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Effectiveness of neuraminidase inhibitors in preventing hospitalization during the H1N1 influenza pandemic in British Columbia, Canada

Fawziah Marra[1]*, Mei Chong[2], Bonnie Henry[1,2], David M. Patrick[1,2] and Perry Kendall[3]

[1]*University of British Columbia, Vancouver, BC, Canada;* [2]*BC Centre for Disease Control, Vancouver, BC, Canada;* [3]*Ministry of Health, Victoria, BC, Canada*

*Corresponding author. Tel: +1-604-822-7898; Fax: +1-604-822-3035; E-mail: fawziah@mail.ubc.ca

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Objectives: In British Columbia (BC), Canada, neuraminidase inhibitors (NIs) were publicly funded during the 2009 A(H1N1)pdm09 pandemic for treatment of high-risk patients and/or anyone with moderate-to-severe illness. We assessed antiviral effectiveness (AVE) against hospitalization in that context.

Methods: A population-based cohort study was conducted using linked administrative data. The cohort included all individuals living in BC during the study period (1 September to 31 December 2009) with a diagnostic code consistent with influenza or pandemic H1N1. The main study period pertained to the second-wave A(H1N1)pdm09 circulation (1 October to 31 December 2009), with sensitivity analyses around the more specific pandemic peak (18 October to 7 November). Exposure was defined by same-day NI prescription. The main outcome was all-cause hospitalization within 14 days of the outpatient influenza diagnosis. Cox proportional hazards models assessed AVE with 1:1 propensity-score matching and covariate adjustment.

Results: After matching, there were 304/58 061 NI-exposed and 345/58 061 unexposed patients hospitalized during the main study period. The very young [<6 months (35.0; 95% CI 16.7–73.4)], the old [65–79 years (13.7; 95% CI 10.1–18.6)] and the very old [≥80 years (38.7; 95% CI 26.6–56.5)] had the highest hospitalization rate per 1000 patients overall. Fully adjusted AVE against all-cause hospitalization during the main study period was 16% (95% CI 2%–28%), similar to the pandemic peak (15%; 95% CI −4%–30%).

Conclusions: The use of NIs was associated with modest protection against hospitalization during the 2009 pandemic, but appeared underutilized in affected age groups with the highest hospitalization risk.

Keywords: oseltamivir, zanamivir, antivirals, mortality, population-based, cohort

Introduction

A novel strain of influenza A(H1N1)pdm09 virus was first detected in Mexico[1] and the USA[2,3] in April 2009. After its initial detection, the pandemic virus spread to many parts of the world, including Canada.[4–6] In British Columbia (BC), Canada, the first wave of A(H1N1)pdm09 activity during spring/summer of 2009 was limited, but was followed by a second, more substantial and widespread wave in the autumn that began in early October, peaked during the last week of October and resolved by the end of 2009.[7,8] Alongside other provinces of Canada, BC provided two pharmaceutical interventions free-of-charge as part of public health population efforts to mitigate overall impact of the pandemic: an AS03-adjuvanted vaccine as prevention and a neuraminidase inhibitor (NI) strategy as treatment.[8]

The adjuvanted A(H1N1)pdm09 vaccine used in Canada was ultimately shown to be highly effective (>90%) against medically attended, laboratory-confirmed A(H1N1)pdm09 illness,[9] but was delayed in availability such that initial administration coincided with the pandemic peak.[8,9] Prior to the pandemic, Canada had stockpiled antivirals, namely the two NIs oseltamivir and zanamivir, for treatment. In anticipation of the second pandemic wave, BC released and distributed NIs from its emergency stockpile for the treatment of people at high risk of influenza illness (regardless of severity) and for previously healthy people experiencing moderate-to-severe influenza-like illness (ILI). The former could also obtain prescriptions in advance to be filled in the event of ILI, minimizing delay from illness onset to the start of treatment. Ultimately, between the weeks of 4 October and 22 November 2009, >120 000 NI prescriptions were filled in BC, with peak administration coinciding with other indicators of peak pandemic activity during the last week of October and the first week of November.[8]

Although NI stockpiles are a component of pandemic preparedness in most developed countries, the 2009 pandemic was the first

pandemic for which widespread NI use was implemented on a population level with a goal of reducing serious disease and the associated healthcare burden. However, studies to assess antiviral effectiveness (AVE) against severe complications of influenza—seasonal or pandemic—remain largely lacking. Here, we assess AVE against hospitalization among patients clinically diagnosed with influenza during the autumn 2009 wave of A(H1N1)pdm09 in BC, Canada.

Methods

Study design and population

We conducted a retrospective cohort study using linked, administrative healthcare data extracted from the Medical Services Plan (MSP) billing information, the Hospital Separations and the *PharmaNet* prescription databases, provided by the BC Ministry of Health. Each eligible resident of BC is assigned a unique patient identifier, the personal health number, which is captured in all the databases and was used to link patients' records across the various data files. The final anonymized dataset was sent to the BC Centre for Disease Control in Vancouver, BC, for analysis. This study received approval from the University of British Columbia Research Ethics Board.

The cohort(s) included all BC residents since 1 September 2009 with an outpatient clinical diagnosis of influenza defined by an MSP fee-service billing code specific for A(H1N1)pdm09 or referring to the International Classification of Diseases (ICD) 9th revision for influenza (ICD-9 code 487). The date of clinical influenza diagnosis became the referent for establishing exposure and outcome status. If the patient had more than one MSP diagnosis of influenza since 1 September, only the first was counted and used as the referent for both exposure and outcome classification.

The main study period spanned clinical influenza diagnosis during the dominant second-wave A(H1N1)pdm09 activity (1 October to 31 December 2009), with sensitivity analyses conducted around the more specific peak period (18 October to 7 November) and the broader, but less specific, autumn period (1 September to 31 December) commencing prior to substantial A(H1N1)pdm09 second-wave circulation in BC.

Antiviral exposure was defined by the filling of an NI (oseltamivir or zanamivir) prescription on the same referent date (day 0), as obtained from *PharmaNet*, a population-based prescription drug database that captures all outpatient prescription drugs dispensed in the province, regardless of the payer/insurer. The referent date was chosen in the absence of information on actual illness onset, recognizing that delay to medical visit and prescription would already tend to underestimate AVE. Those filling an NI prescription before or after the referent date were excluded.

The main outcome was all-cause hospitalization within 14 days of the referent date, obtained from the Hospital Separations database that includes records from all acute care inpatient visits and long-term care holding beds, extended care beds, rehabilitation beds and discharge planning units managed by hospitals. In addition to all-cause hospitalization, we explored outcomes of pneumonia or influenza (P&I; ICD-10 codes: J10–18) and acute respiratory diseases (ARD; ICD-10 codes: J00–06 and J20–22), including where these were coded as the primary cause or anywhere on the hospital discharge record.

Statistical analysis

Cox proportional hazards models assessed AVE with 1:1 propensity score matching and covariate adjustment. Since the assignment of subjects to NI treatment and non-treatment groups was not random during the pandemic, confounding factors may bias treatment effects. Therefore, propensity score matching, estimated by multivariate logistic regression with the smallest Akaike's information criterion, was used to minimize such bias and balance the baseline and clinical characteristics between the two groups. One-to-one matching of NI-exposed to unexposed individuals based on the propensity score was performed by using the 'greedy nearest-neighbour' algorithm.[10] Separate propensity score-matched cohorts were constructed for the main study period and sensitivity analyses.

Participant profiles and hospitalization incidences were derived by NI exposure status before and after propensity score matching, further stratified by relevant subgroups. Multivariable Cox regression analyses compared the hazard of hospitalization in NI-exposed subjects with the hazard of hospitalization in unexposed subjects in the propensity score-matched cohorts by the hazard ratio (HR), adjusted for relevant covariates (see below). AVE was derived as $(1-\text{HR})\times 100\%$.

The baseline covariates used in propensity score construction and Cox regression analysis included age (<6 months, 6–11 months, 1–4 years, 5–9 years, 10–19 years, 20–49 years, 50–64 years, 65–79 years and ≥80 years), gender, health services delivery area, number of physician visits on the referent date (1 and ≥1), number of physician visits (0, 1, 2–4 and ≥5) and hospitalizations (0, 1, 2–3 and ≥4) within 6 months prior to the referent date, use of immunosuppressives within ±30 days of the referent date, cardiorespiratory conditions (myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, asthma, cystic fibrosis and bronchopulmonary dysplasia), immunosuppressive conditions (connective tissue disease–rheumatic disease, cancer, metastatic carcinoma and HIV), metabolic conditions (diabetes mellitus and other metabolic diseases), neurological conditions (stroke and other conditions) and other conditions (liver disease and renal disease). Covariates were entered into the model via a stepwise multivariate Cox regression model (entry criteria of $P\leq 0.1$ and staying criteria of $P\leq 0.05$) and some covariates were recategorized when needed.

Information on comorbid conditions was extracted according to diagnostic codes from the MSP database and Hospital Separations database within 2 years from the reference date (ICD-9/ICD-10 codes applied available upon request). Adjustment for comorbidity was dichotomized as 'yes'/'no' to any of the above chronic conditions, but also explored based on the Charlson index for which a score of 0 indicates no comorbidity.[11] Patients considered immunosuppressed on the basis of therapy were defined by *PharmaNet* record of the following prescriptions: antirheumatic drugs, oral glucocorticoids, antirejection medication and chemotherapeutic agents.

Statistical significance in this study was defined as $P\leq 0.05$. SAS version 9.2 (SAS, Cary, NC, USA) was used for all statistical analyses.

Results

Participants

Table S1 (available as Supplementary data at *JAC* Online) provides a summary of participant profiles before propensity score matching and Table 1 after propensity score matching according to exposure and outcome status for the main analysis period of 1 October to 31 December 2009. Table 2 compares hospitalization events by antiviral exposure for the main and sensitivity analyses before and after propensity score matching.

There were 227 755 people who had a physician visit related to influenza between 1 September and 31 December 2009 (Figure 1). Of those, 10 503 (4.6%) were removed due to missing information ($n=568$) or because they filled an NI prescription after the referent date ($n=9935$). Of the remaining 217 252 subjects, 27% ($n=58\,978$, only 86 were given zanamivir) met NI exposure criteria. The propensity score-matched cohort for the broadest period (1 September to 31 December 2009) included 58 775 records per exposure group (a total of 203 NI-treated subjects were removed due to extreme propensity scores or no matching from the non-NI-treated pool). For the main analysis period spanning

Table 1. Participant profile by exposure and hospitalization, main analysis period (1 October to 31 December 2009), after propensity score matching

Baseline characteristics/ category	Hospitalized				Not hospitalized				Hospitalization rates per 1000 (95% CI)		
	No NI (column %)	NI (column %) (row %)	overall (column %)	*P* value	No NI (column %)	NI (column %) (row %)	overall (column %)	*P* value	No NI	NI	overall
Age											
<6 months	5 (1.4%)	2 (0.7%) (28.6%)	7 (1.1%)	0.088	97 (0.2%)	96 (0.2%) (49.7%)	193 (0.2%)	1.000	49.0 (20.4, 117.8)	20.4 (5.1, 81.6)	35.0 (16.7, 73.4)
6–11 months	1 (0.3%)	1 (0.3%) (50.0%)	2 (0.3%)		362 (0.6%)	367 (0.6%) (50.3%)	729 (0.6%)		2.8 (0.4, 19.6)	2.7 (0.4, 19.3)	2.7 (0.7, 10.9)
1–4 years	24 (7.0%)	21 (6.9%) (46.7%)	45 (6.9%)		4825 (8.4%)	4834 (8.4%) (50.0%)	9659 (8.4%)		4.9 (3.3, 7.4)	4.3 (2.8, 6.6)	4.6 (3.5, 6.2)
5–9 years	25 (7.2%)	18 (5.9%) (41.9%)	43 (6.6%)		7732 (13.4%)	7754 (13.4%) (50.1%)	15486 (13.4%)		3.2 (2.2, 4.8)	2.3 (1.5, 3.7)	2.8 (2.1, 3.7)
10–19 years	36 (10.4%)	26 (8.6%) (41.9%)	62 (9.6%)		12207 (21.2%)	12175 (21.1%) (49.9%)	24382 (21.1%)		2.9 (2.1, 4.1)	2.1 (1.5, 3.1)	2.5 (2.0, 3.3)
20–49 years	174 (50.4%)	138 (45.4%) (44.2%)	312 (48.1%)		24531 (42.5%)	24587 (42.6%) (50.1%)	49118 (42.5%)		7.0 (6.1, 8.2)	5.6 (4.7, 6.6)	6.3 (5.6, 7.1)
50–64 years	57 (16.5%)	52 (17.1%) (47.7%)	109 (16.8%)		6111 (10.6%)	6108 (10.6%) (50.0%)	12219 (10.6%)		9.2 (7.1, 12.0)	8.4 (6.4, 11.1)	8.8 (7.3, 10.7)
65–79 years	14 (4.1%)	28 (9.2%) (66.7%)	42 (6.5%)		1510 (2.6%)	1507 (2.6%) (50.0%)	3017 (2.6%)		9.2 (5.4, 15.5)	18.2 (12.6, 26.4)	13.7 (10.1, 18.6)
≥80 years	9 (2.6%)	18 (5.9%) (66.7%)	27 (4.2%)		341 (0.6%)	329 (0.6%) (49.1%)	670 (0.6%)		25.7 (13.4, 49.4)	51.9 (32.7, 82.3)	38.7 (26.6, 56.5)
Sex											
female	215 (62.3%)	181 (59.5%) (45.7%)	396 (61.0%)	0.469	31541 (54.6%)	31612 (54.7%) (50.1%)	63153 (54.7%)	0.774	6.8 (5.9, 7.7)	5.7 (4.9, 6.6)	6.2 (5.6, 6.9)
male	130 (37.7%)	123 (40.5%) (48.6%)	253 (39.0%)		26175 (45.4%)	26145 (45.3%) (50.0%)	52320 (45.3%)		4.9 (4.2, 5.9)	4.7 (3.9, 5.6)	4.8 (4.3, 5.4)
Immunosuppressive drug use											
yes	39 (11.3%)	50 (16.4%) (56.2%)	89 (13.7%)	0.057	1485 (2.6%)	1520 (2.6%) (50.6%)	3005 (2.6%)	0.531	25.6 (18.7, 35.0)	31.8 (24.1, 42.0)	28.8 (23.4, 35.4)
no	306 (88.7%)	254 (83.6%) (45.4%)	560 (86.3%)		56231 (97.4%)	56237 (97.4%) (50.0%)	112468 (97.4%)		5.4 (4.8, 6.1)	4.5 (4.0, 5.1)	5.0 (4.6, 5.4)
No. of same-day GP visits											
1	309 (89.6%)	289 (95.1%) (48.3%)	598 (92.1%)	0.009	57452 (99.5%)	57455 (99.5%) (50.0%)	114907 (99.5%)	0.111	5.3 (4.8, 6.0)	5.0 (4.5, 5.6)	5.2 (4.8, 5.6)
2	32 (9.3%)	12 (3.9%) (27.3%)	44 (6.8%)		263 (0.5%)	298 (0.5%) (53.1%)	561 (0.5%)		108.5 (76.7, 153.4)	38.7 (22.0, 68.2)	72.7 (54.1, 97.7)
≥3	4 (1.2%)	3 (1.0%) (42.9%)	7 (1.1%)		1 (0.0%)	4 (0.0%) (80.0%)	5 (0.0%)		800.0 (300.2, 2131.6)	428.6 (138.2, 1328.8)	583.3 (278.1, 1223.6)
No. of past GP visits											
0	321 (93.0%)	295 (97.0%) (47.9%)	616 (94.9%)	0.095	56975 (98.7%)	57051 (98.8%) (50.0%)	114026 (98.7%)	0.528	5.6 (5.0, 6.3)	5.1 (4.6, 5.8)	5.4 (5.0, 5.8)
1	17 (4.9%)	5 (1.6%) (22.7%)	22 (3.4%)		592 (1.0%)	569 (1.0%) (49.0%)	1161 (1.0%)		27.9 (17.4, 44.9)	8.7 (3.6, 20.9)	18.6 (12.2, 28.2)
2–4	5 (1.4%)	2 (0.7%) (28.6%)	7 (1.1%)		127 (0.2%)	110 (0.2%) (46.4%)	237 (0.2%)		37.9 (15.8, 91.0)	17.9 (4.5, 71.4)	28.7 (13.7, 60.2)
≥5	2 (0.6%)	2 (0.7%) (50.0%)	4 (0.6%)		22 (0.0%)	27 (0.0%) (55.1%)	49 (0.0%)		83.3 (20.8, 333.2)	69.0 (17.2, 275.8)	75.5 (28.3, 201.1)
No. of past hospitalizations											
0	271 (78.6%)	239 (78.6%) (46.9%)	510 (78.6%)	0.632	54581 (94.6%)	54640 (94.6%) (50.0%)	109221 (94.6%)	0.758	4.9 (4.4, 5.6)	4.4 (3.8, 4.9)	4.6 (4.3, 5.1)
1	47 (13.6%)	39 (12.8%) (45.3%)	86 (13.3%)		2711 (4.7%)	2692 (4.7%) (49.8%)	5403 (4.7%)		17.0 (12.8, 22.7)	14.3 (10.4, 19.5)	15.7 (12.7, 19.4)
2–3	19 (5.5%)	22 (7.2%) (53.7%)	41 (6.3%)		397 (0.7%)	390 (0.7%) (49.6%)	787 (0.7%)		45.7 (29.1, 71.6)	53.4 (35.2, 81.1)	49.5 (36.5, 67.2)
≥4	8 (2.3%)	4 (1.3%) (33.3%)	12 (1.8%)		27 (0.0%)	35 (0.1%) (56.5%)	62 (0.1%)		228.6 (114.3, 457.1)	102.6 (38.5, 273.3)	162.2 (92.1, 285.5)
Charlson index											
0	247 (71.6%)	230 (75.7%) (48.2%)	477 (73.5%)	0.311	54275 (94.0%)	54244 (93.9%) (50.0%)	108519 (94.0%)	0.195	4.5 (4.0, 5.1)	4.2 (3.7, 4.8)	4.4 (4.0, 4.8)
1–2	76 (22.0%)	59 (19.4%) (43.7%)	135 (20.8%)		3155 (5.5%)	3195 (5.5%) (50.3%)	6350 (5.5%)		23.5 (18.8, 29.5)	18.1 (14.0, 23.4)	20.8 (17.6, 24.6)
3–5	13 (3.8%)	13 (4.3%) (50.0%)	26 (4.0%)		213 (0.4%)	252 (0.4%) (54.2%)	465 (0.4%)		57.5 (33.4, 99.1)	49.1 (28.5, 84.5)	53.0 (36.1, 77.8)
6–9	8 (2.3%)	2 (0.7%) (20.0%)	10 (1.5%)		72 (0.1%)	62 (0.1%) (46.3%)	134 (0.1%)		100.0 (50.0, 200.0)	31.3 (7.8, 125.0)	69.4 (37.4, 129.1)
≥10	1 (0.3%)	0 (0.0%) (0.0%)	1 (0.2%)		1 (0.0%)	4 (0.0%) (80.0%)	5 (0.0%)		500.0 (70.4, 3549.7)	0	166.7 (23.5, 1183.2)
Age/Charlson index											
<6 months/≥1	5 (1.4%)	2 (0.7%) (28.6%)	7 (1.1%)	<0.001	97 (0.2%)	95 (0.2%) (49.5%)	192 (0.2%)	<0.001	49.0 (20.4, 117.8)	20.6 (5.2, 82.4)	35.2 (16.8, 73.8)
6–11 months/0	0 (0.0%)	0 (0.0%) (0.0%)	0 (0.0%)		0 (0.0%)	1 (0.0%) (100.0%)	1 (0.0%)		—	—	—
<6 months/0	1 (0.3%)	1 (0.3%) (50.0%)	2 (0.3%)		354 (0.6%)	362 (0.6%) (50.6%)	716 (0.6%)		2.8 (0.4, 20.0)	2.8 (0.4, 19.6)	2.8 (0.7, 11.1)
6–11 months/≥1	0 (0.0%)	0 (0.0%) (0.0%)	0 (0.0%)		8 (0.0%)	5 (0.0%) (38.5%)	13 (0.0%)		—	—	—
1–4 years/0	19 (5.5%)	17 (5.6%) (47.2%)	36 (5.5%)		4515 (7.8%)	4515 (7.8%) (50.0%)	9030 (7.8%)		4.2 (2.7, 6.6)	3.8 (2.3, 6.0)	4.0 (2.9, 5.5)
1–4 years/≥1	5 (1.4%)	4 (1.3%) (44.4%)	9 (1.4%)		310 (0.5%)	319 (0.6%) (50.7%)	629 (0.5%)		15.9 (6.6, 38.1)	12.4 (4.6, 33.0)	14.1 (7.3, 27.1)

Continued

Table 1. *Continued*

Baseline characteristics/ category	Hospitalized				Not hospitalized				Hospitalization rates per 1000 (95% CI)		
	No NI (column %)	NI (column %) (row %)	overall (column %)	*P* value	No NI (column %)	NI (column %) (row %)	overall (column %)	*P* value	No NI	NI	overall
5–9 years/0	14 (4.1%)	11 (3.6%) (44.0%)	25 (3.9%)		7242 (12.5%)	7247 (12.5%) (50.0%)	14489 (12.5%)		1.9 (1.1, 3.3)	1.5 (0.8, 2.7)	1.7 (1.2, 2.5)
5–9 years/≥1	11 (3.2%)	7 (2.3%) (38.9%)	18 (2.8%)		490 (0.8%)	507 (0.9%) (50.9%)	997 (0.9%)		22.0 (12.2, 39.6)	13.6 (6.5, 28.6)	17.7 (11.2, 28.1)
10–19 years/0	30 (8.7%)	23 (7.6%) (43.4%)	53 (8.2%)		11760 (20.4%)	11725 (20.3%) (49.9%)	23485 (20.3%)		2.5 (1.8, 3.6)	2.0 (1.3, 2.9)	2.3 (1.7, 2.9)
10–19 years/≥1	6 (1.7%)	3 (1.0%) (33.3%)	9 (1.4%)		447 (0.8%)	450 (0.8%) (50.2%)	897 (0.8%)		13.2 (6.0, 29.5)	6.6 (2.1, 20.5)	9.9 (5.2, 19.1)
20–49 years/0	137 (39.7%)	119 (39.1%) (46.5%)	256 (39.4%)		23437 (40.6%)	23465 (40.6%) (50.0%)	46902 (40.6%)		5.8 (4.9, 6.9)	5.0 (4.2, 6.0)	5.4 (4.8, 6.1)
20–49 years/≥1	37 (10.7%)	19 (6.3%) (33.9%)	56 (8.6%)		1094 (1.9%)	1122 (1.9%) (50.6%)	2216 (1.9%)		32.7 (23.7, 45.2)	16.7 (10.6, 26.1)	24.6 (19.0, 32.0)
50–64 years/0	34 (9.9%)	28 (9.2%) (45.2%)	62 (9.6%)		5472 (9.5%)	5462 (9.5%) (50.0%)	10934 (9.5%)		6.2 (4.4, 8.6)	5.1 (3.5, 7.4)	5.6 (4.4, 7.2)
50–64 years/≥1	23 (6.7%)	24 (7.9%) (51.1%)	47 (7.2%)		639 (1.1%)	646 (1.1%) (50.3%)	1285 (1.1%)		34.7 (23.1, 52.3)	35.8 (24.0, 53.4)	35.3 (26.5, 47.0)
65–79 years/0	4 (1.2%)	18 (5.9%) (81.8%)	22 (3.4%)		1160 (2.0%)	1154 (2.0%) (49.9%)	2314 (2.0%)		3.4 (1.3, 9.2)	15.4 (9.7, 24.4)	9.4 (6.2, 14.3)
65–79 years/≥1	10 (2.9%)	10 (3.3%) (50.0%)	20 (3.1%)		350 (0.6%)	353 (0.6%) (50.2%)	703 (0.6%)		27.8 (14.9, 51.6)	27.5 (14.8, 51.2)	27.7 (17.8, 42.9)
≥80 years/0	3 (0.9%)	11 (3.6%) (78.6%)	14 (2.2%)		238 (0.4%)	219 (0.4%) (47.9%)	457 (0.4%)		12.4 (4.0, 38.6)	47.8 (26.5, 86.4)	29.7 (17.6, 50.2)
≥80 years/≥1	6 (1.7%)	7 (2.3%) (53.8%)	13 (2.0%)		103 (0.2%)	110 (0.2%) (51.6%)	213 (0.2%)		55.0 (24.7, 122.5)	59.8 (28.5, 125.5)	57.5 (33.4, 99.1)

1 October to 31 December 2009, there were 58 061 per group; for the most specific pandemic peak period spanning 18 October to 7 November, there were 36 771 records per group.

Before propensity score matching, the two cohorts (NI exposed and unexposed) differed significantly on almost all baseline characteristics (11 showed a *P* value of <0.0002 and only cardiorespiratory condition had a *P* value of 0.7). These variables were used to derive propensity scores upon which the treatment groups were individually matched in each analysis period. After 1:1 propensity score matching, no baseline characteristics, including those considered as possible confounders, showed significant differences between groups. The distribution of all baseline covariates was completely balanced between NI-exposed and unexposed groups by the propensity score matching. Since only 203 subjects (0.03%) from the NI-treated subjects were lost during the matching algorithm, the final matching sample retains the representativeness of the population. Both before and after propensity score matching, data showed similar patterns in NI-exposed and unexposed groups with respect to the distribution of intervals between influenza visit and subsequent hospitalization. More than 50% of hospitalized subjects were admitted by day 3.

Overall and among subjects in both NI-exposed and unexposed groups, the highest hospitalization rates after propensity score matching were in the very young (<6 months old) as well as the old (65–79 years old) and the very old (≥80 years old) (Table 1). Overall rates of hospitalization per 1000 patients in the exposed and unexposed cohorts, within 2 weeks of an outpatient influenza diagnosis, were significantly higher in these age groups than in any other: 35.0 (95% CI 16.7–73.4), 13.7 (95% CI 10.1–18.6) and 38.7 (95% CI 26.6–56.5), respectively (Table 1). These ages comprised 0.2%, 2.6% and 0.6% of participants with outpatient influenza diagnosis.

About 6% of subjects with an outpatient physician diagnosis of influenza who were not subsequently hospitalized (i.e. within 14 days) had an underlying comorbidity (Table 1). Conversely, among hospitalized patients, about one-quarter of the exposed and unexposed groups had an underlying comorbidity and this was mainly due to age groups 20–49 and 50–64 years.

AVE

The crude and adjusted baseline HRs and the 95% CIs for all-cause hospitalization associated with the use of antivirals are illustrated in Table 3. During the main analysis period (Table 4), spanning 1 October to 31 December 2009, antivirals were associated with a statistically significant reduction of 16.1% in the risk of hospitalization (HR 0.839; 95% CI 0.719–0.980), comparable to the narrower, but more specific, pandemic peak period of 18 October to 7 November 2009 (AVE 15%; 95% CI −4%–30%). For the broader, but less specific, period spanning 1 September to 31 December 2009, AVE was higher (36%; 95% CI 20%–49%), but there was greater variability in this estimate. During the main analysis period, the use of more specific causes of hospitalization (P&I or ARD) also paradoxically resulted in lower AVE estimates.

For the main analysis period, crude AVE among those with comorbidity was significant at 52% (95% CI 29%–68%) as was the fully adjusted model (59%; 95% CI 39%–73%). For those individuals without comorbidity, the crude and the fully adjusted AVE were non-significant at 6% (95% CI −14%–20%) and 6% (95% CI −13%–21%), respectively.

Table 2. Crude all-cause hospitalization and death rate per 100 000 person-days by antiviral exposure status and analysis period before and after propensity score matching

			Before propensity score matching				After propensity score matching			
Time period	Outcome	Antiviral exposure	*n*	no. of events	person-days	rate (95% CI)	*n*	no. of events	person-days	rate (95% CI)
Main period (1 October to 31 December)	hospitalization	total	213 022	1343	2 969 756	45.22 (42.87, 47.71)	116 122	649	1 619 569	40.07 (37.10, 43.28)
		antiviral	58 271	310	812 945	38.13 (34.12, 42.62)	58 061	304	810 087	37.53 (33.54, 41.99)
		no antiviral	154 751	1033	2 156 811	47.89 (45.06, 50.91)	58 061	345	809 482	42.62 (38.35, 47.36)
	death	total	213 022	124	6 388 512	1.94 (1.63, 2.31)	116 122	28	3 483 160	0.80 (0.56, 1.16)
		antiviral	58 271	11	1 747 938	0.63 (0.35, 1.14)	58 061	11	1 741 638	0.63 (0.35, 1.14)
		no antiviral	154 751	113	4 640 574	2.44 (2.03, 2.93)	58 061	17	1 741 522	0.98 (0.61, 1.57)
Sensitivity analysis										
peak period (18 October to 7 November)	hospitalization	total	115 037	724	1 603 762	45.14 (41.97, 48.55)	73 542	380	1 025 985	37.04 (33.49, 40.96)
		antiviral	36 962	184	515 755	35.68 (30.88, 41.22)	36 771	175	513 188	34.10 (29.40, 39.55)
		no antiviral	78 075	540	1 088 007	49.63 (45.62, 54.00)	36 771	205	512 797	39.98 (34.86, 45.84)
	death	total	115 037	60	3 450 017	1.74 (1.35, 2.24)	73 542	15	2 205 972	0.68 (0.41, 1.13)
		antiviral	36 962	7	1 108 726	0.63 (0.30, 1.32)	36 771	7	1 102 996	0.63 (0.30, 1.33)
		no antiviral	78 075	53	2 341 291	2.26 (1.73, 2.96)	36 771	8	1 102 976	0.73 (0.36, 1.45)
full autumn (1 September to 31 December)	hospitalization	total	217 252	1398	3 028 415	46.16 (43.81, 48.65)	117 550	668	1 639 264	40.75 (37.77, 43.96)
		antiviral	58 978	317	822 790	38.53 (34.51, 43.01)	58 775	310	820 039	37.80 (33.82, 42.25)
		no antiviral	158 274	1081	2 205 625	49.01 (46.17, 52.02)	58 775	358	819 225	43.70 (39.40, 48.47)
	death	total	217 252	134	6 515 214	2.06 (1.74, 2.44)	117 550	31	3 525 974	0.88 (0.62, 1.25)
		antiviral	58 978	11	1 769 148	0.62 (0.34, 1.12)	58 775	11	1 763 058	0.62 (0.35, 1.13)
		no antiviral	158 274	123	4 746 066	2.59 (2.17, 3.09)	58 775	20	1 762 916	1.13 (0.73, 1.76)

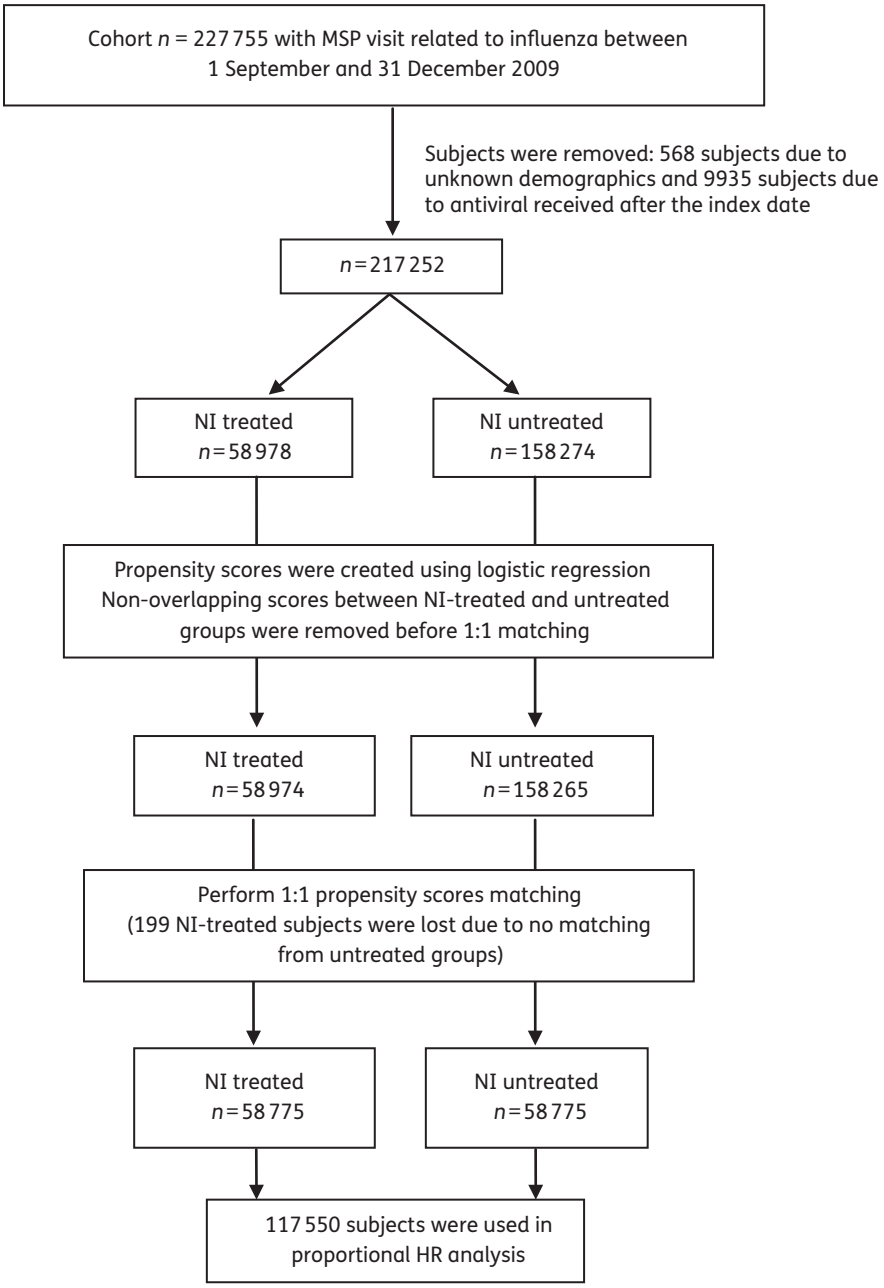

Figure 1. Propensity score matching cohort flow chart during second wave.

Discussion

Our large, population-based study found that antiviral use, as measured by receipt of a prescription for oseltamivir or zanamivir after a physician diagnosis of influenza or A(H1N1)pdm09 pandemic, was associated with a 15%–36% decrease in all-cause hospitalization. Our study is unique in that we used a population-based cohort to evaluate the effectiveness of antivirals; few studies have evaluated AVE in an entire cohort[12,13] and most used case series.[14–18] Nevertheless, our results are consistent with other findings that show that NIs are useful during pandemics when taken within the recommended 48 h. These results support the use of antiviral medications as a key mitigation strategy.

Although the A(H1N1)pdm09 pandemic virus was more likely to infect the younger population, previous studies have showed that when patients aged ≥65 years were infected with influenza, they were more likely to be admitted into hospital and die from it.[19] Our findings were similar and we saw the highest hospitalization rates in the very young (i.e. <6 months of age) and in older adults (i.e. ≥65 years of age). About 6% of subjects with an outpatient physician diagnosis of influenza who were not subsequently hospitalized (i.e. within 14 days) had an underlying comorbidity (Table 1).

Table 3. Crude and adjusted HR for all-cause hospitalization, main analysis period (1 October to 31 December 2009)

	HR (95% CI)	*P* value
Crude estimate	0.881 (0.755, 1.027)	0.1061
Individual covariate adjustment		
age group	0.881 (0.755, 1.028)	0.1067
gender	0.880 (0.755, 1.027)	0.1053
health authority	0.880 (0.754, 1.027)	0.1047
immunosuppressive agent use	0.877 (0.752, 1.024)	0.0964
number of past GP visits	0.883 (0.756, 1.030)	0.1123
number of past hospitalizations	0.881 (0.755, 1.028)	0.1071
number of same-day GP visits	0.738 (0.590, 0.923)[a]	0.0078
Charlson index	0.743 (0.594, 0.929)[a]	0.0093
vaccine availability[b]	0.864 (0.740, 1.009)	0.0643
Fully adjusted estimate	0.839 (0.719, 0.980)	0.0270

Sample size (no. of hospitalizations): antiviral, 58 061 (304); non-antiviral, 58 061 (345).
[a]Indicating model was adjusted to non-proportionality, estimates unstable.
[b]Indicating whether the influenza referent date was during the period that vaccine became available on 26 October 2009.

Conversely, among hospitalized patients, about one-quarter of the treated and untreated groups had an underlying comorbidity. This high proportion was mainly contributed by adults, particularly those in age groups 20–49 and 50–64 years.

As mentioned previously, a number of studies, mostly case series, have evaluated the benefit of antivirals in reducing the severity of infections (reduction in critical care admission), hospitalizations and mortality during the 2009 pandemic.[12,14–18,20,21] Of note, the majority of these studies have been conducted in pregnant women.[15–18,20,21] Like our study, they all demonstrated that NIs decreased the risk of severe disease and hospitalization. Our study databases could not identify pregnant women as a separate category as there was a lack of appropriate ICD-9 or -10 diagnostic codes to identify pregnancy during the pandemic. It would have been interesting to see the effect of the antivirals on this population, given that they are at higher risk of hospitalization and severe disease from influenza.[15,20,21] A few of our patients did go to ICU, but the sample size was not large enough to do propensity score matching for the exposed and unexposed groups; thus, the data are not presented.

Early on in the 2009 pandemic, BC developed a targeted programme to encourage antiviral use in people with severe ILI disease and/or underlying chronic conditions. In our study, we saw that these patients were ≥30% more likely to receive antivirals. The provincial stockpile of NIs was also pre-distributed across the province to pharmacies and remote communities, so that people at risk could have access to the medications in a timely way. This study supports the benefits of this targeted approach to those at highest risk and the strategy of antiviral pre-distribution. In mitigating the pandemic impact, the avoidance of between 16% and 36% of hospitalizations attributable to the antiviral strategy was likely a key factor in the ability of the healthcare system to cope with the peak of infections between October and November 2009, before vaccine was available.

There are several limitations to this study. First, the measure of antiviral exposure we used was a prescription for antivirals being dispensed to an individual on day 0 with the assumption that the patients had symptoms for <48 h prior to their physician visit. During our vaccine effectiveness analysis,[9] the median time from ILI onset to physician visit was 2–3 days and therefore we may have included patients who had had symptoms for >48 h prior to their physician visit; however, if this was the case, AVE would be higher than we observed. Further, we cannot be certain that the medication was actually taken by the recipient or that it was taken for a complete course. We are assuming that all the A(H1N1)pdm09 pandemic viruses were NI susceptible, but it should be noted that oseltamivir resistance is present in many countries and, as of 26 January 2011, 340 instances of oseltamivir resistance have been reported by the WHO Global Influenza Surveillance Network.[22,23]

Individuals may have received antivirals from sources other than a pharmacy and these would not be recorded in the *PharmaNet* database. This was a potential primarily in remote communities where antivirals were pre-positioned within the community to be dispensed by the local healthcare worker. In addition, *PharmaNet* would not have recorded antiviral use for inmates in federal penitentiaries. Additionally, some people would have received a prescription from their physician in advance of the pandemic to be taken should they develop ILI. This was part of a campaign to ensure people at risk had a plan for assessment (often by phone) and treatment should they develop influenza during the pandemic. In either case, failure to capture these individuals would lead to conservative bias and an underassessment of AVE. Oseltamivir may have been administered to the 'healthier' population; a proxy for this could have been past vaccinations. Unfortunately, our merged datasets did not include past vaccinations as we do not have a complete immunization registry for adults. However, we did adjust for the 'healthy' adults by the number of past GP visits as well as the number of past hospitalizations.

Miscoding is always a possibility when using administrative data, especially when related to coding for physician office visits or hospitalization. This could have resulted in an over- or underestimation of AVE. This is particularly true for the varying estimates of AVE seen when we looked at more influenza-specific causes of hospitalizations, such as acute respiratory disease and/or pneumonia. Hospital emergency departments in BC use both physicians who bill for their services and those who are paid a flat fee. As such, if only an outpatient visit was required and the patient was seen by a non-billing physician, we would have not included them in our dataset.

Prior to the pandemic, randomized controlled trials evaluating the efficacy of antivirals for treatment of seasonal influenza A or B had shown them to shorten the course of illness when administered within 48 h of onset of illness,[24–30] although the benefit was greatest when treatment was initiated with 12 h of the onset of symptoms.[31] The use of antivirals in high-risk patients, defined as those over the age of 65 years or with chronic medical conditions, showed that they reduced the time to alleviation of symptoms by ~0.5–1 day.[32] Although these studies showed a modest decrease in symptom duration, not many studies had evaluated antiviral efficacy in preventing hospitalization or mortality. A pooled analysis of 10 randomized controlled trials of oseltamivir used in adults with acute influenza showed that its use was associated with a 50% decline in the hospitalization rate or lower respiratory infections and antibiotic use declined by 26%.[33]

Table 4. Main and sensitivity analyses of antiviral effectiveness by outcome

	HR (95% CI) (*P* value)		
	1 October to 31 December 2009 (main period)	1 September to 31 December 2009 (second wave)	18 October to 7 November 2009 (peak period)
All-cause hospitalizations			
n (no. of hospitalizations) AV	58061 (304)	58775 (310)	36771 (175)
n (no. of hospitalizations) non-AV	58061 (345)	58775 (358)	36771 (205)
HR estimates crude	0.881 (0.755, 1.027) (0.11)	0.674 (0.542, 0.839)[a] (<0.01)	0.853 (0.697, 1.044) (0.12)
fully adjusted	0.839 (0.719, 0.980) (0.03)	0.639 (0.513, 0.796)[a] (<0.01)	0.850 (0.695, 1.041) (0.12)
Primary due to P & I			
n (no. of hospitalizations) AV	58061 (57)	58775 (59)	36771 (34)
n (no. of hospitalizations) non-AV	58061 (40)	58775 (47)	36771 (32)
HR estimates crude	1.425 (0.951, 2.135) (0.09)	1.255 (0.856, 1.841) (0.24)	1.062 (0.656, 1.722) (0.81)
fully adjusted	1.421 (0.947, 2.131) (0.09)	1.221 (0.832, 1.793) (0.31)	1.035 (0.638, 1.679) (0.89)
Due to P & I (anywhere on discharge sheet)			
n (no. of hospitalizations) AV	58061 (77)	58775 (79)	36771 (47)
n (no. of hospitalizations) non-AV	58061 (71)	58775 (81)	36771 (56)
HR estimates crude	1.084 (0.785, 1.497) (0.62)	0.975 (0.715, 1.329) (0.87)	0.839 (0.570, 1.237) (0.38)
fully adjusted	1.041 (0.753, 1.440) (0.81)	0.935 (0.685, 1.275) (0.67)	0.808 (0.548, 1.191) (0.28)
Primary due to acute respiratory diseases			
n (no. of hospitalizations) AV	58061 (11)	58775 (12)	36771 (6)
n (no. of hospitalizations) non-AV	58061 (11)	58775 (11)	36771 (4)
HR estimates crude	1.000 (0.434, 2.307) (1.00)	1.091 (0.481, 2.472) (0.84)	1.500 (0.423, 5.315) (0.53)
fully adjusted	0.975 (0.422, 2.249) (0.95)	1.078 (0.476, 2.444) (0.86)	1.475 (0.416, 5.228) (0.55)
Due to acute respiratory diseases (anywhere on discharge sheet)			
n (no. of hospitalizations) AV	58061 (18)	58775 (19)	36771 (9)
n (no. of hospitalizations) non-AV	58061 (18)	58775 (15)	36771 (8)
HR estimates crude	1.385 (0.678, 2.826) (0.37)	1.267 (0.644, 2.493) (0.49)	1.125 (0.434, 2.915) (0.81)
fully adjusted	1.350 (0.661, 2.756) (0.41)	1.239 (0.629, 2.440) (0.54)	1.130 (0.436, 2.929) (0.80)
Primary due to P & I and acute respiratory diseases			
n (no. of hospitalizations) AV	58061 (67)	58775 (70)	36771 (39)
n (no. of hospitalizations) non-AV	58061 (51)	58775 (58)	36771 (36)
HR estimates crude	1.314 (0.913, 1.891) (0.14)	0.887 (0.564, 1.396)[a] (0.61)	1.083 (0.689, 1.704) (0.73)
fully adjusted	1.257 (0.873, 1.812) (0.22)	0.845 (0.536, 1.331)[a] (0.47)	1.076 (0.684, 1.693) (0.75)
Due to P & I and acute respiratory diseases (anywhere on discharge sheet)			
n (no. of hospitalizations) AV	58061 (91)	58775 (94)	36771 (54)
n (no. of hospitalizations) non-AV	58061 (84)	58775 (96)	36771 (64)
HR estimates crude	0.816 (0.560, 1.189)[a] (0.29)	0.734 (0.505, 1.069)[a] (0.11)	0.844 (0.587, 1.212) (0.36)
fully adjusted	0.772 (0.529, 1.127)[a] (0.18)	0.690 (0.474, 1.006)[a] (0.054)	0.807 (0.562, 1.160) (0.25)

AV, antiviral.
[a]Indicating model was adjusted to non-proportionality, estimates unstable.

Numerous studies have now been published on the A(H1N1)pdm09 pandemic, but most of these looked at risk factors associated with pH1N1. These studies showed that patients at increased risk of hospitalization[6,19,34–37] and severe disease from pH1N1 were those with underlying medical conditions (especially asthma and chronic obstructive pulmonary disease),[6,14,19,32–35] children <2 years of age (especially those with asthma and neurological conditions),[14,19,38,39] obese patients (BMI >35),[40–42] pregnant women[15,20,21] and aboriginal peoples.[6,39,43]

The adjuvanted A(H1N1)pdm09 vaccine used in Canada was ultimately shown to be highly effective (>90%) against medically attended, laboratory-confirmed A(H1N1)pdm09 illness,[9] but was delayed in availability such that initial administration coincided with the pandemic peak in BC. Further, the vaccine was initially available in only limited amounts, requiring sequenced rollout beginning in the last week of October for persons with comorbidity <65 years of age, pregnant women and remote community residents, followed by children <5 years of age, healthcare workers

and other caregivers <65 years in early November, then older children and first responders and, finally, all other BC residents beginning mid–late November. Uptake of the vaccine was ~35%–45% in the province overall and was highest in the elderly (age ≥65 years) in whom vaccine administration had been most delayed.[8] As such, although the use of the NIs may not have slowed down transmission of A(H1N1)pdm09, they were effective in reducing hospitalizations and therefore decreasing the burden on the acute care sector.

Conclusions

Antiviral use in people with influenza who were at risk of severe disease or complications from influenza infection was associated with a reduced risk of hospitalization during the 2009 influenza pandemic. Antiviral strategies should continue to be incorporated into pandemic planning for future influenza pandemics.

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Transparency declarations

None to declare.

Author contributions

F. M. was responsible for the design, implementation and supervision of the study. Statistical analysis was performed by M. C. Write up of the first draft was by F. M. and M. C. All authors contributed to the interpretation of the data and revision of the manuscript for important content.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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