Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Brief report

Association between Influenza Vaccination and severe COVID-19 outcomes at a designated COVID-only hospital in Brooklyn

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A B S T R A C T

Maintaining influenza vaccination at high coverage has the potential to prevent a proportion of COVID-19 morbidity and mortality. We examined whether flu-vaccination is associated with severe corona virus disease 2019 (COVID-19) disease, as measured by intensive care unit (ICU)-admission, ventilator-use, and mortality. Other outcome measures included hospital length of stay and total ICU days. Our findings showed that flu-vaccination was associated with a significantly reduced likelihood of an ICU admission especially among aged <65 and non-obese patients. Public health promotion of flu-vaccination may help mitigate the overwhelming demand for critical COVID-19 care pending the large-scale availability of COVID-19 vaccines.

In the United States, the Coronavirus disease-2019 (COVID-19) pandemic has resulted in 31.3 million confirmed cases and over 562,000 deaths as of April 13, 2021.[1] Experts had warned of a possible second wave in late fall and winter, corresponding with the influenza (flu) season. Influenza co-infection with COVID-19 brings with it challenges of clinically distinguishing both infectious agents, test cross-reactivity and accuracy; and possibly enhancing the risk for severe COVID-19. This can significantly affect downstream public health efforts to properly identify COVID-19 cases and contain the outbreak particularly in resource-limited settings. Flu-vaccination reduces Influenza disease severity and hospitalizations among at-risk populations, such as children, older adults (aged 65>), and pregnant women. Mathematical models suggest that maintaining high influenza-vaccination coverage has the potential to significantly reduce the proportion of COVID-19 morbidity and mortality, and the risk of cross-infection.[2,3] Here, we examined whether prior flu-vaccination reduces the likelihood of COVID-19 disease severity, as measured by hospital length of stay, ICU-admission, ICU length of stay, ventilator-use, and in-hospital mortality.

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METHODS

We conducted a retrospective chart review of 588 COVID-19 hospitalized patients admitted during the height of the pandemic's first wave, between 03/12/2020 and 06/30/2020 at SUNY Downstate Medical Center; a New York State designated COVID-only hospital. Patients reported on admission if they had been previously vaccinated for Influenza (Yes or No) during last flu-season (09/01/19 - 03/31/20). SUNY Downstate Medical Center institutional review board approved this study. Dichotomous (Yes or No) outcome measures included whether patients required ICU-admission, mechanical-ventilation or experienced in-hospital mortality. Continuous outcome measures included hospital length of stay defined as total hospital stay days from admission to discharge or death, and ICU length of stay, defined as total ICU stay days from admission to ICU to discharge from ICU or death. COVID-19 diagnosis was confirmed using quantitative reverse transcription–polymerase chain reaction (RT-PCR) assay of nasopharyngeal swabs.

Statistical analyses

Descriptive statistics were calculated for demographic and clinical data for the sample. Characteristics of the study groups (self-reported flu vaccination Yes vs No) were compared using Pearson's chi-square test, or Fisher's exact test where appropriate, for categorical variables (eg, sex) and t-test for continuous variables (eg, age). Clinical data comparison between flu-vaccinated groups included use of the Charlson's co-morbidity index scores,[4] to account for multiple comorbidities that could be potentially associated with COVID19 infection. Adjusted multivariate logistic regression analyses quantified the effect of flu-vaccination on the rates of ICU-admission, ventilator-use and mortality (Table 2). Adjusted multivariate linear regression analyses quantified the effect of flu-vaccination on hospital and ICU length of stay. Since individuals who are older than 65 years and those who are obese are more likely to develop severe COVID-19 disease,[5] we also conducted stratified analyses by age (<65 and ≥65 y) and BMI (<30 and ≥30 kg/m^2). Covariates/potential confounders were selected *a priori* and were chosen based on the literature and their clinical relevance to COVID-19

Table 1
Characteristics of all 588 RCT-PCR confirmed COVID-19 positives, between 03/12/20 and 05/30/20 SUNY downstate health sciences medical center, Brooklyn, New York

Clinical characteristics	All patients n = 588	Self-reported flu vaccination - No n = 382	Self-reported flu vaccination -Yes n = 206	*P-value*
Female sex no. (%)	277 (47.1)	179 (46.9)	98 (47.6)	.87
Age years mean (SD)				
All Patients	68.4 (14.5)	68.6 (14.1)	68.9 (14.1)	.79
Age years no. (%)				
<65	52.7 (9.8)	53.1 (9.1)	52.3 (9.7)	.56
≥65	76.9 (8.1)	77.0 (7.9)	76.5 (8.4)	
Race/Ethnicity no. (%)				
African American	519 (88.3)	341 (89.3)	178 (86.4)	.7
Non-Hispanic White	40 (6.8)	23 (60)	17 (8.3)	
Other	29 (4.9)	18 (4.7)	11(5.3)	
BMI kg/m^{2**} mean (SD)				
All Patients	30.3 (9.5)	30.8 (10.2)	28.9 (8.3)	.14
BMI kg/m^{2**} no. (%)				
<30	24.8 (3.8)	25.0 (3.6)	24.5 (4.1)	.86
≥30	37.7 (10.1)	38.8 (10.9)	35.4 (8.7)	
Co-morbidities no. (%)				
Hypertension	467 (79.4)	298 (78.0)	169 (82.0)	.31
Diabetes	311 (52.9)	209 (54.7)	102 (49.5)	.22
Hyperlipidemia	205 (34.9)	135 (35.3)	70 (34.0)	.55
coronary artery disease	102 (17.3)	66 (17.3)	36 (17.5)	.54
CVD/Stroke	65 (11.1)	42 (11.0)	23 (11.2)	.23
COPD	47 (8.0)	27 (7.1)	20 (9.7)	.18
chronic kidney disease	79 (13.4)	52 (13.6)	27 (13.1)	.57
ESRD	77 (13.1)	53 (13.9)	24 (11.7)	.15
Asthma	45 (7.7)	32 (8.4)	13 (6.3)	.32
Malignant tumor	32 (5.4)	22 (5.8)	10 (4.9)	.44
Charlson's comorbidity index mean (SD)	2.0 (0.12)	2.0 (0.11)	2.0 (0.13)	.69
Symptoms/signs no. (%)				
Fever	505 (85.9)	318 (83.2)	187 (90.7)	<.01
Cough	450 (76.5)	303 (79.3)	147 (71.0)	.05
Dyspnea	400 (68.0)	264 (69.1)	136 (66.0)	.08
Chest Pain	206 (35.0)	141 (36.9)	65 (31.6)	.19
Respiratory illness	116 (19.7)	76 (19.9)	40 (19.4)	.61
Pneumonia	119 (20.2)	82 (21.5)	37 (18.0)	.31
Anemia	25 (4.3)	18 (4.7)	7 (3.4)	.45
Myalgia	179 (30.4)	111 (29.1)	66 (32)	.46
Diarrhea	192 (32.7)	124 (32.5)	68 (33)	.66
Outcome measures no. (%)				
ICU Admission	110 (18.7)	84 (22.0)	26 (12.6)	<.01**
Ventilator use	82 (13.9)	54 (14.1)	28 (13.6)	.47
Death	232 (39.5)	155 (40.6)	77 (37.4)	.45
Outcome measures mean (SD)				
Hospital length of stay	7.9 (9.1)	8.9 (9.3)	8.8 (8.6)	.98
Total ICU Days	9.5 (8.4)	8.3 (7.5)	10.7 (10.1)	.43

Abbreviations: BMI, body mass index; COVID-19, corona virus disease 2019; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; ESRD, end stage renal disease; ICU, intensive care unit; RCT-PCR, reverse transcription-polymerase chain reaction; mean (SD), mean (standard deviation); no. (%), number (percent); SUNY, State University New York.

*P-value significant at ≤.05;

**P-value significant at ≤.0125 level controlling for family wise error.

disease; and included length of hospital stay (when not used as the outcome); demographic variables, co-morbid conditions and presenting symptoms/signs (Table 2). Statistical analyses were performed using SAS Institute Inc. version 9.4.

RESULTS

Tables 1 shows the demographic and clinical characteristics of the 588 COVID-19 hospitalized patients. Of the 588 reverse transcription-polymerase chain reaction (RCT-PCR) confirmed COVID-19 positives, 35% self-reported being flu-vaccinated, 47.1% were women, 88.3% were black, 18.7% required ICU-admission, 13.9% required ventilator-use, and 39.5% died during in-hospital stay. The mean (SD) age was 68.4 (14.5) years, BMI was 30.3 (9.5) kg/m^2, and length of stay was 7.9 (9.1) days. Hypertension (79.4%), diabetes (52.9%) and hyperlipidemia (34.9%) were also the most common comorbidities. Fever (85.9%), cough (76.5%), and dyspnea (68.0%) were the three most common COVID-19 symptoms. Rates for both self-reported flu-vaccinated statuses (No vs Yes) did not significantly differ for ventilator-use {[54/382] vs [28/206], P = .47 and mortality {[155/382] vs [77/206], P = .45]} respectively. Mean [SD] for both hospital length of stay and total ICU days did not significantly differ for self-reported flu-vaccinated statuses (No vs Yes) {8.9 [9.3] vs 8.8 [8.6], P = .98 and {8.3 [7.5] vs 10.7 [10.1], P = .43, respectively}. Bivariate analysis showed that ICU admission rates differed significantly between self-reported flu-vaccinated statuses (No vs Yes) {[84/382] vs [26/206], OR: 1.95, 95%CI: 1.21-3.15, P <.001}, with adjusted analyses showing a significantly increased likelihood of ICU-admission among self-reported nonflu-vaccinated relative to self-reported flu-vaccinated patients (aOR: 1.88, 95%CI: 1.18-3.99, $P < .01$). Furthermore, stratified adjusted analyses by age and BMI respectively showed a significantly increased likelihood of requiring an ICU admission among self-reported non-flu-vaccinated relative to self-reported flu-vaccinated patients only for ages <65 (aOR: 4.16, 95%CI: 1.03-16.73), and non-obese patients (aOR: 2.61, 95%CI: 1.35-5.03) (Table 2).

DISCUSSION

In this sample of COVID-19 hospitalized patients in Brooklyn, during the first wave of the COVID-19 pandemic, mortality and ventilation rates were actually higher in non-flu-vaccinated patients compared to flu-vaccinated patients but the differences were not statistically significant. However, non-flu-vaccinated hospitalized patients were two times more likely to have required an ICU admission, relative to flu-vaccinated hospitalized patients after adjusting for pertinent confounders. Stratified analysis of this association showed effects significantly stronger and present for ages <65 and non-obese patients. Non-flu-vaccinated patients aged <65 and non-obese patients were four and approximately three times more likely to have required an ICU admission, relative to their flu-vaccinated

Table 2
Adjusted Odds Ratios for the association between Self-reported Flu vaccination (No vs Yes) and categorical outcome measures {RCT-PCR COVID-19 POSITIVES}

Outcome Variable	Crude Odds Ratios (95% CI)	*P-value*	‡Adjusted Odds Ratios (95% CI)	*P-value*
ICU Admission	1.95 (1.21-3.15)	<.01**	1.88 (1.18-3.99)	<.01**
Ventilator use	1.05 (0.64-1.71)	.85	0.94 (0.43-2.06)	.88
Death	1.14 (0.81-1.62)	.45	0.87 (0.47-1.62)	.67
Adjusted risk ratios for the association between self-reported flu vaccination (No vs Yes) and continuous outcome measures {RCT-PCR COVID-19 POSITIVES}				
Hospital length of stay	1.07 (0.42-1.72)	.81	0.84 (0.33-1.94)	.87
Total ICU Days	0.94 (0.36-2.52)	.79	0.72 (0.37-2.07)	.84
Adjusted odds ratios for the association between Self-reported Flu vaccination (No vs Yes) and categorical outcome measures stratified by Age and BMI				
RCT-PCR COVID-19 Positives {Ages <65 only}				
ICU admission	2.81 (1.23-6.45)	.01**	4.16 (1.03-16.73)	.04*
Ventilator use	1.46 (0.61-3.48)	.39	1.89 (0.53-6.77)	.33
Death	1.62 (0.78-3.37)	.20	0.80 (0.24-2.64)	.72
RCT-PCR COVID-19 Positives {Ages ≥65 only}				
ICU admission	1.57 (0.87-2.83)	.1321	2.03 (0.66-6.27)	.22
Ventilator use	0.88 (0.43-1.61)	.68	0.57 (0.20-1.61)	.29
Death	1.07 (0.70-1.62)	.76	1.03 (0.48-2.21)	.95
RCT-PCR COVID-19 Positives {BMI <30 only}				
ICU admission	2.32 (1.31-4.11)	<.01**	2.61 (1.35-5.03)	<.01**
Ventilator use	1.17 (0.66-2.06)	.61	1.21 (0.63-2.30)	.57
Death	1.23 (0.84-1.80)	.29	1.23 (0.79-1.91)	.35
RCT-PCR COVID-19 Positives {BMI ≥30 only}				
ICU admission	1.24 (0.49 - 3.12)	.65	1.12 (0.38-3.31)	.84
Ventilator use	0.74 (0.27 - 2.01)	.55	0.80 (0.27-2.39)	.69
Death	0.79 (0.33 - 1.86)	.58	0.71 (0.23-2.18)	.55
Adjusted risk ratios for the association between self-reported flu vaccination (No vs Yes) and continuous outcome measures stratified by age and BMI				
RCT-PCR COVID-19 Positives {Ages <65 only}				
Hospital length of stay	1.12 (0.47-2.77)	.76	1.00 (0.45-2.57)	.57
Total ICU Days	0.89 (0.41-3.37)	.84	1.01 (0.38-3.63)	.73
RCT-PCR COVID-19 Positives {Ages ≥65 only}				
Hospital length of stay	0.92 (0.34-2.51)	.86	0.89 (0.46-2.32)	.77
Total ICU Days	1.09 (0.41-2.77)	.64	1.02 (0.58-2.46)	.83
RCT-PCR COVID-19 Positives {BMI <30 only}				
Hospital length of stay	1.11 (0.58-2.64)	.41	1.03 (0.43-2.62)	.61
Total ICU Days	1.33 (0.76-3.91)	.49	1.23 (0.69-3.82)	.37
RCT-PCR COVID-19 Positives {BMI ≥30 only}				
Ventilator use	0.86 (0.39-2.33)	.55	1.01 (0.37-2.65)	.58
Death	0.93 (0.47-4.39)	.48	0.81 (0.33-4.28)	.45

Abbreviations: BMI, body mass index; COVID-19, corona virus disease 2019; ICU, intensive care unit; RCT-PCR, reverse transcription-polymerase chain reaction.
*P-value significant at ≤.05;
**P-value significant at ≤.0125 level;
‡Adjusted for the following covariates/potential confounders selected *a priori:* length of hospital stay; age, sex, race and body mass index (BMI); hypertension, diabetes, coronary artery disease, stroke, chronic kidney disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), end stage renal disease (ESRD), asthma, malignant tumor; fever, cough, dyspnea, chest pain, respiratory illness, pneumonia, anemia, myalgia, and diarrhea. Statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, North Carolina, USA).

hospitalized counterparts, respectively. Our findings suggest that the risk of non-obese and ages <65 patients requiring an ICU-admission due to COVID-19 may be reduced if they were flu-vaccinated. A recent study found that higher regional rates of flu-vaccinated adults >65 years old was associated with lower regional rates of COVID−19 deaths.[6] We did not find any association between flu-vaccination and hospital length of stay, total ICU days, mechanical ventilator use, and mortality perhaps due to the low prevalence of flu vaccination in this Brooklyn patient sample and in the US overall (36% vs 48%).[7] Possible explanations of this finding could be the well-documented protective effects of flu-vaccination for co-morbid conditions.[8-10] Flu vaccine behavior is a marker for patients' healthy behaviors and this could possibly explain the findings. It also could be because of an already primed innate immunity from flu-vaccination, especially in <65 year old and non-obese, that results in an effective rapid immunogenic response.[11] However, it seems that once a certain threshold is reached, possibly due to an overwhelming and immunosuppressive inflammatory/cytokine storm,[12] that necessitates an ICU-admission, the protective effect is no longer seen. Importantly, these findings add significant rationale supporting the public health promotion of flu-vaccination suggesting that this could mitigate the enormous demand for critical care that can overwhelm healthcare systems especially with possible escalating COVID-19 infections during the flu season and second wave.

Limitation

The key limitation of this study is the self-report assessment of flu-vaccination. Future studies should use objective measures of flu-vaccination and evaluate possible mechanisms explaining this association.

CONCLUSIONS

Our findings suggest that public health promotion of flu-vaccination may help mitigate the overwhelming demand for critical COVID-19 care that devastated underserved communities and under sourced healthcare systems, especially as we patiently wait for the large-scale availability of COVID-19 vaccines.

Data sharing

Deidentified patient data collected for the study, the statistical analysis plan and a data dictionary defining each field in the set, will be made available upon request. Data will be shared with investigator support after approval of the IRB and a signed data access agreement.

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