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# Influenza Vaccine Administration and Effectiveness Among Children and Adults With Glomerular Disease

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**Introduction:** Influenza infections contribute to excess healthcare utilization, morbidity, and mortality in individuals with glomerular disease (GD); however, influenza vaccination may not yield protective immune responses in this high-risk patient population. The objective of the present study was to describe influenza vaccine administration from 2010 to 2019 and explore the effectiveness of influenza vaccination in patients with GD.

**Methods:** We conducted an observational cohort study using healthcare claims for seasonal influenza vaccination (exposure) as well as influenza and influenza-like illness (outcomes) from commercially insured children and adults <65 years of age with primary GD in the Merative MarketScan Research Databases. Propensity score-weighted cox proportional hazards models and ratio-of-hazard ratios (RHR) analyses were used to compare influenza infection risk in years where seasonal influenza vaccines matched or mismatched circulating viral strains.

**Results:** The mean proportion of individuals vaccinated per season was 23% (range 19%–24%). In pooled analyses comparing matched to mismatched seasons, vaccination was minimally protective for both influenza (RHR 0.86, 95% confidence interval [CI]: 0.52–1.41) and influenza-like illness (RHR 0.86, 95% CI 0.59–1.24), though estimates were limited by sample size.

**Conclusion:** Rates of influenza vaccination are suboptimal among patients with GD. Protection from influenza after vaccination may be poor, leading to excess infection-related morbidity in this vulnerable population.

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Individuals with GD represent 7.4% of the approximately 30 million Americans with chronic kidney disease.[1] Patients with chronic kidney disease, especially those with GD, are at increased risk of vaccine-preventable infections, placing them at high risk for infection-related morbidity and mortality.[2-10] Risk factors include proteinuria resulting in urinary loss of immunoglobulin, immune dysregulation, and exposure to immunosuppression.[11-13] Despite widespread availability of influenza vaccines in the United States, vaccine-preventable influenza infections remain a major burden for patients and the healthcare system, resulting annually in 1 million influenza-related hospitalizations and 80,000 influenza-related deaths.[14] Although influenza vaccination is an efficacious and cost-effective intervention to reduce morbidity and healthcare utilization in the general population, vaccination may not yield protective or sustained immune responses in patients with GD as a result of exposure to immunosuppressive medications, systemic inflammation, altered immune cell function, and urinary loss of immunoglobulin and complement factors.[15,16]

Patients with GD are typically excluded from vaccine efficacy trials[17] and prospective clinical trials are

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time consuming and costly. As a result, clinicians and patients often rely on post-licensure immunogenicity data or expert opinion to inform decisions regarding vaccine timing and likely effectiveness.[10] We used healthcare claims data and year-to-year differences in vaccine-to-circulating strain match to estimate risk of influenza and influenza-like illness following influenza vaccination among individuals with primary GD.

## METHODS

### Participant Population and Cohort Assembly

The Merative MarketScan Commercial Claims and Encounters database includes inpatient and outpatient medical and pharmacy prescription claims from approximately 50 commercial fee-for-service healthcare plans that provide healthcare benefits to >15 million persons annually in the United States, including active or retired employees as well as their spouses and dependents. Incident GD was identified among individuals <65 years of age over a 9-year period (January 1, 2010–December 11, 2018) by identifying the International Classification of Diseases, 9th Revision, Clinical Modification or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-9-CM/10-CM) billing codes for GD during the study period (Supplementary Table S1). Forward-backward mapping[18] using general equivalence mappings[19] were used to identify ICD-10-CM codes for GD from a published list of ICD-9-CM GD codes.[20] In a sensitivity analysis, inclusion or exclusion codes were adapted from a previously validated computable phenotype for GD[21] yielding a smaller GD cohort presumed to have a higher specificity for GD (Supplementary Table S1). To restrict to only new-onset GD, patients were required to have 1 inpatient or 2 outpatient billing codes ≥30 and ≤365 days apart[20] following at least 1 year, and up to 5 years, of continuous enrollment in a fee-for-service insurance plan with prescription drug coverage with no GD billing codes present. To restrict the cohort to primary GDs, a list of exclusion codes was applied, including codes for systemic GDs, vasculitis, hepatitis B and C, HIV, or malignancy occurring up to 5 years prior to enrollment. Those with codes for dialysis or solid organ transplantation were also excluded. After establishing incident GD status, patients were included in yearly influenza season cohorts (2010–2019) until 2019 or insurance disenrollment; each season was considered independently, and a given patient could be included in multiple seasons after their GD diagnosis. To be considered for a given influenza season, a patient's incident GD date must have occurred before the first date of the outcome window (Figure 1).

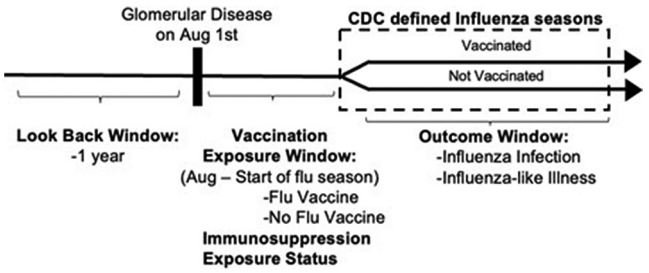


**Figure 1.** Study design. CDC, Centers for Disease Control.

### Exposure: Vaccination

Influenza vaccine exposure was identified separately for each influenza season using CPT codes within an exposure window beginning August 1 and ending at the beginning of the Centers for Disease Control and Prevention-defined flu season[22] (Supplementary Table S2). The exposure window was extended for 2 weeks to allow for vaccination to occur following GD diagnosis when a patient was diagnosed within the final 2 weeks of the exposure window.

Centers for Disease Control and Prevention-reported influenza surveillance data was used to compare components of the Northern Hemisphere seasonal influenza vaccine with the predominant circulating strains during the Centers for Disease Control and Prevention-defined influenza season.[23–31] A weighted "match" score was generated by calculating the relative proportion of circulating seasonal influenza A/B isolates to influenza strains included in the vaccine from the same year (Supplementary Table S2). Seasons were then categorized as matched (2010–2013, 2015–2018) and mismatched (2014).

### Outcomes: Influenza Infection and Influenza-like Illness

Inpatient or outpatient claims for influenza infection and influenza-like illness were defined using ICD-9-CM/10-CM-based definitions and identified during the Centers for Disease Control and Prevention-defined influenza season (Supplementary Table S1). The beginning of the outcome window was delayed for 2 weeks for individuals vaccinated in the final 2 weeks of the exposure window to allow for an immunologic response to vaccination. Individuals who experienced the outcome prior to the start of the outcome window were excluded from that year of analysis.

### Covariates

Indicators for GD severity at time of diagnosis were defined based on claims around the time of GD diagnosis. These included immunosuppressant medication exposure (glucocorticoids, calcineurin inhibitors, biologics [rituximab], cyclophosphamide, and antimetabolites [mycophenolate, azathioprine]), hospitalization

within 30 days of diagnosis, and the presence of a kidney biopsy claim prior to or within 30 days of diagnosis. Additional covariates were defined separately for each influenza season using a 1-year or 5-year lookback beginning on August 1. Past immunosuppressant use, prior clinical encounter with a nephrologist, and number of all-cause infections, hospitalizations, outpatient office visits, and emergency department visits were defined using a 1-year look back window. Current immunosuppression exposure was defined using claims occurring within the annual vaccination exposure window. All other comorbid conditions were identified using ICD-9-CM/10-CM codes within a 5-year lookback window. Comorbidities included acute myocardial infarction, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, dementia, diabetes, liver disease, hemiplegia/paraplegia, peptic ulcer disease, peripheral vascular disease, renal disease, rheumatologic/inflammatory disease, lymphatic and hematopoietic tissue malignancies, and other immune conditions.

## Statistical Methods

Demographic and clinical characteristics, including comorbidities and healthcare utilization prior to cohort entry, were summarized using means and SD and proportions, and were compared across vaccination status using a standardized mean difference. Influenza seasons were first analyzed individually by comparing the incidence rates of infection in vaccinated and unvaccinated individuals during the influenza season. To calculate infection incidence rates, the number of infections was divided by the corresponding person-time stratified by vaccination status and subgroups of interest (i.e., immunosuppressant exposure surrounding vaccination, history of diabetes). To minimize potential confounding by differences in health-seeking behavior, comorbidity, and disease severity, we estimated propensity scores for receiving vaccination using age, sex, geographic region, influenza vaccination in the prior year, current comorbid conditions, and indicators for GD severity at time of diagnosis. We used the propensity scores to calculate standardized mortality-to-morbidity ratio weights, which were then used to standardize the covariate distribution of the unvaccinated to that of the vaccinated groups.[32] Standardized mortality-to-morbidity ratio weighted Cox proportional hazards models were then used to estimate overall and season-specific vaccine effectiveness (VE), the proportion of expected outcome cases avoided due to vaccination, as 1 minus the hazard ratio.[33]

To control for confounding by indication, we used an RHR analysis[34] to compare years with a close match between vaccine composition and circulating influenza strains (2010–2013, 2015–2018), with a mismatched "control" season (2014) where the effect of the vaccine is expected to be minimal. We re-estimated propensity scores by combining all years of data; the same variables plus a year indicator variable were included in the model. To estimate the relative risk reduction conferred by vaccination in matched versus mismatched seasons, new standardized mortality-to-morbidity ratio weights were calculated and used in a weighted Cox model that included an interaction term between vaccination status and vaccine match grouping.[34] Specifically, we exponentiated the beta coefficient for the interaction term, which represents the ratio of 2 hazard ratios:

$$= \frac{vaccinated\ matched\ years / unvaccinated\ matched\ years}{vaccinated\ mismatched\ years / unvaccinated\ mismatched\ years}$$

RHR values close to 1 signify that observed effects were related to unmeasured confounding since those effects were also seen in the mismatched "control" year. Values less than 1 were interpreted to indicate a protective effect from vaccination. The study protocol was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill. Analyses were conducted using SAS 9.2 (Cary, NC).

# RESULTS

## Participant Characteristics

Among 78,861 individuals <65 years of age that met the criteria for GD, 38,642 qualified as having incident GD, and 18,203 remained after the exclusion criteria were applied. From 2010 to early 2019, these patients contributed a total of 45,142 influenza person-seasons (10,370 vaccinated and 34,772 unvaccinated person-seasons). Selected characteristics of the study cohort by person-season are presented in Table 1. Additional information regarding the cohort is available in Supplementary Figure S1 and Supplementary Table S3. Vaccination groups were similar in age and sex

**Table 1.** Selected clinical and demographic characteristics, and indices of healthcare utilization by person-season and vaccination status

| Characteristic | Vaccinated seasons $N = 10,370$ | Unvaccinated seasons $N = 34,772$ | Standardized mean difference |
|---|---|---|---|
| Age on August 1, mean (SD) | 45.2 (18.79) | 45.1 (16.31) | 0.010 |
| Sex, Female | 4547 (43.8%) | 15,012 (43.2%) | 0.014 |
| Season | | | 0.100 |
| 2010–2011 | 372 (3.6%) | 1389 (4.0%) | |
| 2011–2012 | 852 (8.2%) | 2664 (7.7%) | |
| 2012–2013 | 931 (9.0%) | 3991 (11.5%) | |
| 2013–2014 | 1084 (10.5%) | 3687 (10.6%) | |
| 2014–2015 | 1398 (13.5%) | 4828 (13.9%) | |
| 2015–2016 | 1570 (15.1%) | 4881 (14.0%) | |
| 2016–2017 | 1612 (15.5%) | 4969 (14.3%) | |
| 2017–2018 | 1370 (13.2%) | 4423 (12.7%) | |
| 2018–2019 | 1181 (11.4%) | 3940 (11.3%) | |
| Region | | | 0.171 |
| Northeast | 1995 (19.2%) | 5633 (16.2%) | |
| North Central | 2523 (24.3%) | 8201 (23.6%) | |
| South | 3993 (38.5%) | 14,807 (42.6%) | |
| West | 1777 (17.1%) | 5896 (17.0%) | |
| Unknown | 82 (0.8%) | 235 (0.7%) | |
| Selected Comorbidities | | | |
| Rheumatologic or inflammatory conditions | 2576 (24.8%) | 7357 (21.2%) | 0.088 |
| Lymphatic or hematopoietic malignancy | 216 (2.1%) | 633 (1.8%) | 0.019 |
| Other immune conditions | 946 (9.1%) | 2877 (8.3%) | 0.030 |
| CHF | 1888 (18.2%) | 4992 (14.4%) | 0.104 |
| COPD | 3145 (30.3%) | 8573 (24.7%) | 0.127 |
| Diabetes without complications | 5879 (56.7%) | 16,946 (48.7%) | 0.160 |
| Diabetes with complications | 4911 (47.4%) | 13,462 (38.7%) | 0.175 |
| Healthcare utilization (in the prior year) | | | |
| ED visits | | | 0.062 |
| 0 | 5978 (57.6%) | 21,165 (60.9%) | |
| 1 | 2000 (19.3%) | 6398 (18.4%) | |
| ≥2 | 2392 (23.1%) | 7209 (20.7%) | |
| Hospitalizations | | | 0.065 |
| 0 | 7356 (70.9%) | 25,447 (73.2%) | |
| 1 | 1783 (17.2%) | 5836 (16.8%) | |
| ≥2 | 1231 (11.9%) | 3489 (10.0%) | |
| Office visits | | | 0.317 |
| 0 | 130 (1.3%) | 1169 (3.4%) | |
| 1–4 | 1989 (19.2%) | 9733 (28.0%) | |
| 5–7 | 2257 (21.8%) | 8209 (23.6%) | |
| 8–12 | 2822 (27.2%) | 8350 (24.0%) | |
| 13+ | 3172 (30.6%) | 7311 (21.0%) | |
| Nephrology encounter | 4335 (41.8%) | 12,341 (35.5%) | 0.130 |
| Infections (any type) in the prior year | | | 0.154 |
| 0 | 3592 (34.6%) | 14,151 (40.7%) | |
| 1–3 | 5291 (51.0%) | 17,066 (49.1%) | |
| ≥4 | 1487 (14.3%) | 3555 (10.2%) | |

CHF, congestive heart disease; COPD, chronic obstructive pulmonary disease; ED, emergency department. See Supplementary Table S3 for additional characteristics.

distribution. The unvaccinated group was more likely to be from the Southern region of the United States (42.6% vs. 38.5%) and vaccinated individuals were more likely to be from the Northeast (19.2% vs. 16.2%). The vaccinated group had a higher proportion of individuals with a claim for influenza vaccination in the year before each annual influenza season (58.5% vs. 17.0%). The vaccinated group had slightly higher rates of rheumatologic, inflammatory, oncologic, and other immune conditions in the 5 years prior to GD diagnosis compared to the unvaccinated group. In addition, rates of prior immunosuppression exposure and comorbid health conditions were somewhat higher in the vaccinated group, including cardiac, pulmonary, neurologic, hepatic, endocrine, and renal disease. Rates of outpatient office visits (including nephrology specialist visits) were higher in the vaccinated group with a higher proportion of the vaccinated group having ≥8 claims for office visits in the year prior to GD diagnosis (57.8% vs. 45.0%). There was similar utilization of the emergency department and distribution of hospitalizations across vaccination status.

The mean proportion of individuals vaccinated per season was 23% (range 19%–24%). Vaccine uptake varied by age category and from season to season (0–10 years: 39% [28%–46%], 11–18 years: 24% [16%–31%], 19–40 years: 15% [12%–16%], and 41–65 years: 24% [20%–26%]).

## Influenza Infections

In Table 2, we summarize case counts and event incidence rates per 100-person years, overall and by calendar year. Across the 9 influenza seasons analyzed, a total of 757 influenza infections and 1439 influenza-like illness events were identified in the cohort. Incidence rates of infection per 100 person-years were highest in 2014 to 2015, 2016 to 2017, 2017 to 2018, and 2018 to 2019 seasons.

## VE

Seasonal hazard ratio estimates comparing vaccinated to unvaccinated individuals ranged from 0.33 to 1.88 for influenza infection and 0.71 to 1.37 for influenza-like illness and were similar in immunosuppressed patients and those with diabetes. The highest and lowest hazard ratio estimates were observed in the 2011 to 2012 and 2010 to 2011 seasons, respectively. Most years showed null or only minimally protective estimates.

In the RHR analyses comparing matched to mismatched seasons, vaccination was minimally protective for both influenza infection (RHR 0.86, 95% CI: 0.52–1.41) and influenza-like illness (RHR 0.86, 95% CI: 0.59–1.24), though estimates were limited by sample size. RHR estimates did not differ substantially among subgroups of patients immunosuppressed around the time of their influenza vaccination, or among patients with diabetes (Figure 2). A sensitivity analysis using a

**Table 2.** Incidence rate of influenza infection and influenza-like illness for vaccinated and unvaccinated patients (crude and weighted)[a] and seasonal hazard ratio and weighted vaccine effectiveness from fully adjusted models

| | Vaccinated | | | Unvaccinated, crude | | | Crude HR | Unvaccinated, weighted | | Weighted HR | Weighted VE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Season | *N* | Events | Incidence rate (100 person-yrs) | *N* | Events | Incidence rate (100 person-yrs) | HR (95% CI) | Events | Incidence rate (100 person-yrs) | HR (95% CI) | VE (95% CI) |
| Influenza Infection | | | | | | | | | | | |
| Overall | 10,349 | 177 | 4.48 | 34,703 | 580 | 4.36 | 1.02 (0.86, 1.21) | 632 | 4.74 | 0.94 (0.78, 1.15) | 6 (−15, 22) |
| 2010–2011 | 371 | 6 | 4.23 | 1385 | 18 | 3.40 | 1.24 (0.49, 3.13) | 12 | 2.24 | 1.88 (0.73, 4.86) | −88 (−386, 27) |
| 2011–2012 | 850 | 1 | 0.34 | 2658 | 13 | 1.41 | 0.24 (0.03, 1.84) | 9 | 1.02 | 0.33 (0.04, 2.63) | 67 (−163, 96) |
| 2012–2013 | 930 | 12 | 3.20 | 3984 | 64 | 3.98 | 0.80 (0.43, 1.49) | 63 | 3.88 | 0.82 (0.42, 1.62) | 18 (−62, 58) |
| 2013–2014 | 1082 | 9 | 1.74 | 3683 | 41 | 2.33 | 0.75 (0.36, 1.53) | 39 | 2.19 | 0.80 (0.34, 1.86) | 20 (−86, 66) |
| 2014–2015 | 1396 | 35 | 6.30 | 4823 | 87 | 4.51 | 1.40 (0.94, 2.07) | 117 | 6.07 | 1.04 (0.65, 1.66) | −4 (−66, 35) |
| 2015–2016 | 1565 | 12 | 1.96 | 4872 | 41 | 2.16 | 0.91 (0.48, 1.73) | 37 | 1.94 | 1.01 (0.49, 2.09) | −1 (−109, 51) |
| 2016–2017 | 1607 | 28 | 5.06 | 4958 | 76 | 4.45 | 1.14 (0.74, 1.76) | 77 | 4.47 | 1.13 (0.68, 1.90) | −13 (−90, 32) |
| 2017–2018 | 1368 | 37 | 7.50 | 4410 | 150 | 9.47 | 0.79 (0.55, 1.13) | 181 | 11.36 | 0.66 (0.44, 1.00) | 34 (0, 56) |
| 2018–2019 | 1180 | 37 | 9.15 | 3930 | 90 | 6.67 | 1.37 (0.94, 2.01) | 98 | 7.22 | 1.27 (0.76, 2.10) | −27 (−110, 24) |
| Influenza-like Illness | | | | | | | | | | | |
| Overall | 10,043 | 377 | 9.95 | 33,943 | 1062 | 8.23 | 1.21 (1.07, 1.36) | 1254 | 9.71 | 1.03 (0.89, 1.18) | −3 (−18, 11) |
| 2010–2011 | 356 | 10 | 7.39 | 1328 | 52 | 10.39 | 0.71 (0.36, 1.39) | 51 | 10.37 | 0.71 (0.35, 1.47) | 29 (−47, 65) |
| 2011–2012 | 807 | 19 | 6.87 | 2553 | 45 | 5.12 | 1.34 (0.78, 2.29) | 38 | 4.37 | 1.57 (0.86, 2.87) | −57 (−187, 14) |
| 2012–2013 | 901 | 34 | 9.50 | 3892 | 121 | 7.77 | 1.22 (0.84, 1.79) | 137 | 8.77 | 1.08 (0.70, 1.68) | −8 (−68, 30) |
| 2013–2014 | 1053 | 39 | 7.86 | 3603 | 104 | 6.09 | 1.29 (0.89, 1.86) | 124 | 7.20 | 1.09 (0.71, 1.69) | −9 (−69, 29) |
| 2014–2015 | 1358 | 62 | 11.60 | 4723 | 161 | 8.58 | 1.35 (1.01, 1.81) | 186 | 9.91 | 1.17 (0.83, 1.66) | −17 (−66, 17) |
| 2015–2016 | 1516 | 51 | 8.74 | 4768 | 119 | 6.45 | 1.35 (0.98, 1.88) | 133 | 7.14 | 1.22 (0.81, 1.85) | −22 (−85, 19) |
| 2016–2017 | 1565 | 49 | 9.16 | 4860 | 136 | 8.17 | 1.12 (0.81, 1.56) | 153 | 9.08 | 1.01 (0.68, 1.49) | −1 (−49, 32) |
| 2017–2018 | 1339 | 62 | 12.97 | 4342 | 195 | 12.58 | 1.03 (0.77, 1.37) | 264 | 17.00 | 0.76 (0.54, 1.07) | 24 (−7, 46) |
| 2018–2019 | 1148 | 51 | 13.07 | 3874 | 129 | 9.74 | 1.34 (0.97, 1.86) | 180 | 13.62 | 0.96 (0.64, 1.45) | 4 (−45, 36) |

CI, confidence interval; HR, hazard ratio; VE, vaccine effectiveness.
[a]Propensity score SMR weights were re-estimated for each influenza season and overall to standardize the distribution of covariates for each analysis.

narrow definition of GD identified 8712 influenza person-seasons (2359 vaccinated and 6353 unvaccinated person-seasons). In the RHR analyses, vaccination was not observed to be protective for influenza infection (RHR 1.21, 95% CI: 0.50–2.92) or influenza-like illness (RHR 1.14, 95% CI: 0.56–2.33), though estimates were imprecise due to small sample size (Supplementary Table S4).

## DISCUSSION

Patients with chronic kidney disease, especially those with GD, are at increased risk of vaccine-preventable infections, placing them at high risk for infection-related morbidity and mortality.[2–9] Gaps persist in our understanding of infection risk in this patient population, though individual and disease-specific factors are recognized, including treatment-related immunosuppression; dysregulated innate and acquired immunity; persistent chronic inflammation; malnutrition; dysbiosis; and impaired initial and sustained response to vaccination for influenza, pneumococcus, and SARS-CoV-2.[35] In the present study, we describe VE against influenza and influenza-like illness among children and adults with GD using healthcare claims data. We found that uptake is low and that protection from influenza after vaccination is overall poor in this patient population. Although we were unable to identify any subgroups with unique risk profiles, these data provide valuable information regarding real-world effectiveness in a high-risk patient group.

Our findings are consistent with results of a multicenter electronic medical record test-negative case control study of influenza VE during the 2017 to 2018 influenza season.[36] VE against polymerase chain reaction-confirmed influenza hospitalization was 5% (95% CI: −29% to 31%) in immunocompromised adults versus 41% (95% CI: 27% to 52%) in non-immunocompromised adults. Prior studies have also shown negligible influenza VE against influenza hospitalization (VE 2%, 95% CI: −2% to 5%) and influenza-like illness (VE of 0%, 95% CI: −3% to 2%) in patients on hemodialysis.[34] Data from immunosuppressed children with nephrotic syndrome have shown adequate seroprotection following A/H1N1 influenza vaccination,[37] and reduced rates of infection following vaccination.[38]

Strengths of the study include use of a large nationwide database to identify a cohort of individuals with primary GD, resulting in a relatively large and geographically diverse sample for analysis. Healthcare claims data can broadly capture inpatient and outpatient encounters from multiple health systems, time points, and clinical settings, though notably, cannot

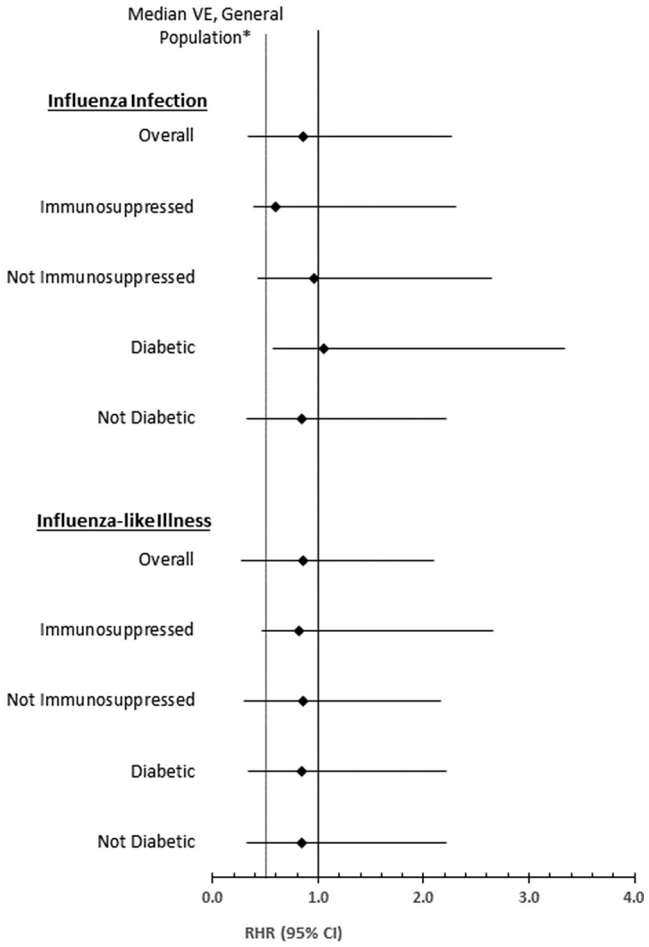


**Figure 2.** Ratio-of-hazard ratios estimates from pooled (fully adjusted) models comparing matched (2010–2013, 2015–2018) to unmatched (2014) influenza seasons. *CDC reported median vaccine effectiveness in the general population 2010–2019 (dashed line) expressed as a HR (HR = 1 − VE). See Supplementary Table S2. CI, confidence interval; VE, vaccine effectiveness.

capture treatments or clinical events not billed through insurance. Our analytic approach addressed confounding that may occur when directly comparing vaccinated to unvaccinated individuals[39] by utilizing a comparator "control" season when little vaccine protection is expected.[34] We hypothesize that residual confounding is a result of patient-level differences across vaccination status in health-seeking behavior and underlying health status, both of which were likely affecting our annual hazard estimates comparing vaccinated to unvaccinated individuals. Because the vaccinated group was generally sicker than the unvaccinated group in our analysis, (i.e., more comorbidities and immunosuppression exposure), we expect that unmeasured confounding would likely make the observed RHRs underestimates of the true risk reduction conferred by vaccination.

Our analysis has several limitations. First, several forms of bias are potentially present in our analysis, including confounding by indication (differences in disease severity across groups). We attempt to adjust for these variables by including markers of disease severity (healthcare utilization and access, hospitalization, immunosuppression exposure, or comorbidities). Second, GDs are heterogenous conditions with wide variability in duration, intensity of disease activity, and degree of immune suppression or dysregulation. A spectrum of therapeutic approaches are now available, ranging from conservative management with renin-angiotensin-aldosterone system inhibitors to prolonged courses of corticosteroids, calcineurin inhibitors, and B-cell depleting agents. In the present analysis we attempt to adjust for disease severity by incorporating early immunosuppression exposure and hospitalization. We were unable to account for periods of disease activity or quiescence, severity of nephrosis, or kidney function decline as these variables are not included in the claims data source. These factors have previously been shown to independently increase infection-risk and may also affect vaccination behavior; likely contributing to residual confounding in our findings.[9,40,41]

In addition, we recognize a number of methodologic limitations related to identifying individuals with GD, capturing vaccination events, and identifying influenza infections. Although ICD-10-CM codes offer improved specificity for GD subtypes compared to ICD-9-CM codes, there is limited validation data available using the ICD-10-CM coding system. When possible, our diagnosis-based outcome definitions were derived from the published literature or generated from an ICD-9-CM to ICD-10-CM crosswalk tool.[42] In the absence of laboratory or biopsy-based diagnoses to aid in a definition of GD, we performed a sensitivity analysis using a narrow set of ICD-9-CM/10-CM GD codes. Although no protective effect was observed, this analysis was limited by a smaller sample size than the main analysis. A second methodological limitation is that MarketScan data may underestimate influenza vaccine coverage, as not all vaccinations are administered in settings that submit claims to insurance carriers. The results of prior studies using MarketScan data have demonstrated that influenza vaccination rates occur within a reasonable range of those expected in the general population, with undercapture most likely in individuals older than 65 years.[13,43] We would expect vaccine undercapture to bias VE estimates toward the null. Lastly, we used medically attended diagnoses to ascertain influenza infection, as opposed to polymerase chain reaction-based laboratory testing, introducing the potential for outcome misclassification, particularly of clinically mild infections.

In summary, rates of influenza vaccination and VE are suboptimal among patients with GD. Despite

potential confounding by indication and uncaptured vaccinations and infections, these data suggest that protection from influenza after vaccination is poor, leading to excess infection-related morbidity in this vulnerable population. Despite these findings, influenza vaccination should continue to be strongly encouraged for patients with GD. Individual risk factors for infection and vaccination timing relative to immunosuppression exposure should be considered to maximize potential benefit from vaccination. Optimized treatment protocols that minimize infection risk are critical to improving patient centered outcomes and reducing morbidity and mortality. The efficacy of high-dose influenza vaccines or enhanced vaccination regimens should be explored further for this, and other, immunosuppressed groups.

## DISCLOSURE

EBW has received funding support from Pfizer, Moderna, Sequiris, Najit Technologies Inc, and Clinetic for the conduct of clinical trials and clinical research; and has served as an advisor to Vaxcyte and consultant to ILiAD biotechnologies. AM reports personal fees from UpToDate and the American Society of Nephrology Diabetic Kidney Disease Consortium; clinical trial support from Pfizer, Calliditas, Alexion, and Chinook, outside the submitted work; personal fees from ProKidney; and has had consultancy agreements with Bayer. JBL is an employee of RTI International, an independent, nonprofit research institute which performs research on behalf of governmental and commercial clients, including pharmaceutical companies. MRD has received grant support from Mallinckrodt Pharmaceuticals. All other authors declare that they have no relevant financial interests.

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Figure S1.** Cohort assembly diagram.

**Table S1.** Study cohort, exposure, and outcome definitions.

**Table S2.** Influenza seasons start and end dates, Centers for Disease Control and Prevention-reported vaccine effectiveness, and weighted match score between circulating seasonal influenza A/B isolates and influenza strains included in the vaccine from the same year.

**Table S3.** Clinical and demographic characteristics of the cohort by person-season and vaccination status.

**Table S4.** Ratio-of-hazard ratios (sensitivity analysis) using a narrow glomerular disease cohort definition. Ratio-of-hazard ratios estimates from pooled (fully adjusted) models comparing matched (2010–2013, 2015–2018) to unmatched (2014) influenza seasons.

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