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Assessing Residual Bias in Estimating Influenza Vaccine Effectiveness: Comparison of High-dose versus Standard Dose Vaccines

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Abstract

Background—Estimating influenza vaccine effectiveness using an unvaccinated comparison group may result in biased effect estimates.

Objectives—To explore the reduction of confounding bias in an active comparison of high-dose versus standard dose influenza vaccines, as compared with vaccinated versus unvaccinated comparisons.

Methods—Using Medicare data from the United States end-stage renal disease program (2009–2013), we compared the risk of all-cause mortality among recipients of high-dose vaccine (HDV) versus standard-dose vaccine (SDV), HDV versus none, and SDV versus none. To quantify confounding bias, analyses were restricted to the preinfluenza season, when the protective effect of vaccination should not yet be observed. We estimated standardized mortality ratio–weighted cumulative incidence functions using Kaplan-Meier methods and calculated risk ratios (RRs) and risk differences between groups.

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Conflict of interest

Dr. Butler has received investigator-initiated support from Amgen and AstraZeneca. Drs. Layton and Krueger are employees of RTI International, an independent, nonprofit research organization that does work for government agencies and pharmaceutical companies. Dr. Layton was formerly an employee of the University of North Carolina, where he received unrestricted salary support from the Center for Pharmacoepidemiology in the Department of Epidemiology; current member companies include GlaxoSmithKline, Merck, and UCB. Dr. Kshirsagar is an advisory board member for Akebia. Dr. McGrath is an employee of and owns stock in NoviSci, LLC, a data sciences company, and previously was an employee of RTI Health Solutions.

Results—Of 350,921 eligible patients contributing 825,642 unique patient preinfluenza seasons, 0.8% received HDV, 70.5% received SDV, and 28.7% remained unvaccinated. Comparisons to unvaccinated patients yielded spurious decreases in mortality risk during the preinfluenza period, for HDV vs. none (RR=0.60 (95% CI: 0.51–0.70)) and SDV vs. none (RR=0.72 (95% CI: 0.70–0.75)). The effect estimate was attenuated in the HDV vs. SDV comparison (RR=0.89 (95% CI: 0.77–1.03)). Estimates on the absolute scale followed a similar pattern.

Conclusions—The HDV versus SDV comparison yielded less-biased estimates of all-cause mortality prior to influenza season compared to those with nonuser comparison groups. Vaccine-effectiveness and safety researchers should consider the active comparator design to reduce bias due to differences in underlying health status between vaccinated and unvaccinated individuals.

Keywords

Active comparator; bias; confounding; epidemiology; influenza; negative control; vaccine effectiveness

The healthy-user bias arises in nonexperimental studies when healthier patients are more likely to receive a preventive drug or intervention and less likely to experience adverse health outcomes due to underlying health status.^{1–4} This bias can lead to exaggerated or spurious beneficial associations. The healthy-user bias is particularly concerning in studies of preventive interventions in populations characterized by individuals in precarious health, such as the elderly or patients with serious clinical conditions.^{5,6} Several studies of influenza vaccine effectiveness comparing vaccinated to unvaccinated individuals have demonstrated implausible reductions in mortality risk before the influenza season,^{7–9} indicating preferential receipt of vaccine by healthier patients.^{10–14} Because influenza is a seasonal infection, a true protective effect of vaccination should be limited to periods during influenza virus circulation.

Recent vaccine-effectiveness studies comparing vaccinated to unvaccinated individuals have demonstrated that the healthy-user bias could not be completely controlled through statistical adjustment, including model adjustment for frailty status and time-varying confounders; however, sample restriction to healthier individuals reduced much of the bias.^{11,13,15} The active comparator design mitigates bias by restricting the study to individuals with an indication for treatment and without contraindications or barriers to receipt, including frailty.¹⁶ In the context of influenza vaccine, the high-dose vaccine (HDV) may be administered as an alternative to the standard-dose vaccine (SDV) among the elderly and immunocompromised populations to elicit a stronger immune response; however, there is no preference stated in national vaccine recommendations between the two vaccine types.¹⁷ Whether the healthy-user bias remains present in comparisons of different vaccine formulations needs to be explored.

We quantified the reduction of bias when comparing HDV to SDV to estimate preinfluenza season mortality, a negative control outcome, among patients receiving chronic hemodialysis. We compared these results to standard analyses comparing HDV or SDV to unvaccinated comparison groups.

METHODS

Study Design and Population

We used Medicare claims data from the United States Renal Data System (USRDS) (2009–2013), a national registry that includes most patients with end-stage renal disease (ESRD) in the United States.¹⁸ We created separate cohorts for four preinfluenza seasons: 2010, 2011, 2012, and 2013. Each cohort included adult patients with ESRD, who had Medicare as a primary payer, were present in the database on August 1 of the given year and who had initiated dialysis prior to October 1 of the preceding year. We required patients to have received in-center hemodialysis from May 1 to July 31. Insurance status and patient characteristics were identified during a 6-month baseline period (February 1–July 31). Follow-up started on August 1 and ended at the earliest instance of all-cause mortality, receipt of unknown influenza vaccine type, receipt of second influenza vaccine, switch to peritoneal dialysis, kidney transplantation, end of Medicare as primary payer status, or start of influenza season. The start of each influenza season was defined as the midpoint of the first week during which >10% of national culture isolates were positive for influenza, using national influenza surveillance data from the Centers for Disease Control and Prevention (CDC) (Table S1, Supplemental Digital Content 1, <http://links.lww.com/MLR/B643>). Patients were eligible for inclusion in multiple yearly cohorts.

Outcome

All-cause mortality during the preinfluenza period was a negative control outcome known to be causally unrelated to the exposure. Given the absence of a biologically plausible mechanism for the vaccine to prevent mortality prior to influenza virus circulation in the community, estimates of reduced mortality or preseason vaccine effectiveness during the preinfluenza period should be null in the absence of confounding.^{10,12,13,19–21}

Exposure

Vaccination status was defined using procedure codes (Table S2, Supplemental Digital Content 1, <http://links.lww.com/MLR/B643>) and categorized as receipt of HDV, SDV, or no vaccine. Vaccination status was modeled as a time-varying covariate, with all cohort members entering yearly cohorts on August 1 as unvaccinated. To allow for an immune response, patients were not considered vaccinated until 14 days post vaccination; this study design decision will allow for interpretation of the magnitude and direction of bias in future studies of influenza vaccine effectiveness during the influenza season.

Statistical Analyses

We estimated crude and weighted cumulative incidence functions for all-cause mortality using Kaplan-Meier methods. Confounding was addressed by applying standardized mortality ratio (SMR) weights to the Kaplan-Meier estimator.^{6,22} Specifically, multivariable logistic regression models were fit to estimate propensity scores (*ps*) for the receipt of a certain vaccine type, accounting for prespecified potential confounders (i.e., age, race, sex, network, cause of ESRD, years on dialysis, hospital days, mobility aids, comorbidities, and frailty markers). The exposure of interest received a weight of 1, and comparators received a

weight based on the following formula: $ps/(1-ps)$. Separate propensity scores and SMR weights were estimated for each contrast. We calculated risk differences (RDs) and risk ratios (RRs) of the cumulative incidence functions over the entire preinfluenza period. A nonparametric-based bootstrap (N=250 resamples) was used to estimate 95% confidence intervals (CIs) for daily RDs and RRs between groups; the bootstrap procedure was performed to mimic the main analysis, and thus, similarly analyzed records at the level of the person-year and recalculated the propensity score within each bootstrap sample. We compared RRs by calculating percent difference. An institutional review board of the University of North Carolina approved this research. Analyses were conducted using SAS 9.4 (Cary, NC) and the R Statistical Software 3.3.²³

RESULTS

We identified 350,921 eligible patients contributing 825,642 unique patient preinfluenza seasons. Cohort sizes ranged from 194,969 (2010) to 215,156 (2013). During these preinfluenza seasons, 6,258 patients (0.8%) received HDV, 582,436 (70.5%) received SDV, and 236,678 (28.7%) remained unvaccinated. HDV recipients were older (mean: 72 years versus 62 years for both SDV and unvaccinated patients). Compared to SDV recipients or unvaccinated patients, HDV recipients were more likely to be white, Midwestern, and have shorter duration of dialysis. HDV recipients were also more likely to receive care at smaller, hospital-based, or nonprofit dialysis facilities (Table 1).

The distribution of comorbidities across exposure groups varied widely. Compared to HDV and SDV recipients, unvaccinated patients were more likely to exhibit signs of frailty and less likely to receive preventive care. In general, the reduction of standardized differences to close to zero after weighting demonstrates creation of comparator cohorts with the same covariate distribution, which removes confounding by these covariates (Table S3, Supplemental Digital Content 1, <http://links.lww.com/MLR/B643>). In our study, the SMR weighting was less successful in balancing measured covariates in the vaccinated vs. unvaccinated comparisons than in the HDV vs. SDV comparison, likely due to the underlying inherent differences between vaccinated and unvaccinated patients.

During the follow-up period, 274,467 person-years of follow-up accrued, during which 48,182 deaths were observed, yielding a rate of 17.6 deaths per 100 person-years. Counts of deaths, total person-years of follow-up, and death rates are presented for all exposure groups (Table 2).

The overlap between propensity score distributions for each comparison is shown in Figure S1, Supplemental Digital Content 1, <http://links.lww.com/MLR/B643>. Figures S2, Supplemental Digital Content 1, <http://links.lww.com/MLR/B643> and 1 present crude and weighted RRs (95% CIs) for all contrasts, respectively. After adjustment, HDV (RR=0.60; 95% CI, 0.51–0.70) and SDV (RR=0.72; 95% CI, 0.70–0.75) recipients demonstrated a decreased mortality risk compared to the unvaccinated group. The HDV versus SDV comparison yielded an attenuated effect estimate, with CIs crossing the null (RR=0.89; 95% CI, 0.77–1.03), indicating less bias. The RR estimates were attenuated by 77% on the logarithmic scale (RR=0.60 vs. 0.89) when referencing the active comparators rather than

the unvaccinated group (Table S4, Supplemental Digital Content 1, <http://links.lww.com/MLR/B643>). In analyses stratified by year, we observed similar associations between vaccine type and mortality (Figure 1).

SMR weighting generally moved estimates closer to the null than the crude estimates, and similar associations were observed on the absolute scale, both overall and by year (Table S4, Supplemental Digital Content 1, <http://links.lww.com/MLR/B643>).

DISCUSSION

In this population-based study of preinfluenza season mortality among patients receiving chronic hemodialysis, the HDV versus SDV comparison yielded less-biased negative control estimates compared to those with nonuser comparison groups. Implausibly large protective associations of the vaccine related to all-cause mortality were demonstrated when using an unvaccinated comparator group versus either HDV or SDV, similar to those in previous studies.^{10–13} These spurious protective associations were observed before seasonal influenza began circulating widely in the community, despite accounting for demographic and clinical factors. This outcome is expected given major differences in underlying characteristics between vaccinated and unvaccinated patients; importantly, unvaccinated patients were more likely to exhibit signs of frailty and less likely to receive preventive care. In contrast, our comparison of HDV to SDV recipients yielded attenuated effect estimates. While the overall estimate remained below the null ($RR = 0.89$), the 95% CI covered the null. It is possible that some residual confounding remained which may have resulted in bias down and away from the null. However, the magnitude of the bias was much lower than the bias evident in the comparison of vaccinated versus unvaccinated patients.

An ideal active comparator has a similar indication to the treatment or intervention of interest and is administered to a population with a similar distribution of measured and unmeasured patient characteristics.¹⁶ SDV appears to be a reasonable choice as an active comparator for HDV based on equipoise reflected in clinical guidelines; influenza vaccine is recommended for patients on dialysis, but neither the CDC nor nephrology-specific organizations have issued recommendations stating a preference for administration of SDV or HDV in this population.¹⁷ In studies comparing HDV versus SDV among older adults, the distribution of patient characteristics has been similar with respect to baseline covariates, including health conditions, low-income status, and frailty indicators.^{24,25} A similar distribution was also observed in our vaccinated dialysis population. However, compared to SDV recipients, HDV recipients were more likely to receive care at smaller, hospital-based, or nonprofit dialysis facilities, possibly because HDV was not included on private dialysis facilities' formularies during the study period. Despite these provider-level differences, comparison of HDV to SDV recipients instead of unvaccinated patients moved the negative control estimates of preinfluenza mortality reduction toward the null, indicating more similar treatment groups as well as reduced measured and unmeasured confounding.

In our study, restriction of the study population to vaccine recipients resulted in better balance of potential measured confounders, and likely also resulted in better balance of unmeasured confounders. Influenza vaccine receipt is driven by patient preference, health

status, healthcare access, perceived benefit, and other factors potentially associated with outcomes.²⁶ Our results are consistent with previous reports that restricting analyses to increasingly healthy people reduced residual bias.^{11,13}

Similar to several studies on influenza vaccine effectiveness, we used the non-specific outcome of all-cause mortality. Influenza-specific mortality is notoriously difficult to measure because influenza infections are generally not confirmed virologically or specified on hospital discharge forms or death certificates. In addition, many influenza-related deaths occur from secondary complications or exacerbations of chronic illnesses when influenza viruses are no longer detectable.²⁷ Here, we selected all-cause mortality as our outcome based on previous research that all-cause mortality in the period before influenza season is associated with the greatest (spurious) reduction in risk associated with influenza vaccination compared to other outcomes such as hospitalization related to other diagnoses or events (e.g., pneumonia or influenza, ischaemic heart disease, congestive heart failure, cerebrovascular diseases, or injury or trauma).¹⁰ In principle, by reducing the residual bias present in the scenario of the most biased outcome (i.e., all-cause mortality), we assume this method will sufficiently reduce bias when investigating more specific outcomes, leading to more valid estimates of vaccine effectiveness.

Our findings are subject to limitations. First, inability to identify all influenza vaccinations paid out of pocket would result in exposure misclassification, which would likely bias the mortality estimates toward the null because relatively healthy vaccinated individuals would be classified as unvaccinated.²⁸ However, we expect misclassification to be rare, given that dialysis patients have frequent health care encounters at dialysis clinics, where influenza vaccines are commonly administered and reimbursed by Medicare.¹² Second, our analysis accounted for patient characteristics measured at baseline, but not for time-varying covariates such as rapid declines in health status which occur commonly in patients with ESRD. However, a previous study of influenza vaccine effectiveness among patients with ESRD showed that accounting for time-varying confounders of health status measured from both clinical and claims data did not reduce bias.¹³ Third, only 0.8% of our study population received HDV, and thus our year-specific RR estimates of mortality during the preinfluenza period are imprecise for comparisons that included HDV recipients. Yet, in every year, the lower 95% CI was closer to the null for the comparison of HDV versus SDV relative to the comparison of HDV versus no vaccination. Fourth, we did not include calendar month in the model to account for a possible seasonal effect of mortality due to the short duration of the period prior to the influenza season; future effectiveness studies should account for seasonality given mortality may increase during the winter months. Finally, use of an active comparator design in vaccine effectiveness studies is limited by the availability of a suitable comparator vaccine. For many vaccines, only one formulation or type of vaccine is administered, which precludes use of this study design. But, given rapid vaccine development and approval, the active comparator design may increasingly be a good option in many settings.

In summary, our results demonstrate that active comparator designs should be considered for use in vaccine-related effectiveness and safety studies to reduce residual confounding due to the healthy-user bias.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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FIGURE 1.

Standardized Mortality Ratio-Weighted Estimates of the Prevention of Preinfluenza Season Mortality Using Different Comparator Groups, 2010–2013

Abbreviations: HDV, high-dose vaccine; SDV, standard-dose vaccine.

† Standardized mortality ratio-weighted analysis adjusted for age, race, sex, cause of end-stage renal disease, years on dialysis, hospital days, mobility aids, network, comorbidities, and frailty markers.

TABLE 1.

Characteristics of the Study Population for Four Preinfluenza Seasons, United States, 2010–2013

	Unvaccinated (%)	HDV (%)	SDV (%)
Unique patient preinfluenza seasons, N (%)	236,678 (28.7%)	6,528 (0.8%)	582,436 (70.5%)
Age, mean [SD] (y)	61.6 (14.7)	71.8 (11.0)	62.3 (14.2)
Male sex	53.4	52.6	54.6
Race			
White	49.6	72.3	55.0
Black	45.6	21.9	39.0
Other	4.9	5.8	6.0
Cause of ESRD			
Diabetes	43.4	45.6	45.8
Hypertension	30.9	30.1	29.3
Glomerulonephritis	11.4	9.0	10.9
Other	14.3	15.3	14.0
Region			
Northeast	17.3	14.0	15.2
South	46.3	36.2	46.9
West	15.7	13.1	18.4
Midwest	20.7	36.6	19.5
Medicaid eligibility	51.5	29.8	48.5
Hospital-based facility	15.0	30.8	11.1
Nonprofit facility	19.1	34.1	15.8
Facility size (number of dialysis stations)			
0-19	41.6	55.6	43.5
20-29	40.4	31.7	40.4
30-80	18.0	12.7	16.1
Years with ESRD			
0	4.7	6.5	4.4
1-2	31.1	40.8	30.7
3-4	24.2	23.9	25.1
5-9	26.7	21.6	27.6
10	13.2	7.1	12.2
Hospitalized in last month (weeks)			
0	81.9	88.7	88.4
<1	9.5	7.6	7.4
1	8.6	3.7	4.2
Used skilled nursing facility in last month	6.7	3.7	3.4
Frailty indicators			

	Unvaccinated (%)	HDV (%)	SDV (%)
Mobility aids [†]	11.8	11.2	10.6
Use of oxygen	11.8	16.2	11.6
Ambulance/life support	40.7	32.2	32.2
Skin ulcer (decubitus)	15.1	12.6	11.0
Dementia	8.8	6.7	5.4
Home hospital bed	4.6	3.4	3.5
Difficulty walking	16.4	14.7	12.5
Weakness	17.5	14.4	12.5
Comorbidities			
Sepsis	11.7	7.2	7.0
Pneumonia	12.1	10.0	8.6
Chronic obstructive pulmonary disease	20.3	23.5	17.7
Neurological problem	11.3	7.3	7.6
Psychiatric problem	22.5	18.1	17.1
Screening tests/prevention [‡]			
Pneumonia vaccine	1.2	9.6	10.3
Hepatitis B vaccine/titre	1.6	25.2	21.7
Lipid test	2.5	40.0	31.8
Diabetic eye exam	2.4	40.5	31.2
A1C test	4.2	58.5	58.0
Cancer screening	1.3	18.9	16.2

Abbreviations: ESRD, end-stage renal disease; HDV, high-dose vaccine; SD, standard deviation; SDV, standard-dose vaccine.

[†]Defined as use of walker, wheelchair, or modified bathroom equipment.

[‡]Defined during baseline period until date of influenza vaccine.

TABLE 2

Outcomes for Four Preinfluenza Seasons, United States, 2010–2013

	Unvaccinated (%)	HDV (%)	SDV (%)
Unique patient preinfluenza seasons, N (%)	236,678 (28.7%)	6,528 (0.8%)	582,436 (70.5%)
Person-years, N	165,366	1,076	108,025
Deaths, N	33,157	199	14,826
Death rate/100 person-years	20.1	18.5	13.7

Abbreviations: HDV, high-dose vaccine; SD, standard deviation; SDV, standard-dose vaccine.