ONLINE FIRST

Estimating Influenza Vaccine Effectiveness in Community-Dwelling Elderly Patients Using the Instrumental Variable Analysis Method

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Background: Estimates of influenza vaccine effectiveness in elderly individuals are largely from observational studies, which are susceptible to bias. Instrumental variable (IV) methods control for overt and hidden biases in observational studies.

Methods: We used linked health administrative databases in Ontario to examine the association between influenza vaccination and all-cause mortality among community-dwelling individuals older than 65 years for 9 influenza seasons (2000-2001 to 2008-2009). We examined the composite of hospitalization for pneumonia and influenza and all-cause mortality as a secondary outcome. We used logistic regression modeling and IV analysis to remove the effect of selection bias.

Results: We included 12 621 806 person–influenza seasons of observation. Logistic regression produced adjusted odds ratios of 0.67 (95% CI, 0.62-0.72) for all-cause mortality during influenza seasons and 0.85 (0.83-0.86) during post–influenza seasons when influenza is not circulating, suggesting the presence of bias. In contrast, IV analysis yielded adjusted odds ratios of 0.94 (95% CI, 0.84-1.03) during influenza seasons and 1.13 (1.07-1.19) during post–influenza seasons. For the composite of hospitalization for pneumonia and influenza and death, logistic regression produced adjusted odds ratios of 0.74 (95% CI, 0.70-0.78) during influenza seasons and 0.88 (0.87-0.90) during post–influenza seasons, whereas IV analysis produced adjusted odds ratios of 0.86 (95% CI, 0.79-0.92) and 1.02 (0.97-1.06), respectively.

Conclusions: Influenza vaccination is associated with reductions in the composite of hospitalizations for pneumonia and influenza and all-cause mortality during the influenza season but not mortality alone. Compared with standard modeling, IV analysis appears to produce less-biased estimates of vaccine effectiveness.

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INFLUENZA CAUSES SUBSTANTIAL mortality in people 65 years or older.[1-4] Annual vaccination is recommended to reduce the burden of influenza in this age group.[5,6] However, the evidence in support of vaccinating older adults against influenza stems primarily from observational studies, which are susceptible to bias.[7]

See Invited Commentary at end of article

Past observational studies suggest that influenza vaccines reduce all-cause mortality in the elderly by approximately 50%.[8] Recent studies observing similar mortality reduction among vaccinated individuals during non–influenza seasons suggest potential bias in such studies.[9-13] Because influenza has been estimated to account for less than 10% of all deaths during winter periods, it seems implausible that vaccination could reduce all-cause mortality during influenza seasons by approximately 50%.[14] A recent Cochrane review concluded that the available evidence is of poor quality[15]; thus, the true effectiveness of influenza vaccination in the elderly population is uncertain.[16]

Individuals who engage in health-promoting behaviors may be more likely to get vaccinated, whereas very sick individuals may be less likely to receive vaccine.[9,10,17] This difference in underlying health status between vaccinated and unvaccinated individuals may artificially overestimate vaccine effectiveness.[9,17,18] Traditional analytical strategies (eg, stratification, restriction, matching, and regression modeling) cannot adjust for unobserved confounders or control for nonrandom treatment allocation.[19] No randomized controlled trials to examine the effectiveness of influenza vaccines against mortality have been conducted. The objective of this study was to use instrumental variable (IV) analysis, a method designed to control for unmea-

sured confounding, to obtain unbiased estimates of influenza vaccine effectiveness against all-cause mortality and hospitalizations for pneumonia and influenza (P&I) in the elderly population.

METHODS

STUDY POPULATION AND SETTING

We conducted a population-based cohort study for 9 influenza seasons (2000-2001 to 2008-2009) using health administrative databases in Ontario. Setting the index date as the start of each influenza season, we included all persons older than 65 years. We excluded institutionalized individuals, those with invalid health card numbers, and those with no contact with the health care system within 3 years before an index date. All cohort members (approximately 1.4 million per influenza season) had free access to influenza vaccines, hospital care, physician services, and prescription medications. Ethics approval for the study was obtained from the Sunnybrook Health Sciences Centre Research Ethics Board, Toronto.

DATA SOURCES

Patient records were linked using unique, anonymous, encrypted identifiers across multiple Ontario health administrative databases containing information on all publicly insured, medically necessary hospital and physician services. These included the Discharge Abstract Database,[20] which contains detailed information on diagnoses and procedures for hospitalizations; the Ontario Health Insurance Plan database,[21] which contains billings claims from approximately 98% of Ontario physicians that include patient diagnosis codes and services for outpatient visits; the Ontario Drug Benefit database for outpatient drug prescriptions[22]; and the Registered Persons Database for patient demographic information and deaths.[23]

INFLUENZA SEASON PERIODS

Influenza seasons were defined using influenza surveillance data provided by a network of sentinel laboratories. In accordance with previous studies, the start and end dates of influenza seasons were defined as the first and last occurrences of 2 consecutive weeks with positive findings for at least 5% of weekly influenza isolates tested.[10,24] Post–influenza seasons were defined as July 1 to September 30 after each influenza season. Individuals were followed up from the beginning of the influenza season (index date) to the end of the post–influenza season separately for each influenza season.

INFLUENZA VACCINATION

Influenza vaccination status was ascertained from physician billing claims. We also considered general vaccination codes when they exceeded baseline rates (representing annual influenza vaccination campaigns) because there was gradual uptake of the influenza-specific vaccination codes after their introduction in 1998. Although these claims include other vaccines, during annual influenza vaccination campaigns most claims (96%) likely represent influenza vaccination.[10] We used self-reported influenza vaccination as the criterion standard to determine that the combination of influenza-specific and general vaccination codes among individuals older than 65 years has performance values of 0.75 for sensitivity, 0.90 for specificity, 0.96 for positive predicted value, and 0.54 for negative predicted value.[25] Influenza vaccines are generally administered from October through March, meaning that individuals may have been vaccinated after the start of an influenza season (the index date).

OUTCOMES

The primary outcome was all-cause mortality during influenza season. As a secondary outcome, we examined P&I hospitalizations (codes 480-487 from the *International Classification of Diseases, Ninth Revision*, and codes J10-J18 from the *International Statistical Classification of Diseases, 10th Revision*) coded in any diagnostic field. Hospitalizations for P&I were analyzed as a composite end point with mortality because mortality is a more serious outcome than hospitalization, making it inappropriate to censor the hospitalization analyses for mortality. In addition, the factors causing mortality were likely an exacerbation of those causing hospitalization, so that these events were not independent. We considered only the first admission during each influenza season or post–influenza season.

COVARIATES

We collected data on more than 100 baseline (index date) characteristics, including demographics, comorbidities, health care utilization, current prescription medication use, and receipt of specific medical procedures.

Comorbidities were defined according to an adaptation of the adjusted clinical group as any mention of the diagnosis in the outpatient or hospitalization data sets within 3 years of the index date.[26] The comorbidities of interest were chronic health conditions (ie, cancers, cardiovascular diseases, respiratory diseases, anemias, renal diseases, diabetes mellitus, and immune disorders) that put individuals at elevated risk for complications owing to influenza, as identified by Canada's National Advisory Committee on Immunizations.[5] Diagnoses of other chronic conditions (ie, cerebrovascular disease, chronic liver disease, rheumatologic diseases, and history of aspiration) were also considered. All models also controlled for the number of hospitalizations in the 3 years before the index date, and post–influenza season models controlled for any hospitalization occurring from the index date through the start of the post–influenza season.

STATISTICAL ANALYSIS

All models used individuals as the unit of analysis. We developed a baseline patient risk index using logistic regression to predict outcomes during influenza season, incorporating all baseline patient characteristics (C=0.87 for mortality; C=0.85 for P&I hospitalization or mortality). We used standardized differences, expressed as percentages, to compare characteristics between vaccinated and unvaccinated patients.[27] Statistical models adjusted for all covariates described in the preceding section. We performed a sensitivity analysis excluding 4.5% of vaccinated individuals who were immunized after the index date.

MULTIVARIABLE MODEL RISK ADJUSTMENT

We used logistic regression models to estimate relative outcome rates during influenza season among study participants who did or did not receive influenza vaccination. Each season was analyzed separately. We repeated this analysis to compare outcomes during post–influenza seasons among those who survived until the start of the post–influenza season. Using a pooled random-effects model, we computed a summary measure of effect combining all 9 influenza seasons.[28]

Table 1. Influenza Season Characteristics and Periods

Characteristic	Influenza Season, y									
	2000-2001	2001-2002	2002-2003	2003-2004	2004-2005	2005-2006	2006-2007	2007-2008	2008-2009	All Seasons
No. of adults >65 y	1 297 051	1 321 863	1 343 761	1 370 191	1 394 361	1 426 690	1 452 909	1 487 616	1 527 364	12 621 806
Vaccinated, %[a]	61.5	60.8	58.2	61.3	60.5	59.1	56.0	53.6	53.9	58.2
Influenza season										
Start and end dates[b]	1/28/01-4/14/01	1/20/02-5/11/02	12/8/02-2/8/03	11/16/03-2/7/04	12/12/04-5/7/05	2/12/05-5/27/06	12/31/06-4/14/07	12/2/07-5/17/08	12/28/08-4/25/09	
Duration, wk	11	16	9	12	21	15	15	24	17	15.6
Influenza A(H3N2) predominance, %[c,d]	1	64	2	99	75	39	91	24	NA	49
All-cause deaths										
No. during influenza season	9769	13 940	8318	11 527	19 721	13 389	14 458	23 013	16 397	130 532
Rate per 1000 population per week of influenza season	0.68	0.66	0.69	0.70	0.67	0.63	0.66	0.64	0.63	0.66
No. during post–influenza season[e]	10 923	11 240	11 268	11 090	11 260	11 160	11 276	11 571	11 421	101 209
P&I hospitalizations										
No. during influenza season	5046	7370	4087	6586	10 138	6069	6765	9585	7267	62 913
Rate per 1000 population per week of influenza season	0.35	0.35	0.34	0.40	0.35	0.28	0.31	0.27	0.28	0.33
No. during post–influenza season	4370	4276	3931	3867	3903	4033	3949	4225	4166	36 720

Abbreviations: NA, not available; P&I, pneumonia and influenza.
[a] Determined by physician billing claims in the Ontario Health Insurance Plan database.
[b] Defined as the first and last occurrences of 2 consecutive weeks with at least 5% positive findings of weekly influenza isolates tested.
[c] Indicates percentage of isolated strains that are influenza A(H3N2) (generally more severe seasons in terms of serious outcomes among elderly individuals).
[d] The influenza A(H3N2) predominance for the 2008-2009 season was not available at the time of study completion.
[e] Defined as July 1 through September 30 after the influenza season.

IV ANALYSIS

Instrumental variable analysis is an econometric method used to remove the effects of hidden bias in observational studies.[19,29] An IV has the following 2 key characteristics: it is highly correlated with treatment and does not independently affect the outcome, so it is not associated with measured or unmeasured patient health status.

We used census subdivision (CSD)–specific influenza vaccine coverage as the IV. There were 377 CSDs (ie, municipalities or the equivalent) in Ontario before 2006 and 385 CSDs subsequently. Influenza vaccine coverage was defined as the percentage of individuals older than 65 years living in a CSD who received influenza vaccination for that influenza season. We excluded individuals whose CSD of residence could not be identified and those living in a CSD with fewer than 100 elderly individuals. We constructed this IV separately for each influenza season because of year-to-year variation in vaccine coverage across regions. Study participants were assigned to the vaccine coverage of their CSD of residence as the IV. For reporting purposes, we grouped the CSDs into quintiles of vaccination coverage to facilitate comparisons of patient characteristics across regions of high and low levels of vaccination.

The IV behaves like natural randomization of patients to regional vaccination groups that differ in their likelihood of receiving influenza vaccination. Unlike randomization, the difference in the likelihood of treatment is not 100%, and one can explore but not prove that the groups are similar in unmeasured patient characteristics. Rather than compare patients with respect to whether they received influenza vaccination, IV analysis compares groups of patients that differ in the likelihood of receiving influenza vaccination.[19,29] Excellent nontechnical expositions of the use of geographical IVs exist.[19,29,30]

Because our outcomes are binary variables, we performed IV modeling using 2-stage multivariable probit regression models. For each influenza season, we estimated the IV-adjusted odds of each outcome, with CSD-level influenza vaccine coverage serving as the IV. We transformed the results of the probit regression models into odds ratios (ORs) by multiplying the coefficients by a scaling factor of 1.6, which approximates the log OR coefficients of a logistic regression model.[31] We repeated the IV analysis on outcomes during the post–influenza seasons and pooled the results across all influenza seasons to compute a summary measure of effect. Owing to a greater proportion of individuals living in urban areas in the highest influenza vaccination quintile, we conducted a sensitivity analysis restricted to urban CSDs.

We performed statistical analyses using commercially available software (SAS, version 9.2,[32] and the procedure IVPROBIT in STATA, version 9.2[33]). All tests were 2-tailed. We used $P < .05$ as the level of statistical significance.

RESULTS

During the course of 9 influenza seasons, we followed up 1.3 million to 1.5 million elderly individuals each year, totaling 12.6 million person–influenza seasons of observation (**Table 1**). On average, 58.2% of the cohort was vaccinated annually. We observed 130 532 deaths and 62 913 P&I hospitalizations during influenza season. Vaccinated individuals had more outpatient visits in the preceding year, a higher prevalence of recorded comorbidities, and greater use of prescription medication and medical procedures (**Table 2**).

Influenza vaccine coverage ranged from 0% to 79% across CSDs. The CSDs with vaccination coverage ranging from 0% to 5% represented 2.8% of CSDs but only 0.2% of residents in the study. Coverage increased consistently from the lowest to the highest quintiles (**Table 3**). The partial *F* statistics from the first-stage IV regression models were greater than 950. Although there was a notable difference in rural residence and small differences in specific risk factors, mean predicted influenza season outcome rates—our summary measures of patient risk—were remarkably consistent across quin-

Table 2. Selected Baseline Characteristics According to Receipt of Influenza Vaccine[a]

Characteristic	Patient Groups		Standardized Difference[b]
	Unvaccinated (n = 5 277 839)	Vaccinated (n = 7 343 967)	
Demographics			
Age, mean (SD), y	74.5 (6.8)	75.5 (6.6)	14.5
Male sex	2 299 767 (43.6)	3 220 215 (43.8)	0.6
Rural residence	836 479 (15.8)	953 003 (13.0)	8.2
Neighborhood income quintile[c]			
1	1 097 456 (20.8)	1 405 066 (19.1)	4.2
2	1 117 164 (21.2)	1 579 953 (21.5)	0.8
3	1 030 921 (19.5)	1 466 779 (20.0)	1.1
4	992 881 (18.8)	1 405 877 (19.1)	0.8
5	1 028 765 (19.5)	1 476 807 (20.1)	1.5
Unknown	10 652 (0.2)	9485 (0.1)	1.8
Use of health care services			
No. of hospital visits in past 3 y, mean (SD)	0.44 (1.04)	0.48 (1.01)	4.0
No. of outpatient visits in past year, mean (SD)	13.31 (15.57)	17.52 (14.24)	28.4
Home care use in past 6 mo	306 562 (5.8)	424 239 (5.8)	0.1
Comorbidities			
Cancers	1 035 008 (19.6)	1 805 235 (24.6)	11.9
Cardiovascular diseases	1 652 785 (31.3)	2 939 387 (40.0)	18.2
Respiratory diseases	844 722 (16.0)	1 540 663 (21.0)	12.7
Anemias	516 317 (9.8)	936 881 (12.8)	9.3
Renal diseases	253 110 (4.8)	416 031 (5.7)	3.9
Diabetes mellitus	1 036 175 (19.6)	1 764 751 (24.0)	10.6
Immune disorders	29 614 (0.6)	45 361 (0.6)	0.7
Medications			
No. of medications in past year, mean (SD)	6.66 (6.05)	8.70 (6.10)	33.6
Statin use	1 532 049 (29.0)	2 858 214 (38.9)	20.9
ACE inhibitor use	1 492 016 (28.3)	2 591 436 (35.3)	15.0
β-Blocker use	1 112 200 (21.1)	1 934 863 (26.3)	12.3
Calcium channel blocker use	1 124 459 (21.3)	2 055 567 (28.0)	15.4
Procedures			
Stress test	935 052 (17.7)	1 619 046 (22.0)	10.8
Bone mineral density test	1 245 642 (23.6)	2 205 684 (30.0)	14.5
Echocardiography	1 067 008 (20.2)	1 859 532 (25.3)	12.1
Electrocardiography	3 367 340 (63.8)	5 335 538 (72.7)	19.2

Abbreviation: ACE, angiotensin-converting enzyme.
[a] Data are expressed as number (percentage) of patients unless otherwise noted. Percentages have been rounded and might not total 100.
[b] The standardized difference is the mean difference divided by the pooled SD. We expressed the standardized difference as a percentage by multiplying by 100.
[c] Higher income quintile number represents higher income.

tiles for all influenza seasons. The balance in the distribution of the measured risk factors across CSDs provides reasonable evidence to infer that unmeasurable risk factors are also likely balanced across CSDs. This inference lends support to regional influenza vaccine coverage being a valid and strong IV.

Using logistic regression and pooling across influenza seasons, we determined that influenza vaccination was associated with a 33% reduction in mortality during influenza season (adjusted OR, 0.67 [95% CI, 0.62-0.72]) (**Table 4**). Influenza vaccination was also significantly associated with mortality reduction after influenza season (adjusted OR, 0.85; [95% CI, 0.83-0.86]).

Instrumental variable analysis showed that the pooled adjusted association between influenza vaccination and mortality during influenza season was not significant (adjusted OR, 0.94 [95% CI, 0.84-1.03]) (Table 4). Restricting the analysis to urban areas led to similar results (adjusted OR, 0.93 [95% CI, 0.82-1.04]). According to the IV method, influenza vaccination was not associated with decreased mortality during post–influenza seasons (adjusted OR, 1.13 [95% CI, 1.07-1.19]).

Excluding individuals vaccinated after the index dates did not alter the results (adjusted OR using logistic regression, 0.68 [95% CI, 0.63-0.73]; adjusted OR using IV analysis, 0.94 [95% CI, 0.84-1.04]).

Results for the composite outcome of P&I hospitalization and death demonstrated reductions when using logistic regression (**Table 5**). According to IV analysis, the composite outcome was reduced during influenza seasons (adjusted OR, 0.86 [95% CI, 0.79-0.92]) but not during post–influenza seasons (1.02 [0.97-1.06]).

COMMENT

We found influenza vaccination of community-dwelling elderly individuals to be associated with reductions in all-cause mortality and the composite of P&I hospitalization and mortality during and after influenza seasons when using standard regression modeling. The

Table 3. Selected Baseline Characteristics Across Quintiles of Regional Influenza Vaccine Coverage[a]

Characteristic	Quintile of Regional Influenza Vaccine Coverage				
	1 (n = 2 540 680)	2 (n = 2 389 851)	3 (n = 3 086 662)	4 (n = 2 030 170)	5 (n = 2 574 443)
Mean influenza vaccine coverage, %	46.5	57.9	60.0	61.9	64.9
Mean predicted influenza season mortality, %[b]	1.09	1.00	1.04	0.94	1.08
Mean predicted influenza season P&I hospitalization or mortality, %	1.65	1.48	1.52	1.39	1.59
Demographics					
Age, mean (SD), y	74.84 (6.62)	74.84 (6.63)	75.23 (6.75)	75.01 (6.67)	75.24 (6.77)
Male, sex	1 142 438 (45.0)	1 053 133 (44.1)	1 325 627 (42.9)	886 124 (43.6)	1 112 660 (43.2)
Rural residence	882 357 (34.7)	234 284 (9.8)	153 421 (5.0)	171 433 (8.4)	347 987 (13.5)
Neighborhood income quintile[c]					
1	538 538 (21.2)	441 589 (18.5)	704 234 (22.8)	356 747 (17.6)	461 414 (17.9)
2	549 332 (21.6)	498 788 (20.9)	705 020 (22.8)	421 340 (20.8)	522 637 (20.3)
3	517 441 (20.4)	507 442 (21.2)	552 781 (17.9)	395 142 (19.5)	524 894 (20.4)
4	481 714 (19.0)	473 752 (19.8)	503 262 (16.3)	418 873 (20.6)	521 157 (20.2)
5	445 793 (17.5)	465 963 (19.5)	616 860 (20.0)	435 214 (21.4)	541 742 (21.0)
Unknown	7862 (0.3)	2317 (0.1)	4505 (0.1)	2854 (0.1)	2599 (0.1)
Use of health care services					
No. of hospital visits in past 3 y, mean (SD)	0.56 (1.15)	0.46 (1.02)	0.41 (0.96)	0.46 (1.00)	0.46 (1.00)
No. of outpatient visits in past year, mean (SD)	14.74 (14.32)	15.59 (14.89)	16.38 (15.64)	16.02 (14.99)	15.98 (14.71)
Home care use in past 6 mo	162 319 (6.4)	138 880 (5.8)	171 772 (5.6)	102 437 (5.0)	155 393 (6.0)
Comorbidities					
Cancers	573 858 (22.6)	508 236 (21.3)	669 285 (21.7)	459 260 (22.6)	629 604 (24.5)
Cardiovascular diseases	952 201 (37.5)	856 778 (35.9)	1 115 479 (36.1)	739 296 (36.4)	928 418 (36.1)
Respiratory diseases	497 937 (19.6)	433 178 (18.1)	581 725 (18.8)	380 549 (18.7)	491 996 (19.1)
Anemias	276 353 (10.9)	271 104 (11.3)	379 140 (12.3)	233 615 (11.5)	292 986 (11.4)
Renal diseases	122 455 (4.8)	126 696 (5.3)	184 927 (6.0)	105 643 (5.2)	129 420 (5.0)
Diabetes mellitus	540 588 (21.3)	536 476 (22.4)	732 882 (23.7)	438 661 (21.6)	552 319 (21.5)
Immune disorders	14 843 (0.6)	15 141 (0.6)	17 671 (0.6)	12 615 (0.6)	14 705 (0.6)
Medications					
No. of medications in past year, mean (SD)	7.63 (5.96)	7.89 (6.21)	8.16 (6.45)	7.76 (6.09)	7.71 (6.00)
Statin use	854 700 (33.6)	858 731 (35.9)	1 124 765 (36.4)	688 942 (33.9)	863 125 (33.5)
ACE inhibitor use	843 154 (33.2)	785 642 (32.9)	980 638 (31.8)	645 290 (31.8)	828 728 (32.2)
β-Blocker use	628 693 (24.7)	573 857 (24.0)	743 356 (24.1)	480 873 (23.7)	620 284 (24.1)
Calcium channel blocker use	627 424 (24.7)	613 355 (25.7)	810 076 (26.2)	507 752 (25.0)	621 419 (24.1)
Procedures					
Stress test	503 847 (19.8)	480 825 (20.1)	658 773 (21.3)	423 177 (20.8)	487 476 (18.9)
Bone mineral density test	549 060 (21.6)	697 761 (29.2)	979 151 (31.7)	570 520 (28.1)	654 834 (25.4)
Echocardiography	551 721 (21.7)	566 730 (23.7)	804 503 (26.1)	474 159 (23.4)	529 427 (20.6)
Electrocardiography	1 640 121 (64.6)	1 653 914 (69.2)	2 308 072 (74.8)	1 419 621 (69.9)	1 681 150 (65.3)

Abbreviations: ACE, angiotensin-converting enzyme; P&I, pneumonia and influenza.
[a] Data are expressed as number (percentage) of patients unless otherwise noted. Percentages have been rounded and might not total 100.
[b] Indicates all-cause mortality.
[c] Higher income quintile number represents higher income.

latter suggests the presence of bias because influenza vaccines should have no benefit in the absence of circulating influenza. In contrast, IV analysis indicated that influenza vaccination was not associated with decreased mortality during or after the influenza season. However, it was associated with a reduction in combined P&I hospitalizations and mortality during influenza seasons but not post–influenza seasons. The estimates of vaccine effectiveness obtained using IV analysis appear to be less biased than those from standard regression modeling. We conclude that influenza vaccines may not reduce all-cause mortality among elderly individuals during influenza season but may reduce the combined rates of P&I hospitalization and death.

The estimates of influenza vaccine effectiveness obtained in this study by using standard regression modeling are comparable to estimates from other observational studies: 43% to 55% for all-cause mortality and 31% to 48% for the composite of P&I hospitalization and death.[8,34-36] However, a 40% to 50% reduction in all-cause mortality (not just deaths attributable to influenza) is implausible if influenza accounts for no more than 10% of deaths during winter months.[14] The results of our IV analysis suggest that influenza vaccination may potentially be associated with a 6% reduction (with as much as a 16% reduction or as little as no reduction) in all-cause mortality during influenza seasons and is associated with a 14% reduction in P&I hospitalization or death, which is a more specific outcome. These estimates are more plausible and are similar to a 4.6% reduction in all-cause mortality and a 9% reduction in P&I hospitalizations during influenza season observed in recent studies using case-centered logistic regression, which has been proposed as a bias-minimizing technique.[11,37]

Table 4. Crude and Adjusted Association Between Influenza Vaccination and All-Cause Mortality Using Different Risk-Adjustment Methods

Influenza Season	Death During Influenza Seasons		Death During Post–Influenza Seasons	
	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
		Logistic Regression Modeling		
2000-2001	0.76 (0.73-0.79)	0.74 (0.71-0.77)	0.87 (0.84-0.91)	0.82 (0.78-0.85)
2001-2002	0.80 (0.77-0.83)	0.77 (0.74-0.80)	0.92 (0.89-0.96)	0.87 (0.83-0.90)
2002-2003	0.61 (0.58-0.64)	0.59 (0.56-0.61)	0.93 (0.89-0.96)	0.84 (0.80-0.87)
2003-2004	0.53 (0.51-0.55)	0.51 (0.49-0.53)	0.91 (0.88-0.94)	0.84 (0.81-0.87)
2004-2005	0.74 (0.72-0.76)	0.68 (0.66-0.70)	0.95 (0.92-0.99)	0.87 (0.84-0.91)
2005-2006	0.82 (0.79-0.85)	0.74 (0.71-0.77)	0.91 (0.88-0.95)	0.82 (0.78-0.85)
2006-2007	0.72 (0.70-0.74)	0.66 (0.64-0.68)	0.96 (0.93-1.00)	0.87 (0.83-0.90)
2007-2008	0.73 (0.71-0.75)	0.66 (0.64-0.68)	0.93 (0.89-0.96)	0.83 (0.80-0.86)
2008-2009	0.76 (0.74-0.79)	0.70 (0.68-0.73)	0.98 (0.94-1.01)	0.88 (0.85-0.92)
Pooled	0.72 (0.67-0.77)	0.67 (0.62-0.72)	0.93 (0.91-0.95)	0.85 (0.83-0.86)
		IV Analysis		
2000-2001	0.82 (0.71-0.95)	0.81 (0.68-0.97)	0.85 (0.74-0.98)	0.92 (0.78-1.10)
2001-2002	0.84 (0.74-0.95)	0.80 (0.69-0.94)	1.00 (0.87-1.15)	1.25 (1.05-1.49)
2002-2003	0.97 (0.83-1.13)	1.05 (0.86-1.27)	0.98 (0.86-1.13)	1.22 (1.03-1.45)
2003-2004	0.72 (0.63-0.82)	0.78 (0.66-0.91)	0.87 (0.76-0.99)	1.15 (0.97-1.35)
2004-2005	0.88 (0.79-0.97)	1.08 (0.95-1.23)	0.80 (0.71-0.91)	1.12 (0.96-1.31)
2005-2006	0.76 (0.68-0.85)	0.76 (0.66-0.88)	0.83 (0.73-0.93)	1.08 (0.92-1.26)
2006-2007	0.95 (0.84-1.07)	1.11 (0.95-1.30)	0.85 (0.75-0.97)	1.19 (1.01-1.41)
2007-2008	0.87 (0.79-0.96)	1.00 (0.89-1.13)	0.80 (0.71-0.91)	1.11 (0.95-1.29)
2008-2009	0.90 (0.81-1.00)	1.05 (0.92-1.19)	0.83 (0.73-0.93)	1.14 (0.98-1.33)
Pooled	0.85 (0.80-0.90)	0.94 (0.84-1.03)	0.86 (0.82-0.91)	1.13 (1.07-1.19)

Abbreviations: IV, instrumental variable; OR, odds ratio.
[a] Adjusted for demographics, comorbidities, previous use of health care services, prescription medication use, and receipt of specific medical procedures.
[b] Adjusted for the same variables as for the models during influenza season and an added term for hospitalization since the start of influenza season.

Table 5. Crude and Adjusted Association Between Influenza Vaccination and the Composite Outcome of P&I Hospitalization or All-Cause Mortality Using Different Risk-Adjustment Methods

Influenza Season	P&I Hospitalization or Death During Influenza Seasons		P&I Hospitalization or Death During Post–Influenza Seasons	
	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
		Logistic Regression Modeling		
2000-2001	0.85 (0.83-0.88)	0.80 (0.77-0.83)	0.94 (0.91-0.97)	0.86 (0.83-0.89)
2001-2002	0.87 (0.84-0.89)	0.79 (0.77-0.82)	0.88 (0.96-1.02)	0.91 (0.88-0.94)
2002-2003	0.72 (0.70-0.75)	0.67 (0.65-0.70)	0.98 (0.95-1.01)	0.87 (0.84-0.90)
2003-2004	0.67 (0.65-0.69)	0.61 (0.60-0.63)	0.96 (0.93-0.99)	0.87 (0.84-0.90)
2004-2005	0.83 (0.81-0.85)	0.75 (0.73-0.77)	1.00 (0.96-1.03)	0.90 (0.87-0.93)
2005-2006	0.91 (0.88-0.93)	0.80 (0.77-0.82)	0.97 (0.94-1.00)	0.86 (0.83-0.89)
2006-2007	0.81 (0.79-0.83)	0.72 (0.70-0.74)	1.02 (0.99-1.05)	0.90 (0.87-0.93)
2007-2008	0.83 (0.81-0.85)	0.72 (0.71-0.74)	0.99 (0.96-1.02)	0.87 (0.84-0.90)
2008-2009	0.87 (0.85-0.90)	0.77 (0.75-0.80)	1.04 (1.00-1.07)	0.92 (0.89-0.95)
Pooled	0.82 (0.77-0.87)	0.74 (0.70-0.78)	0.97 (0.94-1.00)	0.88 (0.87-0.90)
		IV Analysis		
2000-2001	0.78 (0.69-0.89)	0.83 (0.71-0.96)	0.78 (0.69-0.88)	0.88 (0.76-1.02)
2001-2002	0.72 (0.65-0.80)	0.75 (0.66-0.85)	0.84 (0.74-0.95)	1.03 (0.89-1.19)
2002-2003	0.83 (0.73-0.94)	0.97 (0.82-1.13)	0.88 (0.78-0.99)	1.11 (0.96-1.29)
2003-2004	0.64 (0.57-0.71)	0.75 (0.65-0.85)	0.77 (0.69-0.87)	1.05 (0.91-1.21)
2004-2005	0.76 (0.70-0.83)	0.98 (0.88-1.10)	0.74 (0.66-0.82)	1.02 (0.89-1.18)
2005-2006	0.67 (0.61-0.74)	0.74 (0.65-0.83)	0.76 (0.69-0.85)	1.04 (0.91-1.19)
2006-2007	0.75 (0.68-0.83)	0.90 (0.79-1.03)	0.73 (0.65-0.82)	1.00 (0.87-1.16)
2007-2008	0.76 (0.70-0.83)	0.90 (0.81-1.00)	0.73 (0.65-0.81)	0.99 (0.87-1.14)
2008-2009	0.75 (0.68-0.82)	0.90 (0.81-1.01)	0.76 (0.68-0.84)	1.02 (0.90-1.17)
Pooled	0.74 (0.70-0.77)	0.86 (0.79-0.92)	0.77 (0.73-0.81)	1.02 (0.97-1.06)

Abbreviations: IV, instrumental variable; OR, odds ratio; P&I, pneumonia and influenza.
[a] Adjusted for demographics, comorbidities, previous use of health care services, prescription medication use, and receipt of specific medical procedures.
[b] Adjusted for the same variables as for the models during influenza season and an added term for hospitalization since the start of influenza season.

The association between influenza vaccination and outcomes during non–influenza seasons is evidence that previous observational studies are biased.[9-11] Because there is minimal influenza circulation outside of influenza seasons, vaccination should confer no benefits during these periods (all OR estimates should be close to the null value of 1.00). However, several studies have demonstrated that vaccinated individuals are approximately 20% to 35% less likely to die during post–influenza seasons,[9-11] which is comparable to our estimate of 15% when using standard regression models. Although our study showed that vaccinated individuals had a higher prevalence of recorded comorbidities and greater use of prescription medications and medical procedures, the protective effect of vaccination during noninfluenza seasons demonstrates the persistence of bias despite adjustment for the factors we described. With IV analysis, influenza vaccination was found not to be associated with reductions in post–influenza season P&I hospitalization or death. This finding increases the confidence that our estimates for the association between vaccination and outcomes during influenza seasons using the IV analysis are unbiased. The estimate for all-cause mortality during post–influenza seasons being significantly greater than 1.00 was unexpected and raises the possibility that we may have underestimated the true effectiveness of the vaccine for this outcome.

Our season-specific estimates also warrant discussion. Based on the framework proposed by Simonsen et al,[7] influenza vaccine effectiveness is expected to be lower when the vaccine does not match the predominant circulating strains and higher during more severe influenza seasons. The 2003-2004 season saw the emergence of the influenza A/Fujian(H3N2) drifted strain that was responsible for 92% of the characterized isolates in Canada but was not included in that season's vaccine.[38] However, that season was also the most severe among the 9 influenza seasons included in this study, with 0.70 all-cause deaths and 0.40 P&I hospitalizations per 1000 population per week of influenza season compared with means of 0.66 and 0.32, respectively, for the other 8 seasons. It is uncertain which of these factors contributed more toward the estimates of vaccine effectiveness for that season being among the largest or whether the finding is due to chance.

In terms of interpretation, IV analysis estimates the treatment effect on the marginal population, defined as patients who would receive influenza vaccination in regions with higher but not lower influenza vaccine coverage.[39] In our study, such individuals would be more likely to be vaccinated if they had better access to influenza vaccination clinics and/or physicians who are more inclined to encourage influenza vaccination.

There have been 2 previous attempts to use IV analysis to estimate influenza vaccine effectiveness among elderly individuals. One study tried various IVs but found that none satisfied the assumptions of a valid IV.[40] Another study used the diagnosis of arthritis or gout as the IV and found that it satisfied both key assumptions; in that study, influenza vaccination was associated with a nonsignificant 10% mortality reduction (confidence intervals were not provided).[41]

Our study had several notable strengths other than the application of the IV analysis method. By including all community-dwelling elderly individuals in Ontario for 9 influenza seasons, we analyzed more than 12 million person–influenza seasons of observation, making our study one of the largest ever conducted to assess influenza vaccine effectiveness. The large sample allowed for more than 100 confounding variables to be adjusted for without compromising statistical power.

Nonetheless, several limitations in our study merit emphasis. First, because approximately 25% of influenza vaccines administered to the elderly are not recorded in the Ontario Health Insurance Plan physician claims database (they were provided outside physician offices, eg, at public health clinics and pharmacies), individual-level vaccination status and regional vaccine coverage may have been misclassified to a certain extent.[25] Such misclassification may have biased our estimates toward the null. Second, cause-specific mortality data were unavailable, so we could not use P&I or respiratory mortality as more specific outcomes. With respect to the IV method, one can strongly infer but not prove that the IV is not related to unmeasured illness variables. However, the fact that there was little relationship with measured variables implies that, for an unmeasured variable to bias these results, it needs to be associated with the outcome and uncorrelated with any of the measured variables.

Application of IV analysis methods to linked health administrative data sets is a valid method for estimating an unbiased estimate of influenza vaccine effectiveness in elderly individuals without the challenges associated with conducting a randomized controlled trial. The results of our study suggest that influenza vaccination may be associated with reductions in the composite of P&I hospitalization and mortality, but not with all-cause mortality alone, among elderly individuals. Nevertheless, current guidelines recommending annual vaccination against influenza for elderly individuals should remain in place until more definitive evidence has been amassed, as even small reductions in outcomes during influenza season as a result of influenza vaccination would be worthwhile because it is a generally safe and relatively low-cost intervention. Improved estimates of influenza vaccine effectiveness will permit better decision making at the individual and population levels and may spur the development of more effective strategies for reducing the burden of influenza.

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