SUBMITTED 21 MAY 2023
REVISIONS REQ. 23 JUL 23; REVISIONS RECD. 3 SEP 23
ACCEPTED 19 SEP 23
ONLINE-FIRST: SEPTEMBER 2023
DOI: https://doi.org/10.18295/squmj.9.2023.053

Frequency of Asthma Exacerbations and Upper Respiratory Tract Infections Among Adult with Asthma According to Vaccination Status

Does the annual influenza vaccine have a protective effect? A retrospective cohort study

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Abstract

Objectives: Annual influenza vaccinations are recommended for patients with asthma to prevent against seasonal influenza and influenza-triggered asthma exacerbations. However, there is conflicting data as to the benefit of the influenza vaccine on the frequency of asthma exacerbations. Therefore, this study aimed to assess the effectiveness of the influenza vaccine in terms of reducing the frequency of asthma-related exacerbations and upper respiratory tract infections among adult patients with asthma. ***Methods:*** This retrospective cohort study was performed from January to December 2018 in Muscat Governorate, Oman. A total of 466 patients attending nine randomly selected primary health centres in Muscat Governorate were enrolled in the study and followed-up for one year post-vaccination. ***Results:*** Most patients were female (70.6%) and had moderate-persistent asthma (42.9%). Overall, there were 203 patients (43.6%) in the vaccinated group and 263 (56.4%) in the non-vaccinated group. A proportion of patients in each group had allergic rhinitis (28.6% and 25.5%, respectively). The frequency of upper respiratory tract infections over

the one-year follow-up period was significant lower in the vaccinated group compared to the non-vaccinated group (37.9% versus 73%; relative risk [RR]: 2.299, 95% confidence interval [CI]: 1.834–2.882; P <0.001); however, there was no significant difference in terms of the frequency of asthma exacerbations (41.9% versus 45.2%; RR: 0.925, 95% CI: 0.750–1.141; P >0.050). ***Conclusion:*** The influenza vaccine significantly reduces the frequency of upper respiratory tract infections over the following year. However, it did not significantly reduce the frequency of asthma exacerbations among adult Omanis with asthma. Further studies are recommended to support the protective effect of the vaccine in this regard.

Keywords: Influenza Vaccines; Immunization; Asthma; Upper Respiratory Tract Infections; Observational Study; Oman.

Advances in Knowledge

- The annual influenza vaccine was found to significantly reduce the frequency of upper respiratory tract infections over the following year among a population of Omani patients with asthma attending randomly selected primary health centres in Muscat Governorate.
- However, there was no significant difference in terms of the frequency of asthma exacerbations between vaccinated and non-vaccinated patients.

Application to Patient Care

- Uptake of the annual influenza vaccine appears to be suboptimal among adult Omani with asthma. As such, primary healthcare providers in Oman should encourage patients with asthma to undergo annual immunisation in order to meet the target coverage rate of 90–100% set by the Ministry of Health.
- Although the study findings indicated that the influenza vaccine conferred no protective effect against asthma exacerbations, patients with asthma should nevertheless still be advised to undergo annual immunisation, as per existing recommendations from the World Health Organization and the United States Advisory Committee on Immunization Practices.

Introduction

Asthma is a pathologic condition of the respiratory tract characterised by chronic airway inflammation and variable airway obstruction.[1] This heterogeneous disease is one of the most common respiratory diseases worldwide, affecting an estimated 262 million people worldwide and causing 455,000 deaths in 2019.[2,3] In addition, asthma also places a significant burden on healthcare systems and communities in terms of medical costs, disability in daily life, and hospitalisation.[4] Much of this is due to asthma attacks—also termed exacerbations—one of the key domains used to determine asthma control in an individual. An asthma exacerbation is defined as an episode of acute or sub-acute worsening of asthma symptoms, including wheezing, coughing, chest tightness, and shortness of breath.[5]

The prevalence of asthma varies from country to country.[1,6] According to the International Study of Asthma and Allergies in Childhood (ISAAC), the national prevalence of asthma in Oman is in the intermediate range in terms of global rankings, despite demonstrating the highest prevalence of paediatric asthma among participating Eastern Mediterranean countries.[6,7] However, ISAAC study data has indicated that urgent evaluation and intervention is required in Oman due to considerable under-diagnosis and under-treatment.[8] Al-Busaidi *et al*. reported that outpatient clinic visits (20%), inpatient hospital stays (55%), and emergency room visits (25%) contribute the majority of asthma-related costs in Oman compared to asthma medications (<0.2%), thereby indicating that asthma control is generally poor.[9] The total direct cost of asthma treatment was estimated to be 61,500,294 Omani riyals per year (equivalent to $159,900,761 USD).[9]

The most common triggers for asthma exacerbations are viral respiratory infections; of these, influenza, a contagious respiratory infection, is believed to contribute to upwards of 80% of asthma exacerbations.[10] Seasonal influenza outbreaks every winter and spring can have a considerable impact on patient with asthma , thereby causing additional strain to local healthcare systems.[11] Both the World Health Organization (WHO) and the United States Advisory Committee on Immunization Practices (ACIP) have recommended that patient with asthma undergo annual immunisation as a preventive measure against seasonal influenza and influenza-triggered asthma attacks.[12,13] In Oman, the influenza vaccine was first introduced in 2010 and was advised for all

high-risk groups, including those with chronic illnesses such as asthma, with a target coverage rate of 90–100% set by the national Ministry of Health (MOH).[14,15]

Despite these recommendations, there remains some controversy as to the efficacy of the influenza vaccine in patients with asthma. Previous studies have reported conflicting findings as to whether influenza vaccination status significantly impacts the frequency of asthma exacerbation and influenza infection.[16,17] In addition, there is inconsistent evidence with regards to the protective effect of the vaccine for individuals aged 65 years or older, regardless of the presence of asthma or other chronic diseases.[18–20] To the best of the authors' knowledge, no local data on this topic have yet been reported from Oman. Accordingly, this study aimed to assess the effectiveness of the influenza vaccine in reducing the frequency of asthma exacerbations and upper respiratory tract infections among adult Omanis with asthma.

Methods

This retrospective cohort study was performed at nine primary health centres in Muscat Governorate between January and December 2018. Three out of the six *wilayats* (districts) of Muscat Governorate were randomly selected, including Al-Seeb, Bausher, and Muttrah *wilayats*, with three health centres randomly selected from each *wilayat*. The study population included all patients with asthma who were followed-up at the respective asthma clinics of the selected health centres during the study period. The inclusion criteria comprised patient with asthma aged 18–60 years who had not been diagnosed with any other respiratory diseases.

Paediatric patients and those with other respiratory illnesses were excluded from the study in order to minimize confounding factors. Patients were followed-up for a one-year period to collect data regarding the frequency of episodes of asthma exacerbation and upper respiratory tract infection. The follow-up period was initiated from the date of receiving the vaccine among patients in the vaccinated group. In terms of sample size requirements, a minimum of 148 subjects in each group (vaccinated versus non-vaccinated) was calculated, based on the results of a pilot study with an estimated risk difference of 16% and at 80% power, 5% alpha error, and using a two-sided test.

Relevant patient data were gathered, including the patients' demographic characteristics (including age, gender and ethnicity), asthma severity classification, smoking status, and the presence of additional comorbidities such as diabetes, hypertension, allergic rhinitis, and gastro-oesophageal reflux disease (GERD). Data were sourced from the Al-Shifa system, a comprehensive healthcare information management system utilised by all government health institutions in Oman. In addition, the asthma registry of each health centre was checked as a source of secondary data. Any visits for episodes of upper respiratory tract infection and asthma exacerbation to non-parent health institutions were tracked via the national electronic health record system that connects all MOH health institutions in Oman using national identification card numbers.

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS), Version 26.0 (IBM Corp., Armonk, New York, USA). Continuous variables were presented as means, medians, standard deviations, and interquartile ranges, while categorical variables were presented as frequencies and percentages. An independent samples t-test and Mann-Whitney U test were used to compare continuous variables and a Chi-squared test, Fisher's exact test, and likelihood ratios were used to determine associations between categorical variables, as appropriate. A *P* value of <0.05 was considered statistically significant. Ethical approval for this study was granted by the Centre of Studies and Research at the MOH, Muscat, Oman. The requirement for informed consent from the patients was waived as the study was conducted using secondary data sources.

Results

A total of 466 patients with asthma attending the nine randomly selected health centres were enrolled in the study. The total number of patients selected from each health centre is shown in Table 1. Most patients were female (70.6%) and were classified as having moderate-persistent asthma (42.9%). There were 203 patients (43.6%) in the vaccinated group and 263 (56.4%) in the non-vaccinated group. Overall, fewer of the vaccinated patients had diabetes compared to the non-vaccinated group (12.3% versus 15.2%); however, the frequency of allergic rhinitis was slightly higher in the vaccinated group (28.6% versus 25.5%). In addition, there were more smokers in the

vaccinated group compared to the non-vaccinated group (16% versus 8.4%). Other sociodemographic and clinical characteristics were comparable between the two groups [Table 2].

By the end of the post-vaccination follow-up period, upper respiratory tract infection symptoms were reported in 77 and 192 vaccinated and non-vaccinated patients, respectively (37.9% versus 73%). According to the analysis, the risk of upper respiratory infection was significantly lower in the vaccinated group compared to the non-vaccinated group (relative risk [RR]: 2.299, 95% confidence interval [CI]: 1.834–2.882; P <0.001). In turn, asthma exacerbations were reported in 85 and 119 vaccinated and non-vaccinated patients, respectively (41.9% versus 45.2%). No statistically significant association was observed between vaccination status and the frequency of asthma exacerbations (RR: 0.925, 95% CI: 0.750–1.141; *P* >0.050).

Similarly, no significant associations were observed between vaccination status and the presence of other comorbidities such as diabetes, hypertension, allergic rhinitis, and GERD (*P* = 0.419, 0.094, 0.462, and 0.110, respectively). There was also no association between vaccination status and frequency of hospitalisation (*P* >0.050), possibly because the overall hospitalisation rate in the enrolled population was so low (n = 2; 0.4%). With regards to smoking status, while there was no significant difference between vaccinated and non-vaccinated smokers in terms of either upper respiratory tract infection or asthma exacerbation rates (*P* >0.050), the frequency of upper respiratory tract infections was significantly higher among non-vaccinated non-smokers (*P* <0.050).

Discussion

The effectiveness of the vaccine is measured by comparing reductions in the frequency of illness among vaccinated compared to non-vaccinated individuals, usually after adjusting for confounding factors related to both the illness itself and the vaccine (e.g., the presence of other chronic medical conditions). [21]

The current observational study sought to assess the effectiveness of the influenza vaccine in terms of reducing the frequency of asthma-related exacerbations and upper respiratory tract infections among adult Omani patients with asthma. In the general population, the influenza vaccine has been

found to reduce illness severity and reduce outpatient visits, hospitalisation rates, and intensive care unit admissions.[12,19] Efficacy of the vaccine reportedly varies according to virus strain and specific season, with the vaccine shown to be significantly effective during epidemic seasons, but not necessarily during non-epidemic seasons.[18,20] For patients with asthma, some studies have shown the vaccine to protect against influenza infection, respiratory illness, asthma attacks, and other influenza-related asthma complications.[22,23] However, conflicting findings have been reported with regards to the protective effect of the vaccine against asthma exacerbations.[16,17]

The present study found that the vaccine effectively reduced the frequency of upper respiratory tract infection symptoms among a cohort of Omani patients with asthma, but had no significant effect on the frequency of asthma exacerbations. In Scotland, Vasileiou *et al*. analysed protection rates over six influenza seasons and found that the vaccine reduced the overall relative risk of subsequent infections by 55% (95% CI: 45.8–62.7%).[23] A recent systematic review and meta-analysis also concluded that the influenza vaccine effectively reduces the incidence of upper respiratory tract infection in patients with asthma by up to 81%, and may reduce the frequency of asthma exacerbations requiring hospitalisation by 59–78%, contributing to the reduction in both influenza infections and asthma attacks.[16] In contrast, Abdoglu *et al*. found no difference in the rate of upper respiratory tract infection between vaccinated and non-vaccinated patients with asthma (48% versus 57%; P >0.050); the researchers also reported that rates of asthma exacerbations remained comparable between the two groups.[17] Elian *et al*. reported a reduction in the frequency and severity of asthma exacerbations in vaccinated children with asthma compared to the non-vaccinated group; however, these differences were not statistically significant (P = 0.441 and 0.422, respectively).[24]

The present study also sought to determine whether influenza immunisation was effective in reducing admission rate among patients with asthma. No association was observed between vaccination status and hospitalisation rate, although this could be due to the low number of hospital admissions overall (0.4%). This low rate of hospitalisation can be explained by the fact that most of the enrolled population had intermittent, mild, or moderate forms of asthma, all of which can be managed in an outpatient setting. Martínez-Baz *et al*. also found that seasonal influenza vaccination did not significantly reduce hospital admission among patients with asthma and

confirmed influenza (adjusted odds ratio: 1.05, 95% CI: 0.51–2.18).[25] In contrast, Elian *et al*. and Jaiwong *et al.* both reported significant reductions in hospitalisation rates among vaccinated patients; however, it is important to note that both of these studies focused on paediatric populations, given that asthma in childhood is known to be more severe than in adulthood.[22,24]

Overall, the influenza vaccine provides moderate protection against the subsequent development of confirmed influenza infection, despite its short-lived effect in some seasons.[18,20] According to the ACIP, no specific type of influenza vaccine is preferable over another in settings where more than one licensed, recommended, and appropriate age-related vaccine is available.[12] Although seasonal influenza vaccines tend to be more efficacious if the vaccines are matched to the circulating strains, with this factor still considered to affect vaccine efficacy, most circulating influenza viruses differ from those used to make the vaccines.[21] There is no evidence to show that live-attenuated influenza vaccines (LAIVs) result in a greater frequency of adverse respiratory events compared to the inactivated influenza vaccine.[26,27] A recent Cochrane review also found no significant differences in asthma exacerbation frequency or pulmonary function with the use of LAIV versus either a placebo or the trivalent inactivated vaccine.[28] However, LAIV are still contraindicated for use in patients with asthma according to expert recommendations.[11,12]

Both the WHO and ACIP recommend annual immunisation for patients with asthma as a preventative measure against influenza.[12,13] Despite existing policies and surveillance systems, influenza vaccine coverage remains suboptimal in many countries, far below WHO recommendations.[29] Vaccine coverage is likely even lower in the Middle Eastern and North African (MENA) region, with few countries monitoring or publishing coverage data.[15,30] One study from Turkey estimated the vaccine coverage rate to be low in all risk groups, especially for the elderly and patients with respiratory diseases for example chronic obstructive pulmonary disease.[31] In Jordan and Saudi Arabia, researchers reported seasonal influenza vaccination coverage rates among adults of 9.9–27.5% and 19.3%, respectively, although the latter study was conducted during the recent coronavirus disease 2019 pandemic which may have had an impact on vaccination uptake and availability.[32,33]

Various factors have been found to affect influenza vaccine uptake among patients with asthma, including cost, convenience, scheduling of appointments, and a lack of understanding of the importance of prophylaxis in asthma.[34] In addition, younger people may not perceive a need to take the vaccine, while others may not be aware of its availability. Some patients may refuse or avoid being vaccinated as a result of fear arising due to uncorrected misinformation, such as the belief that the vaccine will cause asthma exacerbations or prompt flu-like symptoms or other side-effects.[11] The need to be immunised on a yearly basis may also present another obstacle to vaccine coverage. In Oman, previous research has indicated few, if any, barriers to influenza vaccination; elsewhere in the MENA region, barriers to vaccination coverage include the perceived lack of efficacy of the vaccine, fear of side-effects, lack of doctor recommendations, and negative media commentary.[15] Counselling and education remain the cornerstone of healthcare providers' efforts to encourage patients with asthma to take the vaccine. Moreover, automated reminder messaging systems are recommended to encourage annual influenza vaccination uptake in this population.[11]

One major limitation of the current study is the fact that this is retrospective study. As well was the fact that some patient with asthma may have sought medical intervention from health centres and institutions in the private sector, while others may have utilised home remedies to treat asthma exacerbations or symptoms of upper respiratory tract infections without ever seeing a doctor. This could have impacted the findings. Moreover, the results could have been confounded by noncompliance with prescribed medications on the part of certain patients, which would have affected rates of asthma exacerbation. Moreover, several allergens have been found to contribute to exacerbation in patients with asthma, a factor not assessed in the present study.[35]Further more the results cannot be generalized as the study was conducted in only one governorate.

Conclusion

In conclusion, this retrospective cohort study showed a significant reduction in the frequency of upper respiratory tract infections among Omani patients with asthma who had been immunised with the annual influenza vaccine; however, no relevant protective effect was found with regards to the frequency of influenza-related asthma exacerbations in the enrolled population. Further prospective studies with larger sample sizes are recommended to determine whether vaccination

status plays a role in reducing the frequency of asthma exacerbations among adult Omani with asthma.

Authors' Contribution

ZK and RK reviewed the literature, drafted the proposal, collected and analysed the data and drafted the manuscript. RH supervised the work done in the study. All authors approved the final version of the manuscript.

Acknowledgements

The authors wish to thank Mr. S. J., statistics specialist at the Research Section, Medical Simulation and Skills Development Centre, Oman Medical Specialty Board, for his help in analysing the data for this study.

Funding

No funding was received for this study.

Conflict of Interest

The authors declare no conflicts of interest.

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Table 1: Proportion of patients included from each of the nine randomly selected primary health centres in Muscat Governorate, Oman (N = 466)

District	Health centre	n (%)
Al-Seeb	Al Hail	64 (13.7)
	South Mabella	61 (13.1)
	South Mawaleh	25 (5.4)
Bausher	North Khuwair	57 (12.2)
	Khuwair	56 (12)
	Al Ghubrah	56 (12)
Muttrah	Ruwi	54 (11.6)
	Muttrah	53 (11.4)
	Wadi Kabeer	40 (8.6)
Total		466 (100)

Table 2: Sociodemographic and clinical characteristics of patients with asthma attending nine randomly selected primary health centres in Muscat Governorate, Oman (N = 466)

Characteristic	Group, n (%)		
	Total	Vaccinated (n = 203)	Non-vaccinated (n = 263)
Gender			
Male	137 (29.4)	53 (26.1)	84 (31.9)
Female	329 (70.6)	150 (73.9)	179 (68.1)
Asthma severity			
Intermittent	105 (22.5)	32 (15.8)	73 (27.8)
Mild-persistent	154 (33)	75 (36.9)	79 (30)
Moderate-persistent	200 (42.9)	92 (45.3)	108 (41.1)
Severe-persistent	5 (1.1)	3 (1.5)	2 (0.8)
Unknown	2 (0.4)	1 (0.5)	1 (0.4)
Smoking status			
Smoker	48 (10.3)	29 (16)	19 (8.4)
Non-smoker	418 (89.7)	244 (92.8)	418 (89.7)
Comorbidities*			
Diabetes	65 (13.9)	25 (12.3)	40 (15.2)
Hypertension	87 (18.7)	45 (22.2)	42 (16)
Allergic rhinitis	125 (26.8)	58 (28.6)	67 (25.5)
GERD	10 (2.1)	7 (3.4)	3 (1.1)
Other	203 (43.6)	62 (30.5)	141 (69.5)

*GERD = gastro-oesophageal reflux disease. *Percentages for this variable do not add up to 100% as some patients may have had more than one comorbidity.*