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The Impact of Influenza Vaccine Uptake on COVID-19 Infection amongst a Multi-ethnic Population with Multiple Morbidities

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ABSTRACT

Background: *The COVID 19 Pandemic, which appeared in 2019 and is caused by SARS Coronavirus 2, has had a huge impact on the health of millions of people worldwide, with some patients having no symptoms or mild to moderate symptoms and others having prolonged, complicated courses, with some succumbing to the disease. The presence of co-morbidities puts the patient at a greater risk of acquiring a more severe infection. This population are also at a greater risk for more severe influenza infection and Influenza vaccination is recommended for this group on an annual basis.*

Objectives: *To assess whether influenza vaccination may protect against COVID 19 infection, in a Family Medicine population with co-morbidities. The study will shed light on the influence of influenza vaccination on acquiring COVID 19 infection.*

Design: *This is an observational, retrospective study.*

Setting: *Family Medicine Clinic in Saudi Arabia.*

Materials and Methods: *Charts from family medicine patients with one or more co-morbidities who received the influenza vaccine during the 2019/2020 Influenza season, were reviewed. Patients aged between 25 to 75 with comorbidities were included and had received the influenza vaccine from July 2019 to March 2020. Children under 18 and pregnant patients were excluded from the study.*

Sample size: *250 patients.*

Conclusions: *There may be beneficial effects of using the Influenza vaccine in a high-risk community population, with co-morbidities, during the COVID-19 Pandemic.*

Keywords

COVID-19 infection, Coronavirus, Family medicine, Co-morbidities, Influenza virus, Influenza vaccination.

Introduction

Background

The people who are most at risk to influenza are also the most vulnerable to COVID-19 [1]. Studies from China, where the SARS CoV-2 infection was first reported, highlighted that patients with comorbidities had a poorer clinical outcome [2] such as hypertension and respiratory and cardiovascular diseases [3]. A meta-analysis found that hypertension, cardiovascular disease, diabetes, smoking, COPD, malignancy and chronic kidney disease were the most prevalent comorbidities among hospitalized patients

with COVID 19 [4]. A study from Saudi Arabia, reported that 20.1% of COVID-19 patients had one or more co-morbidities, including diabetes, chronic kidney disease, cardiac disease, cancer and immunodeficiency [5].

The COVID-19 disease can be classified according to the presentation: Stage A asymptomatic, stage B mild with acute upper respiratory symptoms or digestive symptoms, stage C moderate symptoms with pneumonia but without hypoxia and chest computerized tomography(CT) shows lesions, and stage D severe disease, characterized by pneumonia with hypoxia, with CT findings of peripheral and basal consolidation which can progress into a critical stage with acute respiratory distress syndrome, and may develop shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury [6].

Regarding influenza, "up to 25% of people in the United Kingdom are designated high risk including all adults aged over 70 and those with underlying health conditions such as respiratory and cardiovascular disease, and cancer" [7]. In 2018-2019, 35.3 million influenza cases were recorded in the United States, with 490,600 hospitalizations and 34,200 deaths [8].

A recent study showed "a correlation between COVID-19 related mortality and morbidity and the status of influenza vaccination, which appears protective". "Influenza is close to SARs-CoV-2 viruses and shares some epitopes and mechanisms" [9]. In a study on the immune response of Influenza A virus (IAV) and human coronavirus (CoV) infections, "host immune responses play both protective and pathogenic roles in IAV and CoV infections"[10]. The stimulation of the immune system with the influenza vaccine "would strengthen the immune system for SARs-CoV-2 infections" [9].

This is the first study from Saudi Arabia that we are aware of, investigating the impact of the influenza vaccination on acquiring COVID-19 infection.

Objectives

The study aimed to assess whether influenza vaccination can protect against COVID 19 infection, in a Family Medicine Department population with comorbidities.

Materials and Methods

This is a retrospective, observational study performed at the Family Medicine Department in Riyadh. The medical records of 250 Family Medicine patients, with one or more comorbidities, who underwent Influenza vaccination at the Family Medicine Department between August 2019 and March 2020, were reviewed at King Faisal Specialist Hospital and Research Center (KFSH&RC), ascertaining whether or not they acquired COVID-19 infection. The patients were between 25 and 75 years old. Among those who developed COVID-19 infection, the severity of the disease was also ascertained. Data was collected from the electronic record search as all the patients' consultations are available there. The study was conducted at a single center in Riyadh but with a very diverse population, covering employees and their dependents and a wide age spectrum.

Statistical Analysis

All the statistical analyses of collected data were performed using the software package SPSS, version 20.0 by the IBM. The continuous variables are reported as median and mean, and categorical variables are summarized as frequencies and percentages. Continues variables will be analyzed using t-test and ANOVA. Categorical variables are compared using the chi-squared test. $p < 0.05$ was considered statistically significant.

Ethical Considerations

The research project will be conducted in accordance with the ethical principles contained in the Declaration of Helsinki (2000), and Good Clinical Practice Guidelines and the policies and regulations of the Research Advisory Council in KFSH&RC. All the collected data will be saved but the confidentiality of the patients will be protected by remaining anonymous. The patient's name or medical record number will not be utilized in datasheets; rather UPN codes will be used for the privacy and confidentiality of the patient has protected health information (PHI). Since no identifying data or PHI will be recorded, a consent is not required (no intervention is needed). All required data already exists in the subject's medical record.

Results

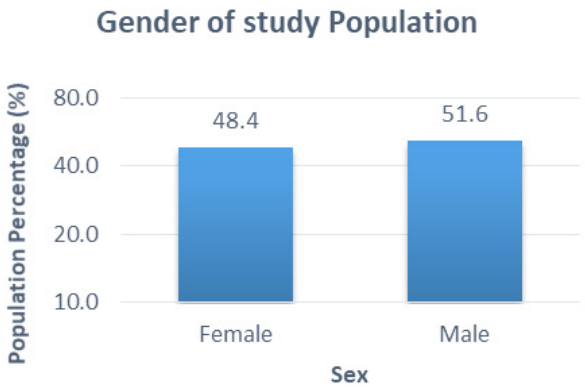
The files of 250 patients with comorbidities who received the influenza vaccine in the Family Medicine Department at KFSHRC from August 2019 to March 2020, were reviewed, which were 52% male and 48% female in the study (Graph 1). A total of 50% of the studied population were of Saudi origin and the other 50% non-Saudi (Graph 2), with the average age of 48.25 and between one and six comorbidities (average 2.3, standard deviation 1.284) (Table 1). Table 2 shows 24% had diabetes, 42% hypertension, 38% obesity, 34.8% dyslipidemia, 20% asthma, 16% hypothyroidism, 4% ischemic heart disease, and 62.4% other comorbidities (Table 2).

We found that 57 out of 250 patients developed COVID-19 infection (22.8%), with 193 (77%) remaining COVID-free, at the time of analysis (Graph 3). Out of the 57 patients affected, 2.8% developed Stage a disease, 8.8% got Stage B, 9.6% developed Stage C with just 1.6% developing Stage D disease, with no mortalities in the affected group (Graph 4). The majority of patients (over 80%) had mild to moderate disease.

Using univariate logistic regression, to look at risk factors for COVID-19 infection, female sex (p- 0.0045, 95% CI 0.216-0.754) and dyslipidemia (p-0.0064) were significant in this population. By multivariate logistic regression, female sex (p=0.0115), dyslipidemia (p=0.0021), and diabetes (p= 0.0257) were all significant. In conclusion, female gender, dyslipidemia and diabetes have a significant effect on having a positive COVID-19 test in this population.

Regarding repeated influenza vaccinations over the last 10 years, we found no association between infection severity and the number of flu vaccines (p=0.053).We also found no association between

the number of morbidities and the number of flu vaccinations over the last ten years (p=0.2973) (Tables 3 and 4).



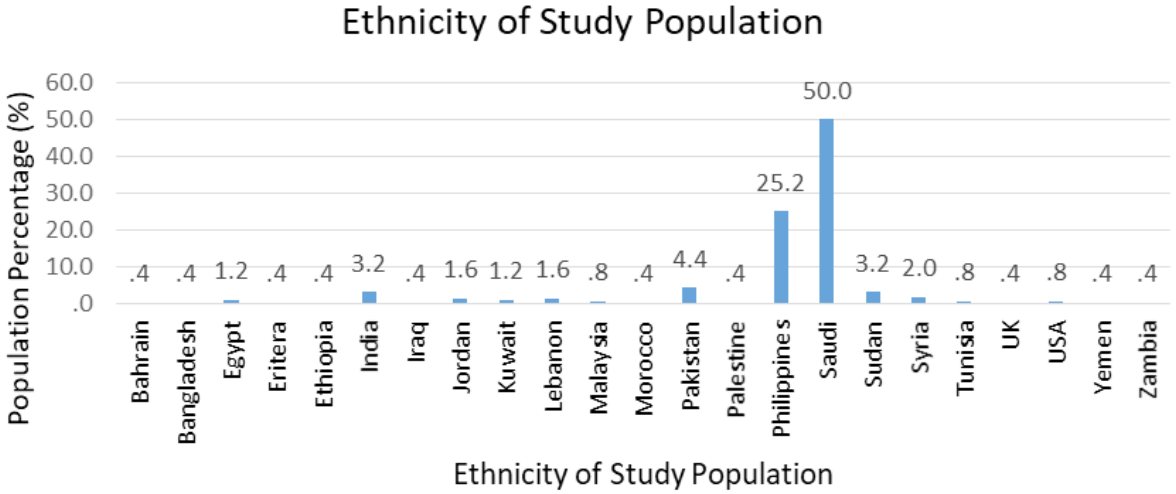
Graph 1: Gender data.

	Age	Comorbidities - Number
N	250	250
Mean	48.25	2.3
SD	12.212	1.284

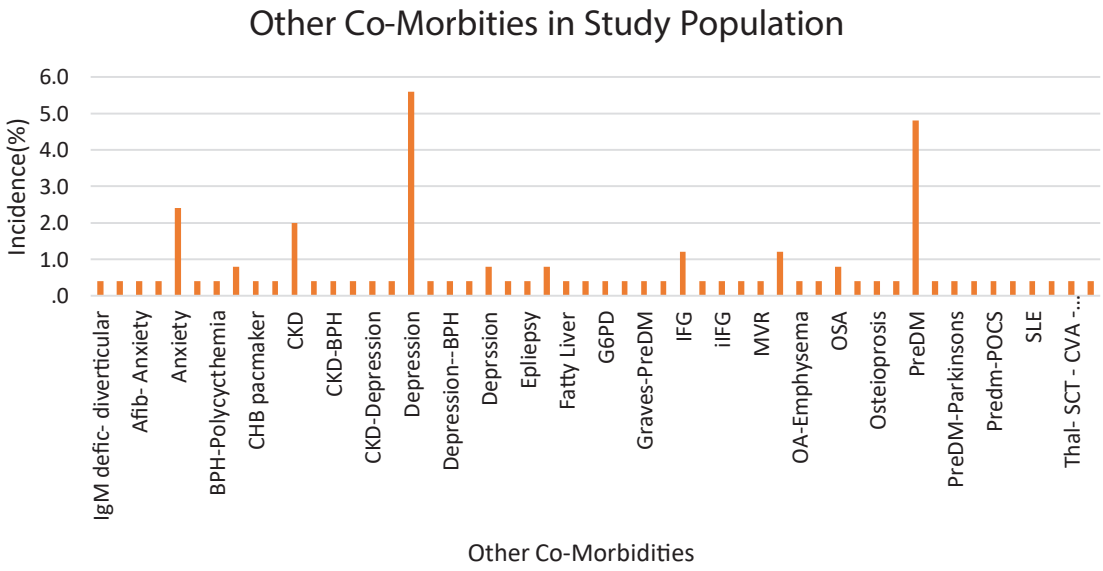
Table 1: The mean age and number of comorbidities of study population.

Co-Morbidities	Number
Hypertension	105 (42%)
Obesity	95 (38%)
Dyslipidemia	87 (34.8%)
Diabetes	61 (24.4%)
Asthma	51 (20.4%)
Hypothyroidism	40 (16%)
Ischemic Heart Disease	10 (4%)
Other comorbidities	156 (62.4%)

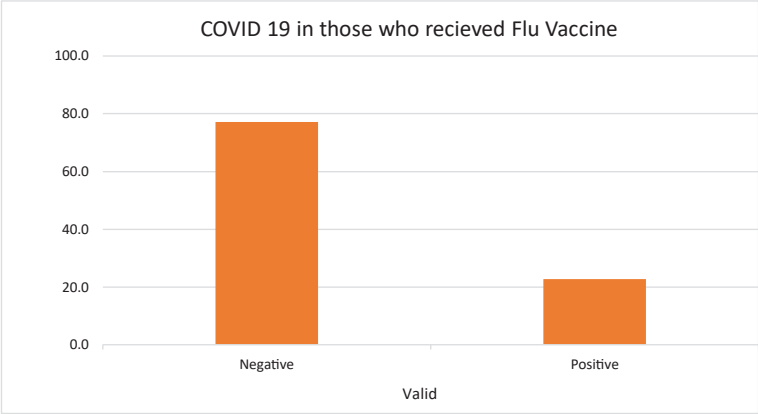
Table 2: Comorbidities in the study population.

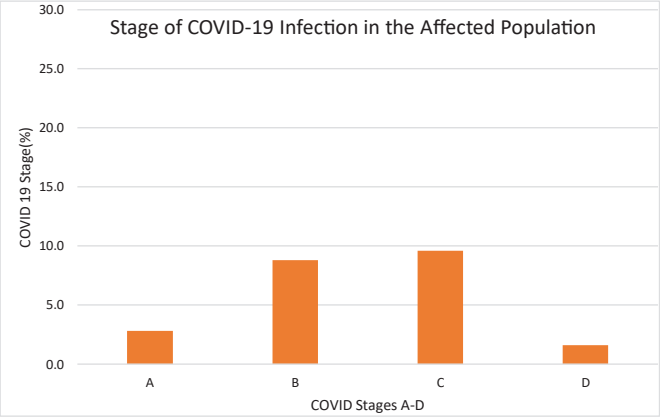


Graph 2: Ethnicity data.



Graph 3: COVID-19 incidence in study population (as a percentage).





Graph 4: COVID-19 stages in the affected population.

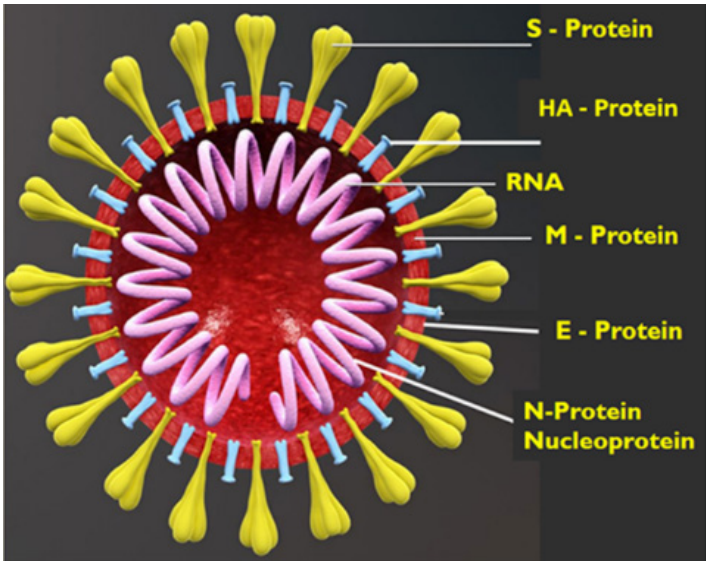


Diagram 1: Morphology of CoV (Rohde RE. Novel coronavirus (2019-nCoV) update uncoating the virus. Am Soc Microbiol. 2020).

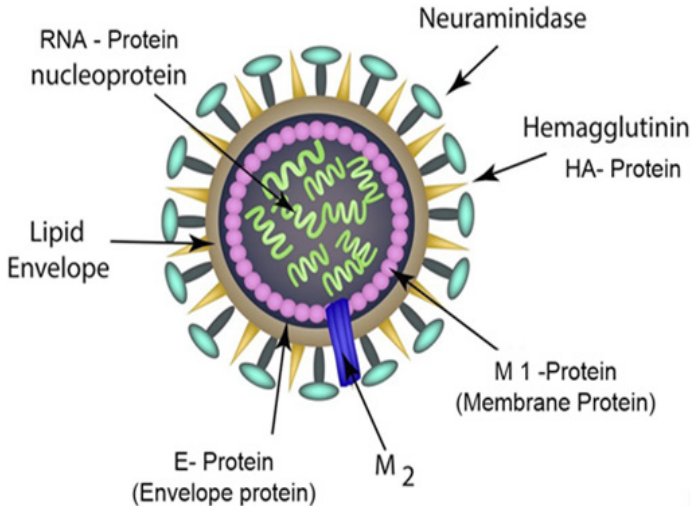


Diagram 2: Morphology of influenza virus (cartoon depiction of an influenza virus structure. Different strains are named after their versions of the hemagglutinin (HE) and neuraminidase (N) proteins, as in H1N1 "swine flu." Credit: Timonina/Shutterstock.com).

Sample size 57

Statistic	DF	Value	Prob.
Chi-square	3	7.6977	0.0527
Likelihood ratio chi-square	3	8.6857	0.0338
Mantel-Haenszel chi-square	**Unenlightenment** 1	5.2259	0.0223
PHI coefficient		0.3675	
Contingency coefficient		0.3449	
Cramer's V		0.3675	
WARNING: - 38% of the cells had expected counts of less than 5. - Chi-square may not be a valid test.			

Table 3: Flu vaccine by infection severity.

Statistic	DF	Value	Probability
Chi-square	1	1.0861	0.2973
Likelihood ratio chi-square	1	1.0606	0.3031
Continuity chi-square	1	0.5322	0.4657
Mantel-Haenszel chi-square	1	1.0671	0.3016
PHI coefficient		-0.1380	
Contingency coefficient		0.1367	
Cramer's V		-0.1380	

Table 4: Flu vaccine by comorbidity number.

Discussion

The COVID-19 pandemic has placed a huge burden on healthcare systems worldwide and as the influenza season approaches, the concern is that coinfection will lead to an even greater burden and to an increased number of mortalities, especially in vulnerable groups including the elderly and those with comorbidities. Older individuals and those with underlying diseases have a greater risk of severe COVID-19 infection [11]. It is estimated that "one in five individuals worldwide has an underlying condition that could put them at an increased risk of severe COVID-19 if infected" [12]. Complications and deaths from influenza are also known to be more common in those high-risk groups. According to the Centers for Disease Control and Prevention (CDC), an estimated 24,000-62,000 influenza deaths have been recorded in the United States for the 2019-2020 influenza season [13]. "Annual influenza vaccination has been demonstrated to be effective in reducing morbidity and mortality among high-risk patients" [14]. Of interest, one study suggested that "the resultant immunity against prior influenza infection would, at least in part, foster immunity

against SARS-CoV-2" [15]. In our study, 77% of the participants remained COVID-free which could be explained by some prior immunity from the received influenza vaccine. Arokiaraj had the same conclusion [9]: Influenza vaccination "could be an effective strategy to reduce the severity of the COVID-19 disease in the general population ". To understand this better, we need to look at the pathophysiological features of SARS-CoV2 and influenza viruses. "The pathognomonic spike protein shares common features with Class 1 viral membrane fusion protein including influenza viruses" [9]. This in turn could lead to cross-reactivity between flu and CoV and reduced severity of COVID-19, by the "Flu-induced bystander immunity" [15].

Influenza viruses are ribonucleic acid (RNA) viruses from the Orthomyxoviridae family, with four main types: A, B, C, and D. A and B are the types that cause infection in humans [16]. The CoV resembles the influenza virus in structure and pathogenesis, both containing single stranded RNA, surrounded by lipoprotein layers and containing protein receptors, responsible for host cell attachment. In addition, there are other proteins that are involved in protein synthesis and viral proliferation as well as multiplication in the host cell. Both influenza virus and CoV have a HE protein, which may have a key role in developing immunity against COVID-19 in humans, when they are vaccinated with the influenza vaccine (Morphology Diagrams 1 and 2). Currently, there are 18 known subtypes of HE and 11 known subtypes of N. Influenza viruses are serologically characterized by their H and N proteins. Spike proteins HA and NA play an important role in the viral infectious cycle. Both viruses must go through the following steps, to cause illness in the host: first, attachment to the host cell, followed by penetration, then replication of viral RNA and biosynthesis of viral proteins, and finally maturation and release of the new virus from the host cell [17].

The influenza vaccine can activate immune responses by mimicking the viral infection. It is prepared using viral strains, in accordance with the World Health Organization (WHO) recommendations. Most are trivalent, containing subtypes A and B. There are four types recommended in the UK for 2020/2021: adjuvant trivalent vaccine, egg-grown quadrivalent vaccine, cell based quadrivalent vaccine and live- attenuated vaccine for children 2 to 18 [18]. They are usually manufactured using attenuated virus (weakened by heat or chemicals) or inactive viral particles which are taken from certain circulating inactive virus strains or killed viruses. The inactive fractions of viral components contain viral protein He and N proteins. When the vaccine is injected into the body, it will stimulate the immune system through three mechanisms: via the macrophages, T-lymphocytes and B-lymphocytes [19].

This study has limitations; for instance it is from a single centre in Saudi Arabia and further studies are needed to establish if the influenza vaccine in 2019/2020 will offer some protection against COVID-19 infection.

Conclusion

Clear conclusions on the relationship between COVID-19 infection and influence vaccination are yet to be established. However, influenza vaccination is strongly recommended to be given to patients with chronic illnesses. In a meta-analysis, the efficacy of the influenza vaccine was almost 60% in those aged 18 to 65 [21]. In the elderly population, influenza vaccination reduces severe disease, especially the adjuvanted trivalent vaccine [18].

This study shows that 77% of patients who received the influenza vaccine did not develop COVID 19 infection and in those who developed COVID-19, the majority had mild to moderate symptoms, with no mortality. It is critical that we try to reduce the risk of influenza and COVID-19 coinfection, as this will lead to a higher mortality [22]. In the UK, the influenza vaccination target has been set at 75% in those aged 65 and above and similarly in at-risk groups, school-aged children, pregnant women, and those working in the health sector and social care [23].

We should therefore encourage patients, especially those with comorbidities, to get the influenza vaccine as early as possible in the 2020/2021 influenza season. "High vaccine coverage would reduce influenza-related mortality" while helping healthcare systems to cope "during circulation of influenza viruses and severe acute respiratory syndrome coronavirus 2" [24].

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