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Original Articles

Influenza prevalence and vaccine efficacy among diabetic patients in Qatar

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ABSTRACT

Seasonal influenza viruses may lead to severe illness and mortality in patients with comorbidities, including Diabetes Mellitus (DM). Vaccination against influenza in DM patients may reduce influenza incidence and severity. Before the emergence of the COVID-19 pandemic, influenza infections were the most prevalent respiratory infections in Qatar. Still, reports about influenza prevalence and vaccine efficacy in DM patients have not been reported. This study aimed to analyze influenza prevalence among other respiratory infections and assess influenza vaccine efficacy in DM patients in Qatar. Statistical analysis was performed on data obtained from Hamad Medical Corporation (HMC) database for patients that visited the emergency department (ED) with respiratory-like illnesses. The analysis was done for the period between January 2016 to December 2018. Among 17,525 patients who visited HMC-ED with clinical symptoms of respiratory infections, 2611(14.9%) were reported to have DM. Among DM patients, influenza was the most prevalent respiratory pathogen at 48.9%. Influenza virus A (IVA) was the most circulating type, contributing to 38.4%, followed by IVB contributing to 10.4% of total respiratory infections. Among the typed IVA-positive cases, 33.4% were H1N1, and 7.7% were H3N2. A significant decrease in influenza infections was reported in vaccinated DM patients (14.5%) when compared to non-vaccinated patients (18.9%) (p-value = 0.006). However, there was no significant relaxation in the clinical symptoms among vaccinated DM patients compared to their non-vaccinated counterparts. In conclusion, influenza was the most common etiology for respiratory viral infection among diabetic patients at the leading healthcare provider in Qatar. Although vaccination reduced the incidence rate among DM patients, it was less effective in preventing symptoms. Further studies on a larger cohort and for a more extended period are required to investigate influenza prevalence and vaccine efficacy among DM patients.

Introduction

Influenza accounts for up to one billion infections annually, with 3–5 million severe cases and around 400,000 to 500,000 deaths reported [1]. Two main influenza types cause infection in humans, influenza virus A (IVA) and influenza virus B (IVB) [2]. Further, IVA is classified into different subtypes based on two surfaces glycoproteins: the hemagglutinin (HA; n = 18 subtypes) and neuraminidase (NA; n = 11 subtypes) present on the surface of the virus [3]. The most common subtypes that infect humans are H1N1 and H3N2 [3],

Abbreviations: DM, Diabetes Mellitus; IVA, Influenza Virus A; IVB, Influenza Virus B; MOPH, Ministry of public health; HMC, Hamad medical corporation; ED, Emergency department; CDC, Communicable disease center

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which cause annual epidemics, whereas IVB causes acute respiratory infections (ARIs) [4–6]. IVB is classified into two lineages: B/Yamagata and B/Victoria [7]. Influenza virus infection is characterized by the sudden onset of fever, headache, cough, prostration, coryza, and tracheal and upper respiratory tract inflammation [6,8]. These symptoms had been reported to be more severe in people with undermining health conditions, including chronic cardiac diseases and diabetes mellitus (DM) [8].

DM is a metabolic disease resulting in elevated blood glucose levels, which occur due to the absence or impaired action of insulin [9,10]. Among the two types of DM, type 2 diabetes mellitus (T2DM or T2D) is the most common and is predominantly seen in adults [11]. Around 422 million people are diabetic worldwide, and up to 1.5 million deaths are directly attributed to DM yearly [9,12]. DM patients are at higher risk for respiratory viral infections, including influenza infections [13–15]. During the 2009 H1N1 pandemic, it was reported that DM doubled the risk of severe H1N1 infection and its fatal outcome [16]. Further, DM patients' hospitalizations increased after H1N1 infection [14]. Indeed, people with DM are 3–6 times more likely to develop severe infections and be hospitalized during the influenza season [13,17–19]. The reason for this increased susceptibility is poorly understood; however, the impaired immune response in DM patients, which is associated with higher hospitalizations and morbidity, is reported [20–22]. The cellular immunity in DM patients to different infections is studied and reported to be associated with impairment of cytokine production[23,24], inhibition of leucocyte recruitment [25], neutrophil dysfunction[26], imperfections in pathogen recognition[27], and abnormalities in complement activation [28]. Therefore, it is logical to assume that vaccine introduction may be a potential solution to mitigate the severity of influenza infection in DM patients. A Study reported that influenza vaccination could produce an adequate immunologic response in DM patients, significantly reducing morbidity and mortality rates due to influenza infection [29–31]. In a comparative study between age-matched diabetic and non-diabetic influenza-vaccinated individuals, the hospitalization of DM patients was reduced by half, and the protective effect of vaccination was significant [32].

In Qatar, the most critical health challenge is T2D. In 2015, when the global rate of diabetes was 8% of the total population, Qatar reported 17% of diabetic cases in its total population [33]. The International Diabetes Federation (IDF) reported the incidence of DM patients in 2021 at 19.8% and is predicted to reach 22.8% of its total population [34]. On the other side, influenza was the most prevalent infection among respiratory infections in Qatar before COVID-19's emergence [35,36]. Qatar's population is increasing every year, with a 40% increase since 2010 due to the inflow of foreign workforce [37]. Tourism brings over a hundred thousand visitors to Qatar every year [38]. Hence there are many challenges in the healthcare sector, especially in providing good healthcare for DM patients [39]. The country offers a yearly "seasonal influenza campaign" to reduce influenza complications in people, especially with undermining health conditions, including DM [40]. In this study, we analyzed influenza prevalence among respiratory infections in DM patients between January 2016 and December 2018 and also evaluated influenza vaccine uptake and effectiveness in DM patients in Qatar.

Research design and methodology

This is a retrospective study of data collected from Hamad Medical Corporation (HMC, the primary healthcare provider in Qatar) between January 2016 and December 2018. The study targeted patients who reported symptoms of respiratory diseases in Qatar during the described period. Data, including demography and laboratory test results, were used in statistical analysis to study the prevalence and burden of influenza infections and the efficacy of influenza vaccination in DM patients.

Samples and virology testing

Samples (nasal swabs) were collected from patients with flu-like symptoms such as a body temperature of ≥ 38 °C, sore throat, headache, cough, shortness of breath, and runny nose. Samples were screened for twenty-one respiratory pathogens using the Respiratory pathogen 21 kits (Fast-Track diagnostics, Luxembourg). This kit offers pathogen analysis against a panel of twenty respiratory viruses and one bacteria that generally causes upper respiratory tract infections (Table 2).

Data acquisition

Data, including viral diagnosis results, DM status, and demographic data, were extracted by the HMC-Communicable Disease Center (HMC- CDC) from the HMC Cerner database using the patients' unique health card numbers as the reference. Clinical data included symptoms reported at the time of the HMC-ED visit, influenza vaccination status (whether vaccinated within the last two years) as recorded in the HMC patient database at the time of vaccination and DM status based on the available records at the HMC Cerner database. Demographic characteristics included age, gender, and nationality.

Selection of study and control group

We utilized the records available at the HMC Cerner database to segregate the patients into DM and control groups. Comorbidities other than DM condition were also analyzed for the DM category. For this, we collected the data of comorbid illness of DM patients as recorded in the HMC patient's database.

Statistical analysis

Before conducting any analysis, duplicates were removed to generate clean data. The data was analyzed in year-wise batches, from January to December, as one batch for each year and all three years. The demographic and clinical characteristics were studied using the chi-square test and two proportion Z-test using SPSS statistics for windows version 20 and GraphPad prism 9. The significance of the results was considered based on the p-value. The correlation was considered significant when the p-value was < 0.05. We observed that some information is missing in the control data for the year 2018; hence we excluded 2018 data from some of the comparative analyses. The analysis performed for this study is a set of comparisons of different respiratory pathogens and the rate of infection caused by them between DM and control. The analyses are a). A comparison of the rate of infection by influenza virus and other respiratory pathogens in DM and control groups, b). A comparison of the rate of infection by four different strains of influenza strains in DM, c). The efficacy of influenza vaccination in terms of test positivity to influenza virus. To perform analyses b and c, we selected an equal sample size with age and gender-matched patient data. We also used different demographic characteristics, including gender, age, and nationality, to characterize influenza vaccine efficacy between vaccinated and non-vaccinated DM patients.

Results

Demographic data

Medical records were collected for 17,525 patients who visited HMC-ED between 2016 and 2018 with respiratory infection

Table 1
Demographic characteristics of the enrolled participants, number (%) of total participants.

Category	DM				Control			Total
	2016	2017	2018	Total	2016	2017	Total	
Age								
< 20	18 (0.1)	21 (0.1)	8 (0.0)	**47 (0.26)**	472 (2.7)	299 (1.7)	**771 (4.4)**	818 (4.7)
20–39	92 (0.4)	115 (0.7)	56 (0.3)	**263 (1.5)**	3708 (20.1)	3291(18.3)	**6999 (39.9)**	7262 (41.4)
40–59	303 (1.5)	416 (3.2)	193 (1.0)	**912 (5.2)**	2079 (11.7)	2073(11.9)	**6231 (35.6)**	5064 (28.9)
60–79	374 (1.8)	527 (3.8)	231 (1.1)	**1132 (6.5)**	1202 (7.4)	1250 (7.6)	**2452 (14.0)**	3584 (20.5)
> 80	76 (0.4)	118 (0.7)	63 (0.3)	**257 (1.5)**	278 (1.7)	262 (1.7)	**540 (3.1)**	797 (4.5)
Gender								
Male	441 (2.2)	570 (4.1)	271 (1.3)	**1282 (7.3)**	4689 (25.6)	4400 (25.7)	**9089 (51.9)**	10,371 (58.2)
Female	422 (2.1)	627 (4.4)	280 (1.4)	**1329 (7.6)**	3044 (15.5)	2773 (15.5)	**5817 (33.2)**	7146 (40.8)
Missing	0	0	0	0	6	2	**8 (0.04)**	8 (0.04)
Nationality								
Qatari	395 (2.3)	548 (3.1)	231 (1.3)	**1174 (9.8)**	2916 (16.6)	2458 (14.0)	**5374 (30.6)**	6548 (37.3)
Indian	86 (0.5)	139 (0.8)	53 (0.3)	**278 (2.6)**	1191 (6.8)	1204 (6.9)	**2395 (13.7)**	2673 (15.3)
Pakistani	63 (0.4)	80 (0.5)	42 (0.2)	**185 (1.1)**	495 (2.8)	431 (2.5)	**926 (5.3)**	1111(6.3)
Egyptian	47 (0.3)	43 (0.2)	25 (0.1)	**115 (0.7)**	568 (3.2)	536 (3.1)	**1104 (6.3)**	1219 (7.0)
Bangladesh	36 (0.2)	41 (0.2)	30 (0.2)	**107 (0.6)**	553 (3.2)	652 (3.7)	**1205 (6.9)**	1312 (7.5)
Palestinian	34 (0.2)	42 (0.2)	23 (0.1)	**99 (0.6)**	165 (0.9)	143 (0.8)	**308 (1.8)**	407 (2.3)
Iranian	21 (0.1)	31 (0.2)	24 (0.1)	**76 (0.4)**	134 (0.8)	117 (0.7)	**251 (1.4)**	327 (1.9)
Sudanese	19 (0.1)	21 (0.1)	22 (0.1)	**62 (0.4)**	397 (2.3)	383 (2.2)	**780 (4.4)**	842 (4.8)
Yemen	20 (0.1)	32 (0.2)	11(0.1)	**63 (0.4)**	187 (1.1)	132 (0.7)	**319 (1.8)**	382 (2.2)
Srilankan	14 (0.1)	22 (0.1)	21 (0.1)	**57 (0.3)**	205 (1.2)	232 (1.3)	**437 (2.5)**	494 (2.8)
Others	128 (0.7)	198 (1.1)	69(0.4)	**395 (2.3)**	928 (5.3)	887 (5.1)	**1785 (10.2)**	2210 (12.6)
Total	**863 (4.2%)**	**1197 (8.5%)**	**551 (2.7%)**	**2611 (14.9%)**	**7739 (43.4%)**	**7175 (41.2%)**	**14,914 (85.1%)**	**17,525 (100%)**

symptoms. Participants with a glucose test value of 5.4 mmol/L and below and HbA1c below 6.5 were grouped under the control group, whereas those above this value were grouped under the DM group. Among the total participants for all three years, 2611 (14.9%) were diagnosed with DM based on the glucose and HbA1c test results. Of the total participants (N = 17,525) in this study,10,371 (59.7%) were males, while the rest, 7146 (40.2%), were females. The gender information was missing for eight (0.04%) participants. However, the male-to-female distributions were 7.3% (N = 1282) and 7.6% (N = 1329), respectively, in the DM group, whereas in the control group, 51.9% (N = 9089) and 33.2% (N = 5817), respectively. We considered participants above 15 years for this study as the DM status information was missing for the below-15 years. The study participants aged between 15 and 106 for both control and DM groups, where the mean age was 43 ± 17.9, and the median was 38 years old. For the analysis, we grouped the participants into five different age groups: < 20 years, 20 – 40 years, 40–60 years, 60–80 years, and > 80 years. Moreover, the majority of participants were between 20 and 80 years (N = 2307 in DM and N = 13,603 in control). The demographic characteristics of the total participants are shown in Table 1. After removing duplicates and missing information, we included 2611 DM patients and 14,914 non-DM (control) patients for further analysis. We also collected the nationality information of all participants. A total of 49 nationalities were reported both for control and DM groups. The top 10 nationalities were considered for analyzing influenza-positive rates among vaccinated and non-vaccinated DM patients (Table 1).

Etiology of respiratory infections

All participants in the study were screened for respiratory pathogens. A total of twenty-one pathogens were diagnosed by PCR test using the nasal samples from the patients (Table 2). The percentage of infection caused by each pathogen was compared between DM and control groups. The percentage of infection was calculated from the number of positive cases for that specific pathogen divided by the total positive cases for DM and the control group, respectively. Among the total positive samples in DM and control group (DM = 1016 and control = 9239), influenza was the most prevalent one, representing 48.9% of total infections in DM and

Table 2
The type of pathogens and the rate of infection in DM and control group.

Pathogen		Number (%) infected in DM (2016–2018)		Number (%) infected in Non-DM (2016–2017)	
Influenza virus	Influenza A	392 (38.6%)	48.9%	3722 (40.3%)	51.7%
	Influenza B	104 (10.4%)		1058 (11.4%)	
Adenovirus		30 (2.9%)		271 (2.9%)	
MERS Coronavirus		9 (0.9%)		1 (0.01%)	
Rhinovirus		146 (14.4%)		1648 (17.8%)	
H-CoV	229E	22 (2.2%)		161 (1.7%)	
	NL63	22 (2.2%)		84 (0.9%)	
	OC43	29 (2.8%)		235 (2.5%)	
	HKU1	16 (1.6%)		132 (1.4%)	
Human Parainfluenza virus	Parainfluenza 1	9 (0.8%)		72 (0.8%)	
	Parainfluenza 2	8 (0.8%)		44 (0.5%)	
	Parainfluenza 3	43 (4.2%)		205 (2.2%)	
	Parainfluenza 4	15 (1.5%)		85 (0.9%)	
Human Metapneumovirus A &B		69 (6.8%)		420 (4.5%)	
Human Bocavirus		13 (1.3%)		104 (1.1%)	
Respiratory Syncytial virus		47 (4.6%)		399 (4.3%)	
Enterovirus		8 (0.7%)		144 (1.6%)	
Parechovirus		4 (0.3%)		11 (0.1%)	
Mycoplasma		30 (3.0%)		444 (4.8%)	
Total		**1016 (100%)**		**9239 (100%)**	

51.7% in control. On the other hand, parechovirus was the least prevalent virus at 0.03% and 0.1% in the DM and control, respectively. MERS-CoV infections, which are prevalent in camels in the Middle East, was detected at 0.9% in DM and 0.01% in the control group. The four strains of the seasonal human coronavirus (HCoV; 229E, NL 63, OC43, and HKU1) that cause the common cold represented a low percentage of infection that ranged between 0.9% and 2.8% in both DM and control groups. Similar ranges (0.5–4.2%) were also reported for the four different human parainfluenza strains 1, 2, 3, and 4. Rhinoviruses were also detected in DM and control groups, with infection percentage of 14.4% and 17.8%, respectively. Enterovirus contributed to 0.7% of positive cases in DM and 1.6% in control. Other pathogens, including adenovirus, human metapneumovirus A & B, human bocavirus, Respiratory Syncytial virus (RSV), and mycoplasma were detected in a range between 0.7% and 6.8% in both groups.

Table 3
Pathogens incidence rates in the DM group for the years 2016, 2017, and 2018.

Pathogen		Number (%) infected in DM for the respective year			
		2016	2017	2018	Total
Human Influenza Virus	Influenza A	108 (31.9)	185 (43.5)	99 (44.0)	392 (38.6%)
	Influenza B	44 (13.0)	32 (7.1)	28 (12.4)	104 (10.4%)
Adenovirus		4 (1.2)	20 (4.4)	6 (2.7)	30 (2.9%)
MERS Coronavirus		3 (0.9)	6 (1.3)	0 (0.0)	9 (0.9%)
Rhinovirus		45 (13.2)	75 (16.6)	26 (11.6)	146 (14.4%)
Human Coronavirus	229 E	7 (2.1)	12 (2.7)	3 (1.3)	22 (2.2%)
	NL63	6 (1.8)	10 (2.2)	6 (2.7)	22 (2.2%)
	OC43	15 (4.4)	8 (1.8)	6 (2.7)	29 (2.8%)
	HKU1	5 (1.5)	9 (2.0)	2 (0.9)	16 (1.6%)
Human Parainfluenza virus	Parainfluenza 1	1 (0.3)	3 (0.7)	5 (2.2)	9 (0.8%)
	Parainfluenza 2	1 (0.3)	4 (0.9)	3 (1.3)	8 (0.8%)
	Parainfluenza 3	16 (4.7)	16 (3.6)	11 (4.4)	43 (4.2%)
	Parainfluenza 4	7 (2.1)	7 (1.5)	1 (0.4)	15 (1.5%)
Human Metapneumovirus A & B		31 (9.1)	22 (4.9)	16 (7.1)	69 (6.8%)
Human Bocavirus		6 (1.8)	6 (1.3)	1 (0.4)	13 (1.3%)
RSV		17 (5.0)	20 (4.4)	10 (4.4)	47 (4.6%)
Enterovirus		3 (0.9)	4 (0.9)	1 (0.4)	8 (0.7%)
Parechovirus		1 (0.3)	2 (0.4)	1 (0.4)	4 (0.3%)
Mycoplasma		19 (5.6)	11 (2.4)	0 (0.0)	30 (3.0%)
Total PCR positive		**339 (100)**	**452 (100)**	**225 (100)**	**1016 (100%)**
Not Determined		**523**	**742**	**330**	**1595**
Total		**862**	**1194**	**555**	**2611**

We also compared the rate of infection year-wise (2016–2018) in the DM group for all 21 pathogens. The rate of infection caused each year was calculated by the total infected participants confirmed by PCR test. Out of 2611 participants with symptoms of respiratory infections for all three years, only 1016 were PCR positive for at least one pathogen. Among these positive samples, 33.4% (N = 339) was in 2016, 44.3% (N = 450) was in 2017, and 22.1% (N = 225) was in 2018. Among the total pathogens tested over the three years, the most prevalent infection was IVA (38.6%), followed by IVB (10.4%) and Rhinovirus (14.5%) of the total PCR-positive samples (N = 1016) (Table 3).

Influenza prevalence among other respiratory pathogens

We next analyzed the rate of infection by the different influenza virus types/subtypes among DM patients (Table 4). In both DM and control groups, influenza was the most circulating virus compared to other respiratory pathogens. To compare the infection rate in the DM and control groups, we selected the same number of age- and gender-matched participants from both groups (N ~500). The percent of infection caused by IVA, IVB, and the subtypes were calculated against the total samples selected for that group. IVA was the most prevalent strain, accounting for ~79% in both DM (N = 392) and control groups (N = 402). In both groups, not all IVA-positive samples were typed for H1N1 or H3N2. In DM, only 161 (41.07% of total IVA detected) were further PCR tested to determine the subtype. H1N1 had a prevalence rate of 26.4% (N = 131) and H3N2 6.0% (N = 30) of total influenza-positive cases. In the control group, out of 503 samples, only 133 (26.5%) were further typed, and the rate of infection caused by H1N1and H3N2 was 21.2% (N = 107), and 7.1%, (N = 36), respectively. IVB contributed to ~ 21% of total influenza infections in both DM (N = 104) and the control group (N = 101).

Table 4
The rate of infection by different strains of influenza virus.

Pathogen		Number (%) infected in the DM group	Number (%) infected in the control group
Influenza A(Not subtyped)		231(46.6%)	259 (51.4%)
Influenza A Subtyped	H1N1	131(26.4%)	107 (21.2%)
	H3N2	30 (6.0%)	36 (7.1%)
Total		392 (79. 0%)	402 (78.7%)
Influenza B		104 (21.0%)	101 (20.1%)
Total		**496 (100%)**	503. **(100%)**

*Percentage of influenza infection in DM and control group in age-gender matched randomly selected samples from each groups.

Influenza vaccination among DM patients

The influenza vaccination among DM patients within two years of their reported infection (2016 and 2018), along with the virology test results, were considered to estimate vaccine effectiveness. As the same data was not available for the control group all analyses were done only using DM data. We considered vaccination status in the past two years as per the patients' records. Only 21.3% (557 of 2611) of the DM patients were vaccinated. This information was confirmed using the HMC patient's database using the date of vaccination.

We analyzed the data under different classifications, including the time of infection, age, nationality, and gender. We observed an increasing trend of vaccination among DM patients from the year 2016–2018. DM patients who received influenza vaccine within the last two years of their reported infection were 7.3% (63 of 863), 27.7% (332 of 1197), and 29.4% (162 of 551) for 2016, 2017, and 2018, respectively, (Fig. 1A). We further analyzed the rate of vaccination per different age groups: < 20 years, 21–40 years, 41–60 years 61–80, and > 80. This analysis revealed that vaccine recipients were 19.1% (9 of 47) in the < 20 years, 20.4% (471 of 2307) in the 20–80 years, and 29.9% (77 of 257) in the > 80 years age group (Fig. 1A). We also analyzed the percentage of vaccine recipients between males and females. Among the total DM patients who reported any symptom of respiratory infection, 8.0% (222 of 2611) of males and 12.1% (335 of 2611) of females were vaccinated. However, among all DM-male patients (N = 1282), vaccinated males were 17.3% (222/1282). In the DM-female group (N = 1329), vaccinated females were 25.3% (335 of 1329). Among total vaccinated DM patients (N = 557), 39.4% were males, and 60.1% were females (Fig. 1B).

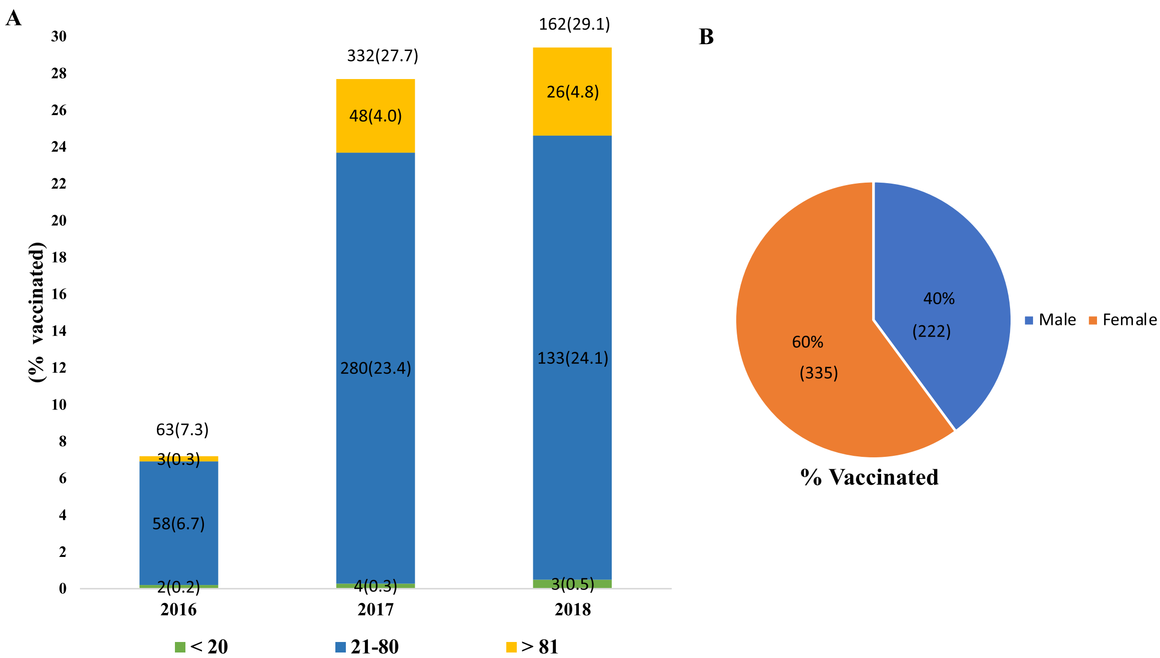

Fig. 1. : Influenza vaccination among DM patients. A) Percentage of DM patients vaccinated between 2016 and 2018 per age group. B) Percentage of male and female DM patients vaccinated for all three years.

Table 5
Test positivity for influenza in vaccinated and non-vaccinated DM patients.

PCR Results	Non-vaccinated DM Patients; N (%)	Vaccinated DM Patients; N (%)	Two proportion Z test; p-value
Influenza Negative	453 (80.9)	476 (85.5)	
Influenza positive	107 (19.1)	81(14.5)	0.006
Total	**560**	**557**	

*The test positive rate between vaccinated and non-vaccinated DM patients were analysed using two proportion Z test. Equal sample size was used from both groups for the analysis.

Influenza incidence among vaccinated DM patients

We further studied influenza positivity among vaccinated (N = 557) and non-vaccinated (N = 2054) DM patients. To perform this analysis, we selected approximately a similar sample size of age-gender-matched patients from non-vaccinated DM patients. Influenza-positive rates among vaccinated individuals were lower compared to non-vaccinated ones (Table 5). Among total vaccinated DM patients (557), only 81(14.5%) tested positive for any of the influenza strains; while among non-vaccinated DM patients (N = 560), 107 (19.1%) tested positive (Two proportion Z test; P-value 0.006).

Table 6
Vaccination and rate of infection among different age groups in DM patients (N = 2611).

Age group (Years)	Vaccinated	Influenza positive in vaccinated	Influenza positive in non-vaccinated	P value
N (%)				
< 20 (N = 47)	9 (19.1)	1 (2.1)	2 (4.3)	-
20–40 (N = 263)	20 (7.6)	3 (0.5)	74 (3.4)	-
41 – 60 (N = 912)	152 (16.6)	30 (5.4)	152 (6.9)	0.009
61 – 80 (N = 1132)	299 (26.4)	37 (6.6)	160 (7.3)	0.010
> 80 (N = 257)	77 (30.0)	10 (3.9)	28 (10.8)	0.291
Total (N = 2611)	**557 (21.3)**	**81 (3.1)**	**416 (15.9)**	**0.005**

*Influenza-positive rate in vaccinated and non-vaccinated DM patients, in different age groups was analyzed by two proportion Z-test. The percentage vaccinated and infected in each age group was calculated against the total reported participants in that DM age group.

Vaccination and test positivity in different age groups/ Nationality and gender

We evaluated DM patients' influenza infection rates in different age groups (Table 6). For the whole study period (2016 – 2018), among all vaccinated DM patients, the percentage vaccinated was 19.1% (9 of 47) among the < 20 years, 7.6% (20 of 263) among the 20–40 years, 16.6% (152 of 912) among the 41 – 60 years, 26.4% (299 of 1132) among the 61 – 80 years and 30.0% (77 of 257) among the > 80 years age groups. Similarly, we also analyzed the influenza infection rate among these age groups. The influenza-positive rate in the vaccinated DM group was 2.1%, 0.5%, 5.4%, 6.6%, and 3.9% in the < 20 years, 20 – 40 years, 40 – 60 years, and > 80 years age groups, respectively. However, in the non-vaccinated DM group, the infection rate was 4.3%, 3.4%, 6.9%, 7.3%, and 10.8% in the < 20 years, 20 – 40 years, 40–60 years, 60 – 80 years, and the > 80 years age groups, respectively.

In all three years (2016–2018), influenza-positive cases were low among vaccinated patients compared to non-vaccinated DM patients, with two proportion Z tests (P value 0.005). Influenza infections among vaccinated DM patients ranged between 2% and 4%; however, among non-vaccinated DM patients, it was between 4% and 19%.

Further, we analyzed the vaccination status of DM patients among different nationalities. We found 49 different nationalities in the DM group. The highest vaccination rate was among Yemenis 33.3% (22 of 66), followed by Sudanese 30.4% (21 of 69) and Palestinians 30.0% (33 of 110), Iranians 27.8% (22 of 79), and Qataris 23.4% (296 of 1264). We selected the top 10 nationalities according

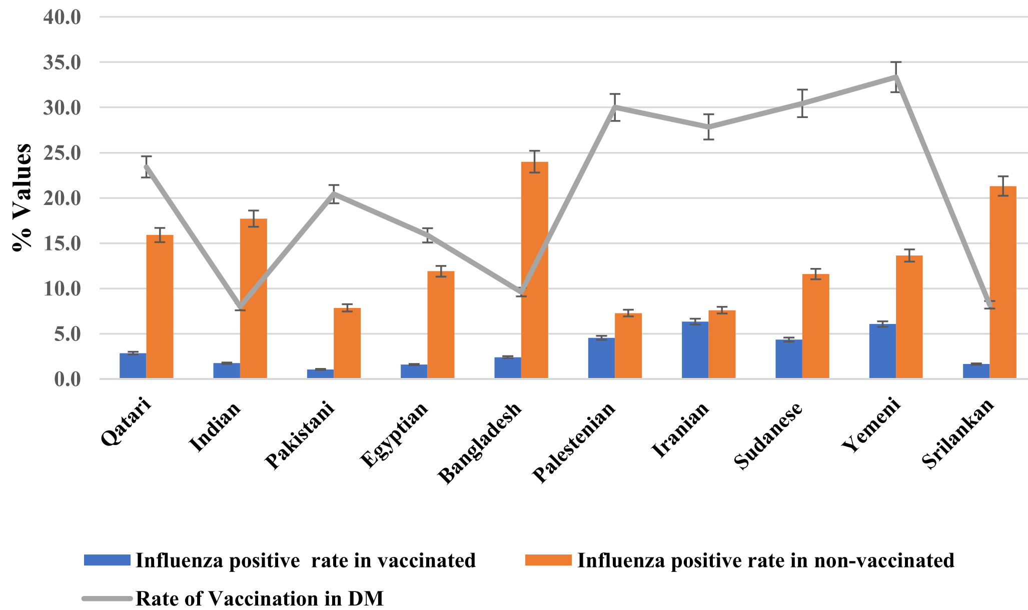

Fig. 2. Influenza infection rates in vaccinated groups of different nationalities.

to the vaccination rate and analyzed the influenza infection rate. The highest influenza-positive rate among vaccinated DM patients was Iranians (6.3%), followed by Yemenis (6.1%), Palestinians (4.5%), Sudanese (4.3%), Qatari (2.4%), and Bangladeshis (2.3%). We then analyzed the correlation of influenza-positive cases between vaccinated and non-vaccinated DM patients in each nationality. Interestingly non-vaccinated DM patients from Bangladesh and Srilanka showed the highest infection rate (~23%), whereas the percentage of infection in the vaccinated group from the same country was ~2%. Similarly, most countries showed reduced influenza positivity among vaccinated DM patients compared to non-vaccinated. The results are depicted in Fig. 2.

The top 10 nationalities were selected, and the rate of vaccination among DM patients of these nationalities and the rate of infection among vaccinated and non-vaccinated DM patients were compared. Further, we analyzed the vaccination rates among males and females. Of the total 557 DM vaccinated patients, there were 222 males (8.0% of total DM patients and 39.9% of total vaccinated DM patients) and 335 females (12.1% of total DM patients and 60.1% of total vaccinated DM patients) (Table 7). Further, the year-wise analysis of vaccinated DM patients showed that 38 – 44% of vaccinated DM patients are males and 56–62% are females (Table 7).

We also analyzed influenza infection versus vaccination status among different genders. We conducted a Two proportion Z test to analyze the association between influenza infection and vaccination among males and females. The percentage of infection among males was 10.7% and 15.5% in 2016, 14.2% and 15% in 2017, and 22.4% and 29.1% in 2018 in vaccinated and non-vaccinated DM patients, respectively. However, among females, the percentage of infection was 17.1% and 20.7% in 2016, 13.2% and 19% in 2017, and 12.6% and 21.4% in 2018 in vaccinated and non-vaccinated DM patients, respectively.

Table 7
Vaccinated DM patients year-wise (%).

	2016	2017	2018	Total Vaccinated N (%)	Vaccinated in DM group (%) (N = 2611)
Male	44	38.3	41.1	222 (39.9)	8.0
Female	56	61.7	58.6	335 (60.1)	12.1
NA			0.3	0.3	
Total	100	100	100	**557 (100)**	**20.2**

The association between vaccination and infection among male DM patients was not significant (p-value = 0.29), and among female DM patients was significant (p-value = 0.013). (Table 8).

Discussion

DM is a chronic health condition of this century and is the fastest-growing underlying comorbidity[11]. Due to glycemic variation, DM patients are reportedly immune-compromised and susceptible to viral infections, particularly respiratory infections [31]. In 1982, Rayfield et al. reported a striking correlation between variable glucose levels and certain infections [41]. Further, DM condition can reduce complement activation, neutrophil degranulation, and impairment in phagocytosis, which in turn affect the susceptibility to infection [42–44]. After the 2009 pandemic, severe influenza infections were reported among DM patients [3]; however, the complete mechanism of disease pathogenesis remains unclear. Influenza infection affects 5–15% of the world's total population annually [45]. Previous studies reported that influenza is the most predominant infection among all respiratory infections in Qatar [45] and the Middle East region [3]. Influenza vaccination is the major measure recommended by WHO to control influenza infection worldwide, especially among people with undermining health conditions [45]. In Qatar, the Ministry of public health's (MOPH) influenza vaccine campaign recommends the annual administration of influenza vaccine for people with undermining health conditions, including DM [45], similar to many countries in the Gulf region [46]. Recent studies indicated that vaccination rates are improving in Qatar. A study among healthcare professionals in Qatar showed that the influenza vaccination rate is relatively high among them (67.7%) [45].

In this study, we investigated the influenza prevalence among other respiratory infections in DM patients in Qatar. We also investigated vaccination rates among DM patients and analyzed influenza vaccine efficacy under different demographic contexts. Influenza was the most circulating respiratory pathogen in Qatar during our study period in both DM and control groups, contributing up to 50% of total respiratory pathogens reported. In both DM and non-DM groups, IVA was the most prevalent type, at 79.0% and 78.7%, respectively. In the DM group, among typed IVA samples (only 41.07% were typed), 26.4% were H1N1, and 6.0% were H3N2. However, in the control group, it was 18.5% and 7.7%, respectively, of

Table 8
Rate of vaccination and infection among male and female DM patients.

	Vaccinated (N = 557)				Non-Vaccinated (N = 2054)				
Gender	Influenza Positive in Vaccinated Group				Influenza Positive in Non-Vaccinated Group				
	% values								
	2016	2017	2018	**Total**	2016	2017	2018	**Total**	**P value**
Male	10.7	14.2	22.4	**16.2**	15.5	15	29.1	**19.9**	0.29
Female	17.1	13.2	12.6	**13.4**	20.7	19	21.4	**20.5**	0.013
Total				**14.5**				**20.3**	

*Influenza-positive rates in males and females were analyzed using two proportion Z-test. The percentage vaccinated and infected for 2016, 2017, and 2018 for males and females are presented, and the P-value is calculated for the total vaccinated and infected in both gender.

total influenza infections. These findings are similar to the previous study reports from Qatar for the period of 2012–2017[47,48].

Vaccination in the general population and DM patients, in particular, is the main measure to reduce infection severity. Influenza vaccination rates in individuals with undermining health conditions, including DM, are reportedly high globally [3]; however not well investigated in Qatar. Our analysis showed an increasing vaccination trend among DM patients in the successive three years, ranging from 7.3% in 2016 to 29.1% in 2018. Recent studies in Qatar reported that influenza vaccination rates among high-risk people increase yearly [46]. During the 2018–2019 influenza seasons, 52.3% of the population with any high-risk health condition (Cardiovascular disease, DM, Hypertension, and Asthma) were vaccinated [45]. The study reported that among the total vaccinated with influenza-like illness, 31% tested positive, and 69% tested negative for influenza. On the other hand, recent studies reported similar vaccination rates in the USA (50–62%) [45], Netherlands (~70%), [49], Spain (~66%) [50], Germany (~40%) [51], but much lower in other countries such as Poland (10%) [51]. On the other side, studies reported that vaccination reduces hospitalization and disease severity due to influenza infection among high-risk category patients [31].

Our analysis showed that influenza vaccination among DM patients is associated with reduced influenza infection, regardless of gender, age, and nationality. Among all DM patients, the influenza-positive rate is 14.5% in the vaccinated group compared to 19.1% in the non-vaccinated. This is supported by a recent study among the general population in Qatar [45]. The study reported a strong association between vaccination and reduced influenza occurrence cases in the nation and among high-risk categories, including DM. The study discusses that the higher influenza occurrence among high-risk categories was due to a lower vaccination rate. Globally several other studies showed that influenza vaccination effectively reduced hospital visits by up to 50–60% due to severe illness [45] and reduced ICU admissions by up to 26% [45]. As per a report from the Centers for Disease Control and Prevention (CDC) during the 2019–2020 period among all category populations, influenza vaccination reduced 105,000 hospitalizations and 6300 deaths associated with influenza infections in the year 2019–2020 globally, confirming the effectiveness of influenza vaccination in reducing influenza occurrence among DM patients [45].

Interestingly, our study observed that the vaccination rate is higher in females than in males (60.1–39.9%, respectively). Although a noticeable decline in influenza infection was reported among vaccinated males compared to non-vaccinated males, a significant drop was only recorded in vaccinated females compared to non-vaccinated. Further, the analysis of different DM age groups reported reduced rates of influenza infection. Specifically, the 41–60 years and 61–80 years groups showed a significant reduction in influenza-positive cases among the vaccinated DM group. This result indicates that influenza vaccination prevents influenza infection among DM patients. Other studies have also reported that seasonal influenza vaccination is associated with reduced influenza infection and hospitalization in DM patients, especially older adults (age above 60) [45]. Another analysis in our study, the nationality-wise analysis of vaccination rate and positive influenza rate, also indicated that vaccination can reduce influenza incidents among DM patients. However, the significance was only seen in some nationalities due to the small sample size. Overall, we saw an inverse correlation between vaccination and infection rates in DM patients. Studies on other viral vaccines, including SARS-CoV-2, reported that in DM patient's vaccination is necessary to ensure adequate immune response [52]. Similar to our study, another study reported the prevalence of influenza infections (48.6%) among other respiratory pathogens in adults in Qatar [47]. However, the severity and complications of influenza and vaccine efficacy among DM patients in Qatar are not reported before.

Limitation and strength

DM is a major challenging problem in the Gulf States. This is one of the very few studies study that investigates influenza burden and vaccine effectiveness in diabetic patients in Qatar and surrounding countries. Still, our study suffers from multiple limitations. This includes some missing information in the control group (no data available for the control group for the year 2018) as well as missing information on vaccination status for the entire control group. To study the effectiveness of influenza vaccination among DM patients, it is imperative to study disease severity and hospitalization of influenza-infected between vaccinated and non-vaccinated DM patients. In our study, the data from hospitalized influenza patients were not included. On the other hand, an extended study period is essential for a better comprehensive analysis of influenza vaccine effectiveness, knowing that the influenza vaccine needs to be administrated yearly.

Further studies involving severely infected DM patients, especially ICU patients, may enable a better analysis of influenza vaccine efficacy among patients with comorbidities. Studies among DM patients with other comorbidities, including asthma, cardiovascular diseases, and hypertension, are also needed.

Conclusion

After more than two years of the COVID-19 pandemic, influenza returned as a major pathogen that affected millions of people around the globe. This could be partially explained by the low influenza vaccination rate in the population. Our study evaluated the influenza burden and effectiveness of the influenza vaccine in the diabetic population in Qatar, before the COVID-19 pandemic. Regardless of all limitations, our data suggest that influenza vaccination significantly reduces influenza infections in DM patients in Qatar. These findings support studies from a few other countries which reported that routine vaccination can reduce disease severity and hospitalization of DM patients during seasonal influenza infections. A considerable benefit of influenza vaccination in adults with Type 2 diabetes was reported in Netherlands, Taiwan, and Italy. Similar findings were also reported for COVID-19, knowing that the respiratory viral vaccine is only available for these two viruses. Hence, vaccination against respiratory viral infections is highly recommended for patients with comorbidities, including DM. Further, there should be a regular evaluation of vaccine effectiveness in DM considering the continuous virus evolution as well as the impaired immune response in this population.

Ethical approvals

The study was approved by ethical committees at HMC and QU (Approval # MRC-03–19–017 & QU-IRB 903-E/18).

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CRediT authorship contribution statement

Conceptualization: HMY, MAA, and AAA; Data acquisition and analysis: ST, JDN & PVC; Funding: HMY; Initial writing: ST, ME and GKN; Final editing and approval: All authors.

Data Availability

Raw data of this study are available on request from the corresponding authors (HMY AND MAA).

Conflict of interest

There is no conflicts of interest declared by any author.

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