

Influenza vaccine uptake and its determinants among adult population in the Kingdom of Bahrain: a cross-sectional study to identify areas for intervention

Influenza
vaccine uptake
in Bahrain

1577

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Abstract

Purpose – Seasonal influenza epidemics accounted for significant morbidity and mortality loads worldwide despite the availability of a safe vaccine as an efficient tool against severity of the disease. However, the uptake of the latter was sub-optimal. This study aims to identify predictors and barriers related to seasonal influenza vaccine uptake in the Kingdom of Bahrain.

Design/methodology/approach – A cross-sectional study enrolled 502 individuals attending primary healthcare centers in Bahrain for ambulatory care between July and August 2022. The data were collected using an interviews-based questionnaire which included questions on demographic data, knowledge and attitudes and practices toward influenza vaccine. The authors identified the barriers as well as the determinants of the vaccine uptake and its recommendation to others.

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Findings – The mean age of participants was 35.07 years (SD = 13.9). Most of the respondents were Bahraini (86.5%) and 53.4 % were females. The results revealed that 34.1% have previous information about the influenza vaccine and 36.9% versus 69.9% are willing to receive the vaccine or advice it to others, respectively. Determinants of vaccine uptake were identified.

Originality/value – This study confirmed a sub-optimal influenza vaccine acceptance in the general community of Bahrain despite a global access in primary care. Health professionals need to be more proactive in mobilizing the community and particularly females toward influenza vaccination.

Keywords Influenza vaccine, Knowledge, Attitudes, Uptake, Source of information, Bahrain

Paper type Research paper

Introduction

Seasonal influenza epidemics have been a major source of illness and death worldwide over almost the past 100 years despite the availability of an effective vaccine (Cox, 2014). Many published studies have attributed the reluctance in the uptake of seasonal influenza vaccine to demographic, sociocultural factors as well as misperceptions about the benefits and the harms of the vaccine (Alsuwaidi, Hammad, Elbarazi, & Sheek-Hussein, 2023; Flannery *et al.*, 2018; Grohskopf *et al.*, 2016, 2020). More recently, the COVID-19 pandemic and its impact on the perceptions and the practices of humans has raised hopes that people are now more willing to take annual vaccinations, particularly seasonal influenza vaccines as a measure to reduce the mortality and morbidity load of seasonal influenza. Furthermore, new strategies of severe acute respiratory infections surveillance are recently focused on monitoring influenza virus and SARS-COV2 infections and related burdens after the COVID-19 pandemic, which raised the importance of influenza disease management and prevention including vaccination (Lana *et al.*, 2020; Petersen *et al.*, 2020; Zheng *et al.*, 2020).

Many studies focused on influenza vaccine uptake identified barriers and motivators (Bhat-Schelbert *et al.*, 2012; Kharbanda *et al.*, 2011; Matsui *et al.*, 2011). They emphasized the importance of accurate information about the high-risk factors, the severity of the disease, the safety of the vaccine as well as the need for innovative communication initiatives and approaches to mobilize communities. In the context of Arab Gulf countries, motivators included a medical source of indication and barriers are mainly related to knowledge about the vaccine, a perceived low effectiveness, safety concerns and perceived low severity of the influenza (Abalkhail *et al.*, 2017; Alolayan, Almotairi, Alshammari, Alhearri, & Alsuhaibani, 2019; Sales, Syed, Almutairi, & Al Ruthia, 2021).

Many studies confirmed the important role of health professionals as source of information for the vaccine uptake by high-risk groups. Surprisingly, they were sometimes advising against the vaccine particularly for pregnant women and healthy immune-competent persons (Dhaouadi *et al.*, 2022). This is coherent with their sub-optimal uptake of this vaccine particularly among female health workers due to the fear from side effects despite the availability of the vaccine (Mojamamy, Albasheer, & Mahfouz, 2018). Moreover, a recent study reported that parental perception and beliefs about seasonal influenza and its vaccines affected their intentions to vaccinate their children, which resulted in a high proportion of parents in the Arab region who are unwilling to vaccinate their children against influenza (Fadl *et al.*, 2023). A systematic review in these countries revealed that in addition to accessibility, recommendation from authorities and evidence-based training about the vaccine and its indications are key determinants to improve its uptake among healthcare workers (Alfouzan, Almujiil, Demyati, & AlOtaybi, 2022).

Immunization has always been among the top priorities of the healthcare system in the Kingdom of Bahrain. The vaccination program is implemented mainly through the governmental public healthcare system, beside the private sectors. Vaccines are provided

free of charge to everyone residing in the country irrespective of their nationalities. Moreover, Bahrain reported inclusion of influenza vaccine in their National Immunization Program (NIP) and recommended it for all the WHO strategic advisory group of experts on immunization (SAGE) groups (Attia, Abubakar, Bresee, Mere, & Khan, 2023; Saleem, Ahmed, Faisal, Abdulhadi, & Mirza, 2022). Although a recent meta-analysis suggested varied COVID-19 vaccine hesitancy prevalence across different Arab countries (Alam *et al.*, 2023), the Arab Gulf Cooperation Council (GCC) countries reported a relatively high uptake of the COVID-19 vaccine and its booster doses (Itani *et al.*, 2022), yet available information from different sources still point out to relatively low rates of uptake of influenza vaccination among the adult Bahraini population, despite its recommendation for all SAGE recommended groups and its availability at the primary healthcare (Attia, *et al.*, 2023). The bottle necks seem to be rather related to misconceptions or inappropriate information related to the influenza and its vaccine. There is a need to investigate the different barriers hampering an optimal use from the perspective of users to provide the evidence base for pertinent policies to address this gap.

This study aims to estimate the proportion of adult Bahraini willing to receive the influenza vaccine and to identify the source of information and perceived barriers for its uptake. Customized communication and promotion programs will ultimately benefit from these findings.

Methods

A cross-sectional study was conducted among adults attending primary healthcare centers in Bahrain. Two main outcomes are targeted: the willingness to uptake of the vaccine as well as its recommendation to others. Independent variables included sociodemographic, identification of high-risk target groups, attitudes toward the vaccine as well as source of information about the vaccine.

Sampling process and data collection

One health center from each of the five health regions in the Kingdom of Bahrain was randomly selected for data collection, namely 'National bank of Bahrain Health Center', 'Sh. Sabah Al Salem Health Center', 'Jidhafs Health Center', 'East Riffa Health Center' and 'Budayia Health Center'. A stratified clustered random sampling approach permitted to enroll eligible participants in the study from adult patients attending primary healthcare centers in Bahrain. The sampling method was intended to achieve the best generalizability, as patients consulting for ambulatory care at the primary level are the most representative of the general population in the absence of a house survey. This is particularly true in Bahrain, where the geographic accessibility and coverage by health centers is optimal. The study team has approached the participants to solicit their interest and consent to enroll in the study. The data were collected by face-to-face interview-based survey conducted by the researchers in Arabic and English languages as both versions were available with them. The survey included questions on demographic data, knowledge and attitudes and practices toward influenza vaccine using a five-point Likert scale. Inclusion criteria: patients (Bahrainis and non-Bahrainis) attending primary healthcare centers in the Kingdom of Bahrain. Exclusion criteria: Individual refusal to participate in the survey.

Sample size

The sample size was determined based on the random sample calculation formula multiplied by a design effect to account for enrolling from the same centers.

$$n = \frac{z^2 P(1-P)}{d^2} * \text{design effect}$$
, where, n = sample size, $z = 1.96$, $P = 0.6$, $d = 6\%$ and design effect = 2. The needed sample size is 512 individuals.

Data analysis

The data were first entered on an excel sheet, double-checked and then exported to the statistical software for analysis. Descriptive statistics, including means, standard deviation and percentages permitted to describe continuous variables. Chi-square test or Fischer's exact test tested the association between the categorical variables. The binary logistic regression model analysis was performed to assess the relative importance of factors determining with intent to uptake flu vaccine this year and recommendation of flu vaccine for others considering confounders and effect modifiers. A p-value less than 0.05 were considered as statistically significant. Adequacy of the model was tested by the Hosmer-Lemeshow test ($p > 0.05$). All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS- version 28) and GraphPad Prism 9 software for graphical presentations.

Ethical consideration

This study was approved by the Research and Ethics Committees of the College of Medicine and Medical Science at Arabian Gulf University (approval number: E032-PI-4/19). The participants provided written informed consent and were interviewed in private rooms located in the selected primary healthcare centers to ensure confidentiality.

Results

Participant characteristics

Overall, 502 out of 512 expected (98.6%) respondents answered the survey between July 20 and August 28, 2022. Sociodemographic data indicated that mean age was 35.07 years ($SD = 13.9$). Most of respondents ($n = 268$, 53.4%) were female and the majority were Bahraini nationals (86.5%). Regarding the age group category, the majority of the respondents were 20–40 years old (61%), followed by 41–60 years old (23.3%), less than 20 years old (9.8%) and more than half of the respondents (62.1%) were married. Distribution of the sample according to occupation showed that (46.5%) were employees, (18.9%) were students and (11.2%) were retired. More than three quarters of the respondents (86.3%) had public insurance coverage, while (10.4%) had a private one (Table 1).

Source of information about the influenza vaccine

Information about the influenza vaccine is mainly conveyed by the family members, the health professionals (treating physician, nurse and pharmacist) as well as the platform of information of the ministry of health. However, the social media remain an important source of information to the individuals (Figure 1).

Interestingly, the study group recognized elderly, pregnant women and children as high-risk groups eligible to receive the flu vaccine; however, they did not identify the health professionals as such. Furthermore, patients suffering from chronic diseases were identified apart from elderly (Figure 2). Flu-vaccine hesitancy is justified by a perceived low severity of influenza, the preference of acquiring natural immunization by contracting the wild virus, a reduced effectiveness of the vaccine compared to a high risk of vaccine-related side effects (Figure 3).

Determinants of intention to take the influenza vaccine and its recommendation to others

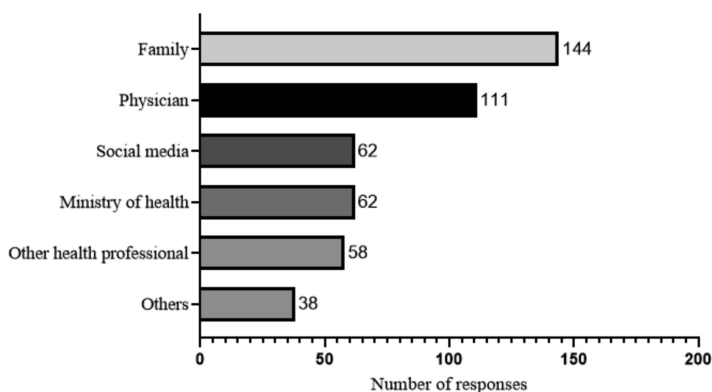
Our study results revealed that 34.1% (171/502) have previous information about the influenza vaccine, on the other hand 36.9% (185/502) individuals intend to receive the influenza vaccine in the current year and males are more willing to receive the flu vaccine compared to females (43.2% vs 31.3%, $p = 0.006$). Regarding nationality, the results showed that non-Bahraini participants are more willing to receive the flu vaccine compared to Bahraini (51.5% vs 34.6%, $p = 0.007$).

Characteristic	n (%)	Influenza vaccine uptake in Bahrain
<i>Gender</i>		
Male	234 (46.6)	
Female	268 (53.4)	
<i>Nationality</i>		
Bahraini	434 (86.5)	
Non-Bahraini	68 (13.5)	
<i>Age group</i>	Mean $\pm$ SD = 35.07 $\pm$ 13.9	
<20 Years	49 (9.8)	
20–40 Years	306 (61.0)	
41–60 Years	117 (23.3)	
>60 Years	30 (6.0)	
<i>Marital status</i>		
Single	182 (36.3)	
Married	312 (62.1)	
Divorced or widowed	8 (1.6)	
<i>Occupation</i>		
Student	95 (18.9)	
Employee	234 (46.5)	
Self-employed	28 (5.6)	
Housewife	50 (10.0)	
Retired	56 (11.2)	
Unemployed	39 (7.8)	
<i>Health coverage</i>		
Public coverage	428 (86.3)	
Discounted	16 (3.3)	
Private coverage	52 (10.4)	

Source(s): Table by authors

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Table 1.
The sociodemographic characteristics of participants (n = 502)



Source(s): Figure by authors

Figure 1.
Source of information about the influenza vaccine uptake

The results showed that 66.9% are willing to recommend the influenza vaccine to others, however, males are more likely to advise the others to receive the flu vaccine than females (71.8% vs 62.7 %, $p = 0.03$). [Table 2](#) and [Table 3](#).

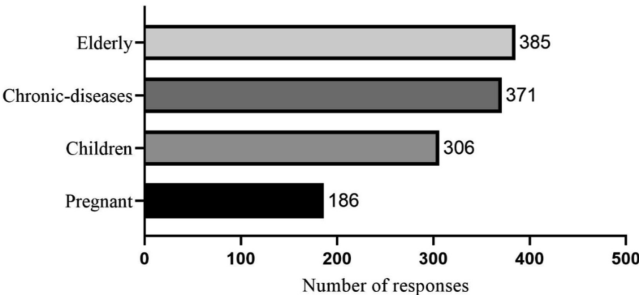
The results of the binary logistic regression examining the association between flu vaccinations intended uptake and a set of predictors (independent variables) are shown in Table 4. Female participants were 0.621 (CI: 0.412–0.938, $p = 0.024$) times less likely to be willing to uptake the vaccine. As expected, participants who indicated that they had enough information about the vaccine were 2.159 (CI: 1.426–3.269, $p < 0.001$) times more likely to accept the vaccine. Similarly, participants who indicated that the vaccine reduces spread of influenza in the community were 7.657 (CI: 4.286–13.678, $p < 0.001$) more favorable to its uptake (Table 4).

Regarding the advice of the flu vaccine to others, the results of the binary logistic regression model revealed that female participants were 0.609 (CI: 0.394–0.942, $p = 0.026$) times less likely to advise others to take the vaccine. Whereas the results indicated that participants who received enough information about the vaccine were 3.567 (CI: 2.151–5.916, $p < 0.001$) times more likely to advise others to take it. In addition, participants who indicated that the vaccine reduces spread of influenza in the community were 7.668 (CI: 4.910–11.975, $p < 0.001$) times more likely to advise others to take the vaccine (Table 5).

The independent samples t -test revealed that there was no significant difference between the mean ages of participants who are willing to receive the influenza vaccine (Mean = 35.16 years, S.D. = 14.64) and the others who are not (Mean = 35.02 years, S.D. = 13.48). Likewise, the results indicated that there was no statistically significant difference between the mean age of participants who recommend the flu vaccine to others (Mean = 35.04 years, S.D. = 14.17) and those who will not recommend it (Mean = 35.12 years, S.D. = 13.49).

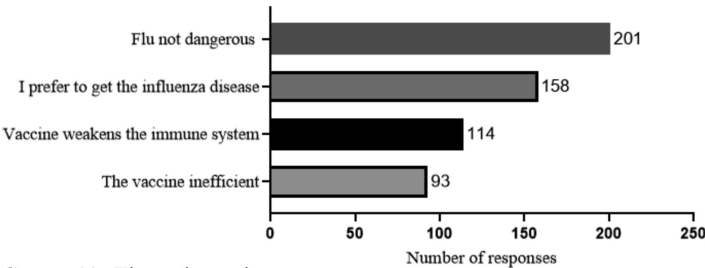
Discussion

This cross-sectional study was undertaken in the primary healthcare centers of Bahrain among patients to reveal the importance of the flu vaccine uptake and its willingness to



Source(s): Figure by authors

Figure 2.
Eligible target groups
for the influenza
vaccine according to
interviewees



Source(s): Figure by authors

Figure 3.
Reasons for refusing to
receive the influenza
vaccine

				Influenza vaccine uptake in Bahrain
Characteristic	Flu vaccination (last 12 Months)		<i>p</i> -value	1583
	Yes n (%)	No n (%)		
<i>Gender</i>				
Male	101 (43.2)	133 (56.8)	0.006*	
Female	84 (31.3)	184 (68.7)		
<i>Nationality</i>				
Bahraini	150 (34.6)	284 (65.4)	0.007*	
Non-Bahraini	35 (51.5)	33 (48.5)		
<i>Marital status</i>				
Single	74 (40.7)	108 (59.3)	0.272	
Married	107 (34.3)	205 (65.7)		
Divorced or widowed	4 (50.0)	4 (50.0)		
<i>Age group</i>				
<20 Years	22 (44.9)	27 (55.1)	0.355	
20–40 Years	105 (34.3)	201 (65.7)		
41–60 Years	48 (41.0)	69 (59.0)		
>60 Years	10 (33.3)	20 (66.7)		
<i>Occupation</i>				
Student	40 (42.1)	55 (57.9)	0.561	
Employee	85 (36.3)	149 (63.7)		
Self-employed	13 (46.4)	15 (53.6)		
Housewife	15 (30.0)	35 (70.0)		
Retired	20 (35.7)	36 (64.3)		
Unemployed	12 (30.8)	27 (69.2)		
<i>Health coverage</i>				
Public coverage	150 (35.0)	278 (65.0)	0.107	
Discounted	6 (37.5)	10 (62.5)		
Private coverage	26 (50.0)	26 (50.0)		
<i>Enough information about vaccine</i>				
No	101 (30.5)	230 (69.5)	<0.001*	
Yes	84 (49.1)	87 (50.9)		
<i>Vaccine reduces spread of flu</i>				
No	15 (10.1)	134 (89.9)	<0.001*	
Yes	170 (48.2)	183 (51.8)		
Note(s): *Statistically significant at the 0.05 level				Table 2. Factors associated with the uptake and willingness to receive the flu vaccine this year – bivariate analysis
Source(s): Table by authors				

recommend it to others as a surrogate of acceptance. The prevalence of uptake of 36% in our study is suboptimal in a context, where the flu vaccine is available and free for all high-risk groups at the primary healthcare-level. This proportion is higher than the prevalence around 20% reported in Europe (Korkmaz, Paşali Kilit, Onbaşı, Mistanoglu Özatağ, & Toka, 2019). On the other hand, it was lower than this proportion in the Kingdom of Saudi Arabia (Almusalam, Ghorab, & Alanezi, 2019) as well as other countries at the global level (Attia *et al.*, 2023; Chen & Stoecker, 2020). This finding agrees with other studies performed at the global level (Bof de Andrade, Sayuri Sato, Moura, & Ferreira Antunes, 2017), the eastern Mediterranean region (Kharroubi *et al.*, 2021) and other Gulf Cooperation Countries (GCC). However, this proportion is significantly higher in other studies at the global and regional levels (Alshahrani & Zahrani, 2023; Barry, Aljammaz, & Alrashed, 2020; Takayama,

Factor	Advise others to receive the flu vaccine		<i>p</i> -value
	Yes n (%)	No n (%)	
<i>Gender</i>			
Male	168 (71.8)	66 (28.2)	0.030*
Female	168 (62.7)	100 (37.3)	
<i>Nationality</i>			
Bahraini	292 (67.3)	142 (32.7)	0.675
Non-Bahraini	44 (64.7)	24 (35.3)	
<i>Age group</i>			
<20 Years	37 (75.5)	12 (24.5)	0.088
20–40 Years	198 (64.7)	108 (35.3)	
41–60 Years	85 (72.6)	32 (27.4)	
>60 Years	16 (53.3)	14 (46.7)	
<i>Marital status</i>			
Single	128 (70.3)	54 (29.7)	0.470
Married	203 (65.1)	109 (34.9)	
Divorced or widowed	5 (62.5)	3 (37.5)	
<i>Occupation</i>			
Student	73 (76.8)	22 (23.2)	0.100
Employee	158 (67.5)	76 (32.5)	
Self-employed	16 (57.1)	12 (42.9)	
Housewife	28 (56.0)	22 (44.0)	
Retired	34 (60.7)	22 (39.3)	
Unemployed	27 (69.2)	12 (30.8)	
<i>Health coverage</i>			
Public coverage	284 (66.4)	144 (33.6)	0.106
Discounted	8 (50.0)	8 (50.0)	
Private coverage	40 (76.9)	12 (23.1)	
<i>Enough information about vaccine</i>			
No	14 (8.4)	152 (91.6)	<0.001*
Yes	171 (50.9)	165 (49.1)	
<i>Vaccine reduces spread of flu</i>			
No	52 (34.9)	97 (65.1)	<0.001*
Yes	284 (80.5)	69 (19.5)	
Note(s): *Statistically significant at the 0.05 level			
Source(s): Table by authors			

Table 3.
Factors associated
with recommendation
of flu vaccine to others
– bivariate analysis

Wetmore, & Mokdad, 2012). These discrepancies reflect different characteristics of study samples. Overall, our study shows a reasonable proportion among the general population., however, it is sub-optimal when compared to the target of 75% for high-risk groups as reported in other studies (Oakley, Bouchet, Costello, & Parker, 2021; World Health Organization, 2020).

Knowledge about high-risk groups identified elderly, patients with chronic diseases pregnant women and children is good while health professionals are still not recognized by patients as a target for this vaccine. This is expected from the perspectives of the general population which is mainly influenced by the messages of the awareness campaigns who tend to adapt their contents to the target groups in the community. Indeed, the source of information about the vaccine is dominated by the family and to a less extent by the treating

					Influenza vaccine uptake in Bahrain
Factor	C.OR* (95% C.I)	p-value	A.OR** (95% C.I)	p-value	
<i>Gender</i>					
Male	Ref		Ref		
Female	0.601 (0.417–0.866)	0.006**	0.621 (0.412–0.938)	0.024**	
<i>Nationality</i>					
Bahraini	Ref		Ref		
Non-Bahraini	2.008 (1.200–3.361)	0.008**	1.420 (0.800–2.521)	0.231	
<i>Enough information about vaccine</i>					
No	Ref		Ref		
Yes	2.199 (1.503–3.216)	<0.001**	2.159 (1.426–3.269)	<0.001**	
<i>Vaccine reduces spread of flu</i>					
No	Ref		Ref		
Yes	8.299 (4.679–14.719)	<0.001**	7.657 (4.286–13.678)	<0.001**	
Hosmer–Lemeshow goodness of fit statistic		$\chi^2 = 9.691$	p = 0.207		
Note(s): *C.OR: Crude odds ratio, **A.OD: Adjusted odds ratio and C.I: Confidence interval **Statistically significant at the 0.05 level Source(s): Table by authors					Table 4. Factors determining flu vaccine uptake (last 12 months) – bivariate and multivariate analysis

Factor	C.OR (95% C.I)	p-value	A.OR (95% C.I)	p-value	
<i>Gender</i>					
Male	Ref		Ref		
Female	0.660 (0.453–0.962)	0.031*	0.609 (0.394–0.942)	0.026*	
<i>Enough information about vaccine</i>					
No	Ref		Ref		
Yes	3.278 (2.088–5.145)	<0.001*	3.567 (2.151–5.916)	<0.001*	
<i>Vaccine reduces spread of flu</i>					
No	Ref		Ref		
Yes	7.678 (5.007–11.772)	<0.001*	7.668 (4.910–11.975)	<0.001*	
Hosmer–Lemeshow goodness of fit statistic		$\chi^2 = 4.366$	p = 0.498		
Note(s): *Statistically significant at the 0.05 level Source(s): Table by authors					Table 5. Factors determining advise the vaccine for others – bivariate and multivariate analysis

doctor. Noticeably, untrusted social media remain an important source of information for the community, similar findings were reported in other Arab populations as exposure to vaccine-related misinformation on social media may shape the behavior of the public toward the vaccines in general, and influenza vaccine in particular (Alfatease, Alqahtani, Orayj, & Alshahrani, 2021; Biswas, Ali, Ali, & Shah, 2022). This finding is corroborated by the determinants of vaccine uptake and recommendation to others (Hwang, 2020). Indeed, males, those who received pertinent information about this tool and those who perceive its benefits to reduce transmission of influenza virus in the community are those who are more likely to uptake the vaccine and advice it to others. Reluctance of females about the influenza vaccine reflects a gap in their knowledge about its safety for their health and fetus as reported elsewhere (Dhaouadi *et al.*, 2022), similar results were reported in Saudi Arabia and were

linked to lack of knowledge about the vaccine and concerns regarding its side effects (Albattat, Alahmed, Alkadi, & Aldrees, 2021). As participants reported that physicians and other healthcare professionals were among the main sources of information they receive about the influenza vaccine; this finding advocates for the need of better training of health professionals in this area, which is in line with other reports from other Arab countries (Alshammari, AlFehaid, AlFraih, & Aljadhey, 2014; Elbarazi *et al.*, 2021; Saddik *et al.*, 2022; Salam & Honein-AbouHaidar, 2023).

On the other hand, in agreement with other studies, the main barriers remain the low perceived susceptibility and severity of influenza contrasted with perceived exposure to side effects of sub-optimal influenza vaccine (Yan *et al.*, 2021).

Conducting the study on patients in health centers has a limitation as it might lead to a social desirability bias where individuals tend to provide an answer that would please the interviewer despite all the explanations and the ethical safeguards to secure the individuals (written informed consent, private interview room, emphasis on any risk to lose benefits).

Conclusion

The present study confirmed a sub-optimal uptake and acceptance of the influenza vaccine in Bahrain despite the availability of this preventive tool free of charge at the primary healthcare. The dominant source of influence remains the family, the health professionals and the social media. This finding supports the need to mobilize more intensively providers of health to promote this service using modern communication tools. Main source of vaccine hesitancy remains the lack of appropriate awareness related to safety and effectiveness of the vaccine compared to a low susceptibility and severity of influenza disease. This pattern of beliefs is shown to be a real barrier to the uptake of health tools as proposed by the health belief model. More studies on different high-risk groups using the mixed methods would permit a more comprehensive assessment of the communication and promotion strategies of influenza vaccine. More training of health professionals regarding the vaccine features and indications is required to promote this preventive tool and increase the uptake by the target groups and particularly females during pregnancy.

Acknowledgments

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Abbreviations: SAGE: Strategic Advisory Group of Experts, S.D: Standard deviation, C.OR: Crude odds ratio, A.OR: Adjusted odds ratio and C.I: Confidence interval.

Ethics approval and consent to participate: This study was approved by the Research and Ethics Committees of the College of Medicine and Medical Science at Arabian Gulf University (approval number: E032-PI-4/19). The participants were interviewed in closed rooms located in the selected primary healthcare centers. Confidentiality was secured.

Availability of data and material: The datasets generated and/or analyzed during the current study are not publicly available due privacy and confidentiality reasons but are available from the corresponding author on reasonable request.

Competing interests: The authors declared that they have no competing interests.

Authors' contributions: All authors conceived and designed the study; MAS, NA, SA, RB, JH, MA and SAK performed the research process and collected the data; AA and ABS performed the statistical analyses; ABS, AA and SAZ wrote the original draft of the manuscript; AA and ABS prepared the figures and tables; ABS, SAZ, MAS, NA and SAK edited and revised the manuscript; all authors have read and approved the final manuscript.

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