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Flu vaccination effectiveness in Tabuk City, Saudi Arabia

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ABSTRACT

Background: There are controversies about vaccination effectiveness of seasonal influenza and its wide variation across seasons and countries. **Objectives:** This study aimed to estimate the effectiveness of seasonal influenza vaccination among adult population in Tabuk City, Saudi Arabia.

Methods: This prospective cohort study included residents aged 18 years or older. 532 participants were divided regarding vaccination status into two equal groups: the first (vaccine group) received the current influenza vaccine, and the other (control group) received nothing. Data were collected through a structured questionnaire. The vaccine effectiveness was estimated based on self-reported data regarding the incidence of chest infection or flu-like illness (FLI) after the vaccination, duration of the FLI, ability to do the normal daily activity, seeking medical care, need for visiting a clinic, taking medications, and hospital admissions.

Results: The rate of chest infection after vaccination showed no significant difference between the two groups (p=0.879). The incidence of FLI in winter following vaccine intake was significantly higher in the vaccine group compared to the control (p=0.038). The FLI affected the daily life activities of 36 subjects (13.5%) belonging to the vaccine group compared to 28 subjects (10.5%) in the control group (p=0.286). Seeking medical service for the FLI was recorded in 7.5% and 4.5% of the vaccine and the control groups, respectively, with no significant difference (p=0.145).

Conclusions: The seasonal flu vaccine lacked significant effectiveness among adult population in Tabuk City, Saudi Arabia. Regularly improving the immunogenicity and efficacy of influenza vaccines seems a necessity.

Keywords: Effectiveness; Influenza; Saudi Arabia; Seasonal influenza; Vaccination; Tabuk

INTRODUCTION

Seasonal influenza is a highly infectious acute disease. It causes inflammation of the upper respiratory tract leading to a variety of symptoms, such as high fever, sore throat, coryza, body aches, and possibly lower respiratory tract illness [(1)]. It is caused by influenza A and B virus subtypes. Influenza A is the most common type in humans, and it has a characteristic high mutation rate, which is over 300 times faster than influenza B. The mutations in the virus antigenic proteins are attributed to antigenic drift and antigenic shift [(2)].

Globally, seasonal influenza affects about five million people, with approximately 500,000 deaths annually, particularly among young children and the elderly [(3)]. Also, it causes a substantial economic burden because of the associated complications, hospital admissions, and loss of productivity [(4)].

Vaccination can reduce the incidence of flu and lessen the severity of infection by eliciting strain-specific immunity. It constitutes the primary approach for controlling influenza and is recommended by most healthcare providers [(5, 6)].

In Saudi Arabia, seasonal influenza remains a threat with widespread cases and deaths. The prevalence of influenza-like illnesses during the holy pilgrimage in Saudi Arabia ranges from 8 to 78.2%. The Ministry of Health keeps the seasonal influenza vaccine available, free of charge to all Saudi citizens and residents, and it recommends the annual vaccine intake by healthcare professionals as well as the public to prevent influenza pandemics [(7-10)]. Concerns have emerged regarding the impact of influenza vaccination on the burden and severity of influenza. There are controversies about the vaccination effectiveness and its wide variation across seasons and countries [(11-13)].

There is a necessity for monitoring the direct protective effect of the vaccine each season. Therefore, this study was conducted to estimate the effectiveness of seasonal influenza vaccination among adult population in Tabuk City, Saudi Arabia.

METHODS

Study design and settings

This prospective cohort study was conducted in Tabuk City, which is located at the North-Western area of Saudi Arabia.

Sample size calculation

The study sample size was calculated based on an expected incidence in the unexposed of 0.03, an assumed relative risk of 3, a confidence level of 95%, and a desired power of 80. The total sample size was 532.

Eligibility criteria

Residents of Tabuk City aged 18 years or older were included in the study. The criteria for exclusion included history of immediate hypersensitivity reactions to eggs

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(because the vaccine may contain small amounts of residual egg protein) or thimerosal (a preservative in the vaccine), previous vaccination against influenza, and pregnancy or planned pregnancy within three months.
Participants were divided regarding vaccination status into two equal groups (262 participants each): the first group (vaccine group) received injections of the current quadrivalent influenza vaccine (split virion, inactivated), and the other group (control group) did not take either the vaccine or placebo. The two groups were well matched regarding age, gender, work, and the presence of chronic comorbidities.

Outcome measures

The vaccine effectiveness was estimated based on self-reported data regarding the incidence of chest infection or flu-like illness (FLI) after the vaccination, duration of the FLI, ability to do the normal daily activity, seeking medical care, need for visiting a clinic, taking medications, and hospital admissions. Flu-like illness was defined as acute respiratory illness with acute-onset cough combined with systemic symptoms, such as fever, headache, and myalgia.

Data collection methods

The study was conducted between January 2022 and March 2022. The data were collected at the beginning of the winter season (at the time of vaccine uptake) where participants' cell phone numbers were registered, then the outcome measures were reported at the end of the season. Data were collected through a structured questionnaire with information about the participants' age, gender, nationality, occupation, smoking, chronic illness, developing chest infection after the vaccination, FLI during this winter, duration of FLI, seeking medical care, visiting a clinic, taking medications or hospital admissions for this illness, and finally whether the FLI affected the daily activities or not. Further data about developing COVID-19 infection, intake of COVID-19 vaccine, and the doses of the vaccine were also recorded.

Ethical considerations

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The study was approved by the Ethics Committee of King Salman Armed Forces Hospital, Tabuk, Saudi Arabia. Informed consents were obtained from all participants. Adequate precautions have been taken to maintain confidentiality during data collection, storage, analysis, and dispensation.

Statistical analysis

Data analysis was carried out using the Statistical Package for the Social Sciences (IBM SPSS Statistics, version 22) for Windows (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequencies and percentages, and the differences between the two groups were tested using the chi-square test. Numerical variable was checked for normality by Shapiro Wilk test. It was found to be non-normally distributed and was expressed as medians and interquartile ranges (25^{th} - 75^{th} percentile). Comparison between both groups was carried out using Mann Whitney U test. A p-value < 0.05 was considered statistically significant.

RESULTS

The two groups were comparable with no significant differences regarding the age, gender, nationality, smoking status, and the presence of chronic illnesses, such as diabetes mellitus, hypertension, or cardiac diseases (Table 1).

Table 1. Baseline characteristics of the studied groups

		Vaccine group N=266		Control group N=266		P-Value
Age (years)	Less than 30	83	31.2%	90	33.8%	0.800
	30-50	153	57.5%	146	54.9%	
	More than 50	30	11.3%	30	11.3%	
Gender	Male	95	35.7%	92	34.7%	0.810
	Female	171	64.3%	173	65.3%	
Nationality	Saudi	247	92.9%	250	94.0%	0.600
	Non-Saudi	19	7.1%	16	6.0%	
Smoker	Yes	52	19.5%	42	15.8%	0.256
	No	214	80.5%	224	84.2%	
Working in the medical field	Yes	61	22.9%	62	23.4%	0.899
	No	205	77.1%	203	76.6%	
Had any chronic illnesses	Yes	47	17.7%	39	14.7%	0.346
	No	219	82.3%	227	85.3%	

Table 2 shows that the incidence of a FLI in the winter following vaccine intake was significantly higher in the vaccine group compared to the control group. There was no significant difference between both groups in the other parameters, e.g., the rate of chest infection and median duration of the illness.

Table 2. Comparison between the studied groups regarding the vaccine effectiveness indicators

		Vaccine group N=266		Control group N=266		P-Value
Did you experience a chest infection after vaccination?	Yes	24	9.0%	23	8.6%	0.879
	No	242	91.0%	243	91.4%	
Have you had a flu-like illness this winter?	Yes	92	34.6%	70	26.3%	0.038*
	No	174	65.4%	196	73.7%	
Did the flu-like illness affect your daily life activities?	Yes	36	13.5%	28	10.5%	0.286
	No	230	86.5%	238	89.5%	
Duration of illness, days	Median (IQR)	3.0 (2.0-7.0)		3.0 (2.0-5.0)		0.122
Did you seek medical service for it?	Yes	20	7.5%	12	4.5%	0.145
	No	246	92.5%	254	95.5%	
Did you need to visit a clinic?	Yes	21	7.9%	19	7.1%	0.742
	No	245	92.1%	247	92.9%	
Were you admitted to a hospital during that illness?	Yes	9	3.4%	4	1.5%	0.158
	No	256	96.6%	262	98.5%	
Have you taken medication for that illness?	Yes	79	29.7%	75	28.2%	0.702
	No	187	70.3%	191	71.8%	

*Significant at p<0.05, IQR: interquartile range

There were significantly higher percentages of influenza-vaccinated subjects who acquired COVID-19 infection, higher percentage of the vaccine group completed the two doses of COVID-19 vaccines, and greater percentages of the influenza-vaccinated subjects who were planning to uptake the influenza vaccine in the forthcoming year compared to control group. (Table 3).

Table 3. The status of COVID-19 infection, COVID-19 vaccines, and the future planning to uptake the influenza vaccine in the studied groups

		Vaccine group N=266		Control group N=266		P-Value
Did you acquire COVID-19?	Yes	105	39.5%	75	28.2%	0.006*
	No	161	60.5%	191	71.8%	
Did you take COVID-19 vaccines?	Yes	257	96.6%	255	95.9%	0.648
	No	9	3.4%	11	4.1%	
Did you complete the two doses of COVID-19 vaccines?	Yes	255	95.9%	235	88.3%	0.001*
	No	11	4.1%	31	11.7%	
Are you planning to uptake the influenza vaccine in the forthcoming year?	Yes	235	88.3%	131	49.2%	<0.001*
	No	31	11.7%	135	50.8%	

*Significant at p<0.05

DISCUSSION

Flu vaccine effectiveness studies are highly warranted to assess the value of the vaccination as a public health intervention, and they should be performed on a regular basis [(14)]. In this regard, the present study estimated the benefits of seasonal flu vaccination among Tabuk City adult population to determine how well the current flu vaccine is working.

Observational studies regarding the vaccine effectiveness have the advantage of evaluating the vaccine performance in real-world conditions that include high risk people, such as health care workers and those with underlying medical conditions [(15)]. The design of these studies helps determine the effect of circulating and evolving different flu viruses on the vaccine performance in actual conditions [(16)]. It has been reported that extremes of age and systemic comorbidities are independent risk factors for the development of the influenza complications; therefore, estimation of the vaccine effectiveness should be adjusted for these confounders

[17]. In the present prospective cohort study, the vaccinated and the unvaccinated control groups were comparable with no significant differences regarding the age group of the participants, the nature of their work whether in the medical field or not, and the presence of chronic medical diseases that may increase the risk of influenza complications, such as cardiac diseases, diabetes mellitus, and hypertension.

This study revealed that the current influenza vaccine exhibited a lack of significant effectiveness in preventing the occurrence of chest infection and FLI during the winter season following the administration of the vaccine. Furthermore, the duration of the FLI, its effect on the daily activities, the need for visiting a clinic, taking medications, and hospital admissions were comparable in the vaccinated and the unvaccinated group, with no significant differences.

Our findings agree with an earlier study that evaluated the effectiveness of the flu vaccine among healthcare worker at King Salman Armed Forced Hospital in Tabuk, Saudi Arabia during the season 2017-2018. Both the vaccinated and the unvaccinated hospital staff showed comparable incidence of FLI, pneumonia, severe acute respiratory infection, the need for hospital admission, and seeking medical care [18].

Nevertheless, the findings in this study are not consistent with several previous studies that reported a significant impact of vaccination in reducing the incidence of infectious diseases and their severity. These studies supported vaccination to protect against severe complications of influenza and other infectious diseases. **Khan *et al.*** [12] have demonstrated the benefit of influenza vaccine in reducing the occurrence and severity of clinically diagnosed FLI among health staff of a tertiary care eye hospital in Saudi Arabia. Also, administration of the flu vaccine in Taiwan has been associated with lower mortality rates in subjects aged more than 65 years [19]. In another study, live influenza vaccines proved to be effective in reducing the incidence of FLI or laboratory-confirmed influenza in children [20]. A study in Germany reported a significant relation between previous influenza vaccination and reduced severity and improved overall survival in patients with community acquired pneumonia during influenza seasons [21]. A surveillance data review in European countries confirmed the health benefits of vaccination in preventing influenza, related clinical visits, hospitalization, and mortality [3, 22].

The observed ineffectiveness of the flu vaccine in Tabuk might be attributed to discordancy between the vaccine targeted viruses and the circulating viruses, which needs further confirmation by isolation and identification of these viruses' strains as stated by **Khan *et al.*** [12]. The conflicting results of vaccine effectiveness studies can also be based on other factors including the study design, the outcomes measured, the population studied, and the season in which the flu vaccine was investigated [10, 13, 23].

There is a need to improve the immunogenicity and efficacy of influenza vaccines regularly. The development of a universal influenza vaccine that confers protection against homologous, drifted, and shifted influenza virus strains could confer long-lasting immunity, prevent the need for annual reformulation, and alleviate the disease burden [24].

The recorded significantly increased incidence of a FLI in the vaccine group (34.6%) compared to the control group (26.3%) in our study might be attributed to recall bias by the case group as subjects who received the vaccine are more likely to be concerned about the disease and more knowledgeable about the vaccine effectiveness [25]. Greater percentages of the influenza-vaccinated subjects (88.3%) showed more motivation, and they were planning to uptake the influenza vaccine in the forthcoming year than in the control group (49.2%), with a statistically significant difference ($p<0.001$). Doubts about the observed high incidence of FLI among the vaccinated subjects is supported by the diagnosis of the FLI on clinical symptoms such as acute cough fever, sore throat, and myalgia rather than laboratory confirmation of influenza infection.

Though influenza laboratory confirmation methods are able to detect the circulating influenza A and B viruses, the designated clinical outcomes used to determine the effectiveness of vaccination against FLI in our study can be applied to most developing countries with limited laboratories resources [18].

In the present study, significantly higher percentages of influenza-vaccinated subjects acquired COVID-19 infection and completed the two doses of COVID-19 vaccines in comparison to the unvaccinated control group. The COVID-19 infection is a novel virus that mainly targets respiratory system, and it produces similar clinical features to influenza. There are controversies about the effects of the flu vaccine in protecting against COVID-19 infection or modifying its severity [26]. **Zanettini *et al.*** [27] have found that higher influenza vaccination coverage in the elderly population was associated with lower mortality from COVID-19. Other studies evaluated the severity of COVID-19 courses in patients with or without prior flu vaccination history and they have found absence of any significant differences regarding the duration of hospitalization or the need for intensive care unit admission [28, 29].

In conclusion, the present findings demonstrate lack of significant effectiveness of the seasonal flu vaccine among adult population in Tabuk City, Saudi Arabia in terms of incidence of chest infection, FLI, the need for medications or hospital admission. Furthermore, the duration of the developed FLI and the effect of the flu on daily activities were comparable in the vaccinated and

the unvaccinated subjects. These findings may indicate the need for regularly improving the immunogenicity and efficacy of influenza vaccines.

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