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The role of influenza vaccination in the COVID-19 infection: Impact on incidence and severity in Iraq

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ABSTRACT

Influenza vaccine was found to have cross-protective effects against heterologous illnesses, so the role of the influenza vaccination in COVID-19 infection is examined. A total of 1475 participants were separated into 2 groups: 194 individuals who got the influenza vaccination and 1,281 that did not. A comparison of positive COVID-19 testing was the primary outcome. From the two groups, 52 patients who got the influenza vaccination and 50 patients who did not get the vaccination were selected to predict the severity of the COVID-19 infection. The results showed that 13.15% of the participants received the influenza vaccine and no significant difference in the COVID-19 infection rates between the two groups was noted (odds ratio = 1.20, 95% CI = 0.890–1.630, p-value ≤ 0.05). In the vaccinated group, outcomes determined a nonsignificant decrease in the infected odds compared to noninfected, while a significant decrease was shown in the unvaccinated group. Finally, only 1 out of 52 patients (1.9%) in the vaccinated group required oxygen therapy or hospitalization versus 9 out of 50 patients (18%) in the unvaccinated group (odds ratio = 0.08, 95% CI = 0.01–0.7, p-value ≤ 0.05). Influenza vaccination could be linked to better clinical outcomes and a lower COVID-19 severity score, without significant effect on the infection rate.

INTRODUCTION

In January 2020, the severe acute respiratory syndrome coronavirus (SARS-CoV-2) was identified as the source of a pneumonia outbreak in Wuhan, and it quickly spread throughout China (Pascarella *et al.*, 2020). Notably, the highest morbidity–mortality of COVID-19 was observed among the elderly (Wu and McGoogan, 2020). COVID-19 causes a wide variety of symptoms, from mild (asymptomatic) to severe sickness and death. The most frequent symptoms are cough, fever, and shortness of breath (Lovato *et al.*, 2020). Clinical signs, viral genome detection by reverse transcription polymerase chain reaction, CT scan or chest X-ray, serological blood tests, and a few additional laboratory procedures are used to diagnose COVID-19 (Paranjpe *et al.*, 2020; Zhu *et al.*, 2020). A large nonstructural polyprotein (ORF1a/b) is encoded by the SARS-CoV-2 genome which is split by proteolytic activity into 15/16 proteins, 5 accessory proteins, and 4 structural proteins (Chan *et al.*, 2020; Ramaiah and Arumugaswami, 2020; Wu *et al.*, 2020). In the United States, influenza and other etiologies of pneumonia are considered the eighth cause of death. In addition, many respiratory viruses have been identified as common pathogens that infect hospitalized patients with community-acquired pneumonia (Jain *et al.*, 2015). Although influenza and COVID-19 possess similar signs and symptoms, huge causalities have been reported due to the novel COVID-19 infection. In some circumstances, the coinfections, including both the infections, can have some serious consequences or result in death (Hashemi *et al.*, 2020; Ma *et al.*, 2020). Unfortunately, both COVID-19 and seasonal influenza individually carry significant risks for elders and those having chronic comorbidities (Kostas *et al.*, 2020; Petrilli *et al.*, 2020). Nonspecific immunity caused by spontaneous influenza infection may reduce the risk of infection

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with other respiratory viruses, while the influenza vaccine protects against influenza infection. Not being infected with influenza, as a result of the vaccine, may lead to an increase in the incidence of other respiratory diseases, according to the so-called phenomenon of viral interference, due to the lack of specific immunity acquired from spontaneous infection (Cowling *et al.*, 2012; Cowling and Nishiura, 2012; Feng *et al.*; Suzuki *et al.*, 2014). Importantly, limited evidence supports the hypothesis that the virus interference process may be associated with the influenza vaccine (Cowling *et al.*, 2012; Rikin and Stockwell, 2018). On the other hand, the influenza vaccination may boost influenza immunity at the expense of SARS-CoV-2 immunity due to some unknown biological mechanism for the noninfluenza respiratory virus (Cowling *et al.*, 2012). Many other studies do not show the correlation between increased respiratory virus risk and influenza vaccination (Cowling and Nishiura, 2012; Sundaram *et al.*, 2013). The influenza vaccine, on the other hand, was found to have cross-protective effects against heterologous illnesses. The long-term enhancement of innate immunity (trained immunity) was the underlying mechanism. Several epidemiological research studies have shown that influenza vaccination and COVID-19 have a cross-protective impact during the current epidemic. However, the mechanism responsible for this effect is undetermined (Debisarun *et al.*, 2020). Previous studies have also found a link between influenza vaccination and COVID-19-related mortality, which might be attributable to heterologous immunity or alterations in innate immunity. Heterologous immunity can cause immunizations to have nonspecific effects that impact other illnesses and disorders, such as boosting the vaccine's protective impact (Agrawal, 2019; Goodridge *et al.*, 2016). Even with the broad use of influenza vaccines, information about the role of the influenza vaccine on the outcome of COVID-19 and other infections is contradictory. The current study intends to investigate if there is a link between influenza vaccination and the incidence of COVID-19 infection and illness severity; nevertheless, a negative link was predicted.

PATIENTS AND METHODS

People who are working in the Iraqi healthcare sector and some medical students were selected as the sample population for the study. It involved physicians, dentists, pharmacists, and medical faculties, including students, who were previously cured of COVID-19 infections during the last few weeks. Because no electronic data about the COVID-19 patients were available in Iraqi hospitals and special centers for COVID-19 management, we depended on the questionnaire to get information from the participants. A total of 1,476 subjects were included in the current study. The age of the participants who were included in the study ranged between 20 and 55 years. The participants was divided into two main groups; group one included 194 participants who had received the influenza vaccination during the previous flu season and group two included 1,281 participants who had not received the influenza vaccine. The primary outcome of interest was COVID-19 incidence (diagnosed by nasopharyngeal swab), with rates compared between the first and second groups of patients, depending on vaccination status. To compare the effect of the influenza vaccine on the severity of COVID-19 infection, 102 patients from the whole sample study were selected: from group one, 52 patients who had taken the influenza vaccine compared

with 50 patients from group two who did not receive the influenza vaccine. They were chosen because they were recently cured of COVID-19 infection and were very cooperative and accessible to get more accurate information about the severity of the infection. The clinical outcomes, including hypoxia [who have saturation of oxygen (SpO_2) <90% on room air measured by a pulse oximeter on the finger by clinician 2–3 times a day], depended on the WHO definition and the need for hospitalization or mechanical ventilation. All the participants who had been positive for COVID-19 were completely cured at the time of the study and nasopharyngeal swabs had been negative. The current study tried to evaluate to what extent receiving the influenza vaccine would affect the COVID-19 infection rate and severity.

Statistical analysis

Chi-squared test was used to measure *p*-value; *Z*-test was used to compare the significant differences between the percentage of different groups; odds ratio was used to determine the effect of influenza vaccination on the COVID-19 infection rate and severity between the study groups. A two-sided *p*-value ≤ 0.05 was used to indicate significance.

RESULTS

The results showed that there was a high percentage (86.8%) of medical staff and medical students who had not received the influenza vaccine compared to a very low percentage (13.15%) of subjects from the same population who received the vaccine (Fig. 1).

Comparing the percentage of COVID-19 patients in the vaccinated group with the unvaccinated group did not show statistical significance (*p*-value > 0.05) (Fig. 2).

The findings also revealed that there was no statistically significant difference in COVID-19 infection rates between the vaccinated and unvaccinated groups, and that COVID-19 incidence was nonsignificantly higher in patients who got the influenza vaccination compared to those who did not (odds ratio = 1.20, 95% CI = 0.890–1.630, *p*-value > 0.05) (Fig. 3 and Table 1).

Within the influenza vaccinated group, the COVID-19 patients were nonsignificantly lower than the noninfected odds, while within the unvaccinated group, the COVID-19 patients were significantly lower than the noninfected odds (Fig. 3).

Interestingly, the outcome of the current study showed no significant association between gender and influenza vaccination status on the percentages of COVID-19 incidence (odds ratio = 1.294, 95% CI = 0.837–2.001, *p*-value > 0.05). A significant (*p* < 0.05) decrease had been seen only in the odds of male patients compared to females in the unvaccinated group (Fig. 4).

Importantly, the results determined that hypoxia and need for hospitalization were significantly less among influenza vaccinated patients [1 out of 52 patients (1.9%)] in comparison with unvaccinated patients [9 out of 50 patients (18%)] (odds ratio = 0.08, 95% CI = 0.01–0.7, *p*-value < 0.05) (Fig. 5).

DISCUSSION

The medical staff and students are the subjects of the present study and have been chosen as they represent the first line of defense against COVID-19. On the other hand, this segment of the society is more susceptible to getting infected due to direct
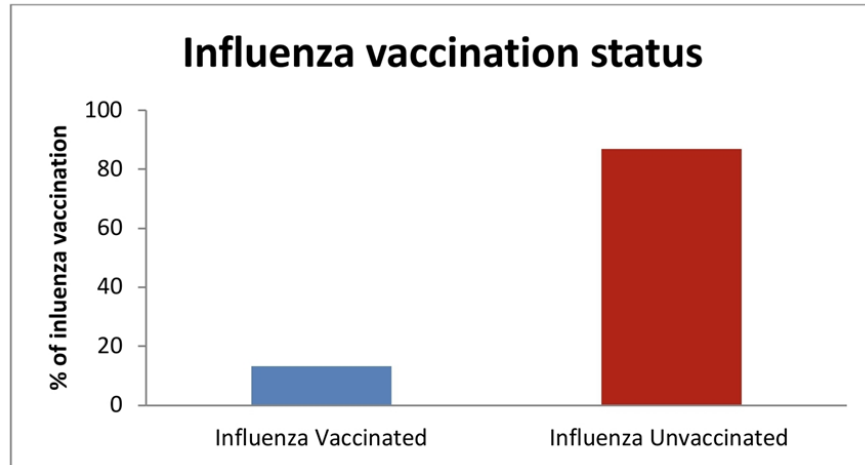
Figure 1. Percentages of vaccinated and unvaccinated members of medical staff and students included in the study.
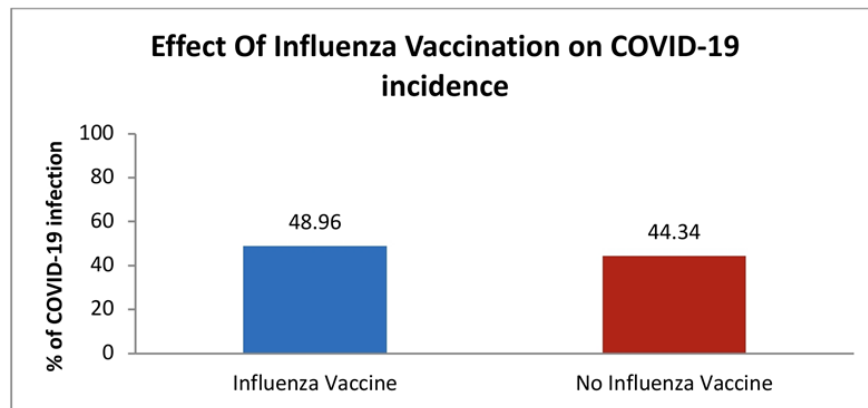

Figure 2. COVID-19 infection incidence in influenza vaccinated and unvaccinated subjects (p- value > 0.05).
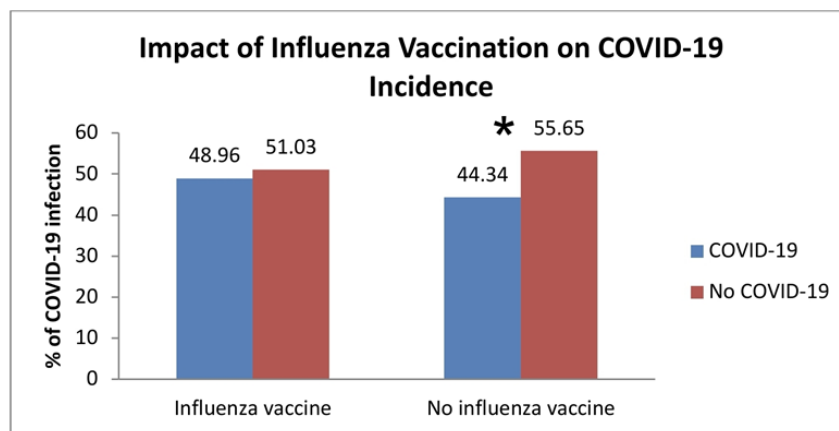
Figure 3. Comparison of COVID-19 infection rates in influenza vaccinated and unvaccinated subjects.

Table 1. Percentages of vaccinated and unvaccinated subjects who have COVID-19.

Groups	COVID-19 infection			
	No COVID-19		COVID-19	
	713 (55.65%)		568 (44.34%)	
1. Unvaccinated (*N* = 1,281)	Male	Female	Male	Female
	300 (42.1%)	413 (57.9%)	233 (41.02%)	335 (58.97%)
	99 (51.03%)		95 (48.96%)	
2. Vaccinated (*N* = 194)	Male	Female	male	Female
	46 (46.4%)	53 (53.5%)	45 (47.3%)	50 (52.63%)
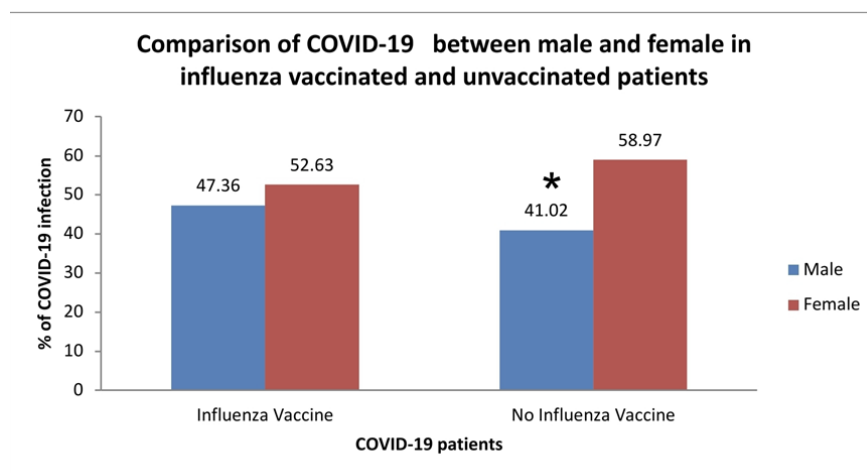
Figure 4. Comparison between males and females in the influenza vaccinated and unvaccinated groups.
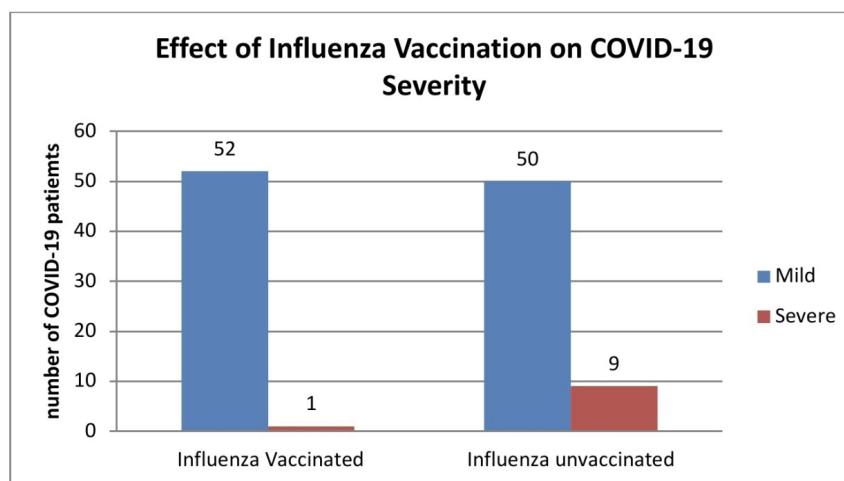
Figure 5. The effect of influenza vaccine on COVID-19 severity.

contact with COVID-19 patients. Our results showed that a very small percentage of the participants received the influenza vaccine. Influenza is not considered a critical illness in Iraq due to lack of proper awareness, in addition to the hot climatic nature of Iraq and short winter season in which the temperature rarely reaches zero. Also, the availability of the influenza vaccine reduces the percentage of vaccinated subjects. Our findings, contrary to predictions, do not support earlier research which found a negative relationship between COVID-19 incidence and influenza vaccination in several clinical investigations. The results showed that the incidence of COVID-19 infection was nonsignificantly higher in the influenza vaccinated group than in the unvaccinated

group. This could be because many influenza vaccinated subjects were given the vaccine due to medical problems or chronic diseases that required vaccination. In addition, many of them were highly susceptible to the influenza virus and other respiratory viruses. Those subjects may be also susceptible to COVID-19 because of the similarity between type and route of transmission of the two viral diseases. Although a nonsignificant difference was reported in the infection rate between the study groups, outcomes of the current study are in line with the clinical investigation carried out by Lisewki (2020), which showed that there was an increase in COVID-19 risk in 28 OECD countries due to influenza vaccination. In Europe and the United States, a recent study found a clear positive link between vaccination rate and the risk of COVID-19 infection among the elderly (65 years of age) (Consortium, 2020). Influenza vaccinations give protection against influenza infection but not against other viral illnesses in patients who have received the vaccination because nonspecific immunity fades with time (Cowling *et al*., 2012), perhaps due to virus interference (Isaacs and Lindenmann, 1957; Seppälä *et al*., 2011; Wolff, 2020). Even though the vaccine adjuvant has a high degree of safety, particularly the influenza vaccine adjuvant should be examined for adverse responses in COVID-19 patients, such as rise in inflammatory markers, which are already high with COVID-19 (Petrovsky, 2015; Qin *et al*., 2020). According to Pawlowski *et al*. (2020), acquired immunity from general vaccines, such as measles, rubella, mumps, varicella, hepatitis A and B, geriatric flu, pneumococcal conjugate (PCV13), polio, Haemophilus influenzae type B 1–5 years, prior to the pandemic resulted in lower rates of infection with SARS-CoV-2. Results from the present study determined that influenza vaccination significantly decreases the need for oxygen therapy and hospitalization. Interestingly, these results indicate that the influenza vaccination may have a role in reducing disease severity. Importantly, many clinical studies support the beneficial impacts of influenza vaccination to reduce mortality and morbidity of COVID-19, indicated by decreasing hospitalization and progression of the disease to severely critical stages. SARS-CoV-2 and influenza viruses share a property, which is enveloped RNA with similar entrance and transmission mechanisms and clinical characteristics that overlap. Recent studies (Arokiaraj, 2020) in Italy (Marin-Hernández *et al*., 2020) and the United States have found an adverse link between influenza vaccine and COVID-19 mortality at the country level. Several linked or separate causes for the influenza vaccine's putative protection against COVID-19 infection have been shown. This may happen if another respiratory virus such as SARS-CoV-2 triggers enough trained innate immune memory to prepare the local immune system of the lung for a rapid response, which might impact the recovery of the COVID-19 infection course. A study by Marín-Hernández *et al*. (2020) showed the epidemiological evidence of an association between increased influenza vaccination rate in elderly individuals and reduced COVID-19-related mortality in Italy. High morbidity and mortality have been linked to an adverse connection between influenza vaccination rates and COVID-19. Furthermore, earlier research has connected the influenza vaccination's potential to reduce COVID-19 infection severity to the cessation of influenza-SARS-CoV-2 coinfections (Arokiaraj, 2020) and tendency to shift in innate immunity (Netea *et al*., 2020). Similarly, research

in OECD countries found a negative relationship between immunization rate and COVID-19-linked morbidity and death in those over 65 years (Arokiaraj, 2020). An Italian study found that the influenza vaccination decreased hospitalization rates, intensive care admissions, and mortality of COVID-19 in the elderly (Amato *et al*., 2020). Zanettini *et al*. (2020) found that the mortality rate of the COVID-19 disease decreased by 28% after recording a 10% increase in vaccination. Another study carried out in Brazil found that those at risk of severe COVID-19 illness may benefit greatly from influenza immunization and have a higher probability of surviving and requiring less extensive hospital care than those who did not receive the vaccine recently. Late vaccination boosts the innate immune response, which may contribute to quick and powerful SARS-CoV-2 clearance, avoiding lower lung tissue invasion and/or suppressing the detrimental proinflammatory host response that occurs at the crucial stage of COVID-19 sickness (Fink *et al*., 2020). Furthermore, in an established *in vitro* model, it has been demonstrated that the tetravalent inactivated influenza vaccination develops trained immunity and improves immune cell responsiveness to SARS-CoV-2 activation (Kleinnijenhuis *et al*., 2012). An increase in cytokines has been reported after the activation of white blood cells by the influenza vaccine (Debisarun *et al*., 2020). This response by cytokines was more specific compared to the response generated by BCG. It has been shown to prevent systemic inflammation and reduce the viral load associated with the microactivation of cytokines (Tanaka *et al*., 2014).

Anti-inflammatory cytokines, like interleukin (IL)-1Ra, are critical for regulating and preventing inflammation. When influenza vaccination and BCG were given, clinical research found that significant levels of IL-6 and IL-1Ra were produced. This supports the idea that these cytokines have a role in keeping the participants' inflammatory condition in check (Moorlag *et al*., 2018). Inactivated influenza vaccination stimulates the innate immune system by activating the toll-like receptor 7, which increases IL-6 and tumor necrosis factor production in peripheral white blood cells in response to antigen challenge and causes functional changes in the natural killer cell compartment for several weeks to months (Fink *et al*., 2020). In conclusion, influenza immunization may reduce the severity of COVID-19 and the negative results, but it does not reduce the occurrence.

CONCLUSION

In this short study, nonsignificant differences in the odds infected with COVID-19 who got the influenza vaccine compared to those who did not get the vaccine are demonstrated. The results also showed no significant association between gender and influenza vaccination status on the percentages of COVID-19 incidence. In addition, the COVID-19 patients who previously received the influenza vaccine had significantly better clinical outcomes; lower complication rates and less hospitalization and hypoxia were noted. The influenza vaccination may have a role in reducing the burden of the COVID-19 disease severity.

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ETHICAL APPROVAL

The present study was approved by the Medical Ethical Committee of the College of Medicine in Wasit University. The ethical number is A/123.

AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to the conceptualization, study design, data acquisition and interpretation, took part in writing-original draft, revising, and final approval for the version to be published and agree to be accountable for all aspects of the work.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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