Original Article

Cost effectiveness of influenza vaccination for specific populations in Iran

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ABSTRACT

Introduction: Influenza viruses are the major respiratory pathogens worldwide and high-risk groups such as healthcare workers may develop severe forms of the disease. The purpose of this study was to evaluate the cost-effectiveness of influenza vaccination for 4 target groups including pregnant women, elderly people (aged over 65 years), healthcare workers and school-age children in Iran. **Methods:** A cost-effectiveness analysis using a decision tree model over a one-year time horizon for the influenza vaccination versus no vaccination in Iran was carried out according to the prospective of the Ministry of Health. Epidemiological data were extracted from the relevant local databases and the literature. The medical and community care costs with sampling of the patients in all 4 groups were estimated. **Results:** The results of the economic evaluation showed that in Iran, incremental costs per Disability-Adjusted-Life-Years (DALY) of influenza were estimated to be US$ 15,069, US$ 104,104, US$ 5,685 and US$ 14,983 for the pregnant women, the elderly people, the healthcare workers and the school-age children, respectively. **Conclusion:** The results of this study indicated that the implementation of influenza vaccination program might be cost effective only for the healthcare workers.

KEYWORDS: Influenza, cost-effectiveness, Iran, school-age children, pregnant women, elderly, healthcare workers.

INTRODUCTION

Influenza viruses A and B are the major respiratory pathogens in the world which cause epidemics, especially during the winter which can cause sporadic cases and outbreaks while influenza A virus can cause pandemics. Trivalent Influenza Vaccine (TIV) is the only vaccine which is licensed to be used for children from 24 months to 6 years, pregnant women and people over 50 years of age. When the vaccine strains match perfectly with the circulating virus, the efficacy of the vaccine in people under 65 years of age is 70-90% [1]. High-risk groups in this regard are healthcare workers as well as other groups with a particular risk for developing severe forms of the disease which may lead to hospitalization or even death. The other concerned groups are pregnant women, children under 5 years of age, the elderly and people with debilitating diseases such as AIDS, asthma and chronic cardiopulmonary diseases. Groups at high-risk of developing influenza complications have received less attention in countries with low and middle income [1]. A world-wide analysis of the burden of different diseases in 2010 has shown that 4 causes of death include ischemic heart disease, ischemic stroke, chronic obstructive pulmonary disease and lower respiratory tract infections [2]. Influenza is a public health problem and has important implications for the healthcare systems due to an increase in the number of in-patient and out-patient clients. The socio-economic burdens of influenza are secondary to impaired quality of life and loss of productivity which all lead to increased healthcare costs either directly or indirectly [3]. Prior to the introduction of a drug or a vaccine, the healthcare authorities in many countries need to assess the cost-effectiveness of such interventions, especially when they require public subsidies or funding [4]. Having specific information from a country about its risk groups, disease burden and the cost-effectiveness of interventions are

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important for the health policy makers at national level to enable the authorities to choose specific populations for vaccinations [1]. The aim of this study was to estimate the cost-effectiveness of public influenza vaccination program in Iran as a major population center in West Asia.

MATERIALS and METHODS

Model structure

A deterministic decision-tree model was used to compare 4 target populations with respect to influenza infection which included pregnant women, the elderly (over 65 years of age), healthcare workers and school-age children based on data obtained from 2014 Ministry of Health and Medical Education prospective regarding vaccination in Iran. In this model, we followed the pathway from the original decision node (i.e. vaccination or no vaccination) to each of the terminal nodes. There were 2 distinct pathways including immune and not immune for the target populations who were not vaccinated as well as for whom the vaccination was not effective, based on the vaccination efficacy rate. We also considered probability of in-patient admissions, out-patient visits and deaths in each of the target populations throughout the decision tree model which was obtained from opinions of an expert panel (Fig. 1).

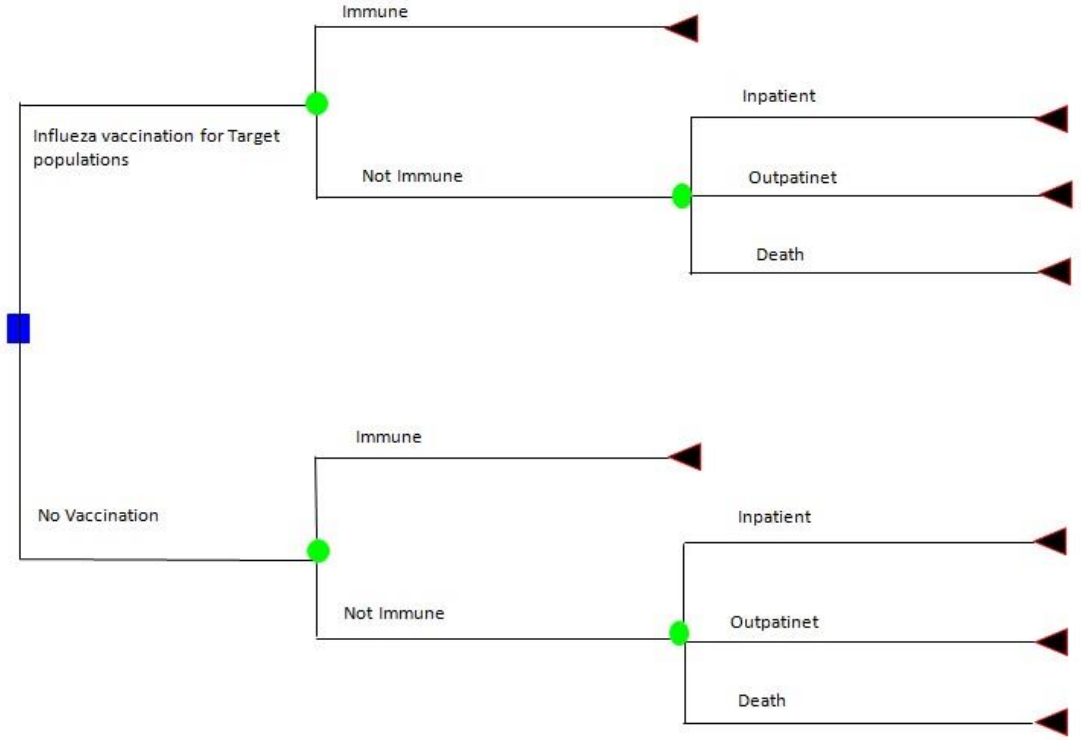

Fig. 1. Decision tree model to assess cost-effectiveness of influenza vaccination program.

The outcome was estimated as a total number of influenza cases averted, as well as Disability-Adjusted-Life-Years (DALYs) averted due to vaccination in each target population. The total costs of the implementation of vaccination program in the intervention scenarios, as well as the direct costs of disease management in non-vaccination scenarios were calculated based on the Ministry of Health and Medical Education prospective. By entering all epidemiological data, the costs and the vaccine efficacy into the model, the cost per DALY averted and the costs per averted cases were then calculated for each scenario. All costs were converted from Iranian Rials (IRR) into the United States Dollars (US$), based on the average exchange rate in the base year of 2014 (1 US$ = 30,000 Rials).

Parameter estimation

Due to lack of epidemiological data from Iran, the required data were extracted from the Global Burden of Disease study (GBD 2013) [2, 5], conducted by the Institute for Health Metrics and Evaluation (IHME) to extract the incidences, deaths and DALYs due to influenza in Iran. For the school-age children, we extracted burden of disease parameters for children aged between 9 and 14 years and we considered the adults older than 65 years for the elderly people group. In order to extract data for the pregnant women, we assumed that pregnant women have a greater likelihood (about 4 fold) of getting influenza compared to non-pregnant women (relative risk: 4.3 (2.3–7.8) [6] and adjusted all epidemiological parameters for pregnant women based on the relative risk of influenza compared to the adult non-pregnant women in pregnancy age range. We also assumed that the relative risk of influenza for the healthcare workers compared to the adults is 1.1 and adjusted the epidemiological parameter for this high-risk population [7]. We used the information obtained from the Center of Prevention and Control of Communicable Diseases in the Ministry of Health and Medical Education which indicated the number of in-patient and out-patients of influenza, as well as the healthcare utilization data of each group (Table 1). Accordingly, among the population of pregnant women, the percentages referred to in-patient and out-patient services were 94.37% and 5.63%, respectively. Such percentages for the population over 65 years, was 72.11% and 27.89%, respectively. Similarly, for the healthcare workers, 94.11% referred to in-patient and 5.89% referred to out-patient services. In school-age children group, the percentages of using in-patient and out-patient services were 97.23% and 2.77%, respectively.

Vaccine efficacies

In order to estimate the efficacy of influenza vaccination in specific populations, we performed a rapid literature review and

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meta-analysis. For the healthcare workers group, we calculated a pooled estimate of vaccine efficacy amongst 10 studies [8-17] for healthy adults aged 18-49 and results of the meta-analysis showed that pooled estimate of vaccine efficacy was equal to 66% (CI: 60-72) and there was heterogeneity between the results of the studies (Q = 13.69, P = 0.250). Regarding the school-age children, 2 studies [18, 19] were included and pooled estimate of the vaccine efficacy was 64% (CI: 51-76). There was no heterogeneity between the results of the studies (Q = 3.15, P = 0.98). Pooled estimate of the vaccine efficacy for the elderly was estimated at 19% (CI: 10-27) between 2 included studies [20, 21] and there was no heterogeneity between the results of the studies (Q = 5.895, P = 0.552). The vaccine efficacy for the pregnant women was equal to 43% (CI: 29-56) [22]. (Table 1)

Vaccination costs

The vaccine's price per dose was taken from the local representative of the vaccine's manufacturer (Jahan Behbood Corporation, Iran) that was US$ 10 per dose. We added 3% surcharge of purchasing from the manufacturer to the price of the vaccine. In addition, 2% was added for transportation, including the insurance, shipping and delivery to the airport. Also 5% wastage rate was assumed, based on the expert opinion for the vaccine. To estimate the vaccine supplies costs, the following formula was used:

$C = P * I \times B \times D \times (1/(1-w)$

P = Vaccine price per dose

I = Immunization coverage rate

B = Birth cohort

D = Number of doses per fully immunized child

W = Wastage rate

The number of doses per children fully immunized for influenza vaccine, the pregnant women , the elderly (aged > 65) and the healthcare workers was considered as 1 dose while for school-age children (aged < 9) 2 doses were assumed. We estimated that the number of Iranian pregnant women in the cohort to be 1,380,000 in the base year. The elderly population was 4,296,769 and the cohort of healthcare workers in the base year was assumed to be 500,000. The total population of school-age children was considered to be 4,437,473. We assumed 99% coverage rate of the vaccination. Consequently, the total vaccine supplies for the pregnant women, the elderly population, the healthcare workers and the school-age children were US$ 14,381,053, US$ 44,664,914, US$ 5,197,500 and US$ 92,255,064, respectively. We used World Health Organization (WHO) guideline to estimate the incremental costs of introducing a new vaccine into the current national vaccination system. To estimate the incremental system cost per dose, we included the costs of cold-chain, surveillance, monitoring, training, maintenance and the required facilities which are needed beyond the currently available facilities of Iran's Ministry of Health and Medical Education. The total annualized capital cost was estimated based on equipment prices and their useful life and an annualizing factor (Table 2).

Health services costs

The direct medical costs of treatment in each of the 4 target groups used for management of influenza were estimated for in-patient and out-patient cases, using sampling done at Imam Khomeini Hospital in Tehran which is the main hub of the influenza treatment for outbreak cases. For this purpose, 20 cases of the hospital treatments for each of the above 4 groups were studied and the average cost of hospitalization, diagnostic tests costs, medications and GP visits were collected and calculated. Furthermore, to calculate the costs for out-patient services, we extracted pharmaceutical items, diagnostic tests and out-patient visits after consultation with an expert's panel including health professionals, GPs, pediatric assistants and pediatricians in public hospitals and estimated the average costs per out-patient visits. (Table 2)

Cost-effectiveness analysis

The analysis of the cost effectiveness of vaccination against influenza of Iranian Ministry of Health and Medical Education's prospective was compared to no vaccination. To estimate the incremental cost-effectiveness ratio (ICER), the difference between the costs in the 2 scenarios was divided by the difference of DALYs averted according to the following formula[23] and WHO threshold was used to interpret the incremental cost-effectiveness ratio.

ICER = (Total Vaccination Cost – Medical Cost Saved) / (DALY without vaccine - DALY with vaccine)

Sensitivity Analysis

A one-way sensitivity analysis was performed on each scenario to detect those parameters which had the most impact on the ICER. We considered upper and lower estimates of DALYs, in-patient and out-patient health services costs and the vaccine efficacy in this regard.

Table 1. Summary of model parameters

Parameter	Pregnant Women	Elderly people	Heath care workers	School age children
Number of Cohort	1,380,000	4,296,769	500,000	4,437,473
Incidence per 100	3.4	12.4	0.9	1.4
Influenza cases	47,472	532,799	4,950	62,125
Inpatient cases	2,673	148,575	291	1,722
Outpatient cases	44,799	384,202	4,659	60,402
Death	30.2(18.2-44.4)	125(71.2-180.1)	22.5(12.8-31.5)	7.7(4.81-10.41)
DALY	2059(1404-2635)	1576(951-2315)	1353(772-2213)	971(605-1541)
Average Inpatient cost	US$400($129.5-$670.6)	US$333($62.5-$603.5)	US$488($217.7-$758.7)	US$113($53.26-$313.7)
Average Outpatient cost	US$39.3($33.4-$45.1)	US$39.3($33.4-$45.1)	US$39.3($33.4-$45.1)	US$38.4($32.5-$44.2)
Vaccine efficacy	0.43(0.29-0.56)	0.19(0.10-0.27)	0.66(0.60-0.72)	0.64(0.51-0.76)

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Table 2. Vaccine cost parameters

Parameter	Pregnant Women	Elderly people	Heath care workers	School-age children
Vaccine Price per dose	US$10	US$10	US$10	US$10
Wastage factor	1.05	1.05	1.05	1.05
Coverage rate %	0.99	0.99	0.99	0.99
Total dose required	1,483,105	4,466,491	519,750	9,225,506
Total vaccine supplied Cost	US$14,381,053	US$44,664,914	US$5,197,500	US$92,255,064
Cold chain storage	US$21,316	US$21,316	US$21,316	US$21,316
Syringe and safety box	US$128,800	US$401,030	US$40,000	US$1,124,146
Training material	US$33,333	US$33,333	US$33,333	US$33,333
Surveillance	US$23,333	US$23,333	US$23,333	US$23,333
Redesign of stationery	US$7,666	US$7,666	US$7,666	US$7,666
Transport maintenance	US$6,667	US$6,667	US$6,667	US$6,667
Cold chain maintenance	US$20,000	US$20,000	US$20,000	US$20,000
Wastage Management	US$9,200	US$9,200	US$9,200	US$9,200
Total Logistic Cost	US$250,316	US$522,526	US$108,483	US$2,558,674
Incremental cost per dose	US$0.17	US$0.11	US$0.20	US$0.27

RESULTS

The average cost of out-patient treatments for influenza was estimated to be US$ 38.4 for the school-age children while this amount was US$ 39.3 for the other 3 population groups. The cost of in-patient admissions totaled US$ 400 for the pregnant women, US$ 333 for the elderly and US$ 488 for the healthcare workers and US$ 113 for the school-age children in Ministry of Health prospective (Table 1). Total cost of influenza disease management for the pregnant women, the elderly, the healthcare workers and the school-age children were US$ 2,995,093 US$ 73, 731,567, US$ 343,351 and US$ 2,621,466, respectively in no vaccination scenario for the base year.

For the pregnant women population, total number of deaths averted was 13.8 and the numbers of influenza cases avoided were 20,413. Furthermore, total costs of influenza saved were calculated to be US$ 1,287,890 during the base year. In the elderly population, total number of influenza cases averted was 101,232 and number of deaths averted was 23.89, total cost of influenza management averted was obtained at US$ 14,008,998. For the healthcare worker population the total number of deaths averted was at 14.9 and the number of influenza cases avoided was 3,267. Moreover, the total cost of influenza saved was US$ 226,612 during the base year. In the school-age population, the total number of influenza cases averted was 39,760 and the number of deaths averted was 4.9. The total cost of influenza management saved was calculated to be US$ 1,677,738 (Table 3).

Incremental cost per DALY averted for vaccination program compared to no vaccination for the target groups of the pregnant women, the elderly people, the healthcare workers and the school age children was estimated to be US$ 15,069, US$ 104,104, US$ 5,685 and US$ 149,839, respectively (Table 3) . Results of the sensitivity analysis showed that ICER for the pregnant women vaccination program was changed from US$ 11,233 to US$ 23,045. This value changed from of US$ 59,399 to US$ 239,897 for the elderly group. Also for the healthcare workers group, the ICER results changed from US$ 3,578 to US$ 99, 69 and for the school-age children program, this value changed from US$ 94,435 to US$ 240,537 (Fig. 2).

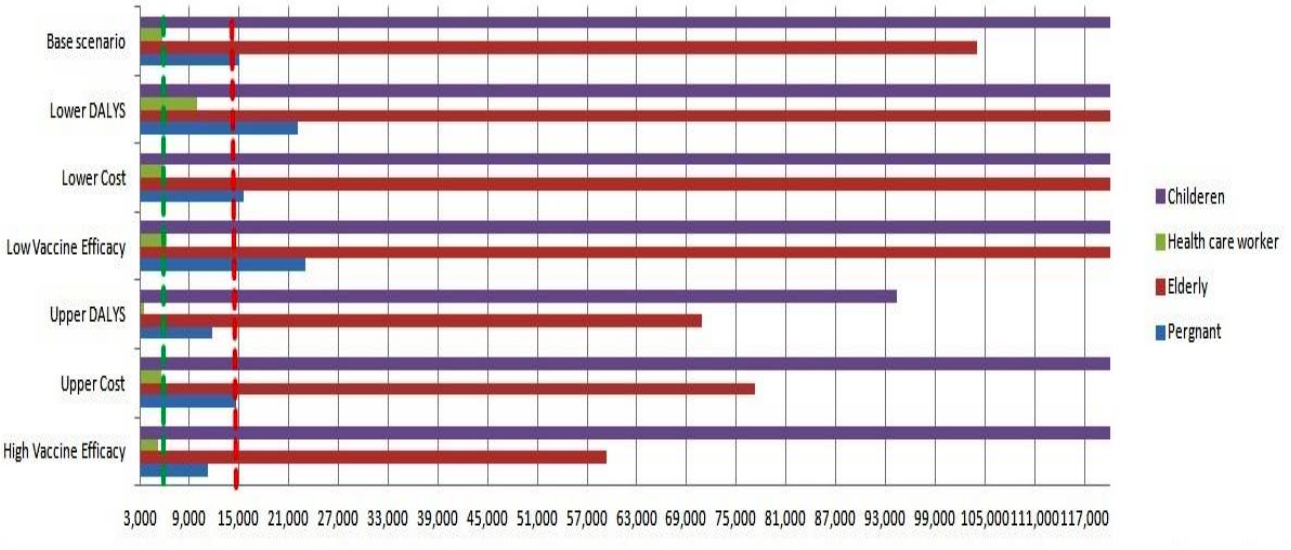

Fig. 2. Scenario analysis of ICER in influenza vaccination program for 4 different Iranian populations studied.

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Table 3. Total estimated costs, healthcare utilization measures and cost- effectiveness results.

Item	Pregnant Women	Elderly people	Heath care worker	School age children
Total Vaccination cost	US$14,631,369	US$45,187,460	US$5,305,983	US$94,813,739
Medical and community care cost	2,995,093	73,731,567	343,351	2,621,466
Medical and community care cost saved	1,287,890	14,008,998	226,612	1,667,738
Number of case averted	20,413	101,232	3,267	39,760
Number of Inpatient admission averted	1,149	28,229	192	1,102
Number of outpatient visit averted	19,263	72,998	3,075	38,675
Number of death averted	13	23	14	4.9
DALY averted	885	299	893	621
Incremental cost per DALY averted	US$ 15,069 Not cost-effective	US$ 104,104 Not cost-effective	US$ 5,685 Cost-effective	US$ 149,839 Not cost-effective

DISCUSSION

According to the threshold of WHO as well as the incremental cost per DALY averted with the basis of per capita GDP in Iran (US$ 4,763 in 2013), and the results of this study, it can be concluded that implementation of influenza vaccination program, only for the healthcare workers will be cost effective and the vaccination programs for the pregnant women, the elderly people and the children of school-age will not be cost effective, given that the incremental cost-effectiveness of such interventions is more than 3 times of the national GDP. Based on the sensitivity analysis, ICER for the healthcare workers group was still cost-effective (less than 3 time of the GDP per capita) in all scenarios. Moreover, in the upper scenario for DALYs, ICER for this group showed highly cost effective intervention ($3,487). However, a vaccination program for the pregnant women will be cost-effective in the upper scenario for DALYs ($11,777) and the upper scenario for the vaccine efficacy ($11,233). Results for other target groups remained constant in terms of cost-effectiveness (Fig. 2).

Regarding the incidence of influenza in the healthcare workers population, there was no significant difference between this group and the other 3 groups. However, due to low population of this group, and lower costs of implementation of vaccination program, the vaccination will be cost effective in this group. The vaccination of the pregnant women, the children of school-age and the elderly people was not shown to be cost-effective due to the high costs of the vaccination program as well as their relatively low incidence.

Among 8 studies, all conducted in high-income countries where the economic evaluation of seasonal vaccination and influenza pandemic were examined, 7 studies were on elderly people in which 4 studies [24-27] evaluated the cost effectiveness for the seasonal influenza vaccine, and 2 studies [25, 28] evaluated the cost-effectiveness of influenza vaccines in addition to pneumococcal vaccine, compared to influenza vaccination alone, and one study [29] assessed the influenza vaccination for pregnant women. One study which has conducted in several countries has evaluated vaccination coverage in terms of gross national income per capita and examined the effects of increased income and education on immunization coverage[30]. Two studies have considered the factors affecting the cost effectiveness of the vaccine before and during the pandemic including the vaccine's strain match, the vaccine's availability and its cost [24, 31]. These studies are discussed in detail as follows.

The study of cost effectiveness of influenza vaccine in Australia, on people aged between 50 to 64 years has shown that vaccination programs in this age group reduced the annual incidences of Influenza-Like-Illness (ILI) to 3,124 cases, in fact, it is considered as 0.09% reduction in the incidence of ILI (reduced from 1.90% to 1.81%). This new policy prevented 1,172 hospitalizations cases, 89 deaths and 2,805 cases of absenteeism from work. From the prospective of the healthcare payers and the government, the incremental costs of influenza vaccination program for years with perfect quality obtained, were US$ 8,908, US$8,338 and US$22,408, respectively [27]. Also, another study have shown that the combined influenza and pneumococcal vaccination strategy has higher effectiveness than influenza vaccination alone [28].

In Japan, following rapid implementation of a national immunization program of influenza vaccination of the elderly, a study was conducted to review the efficiency of the implemented strategies in order to allocate allowances to their vaccination programs. The results indicated that a strategy that pays 100% allowances for all, or 100% allowance for the high-risk elderly, would be cost-effective [25]. In Australia, a model was used to compare the cost-effectiveness of universal influenza vaccination for persons over 50 years of age with recent policies of vaccination of people older than 65 years. According to the available epidemiological data, 2 scenarios were followed. One scenario was related to an estimation of the incidence of ILI in Australia, and the other one in Europe. These scenarios and sensitivity analyses have shown that, ICER compared to the recent policy indicate changes from US$ 6,000 to US$12,000 per DALYs [26].

Another study has examined the cost- effectiveness of influenza vaccination in pregnant women and has shown that, immunization of pregnant women population against influenza would save US$ 50 per woman, gaining 45 quality-adjusted hours, relative to providing supportive care only. This study has determined that influenza vaccination programs for pregnant women are cost-effective [29]. Another study in Hong Kong aimed to answer the question "Does the program of influenza vaccination during a non-pandemic rate (with ILI value of 11%), has the cost-benefit or not?" The results indicated that from the perspective of a susceptible individual, the influenza vaccine was cost-effective [24] . In a study in Singapore, a decision analytic model to assess the cost-benefit and cost effectiveness of vaccination against pandemic influenza was used. This model has compared common strategies for the treatment, including quick treatment with oseltamivir and only treatment with vaccination in addition to the treatment. According to their results, the only treatment strategy led to 690 deaths, 13,950 hospitalization days, and a cost of about US$ 497 million in North America. For immediate vaccination, when vaccine efficiency was 55%, the cost benefit of vaccination was more than vaccination alone. Stockpiling of the vaccines in most scenarios, even when the vaccine effectiveness

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is 100%, is not cost-effective. Based on findings of this study, a vaccination program should be based on severity of the disease and immediate vaccination is most cost-effective; however, it implies that the vaccines be available when required [32]. Furthermore, results of a survey done in 10 countries in Africa, Asia, Oceania, Eastern Europe, Latin America and the Middle East have shown that influenza vaccination coverage rates between countries have considerable differences, and only 1 factor does not make the top cover. The results have indicated that a strong recommendation to perform vaccination is not enough, and the immunization programs will be completed when awareness of the population is increased. In fact, increased awareness is the key to increased coverage of influenza vaccination [30].

The authors here recommended that national immunization program in Iran should be focused on diseases with high morbidity and mortality, including *Haemophilus Influenzae* type b (Hib) infection , diarrhea and other severe infectious diseases based on economic evaluation studies which has been done in this regard [33-35]. In case of influenza, vaccination of high-risk group such as healthcare workers should be taken into consideration.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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