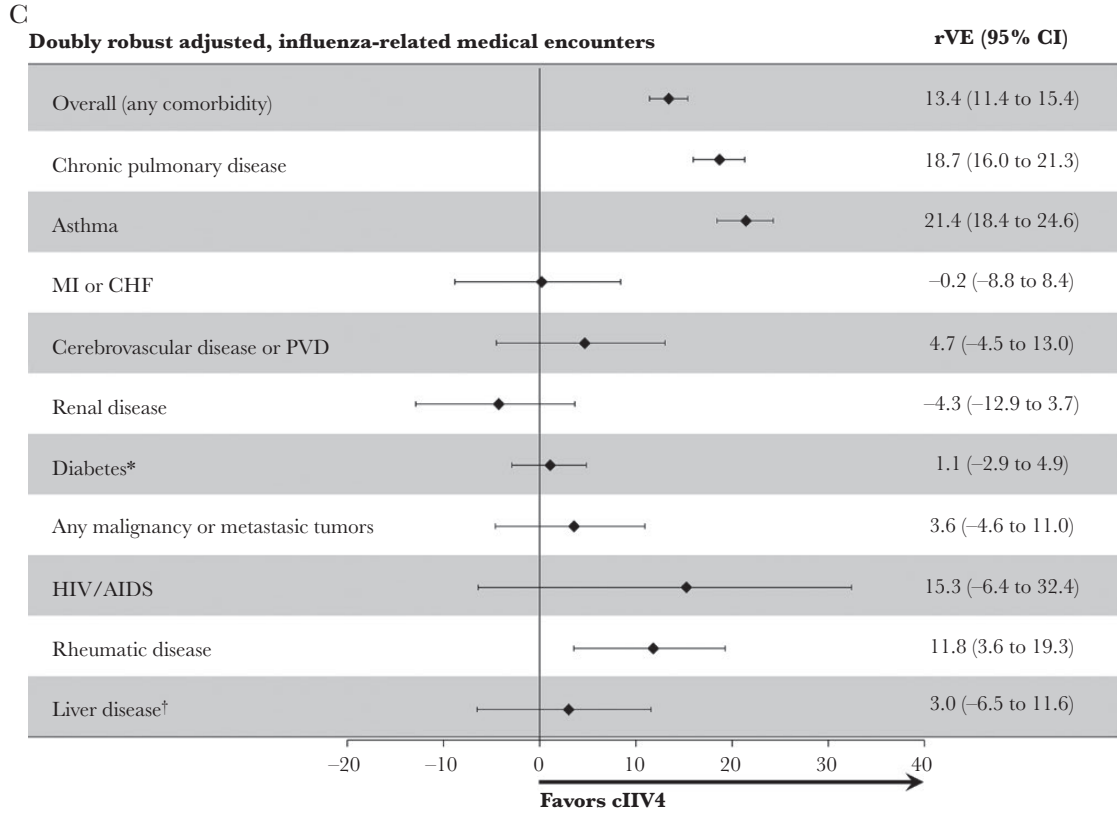

Figure 1. Continued.

between mild-to-moderate and severe renal disease. As such, nuances in vaccine effectiveness caused by these factors may not be captured. Another limitation of this study was that the main analysis did not specifically adjust for functional status, healthcare seeking behavior, or receipt of an influenza vaccine in the previous season. The study population included individuals for whom at least some pharmacy and medical claims data were available, thus limiting the study cohort to insured individuals but not requiring healthcare resource utilization beyond the index date. Moreover, rVE was not estimated by age group within each high-risk condition given the limited sample sizes of some high-risk groups (such as HIV/AIDS, rheumatic disease, and liver disease). As such, point estimates in the overall high-risk categories may mask an interaction effect between age and vaccination. However, the confounding effect of age was adjusted for using the (doubly robust) IPTW methodology. Finally, as with all observational studies, vaccination was not randomly assigned, and unmeasured confounding might bias estimates.

Despite these limitations, this analysis has several key strengths. The use of a large, real-world dataset integrating sources of patient information allowed us to evaluate an effectiveness outcome that is not typically analyzed in randomized trials. The large dataset allowed for the estimation of effects with robust statistical power in the overall cohort of high-risk individuals. Integrated databases linking both EMR and claims data provide the most well rounded picture of the health status and service utilization of both individuals and populations. Inclusion of both EMR and claims data increases the likelihood that most—if not all—medical interventions and diagnoses are captured within the study dataset. Furthermore, the variety and completeness of data also permitted the adjustment of several well established confounders. Exposure, outcome, and covariate information were ascertained retrospectively from the integrated dataset in exactly the same manner for both exposure cohorts, limiting the possibility of differential misclassification. The database allowed the identification of high-risk patients with underlying health conditions and adjustment for health status using validated ICD-9/10 algorithms for CCI categories. In addition, we implemented doubly robust adjustment methodology in our statistical analyses to further control for any residual confounding.

CONCLUSIONS

The results of this study demonstrate that cIIV4 was statistically significantly more effective in preventing influenza-related medical encounters compared with eIIV4 for individuals with at least 1 identified health condition. Findings from this study are consistent with previously published research evaluating the relative benefit

of cIIV4 compared with egg-derived vaccines [19–21, 34, 35, 37]. The results of this study support the use of cIIV4 in individuals at high risk of influenza complications and provides further evidence supporting the improved effectiveness of cIIV4 compared with eIIV4 against influenza-related outcomes.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. J. A. M., C. B., and G. C. S. were responsible the study conceptualization and design; J. A. M., C. B., G. C. S., V. H. N., and T. D. were responsible for study and analyses; all authors contributed to manuscript development and editorial review.

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Potential conflicts of interest. J. A. M., C. B., G. C. S., and M. I. are employees of Seqirus Inc. V. H. N. is the owner and T. D. is an employee of VHN and funding for their work was provided by Seqirus Inc. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Tokars JI, Olsen SJ, Reed C. Seasonal incidence of symptomatic influenza in the United States. Clin Infect Dis **2018**; 66:1511–8.
2. Krammer F, Smith GJD, Fouchier RAM, et al. Influenza. Nat Rev Dis Primers **2018**; 4:3.
3. Restivo V, Costantino C, Bono S, et al. Influenza vaccine effectiveness among high-risk groups: a systematic literature review and meta-analysis of case-control and cohort studies. Hum Vaccin Immunother **2018**; 14:724–35.
4. Rothberg MB, Haessler SD. Complications of seasonal and pandemic influenza. Crit Care Med **2010**; 38:e91–7.
5. Sandrock CE, Norris A. Infection in severe asthma exacerbations and critical asthma syndrome. Clin Rev Allergy Immunol **2015**; 48:104–13.
6. Biancardi E, Fennell M, Rawlinson W, Thomas PS. Viruses are frequently present as the infecting agent in acute exacerbations of chronic obstructive pulmonary disease in patients presenting to hospital. Intern Med J **2016**; 46:1160–5.
7. Mauskopf J, Klesse M, Lee S, Herrera-Taracena G. The burden of influenza complications in different high-risk groups: a targeted literature review. J Med Econ **2013**; 16:264–77.
8. Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2019–20 influenza season. MMWR Recomm Rep **2019**; 68:1–21.
9. Harrison SM, Wei MY, Lamerato LE, et al. Multimorbidity is associated with uptake of influenza vaccination. Vaccine **2018**; 36:3635–40.
10. World Health Organization. Report prepared for the WHO annual consultation on the composition of influenza vaccine for the Northern Hemisphere 2017–2018. Available at: https://www.who.int/influenza/vaccines/virus/recommendations/2017_18_north/en/. Accessed 25 November 2020.
11. Wu NC, Zost SJ, Thompson AJ, et al. A structural explanation for the low effectiveness of the seasonal influenza H3N2 vaccine. PLoS Pathog **2017**; 13:e1006682.
12. Zost SJ, Parkhouse K, Gumina ME, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. Proc Natl Acad Sci U S A **2017**; 114:12578–83.
13. Blanton L, Wentworth DE, Alabi N, et al. Update: influenza activity - United States and worldwide, May 21-September 23, 2017. MMWR Morb Mortal Wkly Rep **2017**; 66:1043–51.
14. Parker L, Wharton SA, Martin SR, et al. Effects of egg-adaptation on receptor-binding and antigenic properties of recent influenza A (H3N2) vaccine viruses. J Gen Virol **2016**; 97:1333–44.
15. Flannery B, Kondor RJG, Chung JR, et al. Spread of antigenically drifted influenza A(H3N2) viruses and vaccine effectiveness in the United States during the 2018–2019 season. J Infect Dis **2020**; 221:8–15.
16. Rajaram S, Van Boxmeer J, Leav B, Suphaphiphat P, Iheanacho I, Kistler K. Retrospective evaluation of mismatch from egg-based isolation of influenza strains compared with cell-based isolation and the possible implications for vaccine effectiveness. Open Forum Infect Dis **2018**; 5:X69.
17. Katz JM, Naeve CW, Webster RG. Host cell-mediated variation in H3N2 influenza viruses. Virology **1987**; 156:386–95.
18. Rocha EP, Xu X, Hall HE, et al. Comparison of 10 influenza A (H1N1 and H3N2) haemagglutinin sequences obtained directly from clinical specimens to those of MDCK cell- and egg-grown viruses. J Gen Virol **1993**; 74(Pt 11):2513–8.
19. Boikos C, Sylvester GC, Sampalis JS, Mansi JA. Relative effectiveness of the cell-cultured quadrivalent influenza vaccine compared to standard, egg-derived quadrivalent influenza vaccines in preventing influenza-like illness in 2017–2018. Clin Infect Dis **2020**; 71:e665–71.
20. Izurieta HS, Chillarige Y, Kelman J, et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among elderly persons in the United States, 2017–2018. J Infect Dis **2019**; 220:1255–64.
21. Divino V, Krishnarajah G, Pelton SI, et al. A real-world study evaluating the relative vaccine effectiveness of a cell-based quadrivalent influenza vaccine compared to egg-based quadrivalent influenza vaccine in the US during the 2017-18 influenza season. Vaccine **2020**; 38:6334–43.
22. Boikos C, Fischer L, O'Brien D, Vasey J, Sylvester GC, Mansi JA. Relative effectiveness of the cell-derived inactivated quadrivalent influenza vaccine versus egg-derived inactivated quadrivalent influenza vaccines in preventing influenza-related medical encounters during the 2018–2019 influenza season in the United States. Clin Infect Dis **2021**. doi: 10.1093/cid/ciaa1944.
23. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care **2005**; 43:1130–9.
24. Centers for Disease Control and Prevention. Most recent national asthma data. Available at: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. Accessed 25 November 2020.
25. Armed Forces Health Surveillance Center (AFHSC). AFHSC Standard Case Definitions: Influenza-Like Illness. Falls Church, VA: Defense Health Agency; **2015**.
26. Eick-Cost AA, Hunt DJ. Assessment of ICD-9-based case definitions for influenza-like illness surveillance. MSMR **2015**; 22:2–7.
27. Sundararajan V, Henderson T, Perry C, et al. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol **2004**; 57:1288–94.
28. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med **2015**; 34:3661–79.
29. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med **2009**; 28:3083–107.
30. Funk MJ, Westreich D, Wiesen C, et al. Doubly robust estimation of causal effects. Am J Epidemiol **2011**; 173:761–7.
31. Belongia EA, McLean HQ. Influenza vaccine effectiveness: defining the H3N2 problem. Clin Infect Dis **2019**; 69:1817–23.
32. Monto AS, Petrie JG. Improving influenza vaccine effectiveness: ways to begin solving the problem. Clin Infect Dis **2019**; 69:1824–6.
33. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis **2016**; 16:942–51.
34. DeMarcus L, Shoubaki L, Federinko S. Comparing influenza vaccine effectiveness between cell-derived and egg-derived vaccines, 2017–2018 influenza season. Vaccine **2019**; 37:4015–21.
35. Eick-Cost A, Hu Z. Relative effectiveness of cell-based influenza vaccines compared to egg-based influenza vaccines, active component U.S. service members, 2017–18 season. International Conference on Emerging Infectious Diseases (Atlanta, GA). August 26–29, 2018. Available at: https://www.cdc.gov/iceid/2018/index.html
36. Izurieta HS, Chillarige Y, Kelman J, et al. Relative effectiveness of influenza vaccines among the United States elderly, 2018-2019. J Infect Dis **2020**; 222:278–87.
37. Bruxvoort KJ, Luo Y, Ackerson B, et al. Comparison of vaccine effectiveness against influenza hospitalization of cell-based and egg-based influenza vaccines, 2017–2018. Vaccine **2019**; 37:5807–11.
38. Zhao L, Young K, Gemmill I. Summary of the NACI seasonal influenza vaccine statement for 2019–2020. Can Commun Dis Rep **2019**; 45:149–55.
39. Public Health England. Influenza: the green book, chapter 19. Available at: https://www.gov.uk/government/publications/influenza-the-green-book-chapter-19. Accessed 21 September 2020.

40. Standing Committee on Vaccination (STIKO) at the Robert Koch Institute. Recommendations of the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute—2017/2018. Epidemiolog Bull **2017**; 34:333–76.
41. Australian Technical Advisory Group on Immunisation. Statement on the administration of seasonal influenza vaccines in 2019. Available at: https://www.health.gov.au/resources/publications/atagi-advice-on-seasonal-influenza-vaccines-in-2019. Accessed 21 September 2020.
42. World Health Organization. Influenza (seasonal). Available at: https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal). Accessed 19 April 2020.