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Severe morbidity among hospitalised adults with acute influenza and other respiratory infections: 2014–2015 and 2015–2016

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Abstract

Our objective was to identify predictors of severe acute respiratory infection in hospitalised patients and understand the impact of vaccination and neuraminidase inhibitor administration on severe influenza. We analysed data from a study evaluating influenza vaccine effectiveness in two Michigan hospitals during the 2014–2015 and 2015–2016 influenza seasons. Adults admitted to the hospital with an acute respiratory infection were eligible. Through patient interview and medical record review, we evaluated potential risk factors for severe disease, defined as ICU admission, 30-day readmission, and hospital length of stay (LOS). Two hundred sixteen of 1119 participants had PCR-confirmed influenza. Frailty score, Charlson score and tertile of prior-year healthcare visits were associated with LOS. Charlson score >2 (OR 1.5 (1.0–2.3)) was associated with ICU admission. Highest tertile of prior-year visits (OR 0.3 (0.2–0.7)) was associated with decreased ICU admission. Increasing tertile of visits (OR 1.5 (1.2–1.8)) was associated with 30-day readmission. Frailty and prior-year healthcare visits were associated with 30-day readmission among influenza-positive participants. Neuraminidase inhibitors were associated with decreased LOS among vaccinated participants with influenza A (HR 1.6 (1.0–2.4)). Overall, frailty and lack of prior-year healthcare visits were predictors of disease severity. Neuraminidase inhibitors were associated with reduced severity among vaccine recipients.

Introduction

It is widely recognised that seasonal respiratory illness, which peaks in fall and winter in temperate regions, is associated with corresponding peaks in doctor's office visits and hospital admissions [1, 2]. Numerous respiratory pathogens are associated with hospitalisation; notably, influenza, human metapneumovirus, respiratory syncytial virus, rhinovirus and parainfluenza virus; all of which cause similar symptoms [3]. However, influenza-associated illness accounts for a substantial proportion of these medical events [2, 4]. Influenza is a viral pathogen that causes an estimated 12 000–56 000 deaths in the USA annually [5]. Influenza-related severe outcomes, such as death, ICU admission or the need for invasive mechanical ventilation, generally occur in elderly individuals or individuals with numerous comorbidities; however, previously healthy adults are also at risk for serious illness [6, 7].

During the 2009 influenza A(H1N1) pandemic, individuals thought to be at low risk for severe influenza, such as those under the age of 65 and without recognised underlying conditions, were hospitalised at a higher than expected rate [8]. During the pandemic, previously unknown risk factors for influenza severity were identified with morbid obesity being one of the most consistently identified factors [9, 10]. In post-pandemic seasons the age of those hospitalised for influenza A(H1N1)pdm09 infection increased along with an increase in the severity of influenza-related pneumonia [11–13]. There was, paradoxically, a corresponding decrease in the use of antiviral treatment initially, though rates of treatment have since risen [13, 14]. With the continued circulation of the A(H1N1) pandemic strain along with A(H3N2) and B viruses, it is critical to identify and monitor groups at risk for severe disease in order to optimise strategies, including the use of neuraminidase inhibitors and vaccine prioritisation when the vaccine supply is limited, to prevent adverse outcomes.

In order to identify predictors of influenza and acute respiratory illness (ARI) severity and, specifically, to understand the impact of vaccination and neuraminidase inhibitor administration on illness severity, we present data from adults hospitalised with ARI from two hospitals in Southeast Michigan over the 2014–2015 and 2015–2016 influenza seasons. Severe outcomes evaluated include ICU admission, length of stay (LOS) and 30-day readmission.

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Methods

Participant enrolment, interview and specimen collection

Participants were adults hospitalised for ARI at University of Michigan Hospital (UMH, Hospital A) in Ann Arbor, Michigan and Henry Ford Hospital (HFH, Hospital B) in Detroit. Enrolment occurred from 5 November 2014 to 6 March 2015, and from 11 January 2016 to 15 April 2016. Staff reviewed electronic medical records (EMRs) daily to identify newly admitted patients (⩽72 h) with ARI as previously described [15]. Eligible participants were approached, and they or their proxy provided written consent for participation in the study. All study procedures were approved by the Institutional Review Boards of the University of Michigan Medical School and the Henry Ford Health System.

Patients were interviewed at enrolment to collect information about demographics, influenza vaccination status, general health status, illness characteristics and subjective assessment of frailty (unexplained >10 pounds weight loss (yes/no), little energy for desired activities (yes/no), difficulty walking 100 yards (no difficulty…unable to do), difficulty carrying 10 pounds (no difficulty…unable to do) and frequency of low/moderate activity (more than once/week…hardly ever/never)). Number of healthcare encounters in the past year and evidence of neuraminidase inhibitor prescription from the study hospital admission were extracted from EMRs. Information about comorbid health conditions was also extracted to calculate the Charlson Comorbidity Index (CCI) for each patient. The following outcome variables were collected from the EMR: death, ICU admission, ventilator use, LOS and 30-day readmission. Outcomes that were experienced by more than 10 influenza-positive participants, including ICU admission, LOS and 30-day readmission, were used in models.

Laboratory methods

Nasal and throat swabs collected at enrolment were combined and tested for influenza viruses using reverse transcriptase polymerase chain reaction (RT–PCR). All primers, probes and protocols were developed and provided by the Influenza Division of the CDC. They were designed for detection of universal influenza A and B, and for subtype and lineage identification. All tests were performed in the investigators' laboratory at the University of Michigan School of Public Health.

Influenza vaccination status

Individuals were considered vaccinated if they had documentation or plausible self-report of influenza vaccine receipt ⩾14 days before illness onset. Documented vaccination status was determined based on documentation from the EMR or state immunisation registry. Plausible self-report was defined as reporting both the approximate date and location of vaccination. Individuals were considered unvaccinated if they had no evidence of documentation of vaccination and self-reported no vaccination. Participants were excluded if they had an incomplete self-report of vaccination (e.g. missing date or location) and no additional documentation or if they were vaccinated <14 days before illness onset.

Statistical methods

CCI scores were categorised as 0, 1, 2 or 3 or greater; high CCI was defined as >2. Frailty was defined as the presence of up to five dichotomised variables taken from the enrolment interview that were summed and weighted by the number of questions answered, as a few participants either refused to answer or answered 'don't know' to either one or two of the frailty questions [15, 16]. Total prior-year healthcare visits were defined as all inpatient and outpatient visits for any reason to a UM or HF Health System affiliated clinic in the previous year. Tertiles of prior-year healthcare visits among all participants were calculated, and the variable was expressed as either 0 visits, or visits falling into the first (1–8 visits), second (9–21 visits) or third (⩾22 visits) tertile. Long LOS was defined as a LOS of >8 days. When used as a continuous outcome, LOS was log-transformed and beta coefficients were analysed as per cent change of LOS.

Participants were compared in frequency models using Pearson χ^2 test or Fisher's exact test. Firth's penalised logistic regression models were used to predict the odds of severe illness by various risk factors. Firth's method was used to reduce small-sample bias and improve model fit in the context of quasi-separation. Hospital site (UMH or HFH), sex, age (18–49, 50–64, 65+), frailty score, and CCI >2 were included in adjusted models *a priori*. Tertile of prior-year healthcare visits was included based on its significance in univariate models; this variable was modelled categorically for the outcomes of ICU admission and hospital LOS and ordinally for 30-day readmission due to the monotonic relationship between these variables. For analyses restricted to influenza A-positive individuals, influenza A subtype and influenza vaccination were included as adjustment factors. Cox proportional hazard models, censoring on death, were used to estimate the impact of antiviral treatment on hospital LOS. Neuraminidase inhibitor administration was modelled as a time-varying covariate indicating the day in the hospital admission when participants were treated. The models were adjusted for covariates associated with increased hospital LOS in the risk factor analysis, weighted frailty score and tertile of prior-year healthcare visits. All statistics were completed using SAS (release 9.4, SAS Institute). Statistical significance was defined as a 95% confidence interval that did not include the null value.

Results

Demographics and outcomes by influenza status

We enrolled 1199 adults with ARI; 727 from the 2014–2015 season and 472 from the 2015–2016 season. Eighty (7%) hospitalisations were excluded due to missing or incomplete information on vaccination status, influenza status, or Charlson score, leaving 1119 participants in the analysis.

Two-hundred sixteen (19%) participants had PCR-confirmed influenza virus infection. Influenza-positive participants were significantly less likely to have received influenza vaccines (Table 1). Half of the participants had a CCI >2 but this percentage was significantly lower in individuals with influenza (41.2%) compared with those testing negative (52.2%). Among influenza-positive participants there were two deaths, 22 ICU admissions, ten invasive ventilations and 19 instances of long LOS (>8 days); these outcomes were observed in similar frequencies between influenza-positive and -negative populations. Thirty-day readmission was significantly less frequent among influenza-positive participants compared with those testing negative (Table 1).

One-hundred and eleven participants were infected with influenza A(H3N2) viruses, 90 with influenza A(H1N1)pdm2009 and 15 with influenza B viruses; models restricted to influenza-positive

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Table 1. Demographics and outcomes of hospitalised adults with ARI by influenza status

Characteristics	Total $N = 1119$ *N* (column %)	Influenza positive $N = 216$ *N* (column %)	Influenza negative $N = 903$ *N* (column %)	*P* value[a]
Sex				0.68
Male	501 (44.7%)	94 (43.5%)	407 (45.1%)	
Female	618 (54.8%)	122 (56.5%)	496 (54.9%)	
Age				0.44
18–49	323 (28.9%)	67 (31.0%)	256 (28.3%)	
50–64	415 (37.1%)	72 (33.3%)	343 (38.0%)	
⩾65	381 (34.0%)	77 (35.7%)	304 (33.7%)	
Race[b]				0.62
White (non-Hispanic)	583 (52.7%)	114 (54.0%)	469 (52.3%)	
Black (non-Hispanic)	392 (35.4%)	76 (36.0%)	316 (35.3%)	
Other	132 (11.9%)	21 (10.0%)	111 (12.4%)	
Site of enrolment				0.47
Hospital A	636 (56.8%)	118 (54.6%)	518 (57.4%)	
Hospital B	483 (43.2%)	98 (45.4%)	385 (42.6%)	
Year				0.12
2014–2015	664 (59.3%)	118 (54.6%)	546 (60.5%)	
2015–2016	455 (40.7%)	98 (45.4%)	357 (39.5%)	
Charlson score				0.01
0	119 (10.6%)	33 (15.3%)	86 (9.5%)	
1	283 (25.3%)	62 (28.7%)	221 (24.5%)	
2	157 (14.0%)	32 (14.8%)	125 (13.8%)	
⩾3	560 (50.0%)	89 (41.2%)	471 (52.2%)	
Frailty score (median (IQR))		0.25 (0.0–0.50)	0.40 (0.20–0.60)	0.04
BMI category[c]				0.51
<18.5	42 (3.9%)	4 (1.9%)	38 (4.3%)	
18.5–24.9	267 (24.7%)	53 (25.7%)	214 (24.5%)	
25–29.9	284 (26.3%)	53 (25.7%)	231 (26.4%)	
30–39.9	315 (29.1%)	65 (31.6%)	250 (28.6%)	
⩾40	173 (16.0%)	31 (15.1%)	142 (16.2%)	
Number of healthcare visits (tertiles)				0.61
0	128 (11.4%)	28 (13.0%)	100 (11.1%)	
1	349 (31.2%)	72 (33.3%)	277 (30.7%)	
2	318 (28.4%)	60 (27.8%)	258 (28.6%)	
3	324 (29.0%)	56 (25.9%)	268 (29.7%)	
Vaccination status				<0.01
Vaccinated	750 (67.0%)	113 (52.3%)	637 (70.5%)	
Unvaccinated	369 (33.0%)	103 (47.7%)	266 (29.5%)	
Death	15 (1.3%)	2 (1.0%)	13 (1.4%)	0.56
ICU	126 (11.3%)	22 (10.2%)	104 (11.5%)	0.58
Invasive ventilator	48 (4.3%)	10 (4.6%)	38 (4.2%)	0.78
LOS >8 days	108 (9.7%)	19 (8.8%)	89 (9.9%)	0.63
30-day readmission	167 (14.9%)	16 (7.4%)	151 (16.7%)	<0.01

[a]*P* values are from χ^2 tests or Fisher's exact tests when appropriate.
[b]12 individuals have missing Race information.
[c]38 individuals have missing BMI information.

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Table 2. Demographics and outcomes of enrolled patients hospitalised with influenza A-associated ARI by subtype

Characteristics	Total $N = 201$ *N* (column %)	H3N2 $N = 111$ *N* (column %)	H1N1 $N = 90$ *N* (column %)	*P* value[a]
Sex				0.20
Male	90 (44.8%)	43 (48.7%)	43 (47.8%)	
Female	111 (55.2%)	68 (61.3%)	47 (52.2%)	
Age				0.10
18–49 years	62 (30.8%)	29 (26.1%)	33 (36.7%)	
50–64 years	68 (33.8%)	36 (32.4%)	32 (35.6%)	
⩾65 years	71 (35.3%)	46 (41.4%)	25 (35.2%)	
Race[b]				0.22
White (non-Hispanic)	106 (53.8%)	63 (57.3%)	43 (49.4%)	
Black	71 (36.0%)	34 (30.9%)	37 (42.5%)	
Other	20 (10.1%)	13 (11.8%)	7 (8.0%)	
Site of enrolment				0.29
Hospital A	111 (55.2%)	65 (58.6%)	46 (51.1%)	
Hospital B	90 (44.8%)	46 (41.4%)	44 (48.9%)	
Charlson score				0.02
0	31 (15.4%)	10 (9.0%)	21 (23.3%)	
1	59 (29.3%)	39 (35.1%)	20 (22.2%)	
2	27 (13.4%)	13 (11.7%)	14 (15.6%)	
⩾3	84 (41.8%)	49 (44.1%)	35 (38.9%)	
Frailty score (median (IQR))	0.25 (0.0,0.40)	0.20 (0.0–0.5)	0.40 (0.0–0.40)	0.89
BMI category[c]				0.11
<18.5	4 (1.7%)	4 (3.6%)	0 (0.0%)	
18.5–24.9	47 (24.0%)	24 (21.8%)	23 (28.4%)	
25–29.9	49 (25.1%)	33 (30.0%)	16 (19.7%)	
⩾30	91 (49.2%)	49 (44.6%)	42 (51.9%)	
Year				<0.01
2014–2015	107 (53.2%)	107 (96.4%)	0 (0.0%)	
2015–2016	94 (46.8%)	4 (3.6%)	90 (100.0%)	
Total number of healthcare visits in the last year (tertiles)				0.05
0	25 (12.4%)	8 (7.2%)	17 (18.9%)	
1	64 (31.8%)	34 (30.6%)	30 (33.3%)	
2	58 (28.9%)	34 (30.6%)	24 (26.7%)	
3	54 (26.9%)	35 (31.5%)	19 (21.1%)	
Vaccination status				0.02
Vaccinated	106 (52.7%)	67 (60.4%)	39 (43.3%)	
Unvaccinated	95 (46.1%)	44 (39.6%)	51 (56.7%)	
Death	2 (1.0%)	1 (0.9%)	1 (1.1%)	1.00
ICU	20 (10.0%)	7 (6.3%)	13 (14.4%)	0.06
Invasive ventilator	9 (4.5%)	1 (0.9%)	8 (8.9%)	0.01
LOS >8 days	18 (9.0%)	5 (4.5%)	13 (14.4%)	0.02
30-day readmission	16 (8.0%)	10 (9.0%)	6 (6.7%)	0.61

[a]*P* values reflect results of Pearson χ^2 tests or Fisher's exact test when appropriate. *P* values for continuous variables represent results of Wilcoxon tests.
[b]4 individuals are missing race information.
[c]10 individuals are missing BMI information.

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Table 3. Predictors of severe disease in participants with all-cause ARI and in patients with influenza A-associated ARI[a]

	ARI ($N = 1119$)			Influenza A positive ($N = 201$)		
Predictors	ICU (OR, 95% CI)	LOS (per cent change, 95% CI)	30-Day readmission (OR, 95% CI)	ICU (OR, 95% CI)	LOS (per cent change, 95% CI)	30-Day readmission (OR, 95% CI)
Male sex	1.5 (1.0–2.2)	6.1 (−0.5 to 13.1)	1.1 (0.8–1.6)	0.7 (0.3–1.8)	−5.0 (−19.2 to 11.7)	0.4 (0.1–1.4)
Age						
18–49	1.0	0.0	1.0	1.0	0.0	1.0
50–64	1.0 (0.6–1.6)	3.6 (−4.4 to 12.3)	0.9 (0.6–1.3)	1.1 (0.3–3.6)	3.2 (−16.1 to 26.9)	1.5 (0.3–7.7)
⩾65	1.0 (0.6–1.6)	0.4 (−7.7 to 9.1)	0.6 (0.4–1.0)	1.0 (0.3–3.4)	6.6 (−13.8 to 31.9)	1.2 (0.3–6.2)
Site of enrolment						
Hospital A	1.0	0.0	1.0	1.0	0.0	1.0
Hospital B	0.8 (0.5–1.2)	−0.7 (−7.3 to 6.2)	1.4 (1.0–2.1)	0.7 (0.2–2.0)	−8.1 (−23.2 to 9.9)	2.7 (0.9–9.0)
Charlson score >2	1.5 (1.0–2.3)	21.7 (13.3–30.7)	1.8 (1.2–2.7)*	1.6 (0.5–5.7)	8.5 (−11.0 to 32.2)	1.1 (0.3–4.2)
Vaccination	–	–	–	1.0 (0.3–3.1)	−6.1 (−22.4 to 13.6)	0.9 (0.3–3.5)
Frailty score[b]	1.5 (0.8–3.0)	22.7 (9.3–37.5)*	1.4 (0.8–2.5)	1.0 (0.1–6.1)	31.4 (−4.5 to 80.9)	8.9 (1.2–78.0)*
Total visits[c] (tertiles)			1.5 (1.2–1.8)*			2.5 (1.2–5.8)*
0	1.0	0.0		1.0	0.0	
1	0.6 (0.4–1.1)	−18.8 (−21.1 to −1.7)*		0.3 (0.1–1.0)*	−11.7 (−33.1 to 16.6)	
2	0.6 (0.3–1.0)	−9.3 (−18.9 to 1.6)		0.2 (0.0–0.8)*	−4.2 (−28.3 to 28.0)	
3	0.3 (0.2–0.7)*	−11.2 (−21.3 to 0.2)		0.1 (0.0–0.8)*	−10.0 (−35.1 to 24.9)	
Influenza A subtype						
H3N2	–	–	–	1.0	0.0	1.0
H1N1	–	–	–	1.9 (0.7–5.2)	11.1 (−5.7 to 30.9)	0.8 (0.3–2.4)

[a]Adjusted models contain male sex, age group, enrolment site, Charlson score, weighted frailty score, total annual healthcare visits and influenza status. Influenza A subtype and vaccination were also included in models restricted to influenza A-positive adults.
[b]OR and per cent changes reflect the impact of a one-unit increase in weighted frailty score.
[c]Total number of annual healthcare visits is modelled categorically except in models predicting 30-day readmission where it is modelled ordinally and OR represent a change in odds for a one tertile increase.
*Indicates significance at the 5% confidence level.

individuals excluded individuals with influenza B virus infection. There was a higher frequency of influenza A(H1N1)pdm09 infection among participants who were 18–49 years old (37% with H1N1 *vs.* 26% with H3N2, $P = 0.10$), though this difference was not statistically significant (Table 2). CCI ($P = 0.02$), tertile of prior-year healthcare visits ($P = 0.05$) and vaccination status ($P = 0.02$) were associated with influenza A subtype; individuals with a CCI of 0, no healthcare visits in the prior year and who were unvaccinated were more frequently infected with influenza A(H1N1)pdm09 (Table 2). A higher percentage of participants infected with H1N1 were admitted to the ICU, put on an invasive ventilator, and had LOS >8 days compared with those infected with H3N2 (Table 2).

Models predicting severe ARI and influenza-associated ARI

Higher frailty and increased tertile of prior-year healthcare visits were associated with increased 30-day readmission among influenza-positive participants (Table 3). Individuals with the highest tertile of prior-year healthcare visits had decreased odds of ICU admission compared to those with no prior-year visits regardless of influenza status (Table 3). Frailty score was associated with longer LOS among all participants but not among participants with influenza-associated ARI (Table 3).

Neuraminidase inhibitor prescription

One hundred forty-seven (68%) influenza-positive participants were treated with neuraminidase inhibitors. Treatment varied by enrolment hospital; over 75% of influenza-positive patients from Hospital A were treated compared to only 57% from Hospital B ($P = 0.01$) (Table 4). Neuraminidase inhibitor administration also varied by time from illness onset to admission; 73% of participants admitted within 2 days were treated compared with 59% of those admitted later ($P = 0.02$) (data not showed). The median LOS was lower among those with timely antiviral treatment (2.0 days) compared with those with late antiviral treatment (3.0 days) or no treatment (3.0); however, the median LOS did not vary significantly.

Clinical testing for influenza varied significantly by enrolment hospital, 74% of influenza-positive participants from Hospital B by research testing received a clinical influenza test compared with 90% from Hospital A. Only 10% of participants from either

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Table 4. Demographics by antiviral prescription timing among participants with laboratory-confirmed influenza

Characteristics	Timely antivirals[a] *N* = 86 *N* (Row %)	Late antivirals *N* = 61 *N* (Row %)	No antivirals *N* = 69 *N* (Row %)	*P* value[b]
Sex				0.75
Male	40 (42.6%)	26 (27.7%)	28 (29.8%)	
Female	46 (37.7%)	35 (28.7%)	41 (33.6%)	
Age				0.31
18–49	31 (46.3%)	21 (31.3%)	15 (22.4%)	
50–64	27 (37.5%)	21 (29.2%)	24 (33.3%)	
⩾65	28 (36.4%)	19 (24.7%)	30 (39.0%)	
Race[c]				0.21
White	51 (44.7%)	32 (28.1%)	31 (27.2%)	
Black	30 (39.5%)	19 (25.0%)	27 (35.5%)	
Other	4 (19.0%)	8 (38.1%)	9 (42.9%)	
Site of enrolment				0.01
Hospital A	54 (45.8%)	37 (31.4%)	27 (22.9%)	
Hospital B	32 (32.6%)	24 (24.5%)	42 (42.9%)	
Year				0.24
2014–2015	42 (35.6%)	33 (28.0%)	43 (36.4%)	
2015–2016	44 (44.9%)	28 (28.6%)	26 (26.5%)	
Influenza Type/subtype				0.23
A/H3N2	37 (33.3%)	35 (31.5%)	39 (35.1%)	
A/H1N1	42 (46.7%)	24 (26.7%)	24 (26.7%)	
B	7 (46.7%)	2 (13.3%)	6 (40.0%)	
Charlson score				0.36
0	17 (51.5%)	8 (24.2%)	8 (24.2%)	
1	17 (27.4%)	21 (33.9%)	24 (38.7%)	
2	14 (43.7%)	9 (28.1%)	9 (28.1%)	
⩾3	38 (42.7%)	23 (25.8%)	28 (31.5%)	
Frailty score	0.20 (0.0–0.40)	0.40 (0.20–0.60)	0.40 (0.20–0.60)	0.20
Obese[d]				0.22
Yes	39 (40.6%)	31 (32.3%)	26 (27.1%)	
No	43 (39.1%)	26 (23.6%)	41 (37.3%)	
Number of healthcare visits (tertiles)				0.52
0	11 (39.3%)	8 (28.6%)	9 (32.1%)	
1	28 (38.9%)	15 (20.8%)	29 (40.3%)	
2	23 (38.3%)	21 (35.0%)	16 (26.7%)	
3	24 (42.9%)	17 (30.4%)	15 (26.8%)	
Vaccination status				0.85
Yes	46 (40.7%)	30 (26.6%)	37 (32.7%)	
No	40 (38.8%)	31 (30.1%)	32 (31.1%)	
LOS (median, IQR)	2.0 (2.0–4.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	0.17

[a]Timely antivirals refer to antivirals within 2 days of symptom onset.
[b]*P* values are from χ^2 tests or Fisher's exact tests when appropriate.
[c]5 individuals are missing race information.
[d]10 individuals are missing BMI information.

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Table 5. Hazards of discharge related to antiviral treatment timing

	Overall ($N = 201$)		Vaccinated ($N = 106$)		Unvaccinated ($N = 95$)	
Predictors	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Antiviral treatment	1.1 (0.8–1.5)	0.44	1.6 (1.0–2.4)	0.04	0.9 (0.5–1.4)	0.52
Frailty score	0.5 (0.3–1.0)	0.04	0.6 (0.3–1.3)	0.17	0.5 (0.2–1.2)	0.11
Total visits (tertiles)						
Tertile 0	Ref		Ref		Ref	
Tertile 1	1.6 (1.0–2.7)	0.05	0.5 (0.1–1.6)	0.23	1.6 (0.9–2.9)	0.09
Tertile 2	1.3 (0.8–2.1)	0.32	0.3 (0.1–1.0)	0.05	1.3 (0.7–2.4)	0.40
Tertile 3	1.5 (0.9–2.4)	0.13	0.4 (0.2–1.2)	0.09	1.6 (0.8–3.5)	0.21

[a]Models contain all predictors in the table.

hospital without a clinically positive influenza test were treated with neuraminidase inhibitors (data not showed).

The influenza-positive population was further stratified by vaccination status. Vaccinated individuals who were treated with neuraminidase inhibitors had a significantly reduced LOS ($HR_{discharge}$:1.6, 95% CI 1.0–2.4; $P = 0.04$) compared with those who were untreated (Table 5). Other severe outcomes were not evaluated in this analysis due to insufficient sample size.

Discussion

Our study identified risk factors for severe influenza-associated ARI and all-cause ARI among hospitalised patients over two influenza seasons. Given that viral aetiology is often unknown at admission when many treatment decisions are made, it is important to understand the severity of ARI of all causes in the hospital. Of note, 65% of participants were tested clinically for influenza and the majority of these tests were initiated the day of or the day after hospital admission. Despite the timely testing, it may take many hours for PCR results to be available to the clinician and rapid influenza tests are known for their low specificity. For these reasons, treatment decisions should be made before viral aetiology is known in most cases. Higher frailty score was associated with longer LOS, and having 0 prior-year healthcare visits was associated with higher odds of ICU admission. Frailty is a well-known predictor of severity and death, especially among the elderly, though many studies do not consider frailty when studying influenza severity [17–19]. The increased severity among those without prior-year healthcare visits may indicate that individuals who are unlikely to seek care present to the hospital with the most severe illnesses. Increased healthcare visits over the prior year were also associated with increased, rather than reduced, 30-day readmission indicating that 30-day readmission may be, in part, a measure of underlying chronic conditions [20].

We evaluated the impact of vaccination and neuraminidase inhibitor administration on influenza severity. Neuraminidase inhibitors were significantly associated with decreased LOS among vaccinated individuals only after stratification by vaccination status. While the association between neuraminidase inhibitor administration and reduced influenza severity has been emphasised, the interaction between vaccination and neuraminidase inhibitors is not well documented or understood [21, 22]. Though this result offers an interesting potential relationship between antiviral treatment, vaccination and influenza severity, the extremely small sample size in this stratified population necessitates repeated demonstration of this association in larger, future studies.

In light of this result and other evidence in the literature, it is critical that hospitalised influenza-positive patients are treated with neuraminidase inhibitors [22, 23]. We found that just 67% of participants with PCR-confirmed influenza were prescribed neuraminidase inhibitors though treatment is recommended for all hospitalised patients with suspected or confirmed influenza. Treatment varied significantly by enrolment hospital; over 40% of influenza-positive participants at Hospital B did not receive neuraminidase inhibitors, compared to 23% at Hospital A. While all participants are tested for influenza by our research team, not every patient receives a clinical influenza test during their hospital stay. This appeared to impact treatment decisions, as very few individuals without a clinically positive influenza test were treated despite the recommendation that hospitalised individuals with suspected influenza be treated empirically. These numbers indicate a need to continue public health messaging directed at nurses and physicians to encourage empiric treatment and to keep influenza on the list of possible diagnoses during influenza season. Additionally, participants were less likely to be treated if they were admitted to the hospital >2 days after symptom onset. This reflects the widely held opinion that antiviral drugs are only effective within 2 days of symptom onset. While studies have shown that effectiveness is higher when neuraminidase inhibitors are given promptly, there is evidence among hospitalised patients with influenza that treatment within 5 days of symptom onset improves survival [21, 22, 24].

Continued interest in the potential for vaccination to reduce influenza severity stems from the vaccine effectiveness (VE) estimates from the 2014–2015 influenza season, which primarily consisted of influenza A viruses that were antigenically drifted from the Northern Hemisphere vaccine strains [15, 25]. VE estimates from the 2014–2015 season were higher in hospital studies than in ambulatory care studies, where they were not significantly different from zero [15, 26, 27]. This could indicate that influenza vaccination reduces severity as well as incidence; this hypothesis has been previously evaluated but results are mixed [28–31]. We did not find an association between severity and vaccination. Observational studies of severity, such as ours, as well as evaluations of interventions such as vaccination, are often impacted by confounding by indication and other challenges.

Overall, the small number of influenza-positive participants in this study led to reduced power, which may explain the few significant predictors of influenza severity. The in-hospital observational

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nature of the study complicated our ability to study some commonly used severity endpoints such as mechanical ventilation and death. Additionally, selection into this study depended on hospital admission prior to enrolment, potentially increasing the number of older individuals with comorbidities who are more likely to be admitted to the hospital with a less severe disease. We accounted for this in our analysis by adjusting for age, CCI, and prior-year healthcare visits, but residual confounding is always a concern. In addition, when calculating the tertile of prior-year healthcare visits, we could only access visits within the hospital study sites or their associated outpatient clinics, and the majority of individuals who had no visits did not get their regular care within these two systems. However, when the population was restricted to those who did get regular care at our study sites in a sensitivity analysis, the trends of increased severity among those with no prior-year visits remained.

In conclusion, we identified frailty and number of prior-year healthcare visits as predictors of all-cause and influenza-associated ARI severity. Our finding that vaccinated patients who received neuraminidase inhibitors had decreased LOS needs confirmation from future studies, but also adds to the evidence that administration of neuraminidase inhibitors to hospitalised patients reduces influenza severity and reinforces current treatment recommendations in the hospital [23, 32–34].

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Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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