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Influenza Vaccine Effectiveness in Preventing Hospitalizations in Older Patients With Chronic Obstructive Pulmonary Disease

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Background. Annual influenza immunization is recommended for people with chronic obstructive pulmonary disease (COPD) by all major COPD clinical practice guidelines. We sought to determine the seasonal influenza vaccine effectiveness (VE) against laboratory-confirmed influenza-associated hospitalizations among older adults with COPD.

Methods. We conducted a test-negative study of influenza VE in community-dwelling older adults with COPD in Ontario, Canada using health administrative data and respiratory specimens collected from patients tested for influenza during the 2010–11 to 2015–16 influenza seasons. Influenza vaccination was ascertained from physician and pharmacist billing claims. Multivariable logistic regression was used to estimate the adjusted odds ratio of influenza vaccination in people with, compared to those without, laboratory-confirmed influenza.

Results. Receipt of seasonal influenza vaccine was associated with an adjusted 22% (95% confidence interval [CI], 15%–27%) reduction in laboratory-confirmed influenza-associated hospitalization. Adjustment for potential misclassification of vaccination status increased this to 43% (95% CI, 35%–52%). Vaccine effectiveness was not found to vary by patient- or influenza-related variables.

Conclusions. During the studied influenza seasons, influenza vaccination was at least modestly effective in reducing laboratory-confirmed influenza-associated hospitalizations in people with COPD. The imperfect effectiveness emphasizes the need for better influenza vaccines and other preventive strategies.

Keywords. chronic obstructive pulmonary disease (COPD); influenza vaccine; vaccine effectiveness.

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide [1] and is costly to healthcare systems. It is also projected to increase in burden over the coming decades due to ongoing exposure to smoking, air pollution, and an aging population. Approximately 70% of COPD exacerbations are believed to be infectious in origin. Although a respiratory virus is not always identified [2, 3], when one is, it is often influenza [4]. Patients with COPD are susceptible to severe complications of influenza, including hospitalization and death [3]. Seasonal influenza vaccination is recommended by all major COPD practice guidelines because it is believed to reduce hospitalizations and death [5]. However, evidence showing reduction of these outcomes in people with COPD—unlike in the general elderly population—is limited [6]. Influenza vaccine effectiveness (VE) in people with COPD may be less than in people without COPD because they have an inherent or corticosteroid-induced decrease in immune response to vaccination and respiratory infection [2]. Despite recommendations for influenza immunization, recent vaccine uptake has only been approximately 60% in high-risk elderly people and lower in other groups [2, 7].

A thorough review of the few, quality-randomized controlled trials (RCTs) examining influenza vaccination versus placebo on hospitalizations or mortality in people with COPD found no significant difference [8]. Future RCTs in this area seem unlikely because recommendations to immunize people with COPD make conducting them ethically questionable.

A few observational studies have also evaluated influenza VE in people with COPD. Those examining various types of

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hospitalizations have noted reductions of 54% to 91%, whereas those measuring all-cause mortality have noted no significant effect to reductions of 55% [2, 3, 9–17]. However, these studies have been limited by small sample sizes, nonspecific outcomes, unmeasured confounding, and lack of generalizability. In addition, although some previous studies have found variation in VE in people with COPD of different ages and severity, there has been little exploration of VE by other patient characteristics [2].

Over the past decade, the test-negative design has been used to study influenza VE that confers advantages over previous designs, including the ability to address confounding and evaluate influenza-specific outcomes. Indeed, influenza VE estimates using the test-negative design have been shown to approximate RCT estimates more accurately than other observational study designs [18]. The only study that we are aware of that has applied this methodology to VE in the COPD population was a Canadian study that found influenza vaccine reduced influenza-related hospitalizations by 38% (95% confidence interval [CI], 27%–46%). However, this study used self-report, a type of measure associated with underreporting, to establish vaccine status as well as many covariables, and a large proportion of subjects had unknown vaccine status and were not accounted for in the analysis [19].

In the current study, we used the test-negative design to determine the effectiveness of influenza vaccination in preventing laboratory-confirmed influenza-associated hospitalizations over several influenza seasons in community-dwelling older patients with COPD using laboratory data linked to longitudinal, complete health administrative data. We examined whether VE differed in those with different patient- and/or influenza-related characteristics.

METHODS

Study Design and Setting

We linked influenza testing data from 11 public health and 8 academic hospital laboratories to health administrative databases and used the test-negative design to determine influenza VE in preventing laboratory-confirmed influenza-associated hospitalizations for older adults with COPD in the province of Ontario, Canada (population 13.9 million in 2016) who had an acute care hospitalization during 6 influenza seasons (2010–11 to 2015–16). A threshold level of 5% influenza test positivity for the province of Ontario was used to restrict the analyses to periods when influenza was circulating.

The test-negative design is commonly used to evaluate influenza VE because it attenuates both biases due to misclassification of infection and due to differences in healthcare seeking behavior between vaccinated and unvaccinated persons [20–27]. This design compares the odds of influenza vaccination between those who test positive for laboratory-confirmed influenza (cases) to the odds of vaccination in those who test negative (controls). Ethics approval was obtained from the Research Ethics Boards of all participating institutions (Supplementary Table S1).

Data Sources

In Ontario's publicly funded health system, the province's residents are insured for all medically necessary services provided by physicians and hospitals, including prescription medications for those aged 65 years or older. Details of healthcare services are captured in several large health administrative databases, detailed below, that were individually linked using unique encoded identifiers and analyzed at ICES.

Study Population and Outcome

Community-dwelling residents of Ontario aged 66 or older with physician-diagnosed COPD who were tested for influenza within 3 days before and during an acute care hospitalization were included. Hospitals in Ontario are guided to systematically identify cases of acute respiratory infection and initiate appropriate care using routine practices that, during influenza season, includes influenza testing [28]. There is further incentive for this testing because it may lead to patients with respiratory symptoms being taken out of isolation, a desirable action due to its scarcity and expense. As per the test-negative design, the index date was the outcome date, which was set as the specimen collection date. Age 66 was used to allow for 1 year lookback for medication use (see below). Those who were vaccinated within 14 days of specimen collection were excluded from the study because their immunity from influenza vaccination was uncertain. People with physician-diagnosed COPD were identified using a COPD case definition, based on COPD ambulatory care visits and hospitalizations, that has been shown to have a positive predictive value of 86% in adults aged 65 years or older compared with clinical evaluation by a physician (Supplementary Table S2) [29, 30]. Although this definition, which has been used in many previous studies, did not require people to have undergone pulmonary function testing, it identified those with COPD in the real world—where less than 50% of individuals receive testing for diagnosis [31]. Information on COPD ambulatory care visits was captured by the Ontario Health Insurance Plan (OHIP) Physician Services Claims database, and information on hospitalizations was captured by the Canadian Institute for Health Information Discharge Abstract Database. We included individuals once per season; if individuals had more than 1 hospitalization associated with influenza testing during the same season, we kept the earliest associated with a positive influenza test or the earliest if all testing was negative.

Influenza Laboratory Testing

Results of subjects' influenza testing were linked to health administrative data using unique encoded identifiers. The linkage success rate was 97.8%. Respiratory specimens were tested

using at least one of polymerase chain reaction (monoplex and multiplex), viral culture, direct immunofluorescence assay, or enzyme immunoassay tests.

Influenza Vaccination

In Ontario, adjuvanted or unadjuvanted inactivated influenza vaccines are available for all older adults through provincial health insurance. We determined influenza vaccination status using physician billing claims (OHIP) and, starting in 2012, pharmacist billing claims, which are captured in the Ontario Drug Benefits (ODB) database (Supplementary Table S2). Physician-administered influenza vaccination has been validated against a self-reported reference standard in people aged 65 years or older with COPD and found to have 68% sensitivity and 92% specificity [32]. A sensitivity analysis that adjusted for possible misclassification was performed.

Covariates

Demographic information including age, sex, neighborhood income quintile, and rural residence was determined through linkage with the Registered Persons Database, a registry of all provincial residents eligible for health insurance. Comorbidities of interest included those identified by Canada's National Advisory Committee on Immunization as indicators of increased risk of influenza complications (Supplementary Table S2) [33]. We also accounted for patient frailty based on methodology developed by Urquhart et al [34], and we combined frailty with dementia due to the overlap in diagnosis codes used in the identification of both conditions. The ODB database was used to determine the receipt of COPD medications. Other influenza factors (including month and influenza season), healthcare utilization, and COPD-related factors were derived from emergency department encounter data (National Ambulatory Care Reporting System), hospitalization data, physician claims data, and home care services data (Ontario Home Care Database) [30]. Community COPD exacerbations were defined by short-term prescriptions for oral steroids and/or respiratory antibiotics within 7 days of a visit to a physician for COPD. These visits could have contributed to a person being identified with COPD and entering the cohort (see above). Although pulmonary function testing is used to establish diagnosis and severity of COPD, it was not used to identify people with COPD because a significant proportion of individuals with COPD do not receive pulmonary function testing and the results are not available in the health administrative data [31].

Analyses

Primary Analysis

Unadjusted and adjusted logistic regression modeling was used to estimate VE, adjusting for age, sex, receipt of home care, income quintile, rural residence, number of hospital visits in past 3 years, number of prescription drugs in past year, number of physician office visits in past year, presence of any comorbidity (ie, composite variable of those listed in the tables), month of specimen collection, season of specimen collection, COPD duration, history of pneumonia hospitalization, history of COPD hospitalization, history of COPD emergency department visit (that did not lead to hospitalization), outpatient COPD exacerbation, receipt of inhaled corticosteroids, receipt of inhaled long-acting anticholinergics, receipt of inhaled long-acting beta-agonist, receipt of inhaled short-acting anticholinergics, receipt of inhaled short-acting beta-agonist, and pulmonary function testing, except when stratifying by one of those variables. Vaccine effectiveness was calculated as (1-adjusted odds ratio) × 100%. We used SAS 9.4 (SAS Institute, Cary, NC) for statistical analyses. All tests were 2-tailed and $P < .05$ was the level of statistical significance.

Subgroup Analyses

A priori, we planned a number of subgroup analyses to determine VE among people with different individual and influenza-related characteristics including age, sex, influenza season, influenza subtype, prior season influenza vaccination, a codiagnosis of asthma, duration of COPD, previous outpatient COPD exacerbations, previous COPD hospitalization, previous receipt of inhaled corticosteroids, and previous pneumonia.

Sensitivity Analyses

Because influenza vaccines are available in both traditional and nontraditional settings in Ontario, and the administrative data only captured influenza vaccines administered in physician offices and pharmacies, the primary analysis was repeated with adjustment for misclassification of the exposure variable (ie, influenza vaccination status) using sensitivity (68%) and specificity (92%) performance measures from a previous study that validated physician-administered influenza vaccination in older adults with COPD [32]. This quantitative sensitivity analysis involved a probabilistic Monte Carlo simulation that assumed nondifferential misclassification of vaccination status [35]. In brief, a range of VE estimates were calculated based on multiple reclassifications of vaccination statuses using the above sensitivity and specificity values and their 95% CIs. To demonstrate specificity of the association between influenza vaccination and laboratory-confirmed influenza, we examined the association between eye exams by an optometrist and laboratory-confirmed influenza as a negative tracer exposure (ie, no association expected). To determine whether confirmation of COPD diagnosis by pulmonary function testing changed results, we conducted subgroup analyses in those who did and did not receive previous pulmonary function testing. Finally, in post hoc analyses, we estimated VE excluding the 2014–15 influenza season, when the influenza vaccine was poorly matched to the circulating A/H3N2 strain, and we also estimated VE for all older adults who did not fulfill our administrative data definition for COPD (ie, no previous physician visits or hospitalizations coded as COPD before index date) [36].

Table 1. Selected Descriptive Characteristics of Influenza Test-Positive and Influenza Test-Negative Adults Aged 66 Years or Older With COPD, 2010/11–2015/16 (for Full List, See Supplementary Table S3)

Characteristic	Test-Positive Patients[a]	Test-Negative Patients[a]	*P* Value
n	3636	18 112	
Vaccinated against influenza, %	1859 (51.1%)	10 315 (57.0%)	<.001
Demographics			
Age group, years, %			
66 to 75	1192 (32.8%)	6668 (36.8%)	<.001
76 to 85	1497 (41.2%)	7392 (40.8%)	
86 and older	947 (26.0%)	4052 (22.4%)	
Male sex, %	1743 (47.9%)	9191 (50.7%)	<.001
Rural residence (compared to urban), %	337 (9.3%)	1547 (8.5%)	.27
Socioeconomic status as per neighborhood income Quintile, %			
1 (lowest)	932 (25.6%)	4782 (26.4%)	.15
2	812 (22.3%)	3918 (21.6%)	
3	692 (19.0%)	3358 (18.5%)	
4	649 (17.8%)	3037 (16.8%)	
5 (highest)	528 (14.5%)	2894 (16.0%)	
COPD-Related Factors, %			
Duration of COPD			
0 to 4 years	1665 (45.8%)	8423 (46.5%)	.26
5 to 9 years	698 (19.2%)	3596 (19.9%)	
10 or more years	1273 (35.0%)	6093 (33.6%)	
Pneumonia Hospitalization			
Less than 1 year previous	112 (3.1%)	731 (4.0%)	.02
1 to 5 years previous	269 (7.4%)	1365 (7.5%)	
More than 5 years or never	3255 (89.5%)	16 016 (88.4%)	
COPD Hospitalization			
Less than 1 year previous	517 (14.2%)	3209 (17.7%)	<.001
1 to 5 years previous	522 (14.4%)	2920 (16.1%)	
More than 5 years or never	2597 (71.4%)	11 983 (66.2%)	
COPD emergency department visit (not resulting in a hospitalization)			
Less than 1 year previous	371 (10.2%)	2275 (12.6%)	<.001
1 to 5 years previous	419 (11.5%)	2265 (12.5%)	
More than 5 years or never	2846 (78.3%)	13 572 (74.9%)	
COPD outpatient exacerbation in previous year	1313 (36.1%)	7253 (40.0%)	<.001
Receipt of COPD Medications in Previous 6 Months			
Inhaled corticosteroids	2069 (56.9%)	10 855 (59.9%)	<.001
Long-acting anticholinergics	1537 (42.3%)	9078 (50.1%)	<.001
Long-acting beta-agonist	1817 (50.0%)	10 024 (55.3%)	<.001
Short-acting anticholinergics	359 (9.9%)	2084 (11.5%)	<.001
Short-acting beta-agonist	1833 (50.4%)	9983 (55.1%)	<.001
Comorbidity, %			
Anemia	807 (22.2%)	4457 (24.6%)	<.001
Asthma	1717 (47.2%)	8327 (46.0%)	.17
Cancer	906 (24.9%)	5173 (28.6%)	<.001
Coronary artery disease	1554 (42.7%)	7855 (43.4%)	.48
Heart failure	1715 (47.2%)	9017 (49.8%)	<.001
Chronic kidney disease	840 (23.1%)	4330 (23.9%)	.30
Diabetes	1611 (44.3%)	7735 (42.7%)	.08
Dementia/frailty	706 (19.4%)	3338 (18.4%)	.16
Immunocompromised condition	547 (15.0%)	2974 (16.4%)	.04
Transient ischemic attack or stroke	474 (13.0%)	2177 (12.0%)	.09
General Healthcare Utilization Factors			
Influenza vaccination in prior influenza season, %	2082 (57.3%)	10 934 (60.4%)	<.001
Number of hospitalizations in past 3 years, median (interquartile range)	1 (0–3)	1 (0–3)	<.001
Number of physician office visits in past year, median (interquartile range)	12 (6–19)	13 (7–20)	<.001
Number of prescribed medications in past year, median (interquartile range)	17 (12–24)	18 (12–25)	<.001
Specimen Collection and Influenza Season Factors, %			

Table 1. Continued

Characteristic	Test-Positive Patients[a]	Test-Negative Patients[a]	*P* Value
Influenza Season			
2010–2011	399 (11.0%)	1996 (11.0%)	<.001
2011–2012	127 (3.5%)	1255 (6.9%)	
2012–2013	760 (20.9%)	3388 (18.7%)	
2013–2014	518 (14.2%)	3735 (20.6%)	
2014–2015	1265 (34.8%)	4476 (24.7%)	
2015–2016	567 (15.6%)	3262 (18.0%)	

Abbreviations: COPD, chronic obstructive pulmonary disease.

[a]Data missing for 23 (0.6%) and 123 (0.7%) test-negative and test-positive patients, respectively.

RESULTS

There were 21 748 community-dwelling individuals aged 66 years or older with physician-diagnosed COPD who were tested for influenza within 3 days before or during a hospitalization over 6 consecutive influenza seasons between 2010 and 2016. Of those, 3636 (16.7%) tested positive for influenza (Table 1 and Supplementary Table S3). Compared to patients who were test-positive, those who were test-negative were slightly younger, more likely to be male, more likely to have been hospitalized for COPD in the previous year, more likely to have been hospitalized for pneumonia and more likely to have a history of cancer or an immunocompromising condition. They were also more likely to have received most COPD medications and pulmonary function testing. Vaccination was less likely to have occurred in a test-positive compared to a test-negative patient (51.1% compared to 57.0%).

Compared to unvaccinated individuals, vaccinated individuals were less likely to test positive for influenza (15.3% vs 18.6%) (Table 2 and Supplementary Table S4). They were also more likely to (1) be slightly older, (2) reside in an urban setting, (3) reside in higher income neighborhoods, (4) have more outpatient visits with a physician in the previous year, (5) have received a prescription for a COPD medication in the last 6 months, (7) have a higher proportion of diabetes, asthma, and immunocompromising conditions, (8) have a longer duration of COPD, and (8) have had an outpatient COPD exacerbation in the past year.

The overall unadjusted estimate of VE was 21% (95% CI, 15%–26%), which was unchanged at 22% (95% CI, 15%–27%) after multivariable adjustment (Table 3 and Supplementary Table S5). Correcting for misclassification of vaccination status among those with COPD resulted in an estimated VE of 43% (95% CI, 34%–52%).

The interaction between VE and influenza season was not statistically significant ($P = .06$), but, as expected, VE was lowest at 11% (95% CI, −1% to 22%) in 2014–15 and ranged from 22% to 35% in other seasons. When specimens from the 2014–15 seasons were removed post hoc, the adjusted VE was 26% (95% CI, 19%–32%). In other post hoc analysis, VE was found to be 20% (95% CI, 15%–25%) among adults aged 66 years or older "without" a diagnosis of COPD.

Correcting for misclassification of vaccination status among those without COPD, using similar methods as for the COPD cohort, revealed an estimated VE of 37% (95% CI, 31%–41%). No association was observed between laboratory-confirmed influenza and eye exams by an optometrist (adjusted "VE" −7% [95% CI, −15% to 1%])

In subgroup analyses, VE was not found to vary significantly by most factors including age, sex, influenza subtype, a codiagnosis of asthma, duration of COPD, previous outpatient COPD exacerbations, previous COPD hospitalization, previous receipt of inhaled corticosteroids, and previous pneumonia. Vaccine effectiveness also did not appear to differ significantly by whether individuals had received previous pulmonary function testing (all *P* values for interactions >.05). However, VE did trend lower in the 2014–15 influenza season, and people who had a prior season influenza vaccination had lower VE than those who had not ($P = .04$) (Table 3 and Supplementary Table S5).

DISCUSSION

We conducted a test-negative design study over 6 influenza seasons in Ontario, Canada and observed receipt of the influenza vaccine to be associated with a 22% to 43% (accounting for misclassification of vaccination status) reduced risk of laboratory-confirmed influenza-associated hospitalization among older adults with physician-diagnosed COPD, a value very similar to that found in older adults without COPD. We found no significant variation by most patient, specimen collection, or influenza season characteristics, with the exception being prior season influenza vaccination. To the best of our knowledge, this is the first large, real-world population study to examine VE in people with COPD using the test-negative design and influenza-specific study outcomes. Influenza vaccination offers prevention against a serious outcome in this high-risk group, but it is far from preventing all hospitalizations. These findings emphasize the need for more effective influenza vaccines for older COPD patients and other preventive strategies.

Table 2. Selected Descriptive Characteristics of Vaccinated and Unvaccinated Adults Aged 66 Years or Older With COPD, 2010/11–2015/16 (for Full List, See Supplementary Table S4)

Characteristic	Vaccinated[a]	Unvaccinated[a]	*P* Value
n	12 174	9574	
Positive influenza test, %	1859 (15.3%)	1777 (18.6%)	<.001
Demographics			
Age group, years, %			
66 to 75	4118 (33.8%)	3742 (39.1%)	<.001
76 to 85	5190 (42.6%)	3699 (38.6%)	
86 and older	2866 (23.5%)	2133 (22.3%)	
Male sex, %	6169 (50.7%)	4765 (49.8%)	.19
Rural residence (compared to urban), %	935 (7.7%)	949 (9.9%)	<.001
Socioeconomic Status as per Neighborhood Income Quintile[a], %			
1 (lowest)	3056 (25.1%)	2658 (27.8%)	<.001
2	2659 (21.8%)	2071 (21.6%)	
3	2266 (18.6%)	1784 (18.6%)	
4	2094 (17.2%)	1592 (16.6%)	
5 (highest)	2035 (16.7%)	1387 (14.5%)	
COPD-Related Factors, %			
Duration of COPD			
0 to 4 years	5303 (43.6%)	4785 (50.0%)	<.001
5 to 9 years	2516 (20.7%)	1778 (18.6%)	
10 or more years	4355 (35.8%)	3011 (31.4%)	
Pneumonia Hospitalization			
Less than 1 year previous	433 (3.6%)	410 (4.3%)	.02
1 to 5 years previous	902 (7.4%)	732 (7.6%)	
More than 5 years or never	10 839 (89.0%)	8432 (88.1%)	
COPD Hospitalization			
Less than 1 year previous	2034 (16.7%)	1692 (17.7%)	.02
1 to 5 years previous	1987 (16.3%)	1455 (15.2%)	
More than 5 years or never	8153 (67.0%)	6427 (67.1%)	
COPD Emergency Department Visit (not Resulting in a Hospitalization)			
Less than 1 year previous	1497 (12.3%)	1149 (12.0%)	.19
1 to 5 years previous	1541 (12.7%)	1143 (11.9%)	
More than 5 years or never	9136 (75.0%)	7282 (76.1%)	
COPD outpatient exacerbation in previous year	5287 (43.4%)	3279 (34.2%)	<.001
COPD Medications Received in Previous 6 Months			
Inhaled corticosteroids	7641 (62.8%)	5283 (55.2%)	<.001
Long-acting anticholinergics	6283 (51.6%)	4332 (45.2%)	<.001
Long-acting beta-agonist	7127 (58.5%)	4714 (49.2%)	<.001
Short-acting anticholinergics	1322 (10.9%)	1121 (11.7%)	.05
Short-acting beta-agonist	6722 (55.2%)	5094 (53.2%)	<.001
Comorbidity, %			
Anemia	3005 (24.7%)	2259 (23.6%)	0.063
Asthma	5933 (48.7%)	4111 (42.9%)	<.001
Cancer	3476 (28.6%)	2603 (27.2%)	.03
Coronary artery disease	5280 (43.4%)	4129 (43.1%)	.72
Heart failure	6046 (49.7%)	4686 (48.9%)	.29
Chronic kidney disease	2883 (23.7%)	2287 (23.9%)	.72
Diabetes	5348 (43.9%)	3998 (41.8%)	<.001
Dementia/frailty	2140 (17.6%)	1904 (19.9%)	<.001
Immunocompromised condition	2076 (17.1%)	1445 (15.1%)	<.001
Transient ischemic attack or stroke	1487 (12.2%)	1164 (12.2%)	1.00
General Healthcare Utilization Factors			
Influenza vaccination in prior influenza season, %	9672 (79.4%)	3344 (34.9%)	<.001
Number of hospitalizations in past 3 years, median (interquartile range)	1 (0–3)	1 (0–3)	<.001
Number of physician office visits in past year, median (interquartile range)	14 (8–21)	10 (5–18)	<.001

Table 2. Continued

Characteristic	Vaccinated[a]	Unvaccinated[a]	*P* Value
Number of prescribed medications in past year, median (interquartile range)	18 (13–25)	17 (11–24)	<.001
Receipt of home care in past year, %	6290 (51.7%)	5326 (55.6%)	<.001
Specimen Collection and Influenza Season Factors, %			
Influenza Season			
2010–11	1231 (10.1%)	1164 (12.2%)	<.001
2011–12	802 (6.6%)	580 (6.1%)	
2012–13	2190 (18.0%)	1958 (20.5%)	
2013–14	2445 (20.1%)	1808 (18.9%)	
2014–15	3315 (27.2%)	2426 (25.3%)	
2015–16	2191 (18.0%)	1638 (17.1%)	

Abbreviations: COPD, chronic obstructive pulmonary disease.

[a]Data missing for 64 (0.5%) and 82 (0.9%) vaccinated and nonvaccinated patients, respectively.

Our results are consistent with several observational studies involving different designs and outcomes demonstrating reductions of influenza-related hospitalization in people with and without COPD [37]. Thus, our study confirms those findings and further extends them by quantifying influenza VE in a large, real-world, North American, COPD population using laboratory-confirmed clinical outcomes and a robust study design. In most comparisons with other observational studies, however, our range of effectiveness was lower [2, 3, 9–17], which could speak to our more robust study design. Indeed, our results were similar to those of one other study using the test-negative design [19].

Our study did not show differences in VE by various patient- and influenza-related characteristics—although apparent trends and wide CIs suggest that it was underpowered to find all but very notable differences. We did note that those who had been vaccinated in the prior season experienced lower VE than those who were not vaccinated in the prior season. This finding may have resulted from the impact of lower VE among those who were vaccinated during both the 2013–14 and 2014–15 seasons compared with those vaccinated in 2014–15 only [38]. However, a recent review concluded that vaccination in the current season is still likely to be beneficial during most influenza seasons, irrespective of prior season vaccination history [39].

A moderate VE in people with COPD might be because of low immunogenicity among this population and/or high susceptibility to respiratory hospitalizations in general. It is interesting to note that our results were not very different from VE in people without COPD. This suggests that it might be the immunosenescence of aging as opposed to the immunosuppression of COPD that leads to lower VE. Our findings speak to the need for more effective influenza vaccines for older COPD patients, and perhaps older people in general, and other preventive strategies. They also reinforce the importance of vaccinating close contacts of patients with COPD, thereby combining the direct benefits of vaccinating a high-risk population with the indirect benefits of vaccinating their contacts.

Our study had limitations that merit emphasis. First, unlike RCTs, observational study designs are susceptible to unmeasured confounding. However, the use of the test-negative design and further controlling for many potential confounders minimized the likelihood of this having biased our results. In addition, in terms of unmeasured confounding, our test-positive patients appeared healthier than our test-negative controls, which means they would be less likely to be susceptible to influenza hospitalization, potentially creating bias in opposition to our positive findings and thereby attenuating the VE observed. A second important limitation was the potential for misclassification of influenza vaccination status; however, this is an improvement over previous studies that relied on self-reported immunization, which is susceptible to recall bias [19]. We also used validation study results to correct for potential misclassification error. A third limitation was the potential for misclassification of COPD given that pulmonary function testing was not done on everyone. However, we used a validated case definition to identify real-world patients with COPD who—as noted above—often do not receive pulmonary function testing [29, 31]. We also found that results did not differ between people who did and did not receive pulmonary function testing. In addition, given that influenza VE was similar among the non-COPD population, any misclassification would not likely have changed our results [40]. Fourth, the VE estimates found in this study are specific to the outcome of influenza hospitalization and may not be generalizable to VE estimates of outpatient outcomes. Finally, we were not able to distinguish the type of vaccine received. Ontario was not administering high-dose Fluzone (Sanofi Pasteur) during the study period.

Although its limitations are important to consider, our study provides an estimate of VE in a large, real-world sample with laboratory-confirmed outcomes and a robust study design. Given that a large pragmatic RCT evaluating influenza vaccination would be unethical, this is likely the most robust estimate of VE for hospitalizations in the COPD population to guide influenza vaccine recommendations for patients with COPD.

Table 3. Selected Adjusted Influenza Vaccine Effectiveness (VE) on Hospitalizations in Adults Aged 66 Years or Older With COPD, Overall and in Subgroups Defined by Various Patient and Influenza-Related Characteristics (for Full List, See Supplementary Table S5)

Characteristic	Test-Positive Patients Number Vaccinated/Total Number	Test-Negative Patients Number Vaccinated/Total Number	Unadjusted VE % (95% CI)	Adjusted VE % (95% CI)	*P* Value for Interaction
Overall	1859/3636	10 315/18 112	21 (15–26)	22 (15–27)	
Demographics					
Age, years					.61
66 to 75	553/1192	3565/6668	25 (15–33)	26 (15–35)	
76 to 85	801/1497	4389/7392	21 (12–30)	20 (10–29)	
86 and older	505/947	2361/4052	18 (6–29)	17 (3–29)	
Sex					.07
Female	977/1893	5028/8921	17 (9–25)	16 (7–25)	
Male	882/1743	5287/9191	24 (16–32)	28 (19–35)	
COPD-Related Factors					
Duration of COPD					.76
0 to 4 years	791/1665	4512/8423	22 (13–29)	21 (12–30)	
5 to 9 years	381/698	2135/3596	18 (3–30)	16 (1–30)	
10 or more years	687/1273	3668/6093	22 (12–31)	25 (15–34)	
COPD Hospitalization					.58
Less than 1 year previous	250/517	1784/3209	25 (10–38)	30 (15–43)	
1 to 5 years previous	272/522	1715/2920	24 (8–37)	21 (4–35)	
More than 5 years or never	1337/2597	6816/11 983	20 (12–26)	20 (12–27)	
COPD Outpatient Exacerbation in Previous Year					.22
Yes	769/1313	4518/7253	14 (4–24)	18 (7–28)	
No	1090/2323	5797/10 859	23 (16–29)	23 (16–30)	
Receipt of Prescription for Inhaled Corticosteroids in Previous 6 Months					.65
Yes	1125/2069	6516/10 855	21 (13–28)	22 (14–29)	
No	734/1567	3799/7257	20 (11–28)	20 (11–29)	
Comorbidity					
Codiagnosis of Asthma					.24
Yes	921/1717	5012/8327	23 (15–31)	26 (17–34)	
No	938/1919	5303/9785	19 (11–27)	18 (9–26)	
Presence of 1 or More Comorbidities					
Yes	1777/3438	9867/17 244	20 (14–26)	21 (15–27)	.474
No	82/198	448/868	34 (9–52)	34 (7–53)	
Specimen Collection and Influenza Season Factors					
Influenza Season					.06
2010–2011	171/399	1060/1996	34 (18–47)	35 (18–49)	
2011–2012	67/127	735/1255	21 (−14 to 45)	27 (−8 to 51)	
2012–2013	356/760	1834/3388	25 (13–36)	22 (7–34)	
2013–2014	272/518	2173/3735	21 (4–34)	26 (10–39)	
2014–2015	710/1265	2605/4476	8 (−4 to 19)	11 (−1 to 22)	
2015–2016	283/567	1908/3262	29 (15–41)	29 (15–41)	
Influenza Type and Subtype					NA
Influenza A/H1N1	140/300	10 315/18 112	34 (17–47)	32 (14–47)	
Influenza A/H3N2	533/1073	103 15/18 112	25 (16–34)	25 (15–35)	
Influenza B	338/652	10 315/18 112	19 (5–30)	31 (18–41)	
Prior Season Influenza Vaccination					
No	355/1554	2147/7178	31 (21–39)	28 (18–37)	.04
Yes	1504/2082	8168/10 934	12 (2–21)	13 (3–22)	

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; NA, not applicable.

CONCLUSIONS

During the 2010–11 to 2015–16 influenza seasons, influenza vaccination was at least modestly effective in reducing laboratory-confirmed influenza-associated hospitalizations in a large population with COPD. Vaccination remains the most effective tool to decrease influenza-associated morbidity and mortality; however, the imperfect effectiveness observed emphasizes the need for more effective influenza vaccines for older patients combined with other preventive strategies.

Supplementary Data

Supplementary materials are available at *The Journal of 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.

Notes

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