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Flu Vaccination Fails to Protect Against COVID-19 Infection; A Cross-sectional Study

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Abstract

Background: Vaccination is likely to be the final solution to stop the COVID-19 pandemic which has been considered as a global public health emergency. Influenza and coronavirus have previously demonstrated antigenic cross-reactivity.

Methods: This cross-sectional study was aimed to evaluate the transmission rate and the severity of coronavirus infection among health care workers with history of previous influenza vaccination. Subjects of the study were asked about their demographics, influenza vaccination history prior to pandemic, infection with COVID-19, and the severity indicators of the disease.

Results: Influenza vaccination has correlation neither with the prevalence of COVID-19 infection rate nor with the severity of the disease process among those who received flu vaccines and those who were not vaccinated. Vaccinated and unvaccinated subjects were equal in terms of sex, age, and comorbidities.

Asthma has not been demonstrated to contribute to the severity of the disease.

Conclusion: Influenza vaccination regardless of the evidence on its antigenic cross reactivity with coronavirus, is not associated with lesser involvement by or any contribution to the severity of the 2019 novel SARS-COV2 disease.

Keywords: Clinical staff, COVID-19, Influenza, SARS-Cov-2, Vaccine

Introduction

SARS-COV-2 or COVID-19 virus infection was initially identified in Wuhan City, China in December 2019 and became a Public Health Emergency of International Concern (PHEIC). To date, the burden brought by this pandemic has accounted to 25 million confirmed cases and 855 thousand deaths worldwide due to the rapid geographical transmission and severity of the disease (1). COVID-19 is associated with 2-14 days of incubation period and a life-threatening respiratory illness, especially for those elderly smoker patients with simultaneous comorbidities (2,3).

It appears that the final solution to cease the pandemic would be a safe and efficient vaccine. Many attempts have been made to find a vaccine and one instance is the non-replicating adenovirus type-5 (Ad5)-vectored COVID-19 vaccine which was introduced by Zhu FC *et al* and has shown appropriate safety and efficacy at the 2nd phase of the clinical trial (4).

Previous studies have implicated the cross-reactivities between corona and influenza viruses on their surface antigens (5-7) which are involved in viral invasion and spread and also the overt inflammatory response to virus (8). There has been also evidences of cross-immunity between coronavirus and BCG (9,10). Hemagglutinin-esterase is another similar component between corona and influenza viruses which mediates virus-cell attachment and membrane fusion (11). Hence, targeting this shared viral component by anti-influenza vaccine is expected to prevent from cellular invasion by the coronavirus.

Influenza vaccination among clinical staff in Iran has been reported to have a coverage rate of 6% which is higher than national statistics among general population (12). Furthermore, the higher rate of clinical staff's exposure to confirmed cases of COVID-19 makes them an appropriate subject for this study.

This study aimed to assess whether previous history of influenza vaccination is effective in both decreasing the rate of the infection by Coronavirus and also enhancing the outcomes of the disease.

Materials and Methods

Clinical staff enrolled in this study were requested to fill out a questionnaire. Subjects were asked regarding their demographics, influenza vaccination history (during the previous year and prior to testing positive for COVID-19), medical history of comorbidities (including asthma, Diabetes Mellitus (DM), Hypertension (HTN), Cardiovascular Diseases (CVD) and immunodeficiencies), symptoms they experienced (respiratory and non-respiratory involvement), COVID-19 PCR or chest CT-scan results and in case of confirmed disease, the severity parameters such as home care, hospital admission, ICU admission, intubation, oxygen saturation, arterial blood gas results and disease duration. The subjects were segregated into three categories: mild, moderate and severe. Subjects who experienced mild clinical symptoms, those tested positive but were asymptomatic and the individuals confirmed positive through chest CT-scan but were treated at home with conservative measures were considered mild cases. Severe cases were those who were admitted to the hospital and in the Intensive Care Unit (ICU), respiratory distress with respiratory rate above 30, Oxygenation Index (OI) (calculated by partial pressure of oxygen (O_2) divided by Fraction of inspired Oxygen (FiO_2) less than 300 *mmHg* and those with oxygen saturation less than 93%. The subjects whose clinical manifestation fell between these spectrums were considered moderate cases. This study was approved by the Research Committee of Iran University of Medical Sciences (IUMS) with a code number: IR. IUMS. REC.1399.414.

Analysis

Statistics of quantitative data were presented by means and variances while qualitative data were reported by their frequencies. Chi-square test was utilized to assess dependence between categorical variables. Parametric data were compared using student T-test and Mann-Whitney U Test. p-value equal or less than 0.05 was considered statistically significant. Analyzes were performed using IBM SPSS version 22.

Results

Of the 510 healthcare staff that participated in the study, 33 were infected by SARS-COV2 accounting to a prevalence rate of 6.47 % among our hospital staff while 132 (25.9%) of the participants had a history of influenza vaccination. 176 were males and 334 were females and the mean age of the participants was

28.94 with a SD deviation of 5.87 years. Furthermore, the subjects of the study were equal in terms of the basic variables such as age and sex.

Individuals in vaccinated and unvaccinated groups were not statistically significant with regard frequency on gender categories (p=0.108) and also were not significantly different in terms of age (p=0.441). The prevalence and duration of comorbidities such as DM, HTN, asthma, Cerebrovascular Diseases (CVD), and immunodeficiencies were not statistically significant (p-value >0.05) (Tables 1 and 2) between vaccinated and unvaccinated participants. Therefore, the samples in two groups were equal in their baseline characteristics.

Prior influenza vaccination was not significantly associated with prevalence rate of infection by COVID-19 (p-value 0.067; Chi-square) (Table 3). Moreover, there was no significant difference in severity of the disease between vaccinated and unvaccinated patients with COVID-19 (p-value = 0.101; Chi-square) (Table 4).

163 of the participants have expressed that they experienced the COVID-19 symptoms during the past 6 months and 57 of these participants subjected themselves to COVID-19 test and this accounted to a 35.0% testing rate among our hospital staff.

Table 1. descriptive of qualitative statistics and comparison between vaccinated and unvaccinated individuals

Variable (N)		All cases	Influenza vaccination		Test	p-value
			Vaccinated	Unvaccinated		
Sex	Male	176	38	138	Chi-square	0.108
	Female	334	94	240		
Asthma	Positive	32	7	25	Chi-square	0.593
	Negative	478	125	353		
HTN	Positive	12	2	10	Fisher's Exact	0.740
	Negative	498	130	368		
CVD	Positive	11	3	8	Fisher's Exact	1.000
	Negative	499	129	370		
Immunodeficiency	Positive	11	2	9	Fisher's Exact	0.737
	Negative	499	130	369		
DM	Positive	5	1	4	Fisher's Exact	1.000
	Negative	505	131	374		

DM: Diabetes mellitus, HTN: hypertension, CVD: cardiovascular diseases

Table 2. descriptive (Mean ± SD)/(Q1, Median, Q3) of quantitative statistics and comparison between vaccinated and unvaccinated individuals

Variable (N)	All cases	Influenza vaccination		Test	p-value
		Vaccinated	Unvaccinated		
Age	28.94 ± 5.87	28.60 ± 4.69	29.06 ± 6.24	Mann-Whitney U Test	0.441
DD in Asthmatics	(0.0, 3.5, 17.0)	12.00 ± 8.29	12.00 ± 7.69	T-test	1.000
DD in HTN cases	(2.0, 4.5, 8.0)	6.10 ± 6.04	(1.75, 4.5, 9.75)	T-test	0.726
DD in CVD cases	(2.0, 11.5, 27.25)	11.33 ± 14.46	14.86 ± 12.79	T-test	0.710
DD in Immunodeficiency cases	5.73 ± 3.95	8.00 ± 9.89	5.22 ± 2.38	T-test	0.760

Table 3. History of vaccination against influenza and involvement by COVID-19 disease

Influenza vaccination / COVID-19	Vaccinated	Unvaccinated	Sum
Healthy	13	20	33
Diseased	119	358	477
SUM	132	378	510

p-value: 0.067 Chi-square test

Table 4. History of vaccination against influenza and severity of COVID-19 disease

Influenza vaccination / Severity	Vaccinated	Unvaccinated	Sum
Mild	4	12	16
Moderate to Severe	9	8	17
SUM	13	20	33

p-value: 0.067 Chi-square test

Table 5. Descriptive of COVID-19 involvement statistics

Variable		All cases	Influenza vaccination		Test	p-value
			Vaccinated	Unvaccinated		
COVID-19 signs	Positive	163	47	116	Chi-square	0.297
	Negative	347	85	262		
COVID-19 test	Performed	114	N/A	N/A	N/A	N/A
	Not performed	396	N/A	N/A		
Manifestations	Cough	40	11	29	N/A	
	Dyspnea	11	4	7		
	Fever	43	9	34		
	Musculoskeletal symptoms	57	16	41		
	Anosmia	28	8	20		
	GI symptoms	26	5	21		
	Asymptomatic	7	1	6		
COVID ward Admission (33)	Positive	1	0	1	Fisher's Exact	1.000
	Negative	32	13	19		
ICU admission (33)	Positive	2	2	0	Fisher's Exact	0.148
	Negative	31	11	20		
Intubation (33)	Positive	2	1	1	Fisher's Exact	1.000
	Negative	31	12	19		
Overall disease duration (33)		(9.50, 14.00, 20.00)	22.08 ± 11.68	12.53 ± 6.29	T-test	0.020
SaO2 (33)		(93.00, 94.00, 97.00)	(91.25, 94.00, 96.50)	95.00 ± 2.53	T-test	0.149

Experiencing the COVID-19 symptoms regardless of the test result was not statistically significant between the vaccinated and unvaccinated participants (p-value = 297) (Table 5). Results of the 114 PCRs or chest CT-scans revealed that 33 of the participants were positive of COVID-19. The most prevalent manifestations of the disease were musculoskeletal pain, fever, and cough. Disease duration was significantly higher on participants with history of influenza vaccination (p-value = 0.020) (Table 5). One participant, positive with COVID-19 without any history of influenza vaccine was admitted to a general ward while 2 of the participants infected with the virus with previous flu vaccination were admitted to the ICU and were intubated. There was no significant difference noted on the oxygen saturation level (SaO_2) between the vaccinated and unvaccinated participants (p-value=0.149) (Table 5). Furthermore, we observed no significant difference in severity of the disease among asthmatic and non-asthmatic patients (p-value=1.000, Fischer exact test).

Discussion

In the present study, no significant correlation was found between influenza vaccination prior to the pandemic to the rate of infectivity and the severity of the disease caused by COVID-19.

Nucleocapsid protein (N protein) and spike protein (S protein) are two major surface components of Coronavirus which are involved in its pathogenesis (8). Both proteins are also present on the surface of influenza virus (13,14). Also, the pathogenesis mechanism of COVID-19 is similar to that of Influenza virus (15). Since N protein is associated with viral assembly and budding and S protein is involved in inflammatory reactions by inducing the host immune response, influenza vaccination was expected to decrease both proliferation and the inflammatory response caused by coronavirus. Hemagglutinin-Esterase (HEs) is another shared viral capsid component of influenza and coronaviruses which mediated host cell membrane invasion and fusion (11).

Regardless of the mentioned shared antigenic components between coronavirus and influenza, the novel SARS-COV2 (COVID-19) virus is not identical in its antigenic components with conventional coronavirus which has made it more pathogenic and consistent with a more severe life-threatening disease. S glycoprotein on the surface of SARS-COV2 has 12.8% antigenic variety with SARS-COV, with this in mind that the spike protein accounts for immune response against the virus (16) There are also additional structural loops on receptor binding (S1) and fusion (S2) domains of the spike protein on SARS-COV2 (17).

The results suggest that previous influenza vaccination has correlation neither with COVID-19 infection nor with the severity of novel SARS-COV2 (COVID-19) disease regardless of the previously reported antigenic similarity between influenza and coronaviruses that could be explained by the antigenic variety of novel 2019 coronavirus from its conventional form which accounts for its higher pathogenicity and severity. However, there has been studies indicating a protective role of prior Influenza vaccination for decreasing the severity of COVID-19 infection and improving the patients' outcomes at 30, 60, 90, and 120 days (18). Previous studies also reported a decreased rate of infection and improved severity of COVID-19 infections in association with prior Influenza vaccination (19,20).

The equality of the baseline characteristics such as demographic parameters and the presence of comorbidities among the vaccinated and unvaccinated participants were ensured and the confounding biases were addressed.

Also, results of the study indicated that there is no significant difference in the severity of the disease between asthmatics and non-asthmatics which is compatible with the literature (21) and this could be explained by the fact that eosinophils have a prominent role in immune response against viral illnesses such as influenza virus as a determinant of the severity (21).

Conclusion

Influenza vaccination is not of potential to prevent or reduce the severity of COVID-19. It neither reduces the rate of infection nor decreases the severity of the 2019 novel SARS-COV2 disease.

Ethics approval

This study was approved by Ethics Committee of

Vice Chancellor for Research & Technology, of Iran University of Medical Sciences (IUMS) by code number: IR.IUMS.REC.1399.414. All patients and control subjects signed the informed consent.

Consent for publication

Informed consent were obtained from all patients whom clinical data were reported in this article to participate in the study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of Interest

Authors declare no financial or non-financial conflict of interest in subject matters of this study.

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