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Retrospective Study

Adherence to the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices vaccine recommendations among patients with diabetes mellitus in Saudi Arabia: A multicenter retrospective study

Alqifari SF *et al*. Vaccines in diabetes

Abstract

BACKGROUND

Patients with diabetes mellitus (DM) are predisposed to an increased risk of infection signifying the importance of vaccination to protect against its potentially severe complications. The Centers for Disease Control and Prevention/Advisory Committee on Immunization Practices (CDC/ACIP) issued immunization recommendations to protect this patient population.

AIM

To assess the adherence of patients with DM to the CDC/ACIP immunization recommendations in Saudi Arabia and to identify the factors associated with the vaccine adherence rate.

METHODS

An observational retrospective study conducted in 2023 was used to collect data on the vaccination records from 13 diabetes care centers in Saudi Arabia with 1000 eligible patients in phase I with data collected through chart review and 709 patients in phase II through online survey.

RESULTS

Among participants, 10.01% (n = 71) had never received any vaccine, while 85.89% (n = 609) received at least one dose of the coronavirus disease 2019 (COVID-19) vaccine, and 34.83% (n = 247) had received the annual influenza vaccine. Only 2.96% (n = 21), 2.11% (n = 15), and 1.12% (n = 8) received herpes zoster, tetanus, diphtheria, and pertussis (Tdap), and human papillomavirus (HPV) vaccines, respectively. For patients with DM in Saudi Arabia, the rate of vaccination for annual influenza and COVID-19 vaccines was higher compared to other vaccinations such as herpes zoster, Tdap, pneumococcal, and HPV. Factors such as vaccine recommendations provided by family physicians or specialists, site of care, income level, DM-related hospitalization history, residency site,

hemoglobin A1c (HbA1c) level, and health sector type can significantly influence the vaccination rate in patients with DM. Among non-vaccinated patients with DM, the most reported barriers were lack of knowledge and fear of side effects. This signifies the need for large-scale research in this area to identify additional factors that might facilitate adherence to CDC/ACIP vaccine recommendations in patients with DM.

CONCLUSION

In Saudi Arabia, patients with DM showed higher vaccination rates for annual influenza and COVID-19 vaccines compared to other vaccinations such as herpes zoster, Tdap, pneumococcal, and HPV. Factors such as vaccine recommendations provided by family physicians or specialists, the site of care, income level, DM-related hospitalization history, residency site, HbA1c level, and health sector type can significantly influence the vaccination rate in patients with DM.

Key Words: Diabetes mellitus; Vaccine recommendation; COVID-19 vaccine; Influenza vaccine; Pneumococcal vaccine; Immunization; Retrospective study

Alqifari SF, Esmail AK, Alarifi DM, Alsuliman GY, Alhati MM, Mutlaq MR, Aldhaeefi M, Alshuaibi SA, Amirthalingam P, Abdallah A, Wasel AS, Hamad HR, Alamin S, Atia TH, Alqahtani T. Adherence to the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices vaccine recommendations among patients with diabetes mellitus in Saudi Arabia: A multicenter retrospective study. *World J Diabetes* 2024; In press

Core Tip: Given the increasing prevalence of diabetes in Saudi Arabia, this national study sheds light on vaccine practices for patients with diabetes mellitus in Saudi Arabia with regard to the Advisory Committee on Immunization Practices vaccine recommendations. The findings of this protocol will aid decision-makers in improving preventative vaccine care for patients with diabetes.

INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disorder characterized by long-term elevated blood sugar levels due to insufficient insulin production, insulin resistance, or both[1]. Globally, data from the International Diabetes Federation reveals that in 2021, approximately 537 million adults worldwide were affected by DM. Projections suggest that this number is expected to increase to 643 million by 2030 and further escalate to 783 million by 2045[2]. In Saudi Arabia, DM impacts roughly 20% of the adult population, with projections indicating that by 2030, the number of cases will more than double[3].

Worldwide, the burden of DM has led to approximate health expenses of 966 billion United States dollars. These expenses are projected to surpass 1.054 trillion United States dollars by 2045[4]. In Saudi Arabia, the escalating prevalence of DM is emerging as a significant contributor to medical complications and fatalities, imposing an economic burden measured at 17 billion Saudi riyals in 2018[5].

Vaccinations play a crucial role in preventing infectious diseases and promoting immunity, particularly for individuals with DM. This significance is evident in the 2011-2020 Global Vaccine Action Plan, built on the ideal that "The benefits of immunization to be equitably extended to all people"[6]. This includes high-risk groups vulnerable to vaccine-preventable diseases, such as patients with chronic and immune-compromising diseases[7]. Factors like impaired immunity, a prolonged course of the disease, poor diabetes control, hyperglycemia, and comorbidities make patients with DM more susceptible to infections and serious complications[8].

According to the World Health Organization, the mortality rate in cases of pneumococcal infection is estimated to be approximately 10%-20%, with rates exceeding 50% in high-risk populations. It is assumed that patients with DM who develop pneumonia-related complications face a nearly threefold higher risk of mortality in comparison to the general population[9]. Annually, influenza is responsible for approximately 10000 to 30000 fatalities, and individuals with DM have a sixfold

increased likelihood of hospitalization during an outbreak compared to those without DM[8]. Through extensive efforts to promote vaccination within this vulnerable population, which have shown promising results, a study indicated that the influenza vaccine effectively reduced rates of hospitalization and mortality, with a number needed to treat of 60, 319, and 250 for all-cause hospitalizations, specific hospitalization, and all-cause mortality, respectively[10]. Another study demonstrated a decline in the risk of invasive pneumococcal disease (adjusted odds ratio = 0.86, 95% confidence interval: 0.78-0.94) among vaccinated patients compared to unvaccinated patients, along with a shorter length of stay at the hospital (-1.27 ± 0.19 d, P = 0.0012)[11]. This reinforces the importance of implementing vaccine recommendations and strictly encouraging adherence to these vaccinations.

Similar to other adults and as recommended by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP), patients with DM should receive vaccinations against coronavirus disease 2019 (COVID-19), influenza, tetanus, diphtheria, and pertussis (Tdap), as well as tetanus and diphtheria boosters. Additionally, individuals with DM must also receive the pneumococcal vaccine, hepatitis B vaccine, human papillomavirus (HPV) vaccine, herpes zoster (Shingles) vaccine, measles, mumps, and rubella (MMR) vaccine, and chickenpox vaccine. The CDC/ACIP recommendations are summarized in Table 1[12].

Worldwide, adherence to these vaccinations among adult patients with DM has been investigated in a few single-center studies. A cross-sectional study conducted at Kent Hospital in the United Kingdom, involving 100 patients, revealed a notably low adherence rate to the ACIP recommendations for hepatitis B, pneumococcal, and influenza vaccines among patients with DM. Specifically, for the hepatitis B vaccine, 39% of vaccine-eligible patients reported non-compliance[13]. Additionally, a recent meta-analysis study noted that 27.8% of patients expressed reluctance to receive the COVID-19 vaccination[14].

To date, only three studies have been conducted in Saudi Arabia to assess vaccination adherence among patients with DM. These studies were either single-centered or

focused on only one to three vaccines. A study conducted in Taif City among 336 patients found that only 43.5% of patients with DM received the influenza vaccine, contradicting the 61% expected adherence rate reported in 2017[15]. Another study at King Abdulaziz University Hospital in Jeddah showed a very low uptake rate of influenza, pneumococcal, and hepatitis B vaccines among admitted patients with DM, with only 1.17% of the 832 participants receiving all three vaccines[16].

MATERIALS AND METHODS

This study was conducted over two phases. Phase I included an observational retrospective chart review from 13 diabetes care centers in Saudi Arabia. Subsequently, in phase II, we administered an online survey with electronic consent to patients with DM who have established care at those 13 diabetes care centers, aiming to gather additional information on socioeconomic, educational, and living status.

Participants' vaccine records were reviewed by two independent teams of physicians and assessed for adherence to the latest vaccine recommendations announced in 2023 by ACIP and the CDC. Demographic data were collected from each participant, including gender, age, education, monthly household income, and living status, which was divided into two categories: City (a large human settlement with a significant population and extensive facilities) and village (a smaller settlement situated in a rural area with a small population ranging from hundreds to thousands), as well as body weight. Additionally, we collected data on hemoglobin A1c (HbA1c) levels, pre-existing conditions, DM duration, healthcare sector (either governmental sector - a public sector that provides free health-related services for Saudi citizens - or private sector - centers that deliver health services for all residents of the country and are funded by self-pay or insurance), preference for diabetic care (whether primary health care centers - centers provided by the Ministry of Health to offer primary health care to the regions it serves through applying a comprehensive care strategy for family medicine - or diabetes care centers - a center with a specialized diabetologist or endocrinologist; or none), frequency of diabetes provider visits (monthly, quarterly, annually, or none), diabetes

regimen (oral medications, insulin, insulin and oral medications, no medications), frequency of total daily medications, and previous hospitalization due to diabetes complications. Finally, data about the reasons for non-adherence to vaccinations among non-vaccinated patients with DM were collected, with patients choosing one of several reasons: "I do not know the importance of these vaccines for diabetes", "fear of side effects", "the vaccines were not suggested by the doctor", "I think the vaccine is not important", "not educated about the importance of vaccines by the doctor", "lack of vaccine", or "reason not disclosed".

We expressed categorical variables as frequencies and percentages, while continuous variables were presented as means and standard deviations or as medians and minimum-maximum ranges. To compare continuous variables between two groups, we utilized an independent Student's *t*-test, while a one-way ANOVA was employed for the comparison of more than two groups. Additionally, we utilized the Tukey test for multiple comparisons of the subgroups. A predetermined significance level of $P < 0.05$ was used to detect differences between study groups. The statistical analysis was conducted using the SPSS version 26.0. Bar diagrams were generated using GraphPad Prism version 9.0. The study protocol (607-43-6007) received IRB approval from the Regional Research Ethics Committee, Ministry of Health, Saudi Arabia.

RESULTS

Baseline characters

Out of 1000 eligible patients whose charts were reviewed in phase I, a total of 709 adult patients with DM consented and participated in phase II, being included in this study. Among the 709 adults with DM surveyed, the majority were between 46 and 55 years old, with 55.7% of participants being female. Most patients were educated, with 55.9% having a bachelor's degree. The majority of participants in our study had a long-standing disease of more than 10 years (42.5%). Baseline characteristics are depicted in Table 2.

Rate of vaccinations among study participants

Figure 1 illustrates the varied vaccination rates among the study participants. It is notable that a small minority, 10.01% (n = 71), have never been administered any form of vaccine. Conversely, a substantial majority, 85.89% (n = 609), have received at least one dose of the COVID-19 vaccine. Additionally, 34.83% (n = 247) of participants had been administered the annual influenza vaccine. However, the reception for other vaccines was notably lower, with only 2.96% (n = 21) having received the herpes zoster vaccine, 2.11% (n = 15) the Tdap vaccine, and a mere 1.12% (n = 8) being administered the HPV vaccine.

Impact of care site on vaccination rates

A one-way ANOVA was conducted to determine if there is a relationship between the site of care and the frequency of vaccines received by patients. Patients were classified into three groups according to their care site: Primary care center, provided by the Ministry of Health to offer primary health care to the region it serves, applying a comprehensive care strategy for family medicine (n = 256), diabetes center (n = 296), and no designated center of care (n = 157). One-way ANOVA indicated the presence of a statistically significant difference between sites of care. Post-hoc Tukey HSD test revealed that when compared to the patients who receive care from the diabetes center, the patients who have no designated center for DM care had a significantly lower mean frequency of vaccines received (mean different = 0.23, P = 0.015). In addition, no significant difference was found between the other groups (Figure 2).

Income-level disparities in vaccine uptake

A one-way ANOVA was conducted to determine if there is a relationship between the frequency of vaccines received and different income levels. Patients were classified into five groups according to their income level: Not disclosed (n = 265), > 9000 Saudi Arabian Riyal (SAR) (n = 145), 6000-9000 SAR (n = 67), 4500-5999 SAR (n = 186), < 4500 SAR (n = 46). One-way ANOVA indicated the presence of a statistically significant

difference between the income groups. Post-hoc Tukey HSD test revealed that, when compared to the > 9000 SAR income group, the 4500-5999 SAR and the 6000-9000 SAR income groups had a significantly lower mean frequency of vaccines received (mean different = 0.25, P = 0.042, and mean different = 0.38, P = 0.014) respectively. In addition, no significant difference was found between the other groups (Figure 3).

Vaccination uptake across various educational levels

A one-way ANOVA was conducted to determine if there is a relationship between the frequency of vaccines received and the educational level of the patients. Patients were classified into four groups according to their education level: Less than primary school (n = 36), school (n = 225), graduate (n = 396), and postgraduate (n = 52). One-way ANOVA indicated a non-significant difference between the different education groups with a P-value of 0.233 (Figure 4).

Comparison of vaccination rates between hospitalized and non-hospitalized patients with diabetes

An independent t-test was performed to compare the frequency of vaccines received by diabetic patients with a history of hospitalization to those without. As seen in Figure 5, the analysis concluded that the group with a hospitalization history (mean = 1.42, SD = 0.83) received a significantly higher frequency of vaccinations [$t(707)$ = 3.10, P = 0.002] compared to the non-hospitalized group (mean = 1.20, SD = 0.78).

Comparative analysis of vaccination rates between city and village residents

We performed an independent t-test to compare the frequency of vaccines received between city residents and village residents. The test concluded that village residents (mean = 1.53, SD = 0.93) had received a significantly higher frequency of vaccinations [$t(707)$ = 2.33, P = 0.02] than city residents (mean = 1.33, SD = 0.79) (Figure 6).

Comparison of vaccination adherence between patients in government and private healthcare sectors

We performed an independent *t*-test to compare the frequency of vaccines received between the patients receiving care from government hospitals and the patients receiving care from private hospitals (Figure 7). The results concluded that patients in government sectors (mean = 1.40, SD = 0.82) had significantly higher adherence to vaccinations [$t(707) = 2.22$, $P = 0.02$] than patients in private sectors (mean = 1.24, SD = 0.80).

Comparative analysis of vaccination frequency in relation to glycemic control levels

We performed an independent *t*-test to compare the frequency of vaccines received between those with HbA1c < 8% and those with HbA1c > 8% (Figure 8). The results concluded that patients with HbA1c > 8% (mean = 1.41, SD = 0.86) had received a significantly higher frequency of vaccinations [$t(707) = 2.14$, $P = 0.03$] than patients with HbA1c < 8% (mean = 1.26, SD = 0.71).

Barriers to vaccine adherence in non-vaccinated patients with DM

Our survey has shown that 71 out of 709 participants did not receive any vaccine. Table 2 demonstrates the most commonly reported barriers to receiving vaccination by patients with DM. The most prevalent reasons were lack of knowledge about the vaccines' importance and fear of side effects, reported by 29.57% ($n = 21$) and 28.16% ($n = 20$), respectively. On the other hand, lack of vaccines was the least commonly disclosed barrier, reported by only 2.81% ($n = 2$).

DISCUSSION

The findings from 709 patients with DM in Saudi Arabia showed that 34.83% of participants received the annual influenza vaccine, and 85.89% received at least one dose of the COVID-19 vaccination. However, there is generally a low rate of other vaccinations, including herpes zoster, Tdap, pneumococcal, and HPV vaccines. In Saudi

Arabia, MMR and varicella (chickenpox) vaccinations are included in the Saudi national vaccine schedule and are required for enrollment in the public education system[17].

Vaccine recommendations delivered to patients, either from their family physicians or specialists, can have an impact on vaccination acceptance by the patient[18]. In our study, we showed that participants without a designated care center exhibited significantly lower mean frequency of vaccination rates when compared to those who received care from a diabetes center. This finding is consistent with another study that showed higher vaccination coverage among patients reporting frequent physician visits[19]. Interestingly, the vaccination rates when comparing primary health care centers and specialized diabetic centers were not significantly different in our report. This contrasts with another report that considered visits to specialists as an independent factor in pneumococcal vaccination compared to family doctors[20]. Additionally, another study reported that patients with DM expressed more trust and willingness to take vaccines when advised by their diabetologist compared to family physicians, at rates of 80.9% and 50.9%, respectively[21].

The impact of socioeconomic status on vaccination rates has been investigated in previous studies. Research conducted in the United States, Thailand, and South Korea has shown that socioeconomic factors are related to unvaccinated status, especially among vulnerable groups such as young adults, individuals without insurance, low-income families, and those lacking access to medical care[22-24]. Our findings align with these studies, highlighting a significantly positive correlation between income levels and vaccination status. In our study, higher income emerged as an important factor associated with the likelihood of being vaccinated.

Regarding education level, findings from previous studies have been conflicting, particularly in relation to the association between education level and vaccination status. A study conducted in South Korea reported that individuals with higher education levels had lower vaccination rates[23]. In our study, we observed a non-statistically significant difference in vaccination status among individuals with varying educational levels, ranging from those below primary school to postgraduates. On the

contrary, multiple previous studies have reported a significant positive correlation between higher educational levels and increased vaccination rates. For instance, a study conducted in Turkey aimed at determining vaccine awareness among patients with DM found a significant positive correlation between influenza vaccine acceptance and education level, suggesting that a higher education level increases the likelihood of accepting the vaccine[25]. Similarly, a study in Turkey also determined that receiving pneumococcal and influenza vaccinations is associated with higher education levels in patients with DM[26]. Additionally, previous studies in Austria, the United States, and Poland reported that individuals with high educational levels show an increase in vaccination coverage[24,27,28]. However, other studies conducted in Italy, China, and Spain reported that low vaccination rates were correlated with high educational levels[24,29,30].

In our current analysis, one of our interests was to investigate whether a previous history of hospitalization could affect the decision of DM patients to receive the CDC/ACIP-recommended vaccines. Our data indicated a significantly higher uptake of vaccines among patients with DM who have a history of hospitalization compared to those who have never been hospitalized due to DM complications. The results presented in a study by Lohan *et al*[31] provide a possible explanation for this finding. The study found an increase in vaccine coverage for influenza, Tdap, and pneumococcal vaccines in patients with DM after being admitted to an endocrinology department. Adherence to vaccines was especially noted in the department units that had an inpatient clinical pharmacist involved. This could be attributed to the fact that clinical pharmacists are more attentive to the patient's medication report and possess skills in educating patients about the importance of vaccinations, thereby facilitating higher vaccine compliance[31]. This privilege of direct access to physicians, clinical pharmacists, and nurses who can provide information about the vaccines and address the patient's concerns may explain the increased rate of vaccination in patients with a history of DM-related hospitalizations. Additionally, our study's findings align with the results of the study of Hung *et al*[32], which demonstrated an increase in influenza

vaccine uptake in patients with DM who reported being hospitalized during the preceding year.

One might assume that patients residing in urban areas, such as cities, would be more likely to get vaccinated for several reasons, including high accessibility to healthcare services, the abundance of vaccine promotion campaigns, increased awareness about infection risks, and the perceived effectiveness of vaccines. However, studies examining the relationship between residency (urban *vs* rural areas) and vaccine adherence have reported inconsistent findings. A cross-sectional study conducted in China investigated the rate of COVID-19 vaccination among hospitalized patients with DM and found that individuals living in rural areas were significantly less likely to be vaccinated with the COVID-19 vaccine[33]. Another study, which included two million patients with chronic diseases, including DM, documented that patients living in rural areas had significantly higher pneumococcal vaccination rates but lower influenza vaccination rates[34]. Conversely, our results showed a significantly higher adherence rate to vaccinations among village residents compared toxicity residents. This could be explained by the Ministry of Health's efforts in rural areas and the periodic vaccination campaigns sent to villages. Additionally, the close connection among people living in village communities could facilitate the spread of vaccination awareness among them. Our results align with findings from a study that evaluated the uptake rate of the pneumococcal vaccine in the United Kingdom among two million at-risk patients, showing higher vaccination rates in patients living in rural areas[35]. An additional large-scale study in China found a higher hesitancy rate for COVID-19 vaccination in residents of rural areas[36].

The impact of governmental and private healthcare sectors on vaccine coverage among patients with DM is an interesting area to investigate due to the lack of research in this domain. Our results revealed that patients with DM who were followed up in governmental centers received more vaccines compared to those seeking healthcare in private centers. This difference might be explained by financial reasons, as vaccines are

provided for free in governmental centers, whereas the cost of vaccines is either covered by patients' own funds or through insurance claims in private centers.

Poor glycemic control increases the likelihood of infection-related morbidity and mortality in patients with DM; thus, vaccination is critical for this population. In our study, patients with poor glycemic control unexpectedly had higher vaccination rates compared to patients with better glycemic control. This could be because healthcare providers may prioritize vaccination for patients with poor glycemic control. Conversely, another study conducted in South Korea revealed that better glycemic control, evidenced by lower HbA1c levels, was associated with higher vaccine coverage. This was rationalized as poor glycemic control correlating with less adherence to medical advice and, therefore, lower vaccine coverage[23].

The adherence of patients diagnosed with DM to the recommended vaccinations is influenced by their attitudes and perceptions, which are shaped by personal beliefs and guidance from healthcare providers. In our analysis, we identified knowledge insufficiency and concerns regarding the potential side effects of vaccinations as the most prevalent barriers among non-vaccinated patients with DM. This observation aligns with findings from a study conducted in Spain, where fear of adverse events was reported as the most prevalent cause of non-adherence to the influenza vaccine among females with DM[37]. Additional reported barriers include misconceptions about the vaccines' efficacy in preventing infectious diseases and their complications, needle aversion, concerns about vaccination costs, and issues related to vaccine availability[38,39]. In our current study, only 2.81% of the participants justified missing their vaccine due to the shortage of vaccine supply at the centers.

The crucial role of healthcare providers, including physicians, nurses, and pharmacists, in shaping the vaccination attitudes and perceptions of patients with DM is notable. This was evident in the study by Lewis-Parmar and McCann[40], which highlighted a pronounced fourteen-fold increase in the vaccination uptake rate among patients with DM following the delivery of vaccination recommendations by a healthcare provider[40]. Barriers hindering the effectiveness of healthcare providers' role

in motivating the adherence of patients with DM to recommended vaccinations include inadequate knowledge about these vaccines and limited participation by diabetologists and endocrinologists in guiding patient attitudes toward vaccines[41].

This calls for several key recommendations, including the utilization of various communication mediums such as social media and awareness campaigns to effectively correct any misconceptions. Furthermore, integrating a reminder system into electronic medical records can aid healthcare providers in educating and encouraging patients with DM to take their recommended vaccinations. Additionally, implementing the Standing Order Protocol, which allows non-physician medical providers to assess the patient's eligibility for vaccines and administer them without a physician's order, can be an effective strategy.

CONCLUSION

In Saudi Arabia, patients with DM showed higher vaccination rates for annual influenza and COVID-19 vaccines compared to other vaccinations such as herpes zoster, Tdap, pneumococcal, and HPV. Factors such as vaccine recommendations provided by family physicians or specialists, the site of care, income level, DM-related hospitalization history, residency site, HbA1c level, and health sector type can significantly influence the vaccination rate in patients with DM. This signifies the need for large-scale research in this area to identify additional factors that might facilitate adherence to CDC/ACIP vaccine recommendations in patients with DM.

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1	Ilaria Dicembrini, Giovanni Antonio Silverii, Alessandra Clerico, Riccardo Fornengo et al. "Influenza: diabetes as a risk factor for severe related-outcomes and the effectiveness of vaccination in diabetic population. A meta-analysis of observational studies", Nutrition, Metabolism and Cardiovascular Diseases, 2023 Crossref	21 words — < 1%
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