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Influenza Vaccine Effectiveness Against All-Cause Mortality Following Laboratory-Confirmed Influenza in Older Adults, 2010–2011 to 2015–2016 Seasons in Ontario, Canada

Hannah Chung,[1,] Sarah A. Buchan,[1,2,3] Aaron Campigotto,[4,5,7] Michael A. Campitelli,[1] Natasha S. Crowcroft,[1,3,6,7] Vinita Dubey,[3,8] Jonathan B. Gubbay,[2,4,7] Timothy Karnauchow,[9,10] Kevin Katz,[11] Allison J. McGeer,[3,7,12] J. Dayre McNally,[9] Samira Mubareka,[13] Michelle Murti,[2,3] David C. Richardson,[14] Laura C. Rosella,[1,2,3] Kevin L. Schwartz,[1,2,3] Marek Smieja,[15] George Zahariadis,[5,16] and Jeffrey C. Kwong[1,2,3,6,17,18]

[1]Institute for Clinical Evaluative Sciences (ICES), Toronto, Ontario, Canada, [2]Public Health Ontario, Toronto, Ontario, Canada, [3]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada, [4]Hospital for Sick Children, Toronto, Ontario, Canada, [5]London Health Sciences Centre, London, Ontario, Canada, [6]Centre for Vaccine Preventable Diseases, University of Toronto, Toronto, Ontario, Canada, [7]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada, [8]Toronto Public Health, Toronto, Ontario, Canada, [9]Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada, [10]Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, Ontario, Canada, [11]North York General Hospital, Toronto, Ontario, Canada, [12]Sinai Health System, Toronto, Ontario, Canada, [13]Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, [14]William Osler Health System, Brampton, Ontario, Canada, [15]McMaster University, Hamilton, Ontario, Canada, [16]Newfoundland and Labrador Public Health Laboratory, St. John's, NF&L, Canada, [17]Department of Family & Community Medicine, University of Toronto, Toronto, Ontario, Canada, and [18]University Health Network, Toronto, Ontario, Canada

Background. Older adults are at increased risk of mortality from influenza infections. We estimated influenza vaccine effectiveness (VE) against mortality following laboratory-confirmed influenza.

Methods. Using a test-negative design study and linked laboratory and health administrative databases in Ontario, Canada, we estimated VE against all-cause mortality following laboratory-confirmed influenza for community-dwelling adults aged >65 years during the 2010–2011 to 2015–2016 influenza seasons.

Results. Among 54 116 older adults tested for influenza across the 6 seasons, 6837 died within 30 days of specimen collection. Thirteen percent (925 individuals) tested positive for influenza, and 50.6% were considered vaccinated for that season. Only 23.2% of influenza test-positive cases had influenza recorded as their underlying cause of death. Before and after multivariable adjustment, we estimated VE against all-cause mortality following laboratory-confirmed influenza to be 20% (95% confidence interval [CI], 8%–30%) and 20% (95% CI, 7%–30%), respectively. This estimate increased to 34% after correcting for influenza vaccination exposure misclassification. We observed significant VE against deaths following influenza confirmation during 2014–2015 (VE = 26% [95% CI, 5%–42%]). We also observed significant VE against deaths following confirmation of influenza A/H1N1 and A/H3N2, and against deaths with COPD as the underlying cause.

Conclusions. These results support the importance of influenza vaccination in older adults, who account for most influenza-associated deaths annually.

Keywords. influenza vaccine; vaccine effectiveness; mortality; older adults.

Each year, seasonal influenza accounts for an estimated 290 000–650 000 deaths globally, largely among older adults [1, 2]. Influenza-associated mortality varies annually depending on circulating strains and vaccine effectiveness (VE) [3, 4].

Influenza vaccines are 24%–63% effective against influenza infection [4, 5], and 31%–54% effective against influenza-related hospitalizations in older adults [6]. However, there is a dearth of high-quality evidence supporting VE against mortality. Conducting randomized-controlled trials (RCTs) is challenging because very large samples would be required to assess the outcome of death, and RCTs would be unethical because vaccination is recommended in older adults [7, 8]. A Cochrane Review found VE against all-cause mortality to be nearly 50% in older adults [9], but the included observational studies likely suffered from frailty selection bias (ie, frail, undervaccinated individuals are more likely to die, resulting in overestimation of VE) and used nonlaboratory-confirmed outcomes, which may also bias VE [7].

The test-negative design (TND) has emerged as the predominant observational study design for evaluating VE [10]. Because it uses a highly specific outcome (laboratory-confirmed influenza) and it controls for differences in healthcare-seeking

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Correspondence: J. Kwong, ICES, G1 06, 2075 Bayview Ave, Toronto, Ontario M4N 3M5, Canada (jeff.kwong@utoronto.ca).

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behavior between vaccinated and unvaccinated individuals by restricting to individuals tested for influenza, the TND is felt to generate unbiased VE estimates [11]. The objective of this study was to estimate VE against all-cause mortality following laboratory-confirmed influenza among older adults using the TND.

METHODS

Study Population, Setting, and Design

We included community-dwelling adults aged >65 years in the province of Ontario, Canada, who were tested for influenza (as part of clinical care, at the clinician's discretion) during periods when influenza was actively circulating (using a province-wide threshold level of 5% weekly influenza test positivity, typically between November and May) for the 2010–2011 to 2015–2016 seasons. We restricted to adults aged >65 years to allow for a 1-year lookback period to identify prescriptions that were used to define certain covariates because Ontario Drug Benefit (ODB) coverage starts at age 65 years. We linked data sets containing results of respiratory virus tests performed by a network of public health and academic hospital laboratories to population-based health administrative databases using both deterministic and probabilistic linkage (proportion linked = 97.8%). These data sets were linked using unique encoded identifiers and analyzed at ICES. Details related to these data sets for estimating VE are described elsewhere [12]. All participating laboratories provided ethics approval for this study, and participant informed consent was not required.

Data Sources and Definitions

Laboratory Data

We included results from respiratory specimens tested for influenza by a variety of methods (eg, nucleic acid detection, antigen detection, viral culture). We combined the results from all specimens collected from the same individual on the same day and defined it as a single testing episode. For individuals tested multiple times in the same season, we included their earliest positive testing episode or their earliest testing episode if all were negative.

Mortality Following Laboratory-Confirmed Influenza

Using the death date in Ontario's Registered Persons Database (RPDB), we restricted the study to those individuals who died from any cause within 30 days of specimen collection, as in other studies [13, 14]. We also considered deaths within 7 days (to minimize uncertainty in the association between influenza vaccination and deaths related to influenza infection) and 90 days (to assess deaths due to underlying chronic conditions that are exacerbated by influenza infection). In addition, we used the Office of the Registrar General–Deaths (ORG-D) database to determine the single underlying cause of death [15]. We grouped them based on common causes of influenza-attributable deaths (Supplementary Table 1) [16]. More details about the mortality data are provided in the Supplementary Methods.

Influenza Vaccination

We used physician and pharmacist billing claims from the Ontario Health Insurance Plan (OHIP) and ODB databases, respectively, to ascertain seasonal influenza vaccination. Individuals who received an influenza vaccine ≥14 days prior to specimen collection (during the same season they were tested) were classified as vaccinated, those who received a vaccine <14 days were excluded from the analysis (because adequate immune responses may take up to 14 days to develop), and all other individuals were considered unvaccinated. During the study period, only trivalent inactivated influenza vaccines were publicly funded for adults ≥65 years in Ontario [12].

Covariates

We identified healthcare encounters associated with each testing episode to determine the setting of specimen collection (intensive care unit [ICU], hospital ward, emergency department, or physician office).

We obtained demographic information (age, sex, neighborhood income quintile, and rurality), and information on healthcare utilization prior to testing (number of hospitalizations, physician office visits, prescription medications, and receipt of home care services) from relevant databases. We also determined the presence of comorbidities that increase the risk of influenza complications (ie, anemia, asthma, cancer, chronic obstructive pulmonary disease [COPD], diabetes, dementia, chronic kidney disease, cardiovascular disease, and immunocompromising conditions). Definitions for these comorbidities and the databases used for all covariates are described elsewhere [12].

Statistical Analysis

We compared characteristics and the underlying causes of death between individuals who died within 30 days of testing positive for influenza (cases) with those who died within 30 days of testing negative (controls), and between vaccinated and unvaccinated individuals using χ^2 tests and analysis of variance (ANOVA).

We used multivariable logistic regression to determine the ratio between the odds of vaccination in cases to the odds of vaccination in controls, and calculated VE as 1 – adjusted odds ratio ×100. We selected variables to include in the models a priori based on clinical importance, adjusting for demographic characteristics, previous healthcare use, presence of any comorbidity, month of test, and influenza season (except when stratifying by season). We estimated VE against deaths after laboratory confirmation of any influenza, A/H1N1, A/H3N2, and B by combining the 2010–2011 to 2015–2016 seasons. We also estimated VE against mortality after laboratory-confirmed

influenza for each season by stratifying by season of testing. In addition, using all seasons combined, we stratified by receipt of the prior season's influenza vaccine. We tested for interaction between receipt of seasonal vaccination and stratifying variables to determine whether VE differed between strata. Finally, we also determined cause-specific VE by pooling seasons and subgrouping individuals based on their underlying cause.

In sensitivity analyses, we conducted a quantitative bias analysis using a publicly available macro [17] to correct for influenza vaccination exposure misclassification (because administrative data do not capture vaccinations delivered outside of physician offices and pharmacies), applying sensitivity (69%) and specificity (90%) parameters for influenza vaccination billing codes in the OHIP database for older adults [18]. Furthermore, we described the causes of death and determined VE against deaths occurring in mutually exclusive and cumulative intervals between specimen collection and death (0–7, 8–30, 31–90, 0–90 days) to assess whether the underlying causes and VE varied by time.

All analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). All tests were 2-sided and used $P < .05$ as the level of statistical significance.

RESULTS

Of 54 116 community-dwelling older adults tested for influenza across the 6 seasons, 6837 (13%) died within 30 days of specimen collection. Test-positive cases were older, less likely to be male, less likely to have specimens collected in the ICU, less likely to receive influenza vaccine during the season they were tested in, and more likely to have influenza recorded as the underlying cause of death (Table 1). Vaccinated individuals were older, more likely to be male, greater users of some health services (physician office visits, prescriptions) and lower users of others (hospitalizations, home care), more likely to have comorbidities, and more likely to have noninfluenza causes as their underlying cause of death.

For the 6 seasons combined, VE against all-cause mortality following laboratory-confirmed influenza before and after adjustment was 20% (95% CI, 8%–30%) and 20% (95% CI, 7%–30%), respectively (Table 2). This increased to 34% (95% CI, 20%–46%) after correcting for exposure misclassification. Adjusted VE was 48% (95% CI, 15%–68%), 30% (95% CI, 11%–45%), and 26% (95% CI, –2%, 47%) against deaths following infection with A/H1N1, A/H3N2, and B, respectively. Adjusted VE against unsubtyped influenza A was lower at –8% (95% CI, –35%, 14%). Among season-specific estimates, VE was only significant for 2014–2015 (VE = 26%; 95% CI, 5%–42%). We did not find significant VE in either stratum based on prior season vaccination, nor did they differ (test for interaction, $P = .21$). We found significant VE against deaths with COPD coded as the underlying cause (VE = 49%; 95% CI, 16%–69%).

Among cases, the proportions with influenza or pneumonia as the underlying cause of death decreased with increasing time since specimen collection, whereas the proportions increased for some non-influenza causes. Among controls, the temporal patterns in the proportions of noninfluenza causes were similar to those of cases other than for COPD and respiratory infections. The proportions and temporal patterns were similar between vaccinated and unvaccinated individuals (Figure 1). VE estimates were comparable when considering death within 7, 90, 8–30, and 31–90 days after specimen collection (Figure 2, Supplementary Tables 2a and 2b). Using these alternate periods, the point estimates were consistently higher among individuals who did not receive the prior season's vaccine. VE was significant against deaths within 90 days with circulatory system diseases as the underlying cause (VE = 24%; 95% CI, 0%–42%) (Supplementary Table 3).

DISCUSSION

We observed that receipt of seasonal influenza vaccine was associated with an overall 20% reduced risk of all-cause mortality following laboratory-confirmed influenza, which increased to 34% after correcting for exposure misclassification. We found significant VE under the following circumstances: against deaths after A/H1N1 and A/H3N2 infection; during the 2014–2015 season; and for deaths coded as being due to COPD. Also, we found consistent results when using different intervals from specimen collection to death.

Other studies that used the TND to determine VE against mortality following laboratory-confirmed influenza in older adults had higher VE estimates than ours, but differences were likely due to the control group used. In assessing the effectiveness of repeated vaccination during the 2013–2014 and 2014–2015 seasons in Spain, Casado et al found that receipt of influenza vaccine during the current season and at least one prior season prevented fatal influenza infections (VE = 70%; 95% CI, 34%–87%) [13]. However, instead of using test-negative patients as controls, they used patients hospitalized for causes other than influenza and acute respiratory illness. Nichols et al examined 30-day mortality among older adults hospitalized for influenza-related reasons during the 2011–2012 to 2013–2014 influenza seasons in Canada, and estimated VE to be 75% (95% CI, 44%–88%) [14]. However, they did not restrict controls to those who died. This likely resulted in frailty selection bias because frail individuals are overrepresented in the unvaccinated test-positive group, which biases VE away from the null [7]. Nation et al determined that VE during the 2010–2017 seasons in Australia among adults ≥65 years was 17% (95% CI, –28%, 46%). However, they measured in-hospital deaths and used test-negative survivors as their control group [19]. Finally, Suzuki et al estimated VE against influenza pneumonia death among older Japanese adults from 2012 to 2014 to be 71% (95%

Table 1. Characteristics of Community-Dwelling Adults Aged >65 Years Who Died Within 30 Days of Influenza Testing (n = 6837) During the 2010–2011 to 2015–2016 Seasons in Ontario, Canada

Characteristic	Influenza-positive (n = 925)	Influenza-negative (n = 5912)	*P* value	Influenza Vaccinated (n = 3465)	Influenza Unvaccinated (n = 3372)	*P* valve
Receipt of seasonal influenza vaccine	424 (45.8%)	3041 (51.4%)	.002	3465 (100.0%)	0 (0%)	N/A
Positive for influenza	925 (100.0%)	0 (0%)	N/A	424 (12.2%)	501 (14.9%)	.002
Age (y), mean ± SD	82.58 ± 8.53	81.06 ± 8.34	<.001	81.64 ± 8.09	80.87 ± 8.66	<.001
Age group, y						
66–75	210 (22.7%)	1727 (29.2%)	<.001	901 (26.0%)	1036 (30.7%)	<.001
76–85	338 (36.5%)	2237 (37.8%)		1370 (39.5%)	1205 (35.7%)	
≥86	377 (40.8%)	1948 (32.9%)		1194 (34.5%)	1131 (33.5%)	
Male sex	477 (51.6%)	3298 (55.8%)	.016	1968 (56.8%)	1807 (53.6%)	.008
Rural residence	81 (8.8%)	462 (7.8%)	.528	257 (7.4%)	286 (8.5%)	.266
Neighborhood income quintile						
1 (lowest)	199 (21.5%)	1311 (22.2%)	.98	732 (21.1%)	778 (23.1%)	.176
2	201 (21.7%)	1292 (21.9%)		770 (22.2%)	723 (21.4%)	
3	174 (18.8%)	1064 (18.0%)		642 (18.5%)	596 (17.7%)	
4	162 (17.5%)	1059 (17.9%)		612 (17.7%)	609 (18.1%)	
5 (highest)	185 (20.0%)	1155 (19.5%)		696 (20.1%)	644 (19.1%)	
Missing information	≤5 (0.4%)	31 (0.5%)		13 (0.4%)	22 (0.7%)	
Season of specimen collection						
2010–2011	99 (10.7%)	760 (12.9%)	<.001	409 (11.8%)	450 (13.3%)	<.001
2011–2012	42 (4.5%)	407 (6.9%)		246 (7.1%)	203 (6.0%)	
2012–2013	184 (19.9%)	1091 (18.5%)		577 (16.7%)	698 (20.7%)	
2013–2014	129 (13.9%)	1153 (19.5%)		696 (20.1%)	586 (17.4%)	
2014–2015	348 (37.6%)	1439 (24.3%)		929 (26.8%)	858 (25.4%)	
2015–2016	123 (13.3%)	1062 (18.0%)		608 (17.5%)	577 (17.1%)	
Month of specimen collection						
November	15 (1.6%)	190 (3.2%)	<.001	65 (1.9%)	140 (4.2%)	<.001
December	203 (21.9%)	856 (14.5%)		483 (13.9%)	576 (17.1%)	
January	328 (35.5%)	1469 (24.8%)		883 (25.5%)	914 (27.1%)	
February	140 (15.1%)	1136 (19.2%)		660 (19.0%)	616 (18.3%)	
March	142 (15.4%)	1109 (18.8%)		668 (19.3%)	583 (17.3%)	
April	83 (9.0%)	773 (13.1%)		485 (14.0%)	371 (11.0%)	
May	14 (1.5%)	379 (6.4%)		221 (6.4%)	172 (5.1%)	
Setting of specimen collection						
Intensive care unit	279 (30.2%)	2120 (35.9%)	<.001	1258 (36.3%)	1141 (33.8%)	.094
Hospital ward	598 (64.6%)	3616 (61.2%)		2100 (60.6%)	2114 (62.7%)	
Emergency department	38 (4.1%)	151 (2.6%)		87 (2.5%)	102 (3.0%)	
Physician office	10 (1.1%)	25 (0.4%)		20 (0.6%)	15 (0.4%)	
Hospitalizations in past 3 years, mean ± SD	1.68 ± 2.11	1.81 ± 2.23	.079	1.71 ± 2.08	1.88 ± 2.34	.001
Physician office visits in past year, mean ± SD	14.00 ± 10.85	15.11 ± 11.78	.007	16.39 ± 11.34	13.50 ± 11.81	<.001
Prescriptions in the past year, mean ± SD	17.02 ± 9.29	17.01 ± 9.21	.991	17.75 ± 8.62	16.26 ± 9.74	<.001
Receipt of home care in past year	574 (62.1%)	3625 (61.3%)	.668	2066 (59.6%)	2133 (63.3%)	.002
Receipt of prior season's influenza vaccine	465 (50.3%)	3438 (58.2%)	<.001	2774 (80.1%)	1129 (33.5%)	<.001
Medical comorbidities						
Anemia	221 (23.9%)	1729 (29.2%)	<.001	1021 (29.5%)	929 (27.6%)	.079
Asthma	260 (28.1%)	1360 (23.0%)	<.001	850 (24.5%)	770 (22.8%)	.099
Cancer	315 (34.1%)	2289 (38.7%)	.007	1314 (37.9%)	1290 (38.3%)	.776
COPD	505 (54.6%)	3014 (51.0%)	.041	1842 (53.2%)	1677 (49.7%)	.005
Arrhythmia	348 (37.6%)	2065 (34.9%)	.111	1272 (36.7%)	1141 (33.8%)	.013
Ischemic heart disease	397 (42.9%)	2375 (40.2%)	.114	1428 (41.2%)	1344 (39.9%)	.254
Congestive heart failure	480 (51.9%)	3026 (51.2%)	.689	1842 (53.2%)	1664 (49.3%)	.002
Chronic kidney disease	274 (29.6%)	1648 (27.9%)	.272	1016 (29.3%)	906 (26.9%)	.024
Diabetes	426 (46.1%)	2480 (41.9%)	.019	1546 (44.6%)	1360 (40.3%)	<.001
Dementia/frailty	258 (27.9%)	1331 (22.5%)	<.001	757 (21.8%)	832 (24.7%)	.006
Immunocompromise	154 (16.6%)	1084 (18.3%)	.215	674 (19.5%)	564 (16.7%)	.003
History of transient ischemic attack or stroke	144 (15.6%)	709 (12.0%)	.002	443 (12.8%)	410 (12.2%)	.434
Any of the above comorbidities	901 (97.4%)	5774 (97.7%)	.628	3412 (98.5%)	3263 (96.8%)	<.001

Table 1. Continued

Characteristic	Influenza-positive (n = 925)	Influenza-negative (n = 5912)	*P* value	Influenza Vaccinated (n = 3465)	Influenza Unvaccinated (n = 3372)	*P* valve
Underlying cause of death[a]						
Influenza	215 (23.2%)	20 (0.3%)	<.001	107 (3.1%)	128 (3.8%)	.002
Pneumonia	146 (15.8%)	979 (16.6%)		605 (17.5%)	520 (15.4%)	
COPD	81 (8.8%)	554 (9.4%)		356 (10.3%)	279 (8.3%)	
Acute and other respiratory infections	45 (4.9%)	526 (8.9%)		296 (8.5%)	275 (8.2%)	
Circulatory system diseases	153 (16.5%)	1183 (20.0%)		686 (19.8%)	650 (19.3%)	
Cancer	75 (8.1%)	1046 (17.7%)		540 (15.6%)	581 (17.2%)	

Abbreviations: COPD, chronic obstructive pulmonary disease; N/A, not applicable; SD, standard deviation.

[a]Sum of counts does not equal the total size of the cohort because either the underlying cause of death was not included in one of the selected categories (n = 1782) or individuals were missing underlying cause of death information either because death was not recorded in the Office of the Registrar General-Deaths (ORGD) database or an underlying cause of death was not determined (n = 32).

CI, –63%, 95%) [20]. This study is the most comparable to ours in terms of control selection; however, it used a more specific outcome.

Despite the variability in VE across study seasons, by pooling data from all seasons, we estimated the overall effect of vaccination against all-cause mortality and observed significant VE against deaths after A/H1N1 and A/H3N2 infection. Influenza B cases were consistently detected in later months (March–May). Thus, waning immunity might explain the apparent diminished protection against severe influenza B infections [21].

Interestingly, we found significant VE only during the 2014–2015 season. This season was known to have markedly

Table 2. Influenza Vaccine Effectiveness Estimates for Community-Dwelling Adults Aged >65 Years Against All-Cause Mortality Following Laboratory-Confirmed Influenza During the 2010–2011 to 2015–2016 Influenza Seasons in Ontario, Canada (n = 6837)

Analysis	Test-positive cases, No. Vaccinated/Total	Test-negative controls, No. Vaccinated/Total	Unadjusted VE% (95% CI)	Adjusted VE%[a] (95% CI)	Misclassification Corrected Adjusted VE% (95% CI)
Any influenza	424 / 925	3041 / 5912	20 (8, 30)	20 (7, 30)	34 (20, 46)
Influenza A	343 / 759	3041 / 5912	22 (9, 33)	18 (3, 30)	35 (21, 48)
A/H1N1[b]	27 / 79	2273 / 4473	50 (20, 69)	48 (15, 68)	66 (32, 79)
A/H3N2	134 / 327	3041 / 5912	34 (18, 48)	30 (11, 45)	52 (34, 64)
A/unsubtyped	182 / 353	3041 / 5912	0 (–25, 19)	–8 (–35, 14)	–5 (–44, 22)
Influenza B	81 / 166	3041 / 5912	10 (–22, 34)	26 (–2, 47)	27 (–14, 52)
By season					
2010–2011	42 / 99	367 / 760	21 (–20, 48)	14 (–36, 46)	29 (–28, 61)
2011–2012	24 / 42	222 / 407	–11 (–111, 42)	–12 (–128, 45)	–42 (–359, 49)
2012–2013	79 / 184	498 / 1091	10 (–23, 35)	–3 (–44, 27)	10 (–39, 41)
2013–2014	62 / 129	634 / 1153	24 (–9, 47)	32 (0, 53)	46 (10, 68)
2014–2015	161 / 348	768 / 1439	25 (5, 41)	26 (5, 42)	43 (22, 59)
2015–2016	56 / 123	552 / 1062	23 (–12, 47)	20 (–19, 46)	36 (–9, 61)
By prior season vaccination					
Yes	330 / 465	2444 / 3438	1 (–23, 20)	–2 (–27, 18)	N/A
No	94 / 460	597 / 2474	19 (–3, 37)	19 (–5, 37)	31 (4, 51)
Underlying cause of death[c]					
Influenza	97 / 215	10 / 20	18 (–106, 67)	18 (–146, 73)	31 (–128, 81)[d]
Pneumonia	75 / 146	530 / 979	11 (–27, 37)	12 (–26, 39)	22 (–28, 53)
COPD	35 / 81	321 / 554	45 (12, 66)	49 (16, 69)	71 (47, 85)[d]
Acute and other respiratory infections	22 / 45	274 / 526	12 (–62, 52)	12 (–70, 54)	22 (–77, 65)[d]
Circulatory system diseases	74 / 153	612 / 1183	13 (–22, 38)	20 (–14, 44)	27 (–17, 55)
Cancer	33 / 75	507 / 1046	16 (–34, 48)	7 (–54, 44)	23 (–53, 61)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; VE, vaccine effectiveness.

[a]Models were adjusted for age, sex, rurality, neighborhood income quintile, receipt of homecare, number of hospitalizations in past 3 years, number of physician office visits in past year, number of prescription drugs in past year, presence of any comorbidity, calendar time, and influenza season (expect when stratifying by influenza season).

[b]1439 test-negative controls from influenza season 2014–2015 were removed from the analysis because there were no cases positive for influenza A/H1N1 in that season.

[c]Sum of counts does not equal the total size of the cohort because either the underlying cause of death was not included in one of the selected categories (n = 1782) or individuals were missing underlying cause of death information either because death was not recorded in Office of the Registrar General–Deaths (ORG-D) or underlying cause of death was not determined (n = 32).

[d] Misclassification corrected unadjusted VE estimates were reported because models for misclassification corrected adjusted VE estimates did not converge.

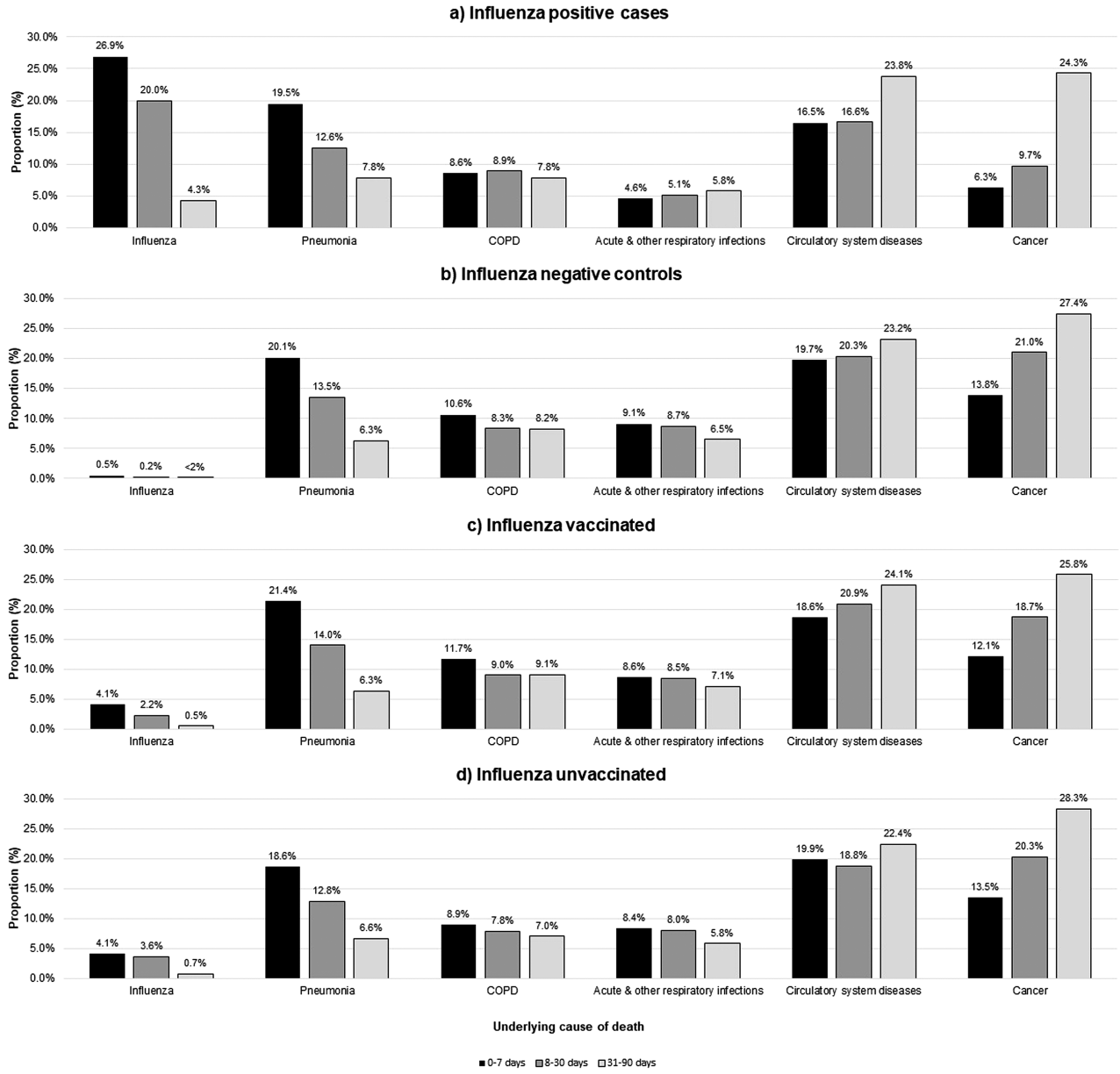

Figure 1. Proportion with underlying causes of death for varying intervals from specimen collection to death among community-dwelling older adults during the 2010–2011 to 2015–2016 influenza seasons in Ontario, Canada. Sum of the proportions for each interval per exposure group does not equal 100%. Of the 10 150 individuals who died within 90 days of specimen collection, 2698 individuals had an underlying cause of death that was not included in one of the selected categories, and 51 individuals do not have an underlying cause of death, because either their death was not registered in the Office of the Registrar General–Death database or their underlying cause of death was not determined. Abbreviation: COPD, chronic obstructive pulmonary disease.

low VE because the predominant circulating A/H3N2 virus was antigenically drifted from the vaccine strain [22]. This suggests that influenza vaccines might be more effective in preventing more severe infections than less severe infections. Two studies observed higher VE against more serious outcomes compared to less serious outcomes. One found significant VE against A/H3N2-related hospitalizations (VE = 43%; 95% CI, 5%–66%) in adults aged ≥18 years during the 2014–2015 season when VE was low in ambulatory settings [23]. Another study of adults aged ≥18 years during the 2012–2015 influenza seasons found VE point estimates to be consistently higher for patients in the ICU than those on general wards [24]. The authors surmised that if vaccination conferred greater protection against more severe outcomes, influenza positivity should be lower for vaccinated ICU patients than vaccinated ward patients. However, the proportions were similar. Thus, the difference in VE was due to higher influenza positivity in unvaccinated ICU patients compared to unvaccinated ward patients [24]. In our study, influenza positivity among vaccinated subjects was lower in those who died within 30 days (12%) compared to those who survived

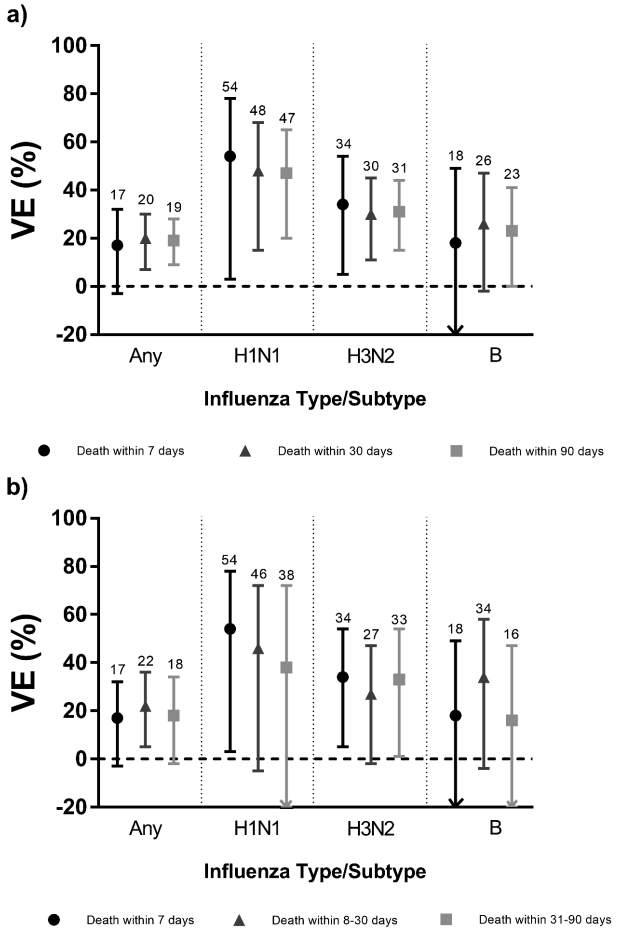

Figure 2. Influenza vaccine effectiveness for community-dwelling adults aged >65 years against all-cause mortality following laboratory-confirmed influenza for cumulative intervals (*a*) and mutually exclusive intervals (*b*) from specimen collection to death for any influenza and by type/subtype. Abbreviation: VE, vaccine effectiveness.

greater than 30 days (19%), and the VE among the latter group was 22% (95% CI, 18%–25%; data not shown). Thus, although mortality can be used to assess whether vaccination is more effective in preventing serious outcomes than less serious outcomes, we did not find a meaningful difference in VE between individuals who died versus those who survived.

We did not find significant VE against mortality based on receipt of prior season's vaccination for most intervals likely due to limited sample sizes, except against deaths within 90 days among individuals who did not receive the prior season's vaccination. Therefore, we could not verify the findings from Casado et al [13]. However, as previously mentioned, that study used a control group that biased their VE estimate away from the null.

Using death certificate data, we found that 23% of influenza-positive individuals had influenza recorded as their cause of death, which was the most frequent cause for deaths within 30 days of testing. Cancer and circulatory system diseases were the most common causes for deaths >30 days after testing, which suggests that deaths can occur later due to exacerbations of comorbidities precipitated by influenza infection and listed instead as the underlying cause [25]. Other studies have also examined causes of death among those with laboratory-confirmed influenza but were limited by small numbers. One study found that among 32 individuals who were aged ≥65 years with laboratory-confirmed influenza hospitalization and died within 30 days of testing, 28% had influenza registered as the underlying cause [26]. Another study found that 25% of deaths within 84 days of laboratory-confirmed influenza among all ages (n = 40) had influenza listed as the underlying cause [27]. To our knowledge, our study is the largest to examine laboratory-confirmed influenza and cause of death among older adults.

We observed significant VE against deaths caused by COPD. We have previously shown that vaccination is associated with reduced influenza-associated hospitalizations among older adults with COPD [28], and the current study reinforces the benefits of vaccination for this population. Furthermore, VE nearly reached significance against deaths within 90 days caused by circulatory system diseases (including cardiovascular events). Influenza infection is known to initiate cardiovascular events that can lead to death [29, 30], and our findings support the vaccine's effectiveness in preventing serious cardiovascular outcomes [31]. We did not find significant VE against deaths with influenza as the underlying cause, possibly due to influenza being less frequently designated as the underlying cause among individuals with comorbidities [26].

By linking laboratory and health administrative data, we created a large cohort to study VE against a rare outcome, overcoming sample size challenges faced by previous studies. However, our study has several limitations. First, the TND assumes that healthcare-seeking behavior between cases and controls is similar, but this can depend on disease severity as those with severe influenza-related illness might have died before seeking medical care [32]. This would underestimate the vaccine's true impact against mortality. Second, we may not have completely eliminated frailty selection bias because our control group may have been less frail and more likely to have been vaccinated than cases [7]. Although the proportions with any comorbidity were similar between cases and controls, cases had a higher proportion specifically with dementia/frailty compared to controls (28% vs 23%, $P < .001$). Furthermore, although vaccinated individuals had a higher proportion with any comorbidity, the proportion with dementia/frailty was lower among vaccinated than unvaccinated individuals (22% vs 25%, $P = .006$). Consequently, because individuals with dementia/frailty are overrepresented among unvaccinated cases, we might be overestimating VE against mortality but not likely to the extent of other studies that used suboptimal control groups. In a post hoc analysis, we controlled for dementia/frailty separately

from all other comorbidities and found that VE changed minimally (VE = 19%; 95% CI, 6%–30%), which suggests that dementia/frailty is not a confounder, which is consistent with a study by Talbot et al [33]. Third, specimens were collected as part of routine clinical care and testing procedures varied by institution. However, we have validated the use of these specimens for estimating VE [12], particularly in inpatients who comprise the majority of our mortality cohort. Fourth, we used specimen collection date rather than illness onset date (due to data availability), which would bias our estimates toward the null because of the inclusion of false-negative controls. However, the VE estimates are similar between groups with mutually exclusive intervals from specimen collection to death. Using illness onset date would lengthen that interval and reassign individuals to the next interval. Fifth, the VE estimate against unsubtyped influenza A was outside of the range between the estimates for A/H1N1 and A/H3N2. However, we have reported elsewhere that individuals positive for subtyped influenza A were representative of all those positive for influenza A in our cohort [34]. Sixth, our main VE estimate increased notably after adjusting for exposure misclassification, underscoring the variability in VE estimates when using Ontario's administrative databases to ascertain vaccination status, with underreporting due to vaccination also occurring in alternative settings. However, imperfect specificity biases VE estimates more than imperfect sensitivity [35, 36] and our estimates (unadjusted and adjusted for exposure misclassification) represent a minimum range of VE against this rare outcome. Finally, despite controlling for potential confounders, residual confounding might have affected our results.

CONCLUSION

We observed 20%–34% VE against all-cause mortality following laboratory-confirmed influenza among community-dwelling older adults across 6 influenza seasons in Ontario, Canada. Influenza vaccination was associated with reduced risk of influenza-associated deaths even during a season when the vaccine was mismatched to the circulating strain. These findings reiterate the importance of influenza vaccination in older adults, who account for most influenza-related deaths.

Supplementary Data

Supplementary materials are available at *Clinical 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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