

# A Review of Influenza Vaccination among Different Population Groups in Iran

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## ABSTRACT

Annual influenza vaccination is the best means of prevention and control of influenza virus infection and its complications. Efforts to increase influenza vaccines coverage, especially in high-risk groups including young children, the elderly, pregnant women and immunocompromised individuals have led to substantial reduction in health burden, severity and duration of infection. This review will focus on vaccination coverage against influenza infection among different population groups in Iran. Also, available evidence suggesting the effectiveness and adverse effects of currently licensed influenza vaccines will be discussed.

**Keywords:** Effectiveness, Immunization, Immunocompromised

## INTRODUCTION

Influenza virus co-infection causes reasserting strains that play a critical role in generating pandemics, such as those of 1957, 1968 and 2009 [1]. During inter-pandemic years, the annual attack rate of influenza is estimated at 5 to 10% in adults and 20 to 30% in children [2]. The World Health Organization (WHO) estimates that the annual epidemics result in 3 to 5 million cases of severe illness and 250,000–500,000 deaths each year around the world [3,4].

Influenza is typically characterized by sudden onset of fever, chills, headache, sore throat, and dry cough. Hence, unlike many other common respiratory infections; it can cause extreme malaise lasting several days [5,6]. More severe diseases can occur in the lungs after an invasion by influenza virus (primary viral pneumonia) or by secondary bacterial pneumonia. Influenza frequently infects individuals who are poorly able to cope with the illness and often require medical attention, including hospitalization, due to their ages or underlying health conditions. Therefore, these persons are taken into account as "medically high risk" subjects during epidemics. [7-9].

Annual administration of the seasonal influenza vaccine is particularly important for people who are at increased risk for serious complications. Influenza vaccines classically contain three components which are target the three main circulating strains of influenza A (H1N1), A (H3N2) and B influenza viruses all of which identified through worldwide surveillance as the most common types during the season. However, since 2004, two antigenic lineages of influenza B viruses (Yamagata and Victoria) have co-circulated; quadrivalent formulations of the flu vaccine containing both lineages have been available from 2013-14 season [10-13].

In several countries, annual vaccination against influenza is implemented both for children and adults in higher-risk groups. The Ministry of Health and Medical Education (MOHME) in Iran provides vaccine for some of the high-risk groups. However, there is no current precise estimate of influenza vaccine efficacy in Iran. This review article focuses on the influenza vaccine efficacy among various high-risk groups in Iran.

## Influenza Vaccination in Immunocompromised Hosts

An immunocompromised host is a patient incapable of effective response to infection due to an either impaired or weakened immune

system. This inability to fight infection can be caused by a number of conditions including those receiving anti-neoplastic therapy, HIV infection, and transplantation. Influenza remains a major cause of morbidity and mortality among immunocompromised patients, resulting in prolonged illness, viral shedding, elevated severity of illness, delayed chemotherapy, and increased frequency of hospitalization [14-16]. Consequently, annual vaccination against seasonal influenza is highly recommended for these high-risk groups. Accompanying such goal, using national immunization guidelines, an inactivated intramuscular vaccine is routinely administered. However, immunosuppression condition may limit their response to the vaccination [17,18].

Several related studies have been performed to evaluate the vaccine responses among Iranian immunocompromised patients so far. In this regard, a study by Vaziri S et al., assessed the immunogenicity and safety of influenza vaccine in 60 HIV-infected patients vaccinated with split influenza vaccine. they showed that the antibody levels against influenza A (H1N1), A (H3N2), and B antigens increased four times in 75%, 45%, and 28.3% of HIV-infected patients, respectively. [19]. In another survey by Hajjabdolbaghi M et al., a total of 203 HIV-infected patients were evaluated to assess the adverse reactions to influenza vaccination. Local and systemic reactions were observed in 61 (30%) and 62 (30.5%) of the subjects, respectively. The most common side effects of the influenza vaccine included skin redness (18.2%), induration (15.5%), and pain (27.1%) as local reactions; and fever (10.8%), myalgia (22.7%), headache (5.9%) and weakness (17.2%) as general reactions [20]. In another study, antibody responses to trivalent inactivated influenza vaccine in 200 HIV-infected patients were evaluated. They showed that seroconversion rate by HI assay for A (H1N1), A (H3N2), and B influenza viruses were 58.5%, 67% and 64.5%, respectively. A significant correlation between specific antibody responses and CD4 cell count was also demonstrated. This result is in consistent with previous studies that have concluded that increased responses to vaccines are associated with higher CD4+ T cells [21,22]. The most common adverse local and systemic reactions to the influenza vaccine were pain in the injection site (20%) and myalgia (6.5%) [23].

Furthermore, Shahgholi E et al., evaluated the immune responses to trivalent influenza vaccine in 30 children with Acute Lymphoblastic

Leukaemia (ALL) treated with immunosuppressive drugs in comparison with 32 healthy individuals. The protective response against virus subunits among patients and healthy controls were 43.4% versus 88% for H1N1, 63.3% versus 80% for H3N2 antigens, and 26% versus 73% for B antigen. It was also shown that the immune responses to virus subunits were significantly lower in patients than healthy controls [24]. A controlled trial was performed by Keshtkar-Jahromi M et al., attempting to evaluate humoral immune response to the trivalent 2006-2007 anti-influenza vaccine in 40 healthy controls and 40 adult Kidney Transplant Recipients (KTRs) who had undergone immunosuppressive therapy. The results led to the conclusion that anti-influenza vaccination was safe in KTRs and induced same HI antibody titers in both KTRs and healthy control groups [25].

### Influenza Vaccination in Pregnancy

Due to a partial immunosuppression in pregnancy and early life, susceptibility to infectious diseases can increase and it is not surprising that pregnant women and newborns are at a higher risk of influenza outcomes such as hospitalization, intensive care unit admission, death [26,27]. Hence, the WHO recommends that all pregnant women at any stage of pregnancy must receive inactivated seasonal influenza vaccine [28]. Until now, there is no solid published data on the efficacy of influenza vaccination among Iranian pregnant women population; only limited studies were performed to determine the uptake rate of influenza vaccination and the reasons for acceptance or rejection among pregnant women [29]. Certainly, the most common reasons for refusing the flu vaccine had to do with the concerns about fetal damages, as well as the lack of sufficient knowledge about influenza.

### Influenza Vaccination in Cardiovascular Patients

Patients with Cardiovascular Diseases (CVD) are mostly at high risk for influenza-related complications [30]. Therefore, vaccination against influenza plays a key role in the prevention of devastating consequences of influenza infections in patients with CVD during the influenza season. Also, several studies have demonstrated that influenza vaccination diminishes the cardiovascular effects [31-33]. An annual influenza immunization can prevent influenza infection and also diminish the complications of acute infection (which promotes inflammation and the progression of atherosclerosis) and serve as a trigger point for acute myocardial infarction [34,35].

In a study by Keshtkar-Jahromi M et al., safety and humoral immune response to the trivalent anti-influenza vaccine (Influvac, Solvay Pharma) in 137 CAD patients and 67 healthy subjects were evaluated. The result of their study did not show any significant difference in the protection rate after vaccination, serologic response, and magnitude of change in antibody titers against each of the vaccine components between CAD and healthy control groups [36].

Another study by Keshtkar-Jahromi M et al., was performed to evaluate the influenza vaccination in reducing cardiovascular effects in 266 patients with CAD (135 CAD-Placebo and 131 CAD-Influvac subjects) during the 2007-2008 influenza season in Iran. They evidenced that the CAD-Placebo group experienced influenza infection significantly more than the CAD-Influvac group ( $p = 0.049$ ) [37].

### Influenza Vaccination in Health Care Workers (HCWs)

During the outbreaks, HCWs are frequently exposed to the influenza virus, and usually, keep on working while infected. Hence, they constitute important sources for viral dissemination between patients and families when the disease is often asymptomatic. It is believed that the administration of influenza vaccine to HCWs is a cost-effective approach to reduce lost work hours, nosocomial transmission, and mortality among hospitalized patients [38,39].

In a study performed by Hajiabdolbaghi M et al., the researchers

reported the frequency and some adverse effects after influenza vaccination in Iranian HCWs at 7 medical centers. Also, they found that among 897 adults who participated in the study, local and systemic reactions were reported in 187 (20.8%) and 198 (22.1%) persons, respectively. The most common local and systemic reactions were pain (20.2%) and myalgia (15.8%); with one case of Guillain-Barre syndrome [40].

Also, in the same survey conducted in Kurdistan province, Iran, safety of a trivalent inactivated influenza vaccine, *Begrivac*<sup>®</sup> (Novartis Company), was evaluated in 936 HCWs. The most common complaints after vaccination were headache (5.3%), fever (7.9%), weakness (9.6%), chills (10.1%), sweating (10.5%), arthralgia (20.2%), and malaise (21.5%). Also, swelling and pruritus in the injection site were seen in 267 (30.3%) and 290 (32.9%) participants. Moreover, redness and induration were recorded in 42.5% of the participants. Their findings have also showed that local adverse reactions after the trivalent inactivated influenza vaccine in HCWs were far more common than also expected [41].

Besides the vaccine efficacy, there are also some studies which focused on influenza vaccine attitude in HCWs. In this regard, one study conducted on 492 HCWs from three teaching hospitals in Tehran between December 2014 and June 2015, to determine factors influencing uptake of influenza vaccination. Their findings showed 27.7% compliance rate. Moreover, principal reasons to undergo vaccination were its effectiveness and personal protection of vaccine which were 30.7% and 28.9%, respectively. On the other hand, the main reasons for refusing vaccination were unavailability (29.9%) and reluctance (24.5%) [42]. Concerning the previous studies, a cross-sectional study was performed on 144 HCWs to evaluate the attitude and knowledge about the influenza and vaccine, allowing the determination of the influenza vaccine coverage. The result showed that the influenza vaccine coverage was 66.9% in 2008-2009. The most common reason for accepting vaccination was effectiveness (51.4%) and the main factor to refuse vaccination was concern about its adverse effects (23.1%) [43].

### Influenza Vaccine among Older Adult Iranian Population

Adults older than 65 years of age are particularly at increased risk for influenza complications, which are responsible for the majority of hospitalizations and deaths each year [44]. Since the immune system's response is compromised in these individuals, the antibody response and protection elicited by the vaccine are lower than those of younger people. Accordingly, to prevent the influenza infection in older adults, more effective vaccines are required [45,46]. Due to the scarcity of investigations regarding the effectiveness of flu vaccine in Iranian older adults, here, we have highlighted some studies focusing on the attitudes, vaccination uptakes, and socioeconomic determinants. In this regard, a study was conducted by Taheri PT et al., on 1,350 of adults who had over 60 years and showed that 10.4% of the older adults had received influenza vaccines. These finding results revealed that the influenza vaccination uptake was dependent on several factors including current occupation, education level, ethnicity, source of income, financial support from relatives, and types of health insurance [47].

### Influenza Vaccination among Hajj Pilgrims

The Hajj is the yearly pilgrimage to Mecca, Saudi Arabia, and is the largest mass gathering in the world [48]. Annually, up to 3 million people from more than 180 countries perform Hajj pilgrimage. Living in shared and crowded accommodations, environmental pollution, and reduced personal hygiene at Hajj may totally lead to an increased transmission of viral respiratory infections such as influenza [49]. Influenza vaccine is recommended for all pilgrims during the Hajj season, especially the elderly and those with essential medical conditions.

In this regard, Razavy S et al., also designed a survey for the

evaluation of influenza vaccine's efficacy in Iranian pilgrims. Among 32370 pilgrims, 3465 individuals (10.7%) had vaccinated themselves against the influenza and the others were not vaccinated. It was shown that the incidence rate of illness among vaccinated and

unvaccinated groups were 56% and 72%, respectively ( $p < 0.001$ ). The efficacy of the vaccine in their study was estimated to be 50% [50].

Target group	Mean age	Total population	Type of vaccine	Study design	Outcome	References
Immunocompromised Host	36.4 Years	60 (HIV positive) 60 (Healthy control)	Split influenza vaccine (Influvac)	Clinical trial	The influenza infection was decrease	[19]
	36.9±7.9 Years	203 (HIV positive)	Influenza virus subunit vaccines (Solvay Pharmaceuticals)	Prospective study	Many side effects were observed.	[20]
	35.57 Years	200 (HIV positive)	TIV (Lyon company, France)	Clinical trial	The seroconversion rate by HI assay for A (H1N1), A (H3N2), and B were measured to be 58.5%, 67% and 64.5%, respectively.	[23]
	10.65 Years	32 (All patients) 30 (Healthy control)	TIV (Influvac)	Clinical trial	The immune responses against virus subunits were significantly lower in patients compared to healthy controls.	[24]
	41.1 Years	40 (Kidney transplant patient) 40 (Healthy control)	TIV (Influvac)	Clinical trial	Anti-influenza vaccination induced the same HI antibody titers in both KTRs and healthy controls.	[25]
Pregnant Women	27.06±5.27 Years	416	NA	Cross-sectional	Education of pregnant women about influenza vaccination has a remarkable effect on flu vaccination uptake among pregnant women.	[29]
Cardiovascular Patients	CAD 54.5 Years and 52.3 Years HC	137 (CAD patients) 67 (Healthy control)	TIV (Influvac)	Clinical trial	Vaccination was safe in CAD patient's and antibody titer were similar healthy controls.	[36]
	NA	266	TIV (Influvac)	Clinical trial	Influenza infection in CAD-Placebo group was significantly more than the CAD-in flu vaccine group.	[37]
Health Care Workers	37.4±7.8 Years male, 33.9±8 Years female	897	Influenza virus subunit vaccines (Solvay Pharmaceuticals)	Prospective study	Inactivated influenza vaccine did not have potential adverse effects in healthy adults.	[40]
	18-64 Years	936	Trivalent inactivated surface antigen influenza vaccine (Begrivac)	Prospective study	Adverse reactions after the trivalent inactivated influenza vaccine in health care workers were far more common	[41]
	35.21 ± 8.76 Years	492	NA	A cross-sectional	The main factors for being vaccinated were vaccine effectiveness (30.7%) and inhibiting factors were unavailable (29.9%) and not interested (24.5%).	[42]
	38.49±7.25 Years	144	NA	A cross-sectional	The main reason for vaccination was the effectiveness of the influenza vaccine (51.4%) and main reason given for not being immunized was the concern about adverse effects (23.1%).	[43]
Elderlies	≥60 Years	1,350	NA	A cross-sectional	10.4% of the older adult had received influenza vaccination and influenza vaccination uptake depended on several determinants such as current occupation, education level, and ethnicity.	[47]
	51 Years	32370	NA	Nested case-control study	The efficacy of the vaccine in this study was estimated to be 50% in 2003.	[50]
	51 Years	51100	NA	Nested case-control study	Vaccine was not efficient in 2004.	[51]
	44.1±9.3 Years (vaccinated), 44.2±9.3 Years (unvaccinated)	203 (vaccinated pilgrim), 203 (unvaccinated pilgrim)	NA	Cohort study	Influenza vaccine efficacy for prevention of influenza like illness symptoms was 20%.	[52]
	≥ 65 Years	325	NA	Cohort study	Result suggests that the high- risk groups should be vaccinated with combination of flu and pneumovax-23 vaccines in Hajj.	[53]
Chronic Pulmonary Diseases	6 months to 5 Years	140 (Asthmatic children)	TIV	Clinical trial	Results support annual influenza vaccination in children with asthma.	[57]
	≥6 Years	517 (Asthmatic children)	NA	NA	Significant relation between Vaccination receiving vaccination and well-controlled asthma was seen.	[58]
	45.83 Years sarcoidosis and 42.23 Years healthy control	23 (Sarcoidosis patient) 26 (Healthy control)	TIV (Influvac)	Clinical trial	Serological response which was equal to HCs did not cause any major adverse effect in SPs	[59]

**[Table/Fig-1]:** Characteristics of studies included in the review.

(TIV: Trivalent Inactive Vaccine; ALL: Acute Lymphoblastic Leukaemia; HC: Healthy Control; HCW: Health Care Worker; NA: Non-Assigned; SP: Sarcoidosis Patient; CAD: Coronary Artery Disease)

Two similar cohort studies were conducted by Razavi SM et al., on 51 100 Iranian pilgrims who had participated in the annual Hajj during 2003-2004 to determine the influenza vaccine efficacy against respiratory diseases. Efficacy of influenza vaccine for prevention of influenza-like disease was 51% in 2003, while no notable efficacy was observed in 2004, it was found that the cause of respiratory disease in Hajj was etiologic agent other than influenza virus [51].

To determine the impact of influenza vaccination on the occurrence of influenza-like illness and other respiratory tract infection symptoms, Kolahi AA et al., performed a cohort study on 406 Iranian pilgrims (vaccinated =203 and control=203) in Hajj 2004. They showed an efficacy of 20% for influenza vaccine to prevent the influenza-like illness symptoms [52]. On the other hand, the previous survey was a cohort study for assessing the effects of influenza and pneumococcal vaccines on preventing respiratory syndromes and their consequences among 295 Iranian pilgrims. In both flu and pneumovax-23 vaccinated groups, duration of coughs significantly reduced in all cases ( $p < 0.01$ ). The vaccine prescription also decreased the complications of the disease ( $p < 0.001$ ). According to the results, the researchers recommended that the high-risk groups should be vaccinated with a combination of flu and pneumovax-23 vaccines in Hajj [53].

### Influenza Vaccination for Patients with Chronic Pulmonary Diseases

Influenza infection is an important cause of global mortality and morbidity with the greatest impact on older people and also those with chronic diseases. Patients with a chronic pulmonary disease are particularly vulnerable to influenza, with evidence for increased incidence and severity of infection [54]. For example, infection with influenza virus causes people with asthma to be more susceptible to bronchoconstriction, exacerbations of asthma symptoms, and even prolonged declines in lung function [55,56], suggesting that the influenza vaccination, and in particular, the use of the seasonal trivalent influenza vaccine is highly recommended for patients with chronic pulmonary diseases.

A randomized, double-blind, placebo-controlled trial was performed by Jahani FF et al., to evaluate the effect of inactivated trivalent influenza vaccine on 140 asthmatic children younger than 5 years. Exacerbation rates among vaccinated and unvaccinated subjects were 13% and 53%, respectively. Cough, as a common sign of the disease, was reported in 48.6% of vaccinated and 76.8% of placebo group. The rate of wheezing report was 20% in vaccinated and 68.6% in unvaccinated group [57]. Furthermore, another Iranian study aimed to determine the association of influenza vaccination status and asthma control in children. The researchers revealed a significant relation between receiving vaccination and well-controlled asthma ( $p < 0.000$ ) [58].

Considering the previous studies, the safety and immunogenicity of influenza vaccine was also evaluated in 23 patients with sarcoidosis and 26 healthy subjects. The results indicated that influenza vaccination did not lead to any significant adverse effects in patients with sarcoidosis, and their serological response was equal to healthy ones in controls [59] [Table/Fig-1].

### CONCLUSION

Since the influenza can aggravate chronic diseases or predispose the patient to secondary infections such as pneumonia or bacterial infections, it can cause severe illness in high risk populations such as children or elderly people, pregnant women, patients with chronic disease, cardiovascular diseases, asthma and immunocompromised patients. As a result, a lack of immunization in these populations can result in serious consequences. Although, several studies have shown that vaccination against influenza infection can reduce illness in high risk groups, and therefore, the evaluation of the influenza vaccination would be of particular importance. The vaccine seems

to be highly efficient, however, a few adverse effects have been also observed. There are limited data on the efficacy of influenza vaccine among various Iranian high-risk groups; particularly children, pregnant women, and elderly people. Hence, further large-scale studies are required to properly evaluate the impact of vaccination program on prevention of influenza infections.

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