

Frequency of Asthma Exacerbations and Upper Respiratory Tract Infections Among Adults With Asthma According to Vaccination Status

Does the annual influenza vaccine have a protective effect?

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ABSTRACT: Objectives: Annual influenza vaccinations are recommended for asthma patients to prevent seasonal influenza and influenza-triggered asthma exacerbations. However, data on the beneficial effect of this vaccine on the frequency of asthma exacerbations are conflicting. 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 9 randomly selected primary health centres in Muscat Governorate were enrolled in the study and followed up for one year post vaccination. **Results:** Most of the patients were female (70.6%) and had moderate persistent asthma (42.9%). There were 203 patients (43.6%) in the vaccinated group and 263 patients (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 significantly lower in the vaccinated group than in 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 does not significantly reduce the frequency of asthma exacerbations among Omani adults 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 adults with asthma attending randomly selected primary healthcare centres in Muscat Governorate.
- There was no significant difference between the frequency of asthma exacerbations among vaccinated and non-vaccinated patients.

APPLICATION TO PATIENT CARE

- Uptake of the annual influenza vaccine appears to be suboptimal among Omani adults with asthma. Consequently, 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 national Ministry of Health.
- Although the study findings indicate that the influenza vaccine conferred no protective effect against asthma exacerbations, asthma patients 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.

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 in the world, affecting an estimated 262 million people worldwide and causing 455,000 deaths in 2019.^{2,3} Furthermore, asthma 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—which is 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 prevalence of asthma in Oman is in the intermediate range in terms of global rankings, despite the country demonstrating the highest prevalence of paediatric asthma among participating Eastern Mediterranean

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countries.^{6,7} However, ISAAC study data indicate that urgent evaluation and intervention is required in Oman due to the considerable under-diagnosis and under-treatment of asthma cases.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 (equivalent to 159,900,761 USD) per year.⁹

The most common triggers for asthma exacerbations are viral respiratory infections; of these, influenza, a contagious respiratory infection, is believed to contribute to more than 80% of asthma exacerbations.¹⁰ Seasonal influenza outbreaks every winter and spring can have a considerable impact on asthma patients, 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 patients with asthma undergo annual immunisation as a preventive measure against seasonal influenza and influenza-triggered asthma exacerbations.^{12,13} In Oman, the influenza vaccine was first introduced in 2010 and was recommended 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 asthma patients. Previous studies have reported conflicting findings as to whether influenza vaccination status significantly impacts the frequency of asthma exacerbation and influenza infection.^{16,17} Additionally, there is inconsistent evidence of the protective effect of the vaccine for individuals aged ≥ 65 years, 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 Omani adult patients with asthma.

Methods

This retrospective cohort study was conducted at nine primary healthcare centres in Muscat Governorate between January and December 2018. Three out of the 6 wilayat (districts) of Muscat Governorate were

randomly selected (Al-Seeb, Bausher and Muttrah wilayat), with 3 health centres randomly selected from each wilayah (district). The study population included all asthma patients who attended follow-ups at the respective asthma clinics of the selected health centres during the study period. The inclusion criteria comprised patients 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 to minimise confounding factors. Patient with respiratory illness such as chronic obstructive pulmonary disease, bronchiectasis and lung fibrosis were excluded. Patients were followed up for a one-year period to collect data regarding the frequency of asthma exacerbation episodes and upper respiratory tract infections. The follow-up period was initiated from the date the patients in the vaccinated group received their vaccine. A minimum of 148 subjects in each group (vaccinated and non-vaccinated) was calculated for the sample size requirements 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. Additionally, 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 (680/2020). 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 9 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 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 patients in the vaccinated group had diabetes compared to those in 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%). Additionally, there were more smokers in the vaccinated group than in the non-vaccinated group (14.3% versus 7.2%). 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 (37.9%) vaccinated and 192 (73%) non-vaccinated patients. According to the analysis, the risk of upper respiratory infection was significantly lower in the vaccinated group than in 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 (41.9%) vaccinated and 119 (45.2%) non-vaccinated

Table 1: Proportion of enrolled patients from each of the 9 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 9 randomly selected primary health centres in Muscat Governorate, Oman (N = 466).

Characteristic	n (%)		
	Total (N = 466)	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 (14.3)	19 (7.2)
Non-smoker	418 (89.7)	174 (85.7)	244 (92.8)
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.

patients. 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%). Regarding 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 a vaccine is measured by comparing reductions in the frequency of the concerned illness among vaccinated and 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 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 Omani adult patients with asthma. In the general population, the influenza vaccine has been found to reduce illness severity, outpatient visits, hospitalisation rates and intensive care unit admissions.^{12,19} The vaccine's efficacy 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 asthma patients, 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 regarding 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 adult patients with asthma, but had no significant effect on the frequency of asthma exacerbations. In Scotland, Vasileiou *et al.* analysed protection rates over 6 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%, thus contributing to a reduction in both influenza infections and asthma attacks.¹⁶ In contrast, Abadoğlu *et al.* found no difference between the rate of upper respiratory tract infection among vaccinated and non-vaccinated asthma patients (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; however, this could be due to the overall low number of hospital admissions (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.* 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 is known to be more severe in childhood 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 when the vaccines match the circulating strains—this factor is still considered to affect vaccine efficacy today—most circulating influenza viruses differ from those used to make the vaccines.²¹ Moreover, experts contraindicate live-attenuated influenza vaccines (LAIVs) in asthma patients.^{11,12} However, there is no evidence to show that LAIVs result in a greater frequency of adverse respiratory events compared to the inactivated influenza vaccine.^{26,27} Also, a recent Cochrane review found no significant differences between asthma exacerbation frequency or pulmonary function with the use of an LAIV and either a placebo or the trivalent inactivated vaccine.²⁸

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} A study from Turkey estimated the vaccine coverage rate to be low in all risk groups, especially the elderly and patients with respiratory diseases such as chronic obstructive pulmonary disease.³¹ Studies in Jordan and Saudi Arabia 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 COVID-19 pandemic, which may have impacted vaccination availability and uptake at the time.^{32,33}

Various factors such as cost, convenience, scheduling of appointments and lack of understanding of the importance of prophylaxis in asthma have been found to affect influenza vaccine uptake among asthma patients.³⁴ Also, younger people may not perceive the need to take the vaccine, and some people may not be aware of its availability. Some patients may refuse or avoid being vaccinated due to fears arising from uncorrected misinformation, such as the belief that the vaccine will cause asthma exacerbations or prompt flu-like symptoms and other side effects.¹¹ The need for yearly immunisation may also present an 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 the vaccine's efficacy, 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 asthma patients 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 its retrospective nature. Also, some patients 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, which could have impacted the findings. Furthermore, the results could have been confounded by noncompliance with prescribed medications on the part of certain patients, which would have affected the rates of asthma exacerbation. Moreover, several allergens have been found to contribute to exacerbation in asthma patients, a factor not assessed in the present study.³⁵ Finally, the results cannot be generalised, as the study was conducted in only one governorate.

Conclusions

This retrospective cohort study showed a significant reduction in the frequency of upper respiratory tract infections among Omani adult patients with asthma who had been immunised with the annual influenza vaccine. However, no relevant protective effect was found regarding 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 Omani adult patients 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.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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