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Original article

Could seasonal influenza virus vaccine reduce the risk and severity of SARS-CoV-2 infection? The first Egyptian experience

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ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) is a serious public health issue worldwide. A safe and effective COVID-19 vaccine is a crucial measure to control the current pandemic. Many efforts have been devoted to the development of COVID-19 vaccines. However, the mistrust of COVID-19 vaccines has a negative impact on the willingness to receive the vaccine. Because of the cross-reactivity between influenza and coronaviruses, influenza immunization may be useful in preventing COVID-19 infection. **Aim:** Assessing the association between seasonal influenza virus vaccination and the acquisition and severity of COVID-19 in Egyptian individuals. **Methods:** This was an observational retrospective cohort study that included sixty participants who were classified into two equal groups based on their influenza virus vaccination status (vaccinated or not). The primary outcome was the susceptibility to COVID-19 infection and the secondary outcome was the severity of COVID-19 symptoms. **Results:** Among the unvaccinated group (n=17/30, 56.7%) had a COVID-19 infection compared to (n=8/30, 26.7%) in the vaccinated group (*p* value =0.02). The calculated OR was 3.6. Regarding the severity of COVID-19 infection, 11 individuals in the unvaccinated group (n=11/17, 64.7%) developed mild infection, (n=5/17, 29.4%) got moderate illness and (n=1/17, 5.9%) developed severe disease whereas (n=6/8, 75%) individuals in the vaccinated group had mild infection and (n=2/8, 25%) developed illness of moderate intensity (*p* value =0.7). **Conclusion:** Seasonal influenza virus vaccine seems to have a protective role against the acquisition of COVID-19 infection but does not reduce the severity of the disease.

Introduction

Coronavirus Disease 2019 (COVID-19) is an emerging infectious disease caused by the novel Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) virus. The clinical manifestations may be asymptomatic or progress to severe disease [1]. A linkage between a robust immune response across diverse cell types and COVID-19 recovery has been reported. These findings have also been described in the context of influenza virus infection [2].

A new theory suggests that the resulting immunity against influenza virus infection may help to boost immunity to SARS-CoV-2. This theory is based on the analogy of the quality of immunity against both viruses as well as the cross-reactivity of immunity due to structural similarities [3]. Furthermore, the anti-flu immune response can also enhance the protection against other viral diseases such as SARS-CoV-2 in a non-specific way [4]. As a result, those who have already been vaccinated against influenza virus infection may only have a

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minor chance of catching or developing severe COVID-19 infection. Furthermore, in vitro studies showed that the quadrivalent inactivated influenza virus vaccine was able to induce an improved cytokine response after the stimulation of immune cells with SARS-CoV-2 [5].

COVID-19 vaccines are being developed by scientists all around the world. Vaccine development has traditionally taken years, if not decades. For example, polio vaccinations took 40 years to develop, but Ebola vaccines required only 5 years. In fact, most vaccinations take an average of 15 years to develop [6,7]. The race is on to discover and license COVID-19 vaccines. However, vaccine development, on the other hand, entails a series of procedures that must be completed in a systematic manner. Attempts to speed up vaccine development may have negative consequences for vaccine research ethics [8]. Given the safety of the seasonal influenza virus vaccine, we carried out this study to investigate the possible protective role of the seasonal influenza virus vaccine against COVID-19 infection in Egyptian individuals.

Methods

2.1 Study design & setting

This was an observational retrospective cohort study that was carried out in Egypt during August 2021. An invitation for an online interview was announced to individuals who received the seasonal influenza virus vaccine (season 2020/2021) to participate. Those who accepted to participate were retrospectively asked if they developed COVID-19 infection following the seasonal flu vaccination at any anytime within two weeks post-immunization till the time of the study. Those who answered yes were asked to mention the clinical symptoms they experienced and to share their SARS-CoV-2 Real-Time Polymerase Chain Reaction (RT-PCR) on nasopharyngeal swabs and chest Computed Tomography (CT) for confirmation of their COVID-19 infection.

The same procedure was repeated for an equal randomized group of volunteers who did not receive seasonal influenza vaccination for the season 2020/2021. They were retrospectively followed for the incidence of COVID-19 infection between October 2020 till the time of the study. Diagnosis of their COVID-19 infection was also confirmed based on clinical, laboratory criteria including RT-PCR on nasopharyngeal swabs, and radiological criteria based on chest CT.

2.2 Variable of interest and study outcomes

The independent variable of interest was the seasonal influenza virus vaccination status. The primary outcome was the incidence of COVID-19 infection and the secondary outcome was the severity of COVID-19 infection in both groups. The severity of COVID-19 infection was determined according to the criteria provided by the Egyptian Ministry of Health management protocol for COVID-19 [9]. Patients were defined to have a mild infection if they had clinical symptoms but no radiological signs for pneumonia. Patients with radiological evidence of pneumonia associated with clinical symptoms were classified as moderate cases. Severe cases were diagnosed by the presence of clinical symptoms, radiological evidence of pneumonia, and resting blood oxygen saturation <92%.

2.3 Study sample

The sample size was comprehensive and included all the individuals who accepted to participate (n=60) divided into two equal groups (1) an influenza-vaccinated group (n=30) and (2) a non-influenza-vaccinated group (n=30). Inclusion criteria: (1) age ≥ 18 years (2) gender: male or female. Exclusion criteria: (1) pregnancy (2) children (3) individuals who received anti-SARS-CoV-2 vaccination.

2.4 Type of the seasonal influenza vaccine

Influenza vaccinated group included individuals who received one dose (0.5 ml) of either the commercially available inactivated trivalent influenza vaccine (VAXIGRIP; SBL vaccine AB, Stockholm, Sweden) or inactivated quadrivalent influenza vaccine (INFLUVAC, ABBOTT) during October-December 2020.

2.5 Ethical approval

The Zagazig University Institutional Review Board (IRB) approved the study protocol (ZU-IRB NO. 9621) which also followed the principles of the Helsinki Declaration. All participants were asked to sign written informed consent.

Statistical analysis

Statistical Package for Service Solution (IBM SPSS version 22) was used for data management. Because data did not follow the normal distribution, median and inter-quartile range (IQR) were used for continuous variables. Mann–Whitney-U test was used to compare continuous variables between the two independent groups. For

categorical variables, we employed a chi-square test. The Odds Ratio (OR) was computed. Individuals with and without influenza vaccination were compared on the probabilities of COVID-19 infection and severity using the unadjusted logistic regression models. In a forced inclusion model, logistic regression analyses were adjusted for possible confounders such as gender, age, hypertension, diabetes, chronic obstructive pulmonary disease, coronary artery disease, and heart failure. *P*-values ≤0.05 were considered statistically significant.

Results

4.1 Characteristics of the studied participants

Baseline demographic and clinical characteristics of the studied groups are shown in **table (I)**. The median age for the vaccinated individuals was 46.5 (range: 39-62) while, for the unvaccinated group, it was 42 (range: 38-59), *p* value= 0.5. Female compromised (n=15, 50%) in the vaccinated group and (n=21, 70%) in the unvaccinated groups, *p* value= 0.1. There was no statistically significant difference between both groups as regard co-morbidities.

4.2 Susceptibility and severity of COVID-19 infection among both groups

Susceptibility and severity of COVID-19 infection among both groups are shown in **table (II).** Among individuals who did not receive an influenza vaccination, (n=17/30; 56.7%) had a COVID-19 infection while (n=13/30; 43.3%) did not. On the other hand, those who received an influenza vaccination had a COVID-19 infection rate of (n=8/30; 26.7%) (*p* value =0.02). Thus, influenza vaccination was associated with a significant reduction of the risk of catching COVID-19 infection.

Concerning the severity of COVID-19 infection among the studied cohort, 6 individuals in the vaccinated group (n=6/8) had a mild infection, while 2 (n=2/8) developed a moderate illness. On the other hand, 11 individuals in the unvaccinated group (n=11/17) developed a mild infection, 5 (n=5/17) got a moderate illness and 1 (n=1/17) developed a severe disease. The significance level between both groups was 0.7. Thus, we could not document that the influenza vaccination could attenuate the severity of COVID-19.

4.3 Predictors of developing COVID-19 infection

Univariate logistic regression for predictors of developing COVID-19 infection is shown in **table (III).** The unvaccinated group had a 3.6 higher risk of developing COVID-19 infection as compared to the vaccinated group, but, we could not document age, gender, or comorbidities as predictors of developing COVID-19 infection.

4.4 Predictors of developing severe COVID-19 infection

Univariate logistic regression for predictors of developing severe COVID-19 infection is shown in **table (IV).** We could not document age, gender, comorbidities, or non-influenza virus vaccination as predictors of developing severe COVID-19.

Table I. Baseline demographic and clinical characteristics of the studied groups.

Variable	Vaccinated (N=30)	Unvaccinated (N=30)	*P* value
Age (years)			
Median (IQR)	46.5 (39-62)	42 (38-59)	0.5
Gender			
Male	15 (50%)	9 (30%)	0.1
Female	15 (50%)	21 (70%)	
Co-morbidities			
Hypertension	10 (33.3%)	6 (20%)	0.2
Diabetes	6 (20%)	4 (13.3%)	0.7
IHD	2 (6.67%)	0 (0%)	0.5
Bronchial Asthma	3 (10%)	0 (0%)	0.2
Others			
• Hypercholesterolemia	2 (6.67)	-	
• FMF	1 (3.3%)	-	
• Chronic Leukemia	1 (3.3%)	-	
• Rheumatoid Arthritis	1 (3.3%)	-	
• Atrial Fibrillation	-	2 (6.67%)	
• Pituitary Adenoma	-	1 (3.3%)	
• Renal impairment	-	1 (3.3%)	

Table II. Susceptibility to and severity of COVID-19 infection among both groups.

Susceptibility to COVID-19	**Vaccinated (N=30)**	**Unvaccinated (N=30)**	***P* value**
Positive COVID-19			
Yes	8 (26.67%)	17 (56.7%)	0.02*
No	22 (73.3%)	13 (43.3%)	
Severity of COVID-19	**Vaccinated (N=8)**	**Unvaccinated (N=17)**	***P* value**
Mild	6 (75%)	11 (64.7%)	0.7
Moderate	2 (25 %%)	5 (29.4%)	
Severe	0 (0%)	1 (5.9%)	

**p value is statistically significant.*

Table III. Univariate logistic regression for predictors of developing COVID-19 infection (n=25).

Variable	**OR (95% CI)**	***P* value**
Age	1.01 (0.97-1.04)	0.7
Gender (Female)	1.33 (0.46-3.83)	0.6
Co-morbidities		
HTN	0.55 (0.16-1.83)	0.3
DM	0.55 (0.13-2.36)	0.4
Unvaccinated Group	3.6 (0.9-8.2)	0.02*

**P value is statistically significant.*

Table IV. Univariate logistic regression for predictors of developing severe COVID-19 infection.

Variable	**OR (95% CI)**	***P* value**
Age	1.05 (0.99-1.12)	0.1
Gender (Female)	2.1 (0.32-13.61)	0.4
Co-morbidities		
HTN	4.5 (0.58-35.1)	0.2
DM	5.3 (0.41-70.2)	0.2
Unvaccinated Group	1.64 (0.1-82.3)	0.6

Discussion

COVID-19 was first identified in Wuhan, China, in December 2019 and was then declared a global public health emergency [10]. Despite that COVID-19 vaccines have been temporarily licensed for emergency use, their efficiency and adverse effects are still being debated [11]. Prior seasonal influenza vaccination may provide protection against COVID-19, according to previous studies [12,13]. As a result, we conducted this research to assess the relationship between seasonal influenza vaccination and COVID-19 susceptibility and severity. Up to our knowledge, this is the first study to assess this topic in the Egyptian citizens.

In the current study, we found that those who did not receive the seasonal influenza virus immunization had a 3.6 higher chance of testing positive for COVID-19. However, we could not prove that the seasonal influenza vaccine could attenuate the severity of COVID-19. In accordance

with our findings, **Conlon et al.** found a probable link between influenza vaccination and a lower incidence of COVID-19 infection in American participants [14]. In addition, Italian researchers found that receiving the influenza vaccine was linked to a decreased risk of contracting SARS-CoV-2 infection [15]. Similarly, Turkish research by **Erismis et al.** found that influenza vaccination may have a protective impact, even if low,on susceptibility to COVID-19 infection [16].

Along the same line, **Noale et al.** studied the relationship between influenza and pneumococcal vaccines and COVID-19 infection and found that anti-pneumococcal and, to a lesser degree, influenza vaccinations were linked to a decreased risk of COVID-19 infection [17]. **Huang et al.** observed that the influenza vaccination may provide a marginal protection against COVID-19 infection [18]. Moreover, a systematic review and meta-analysis revealed that influenza vaccination was associated with a lower risk of SARS-CoV-2 infection [19].

Although we were unable to find statistically significant evidence that the influenza vaccine could reduce COVID-19 severity, a Brazilian study of over 92,000 COVID-19 patients found that those who received the influenza vaccine had a 17% lower risk of death, an 8% lower risk of ICU admission, and an 18% lower risk of requiring invasive respiratory support [20]. Likewise, two epidemiologic investigations, one in Italy and the other in the United States, reported a correlation between increased influenza vaccination rates in people aged over 65 and lower rates of COVID-19 mortality [14, 21]. Another noteworthy Italian study revealed that the regional influenza vaccination coverage was inversely related to SARS-CoV-2 spread and clinical outcomes [22].

On the contrary, a prospective cohort study of Spanish HCWs found that influenza vaccination had no significant effect on reducing the risk of SARS-CoV-2 infection, and that the development of particular SARS-CoV-2 vaccines is necessary [23]. Furthermore, several researches suggested that those who had influenza vaccine had a higher risk of coronavirus infection. However, a systematic review of the association between seasonal influenza vaccination and the risk of SARS-CoV-2 infection found that none of the included studies (n = 12) reported a significant increase in the risk of infection, illness severity, or lethality, and some found significantly inverse associations. As a result, their findings support influenza vaccine campaigns [24].

Despite the fact it is not specific to the virus, cross-reactivity, cross-protection, and immune stimulation are three mechanisms that might explain the potential protective role of influenza vaccination against COVID-19 [25,26]. Surprisingly, several studies proved the ability of non-COVID-19 vaccines, such as the Bacillus Calmette-Guerin (BCG); polio; Haemophilus Influenza type B (HIB); Measles-Mumps-Rubella (MMR); varicella; Pneumococcal Conjugate (PCV13); hepatitis A; or hepatitis B vaccination to reduce SARS-CoV-2 infection rates [27-29].

From other perspectives, many studies have shown that other social variables may contribute to the vaccinated groups' lower risk of SARS-CoV-2 infection. For instance, individuals who choose to be vaccinated may have higher levels of education, awareness, and positive attitude that may be contributed to greater compliance with COVID-19 preventive measures such as hygiene/disinfection practices, physical distance, and the use of personal protective equipment [30]. Despite the fact that we did not incorporate the educational level in our statistical analysis, we noted that the individuals in the unvaccinated group are likewise highly educated.

Regarding influenza vaccine side effects, influenza vaccines are very safe; common adverse reactions may include local (e.g., injection site), systemic (e.g., fever, chills, malaise, myalgia), or hypersensitivity reactions [31]. None of our patients (0/30, 0%) developed local or severe systematic allergic reactions in form of respiratory distress or hypotension. Only one individual (1/30, 3.3%) developed constitutional flu like symptoms after vaccine administration. In addition, Gillian Bare Syndrome (GBS) which is reported to be the most serious adverse effects of influenza vaccine is documented to be as low as 1-3 cases per million [32].

Implications of the study: Individuals who are hesitant to receive COVID-19 vaccine may benefit from seasonal influenza virus vaccination due to the potential preventive impact of influenza vaccination against susceptibility to COVID-19 infection.

Limitation of the study: the study is limited by the small sample size and the retrospective design. Future prospective studies on a larger scale are required.

Conclusion: Seasonal influenza virus vaccination could contribute to significant reduction in the likelihood of developing COVID-19. However, it does not attenuate the COVID-19 severity.

Authors' contribution

Dina M. Ali is the principle investigator responsible for the whole work including concept, study design, acquisition of data, analysis and interpretation of data, writing the draft and critical revision of the manuscript. Khaled Raafat is a co-author responsible for critical revision of the manuscript for the intellectual content.

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Availability of data: The data are available from the corresponding author upon reasonable request.

List of abbreviations

BCG vaccine: Bacillus Calmette-Guerin vaccine, **COVID-19:** Coronavirus Disease 2019, **FMF:** Familial Mediterranean Fever, **GBS:** Guillain-Barré Syndrome, **HCWs:** Healthcare Workers, **HIB vaccine:** Haemophilus Influenza type B vaccine, **IHD:** Ischemic Heart Disease, **MMR vaccine:** Measles- Mumps-Rubella vaccine, **PCV vaccine:** Pneumococcal Conjugate Vaccine, **SARS-CoV-2:** Severe Acute Respiratory Syndrome- Coronavirus 2.

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