Cost–benefit Analysis of Human Papillomavirus Vaccine in Iran

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Research Article

Keywords: HPV, Vaccine, Cost-benefit analysis, discrete choice experiment, cost-of-illness, Iran

Posted Date: September 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-745058/v1

Abstract

Background: Despite increasing global attention to the national human papillomavirus (HPV) immunization program, this program is controversial in Iran. Evidence indicate that HPV vaccination is not cost-effective in Iran. Using cost-effectiveness analysis for decision-making about public health interventions such as vaccination is debated, because its potential benefits may not fit this framework. Our objective was to evaluate economic effects of HPV vaccination by cost-benefit analysis (CBA). In this case, we used bivalent and quadrivalent in Iran in 2020.

Methods: We performed a CBA from a societal perspective. We used two approaches of the vaccine's economic benefit: willingness to pay by discrete choice experiment; and cost of illness. Costs only included the vaccine cost.

Results: The cost of two doses of bivalent and quadrivalent vaccines were US $ 29 and US $ 151, respectively (US $1 =IRR 42,000). The benefits of bivalent and quadrivalent vaccines were US $ -432, and US $ 380 per person using willingness to pay approach and they were US $ 7,375 and US $ 6,590 thorough cost-of-illness approach. The cost-benefit ratio (CBR) of bivalent and quadrivalent vaccines was -15.114 and 2.512 by willingness to pay approach, and it was 258.12 and 43.51, by cost of illness approach.

Conclusions: This study confirms the benefit of both the national bivalent and quadrivalent vaccination program and provide reliable evidence for policy-makers when programming HPV vaccination.

Background

Human papillomavirus (HPV) infections are the most common sexually transmitted infections worldwide [1]. The global prevalence estimated at 11.7% and HPV will infect 80% of women in their lifetime [1, 2]. The HPV prevalence is estimated to be 9.3% among women in the East Mediterranean region (EMR)[3], while its prevalence was 9 % in Iranian females[4]. Persistent HPV infection with high-risk types such as HPV type 6, 11, 16, and 18 cause almost all cases of cervical cancer, genital wart, and some anal, vaginal, penile, and oropharyngeal cancers[5].

Cervical cancer is the fourth most common cancer in women globally, with an estimated 604,127 new cases and 341,831 deaths in 2020[6]. The highest deaths (33.94%) was in the South-East Asia Region (SEAR) and lowest (2.81%) in EMR[7]. International Agency for Research on Cancer (IARC) estimated the age-standardized incidence rate (ASR) and mortality rate of cervical cancer in Iran to be around 2.3 and 1.5 per 100,000 females, respectively, in 2020[8]. Even though these rates are lower than many countries, they are estimated to increase by 2040. By the highest assumption (i.e. 5% annual change), we might observe a 475% excess in the number of cervical cancer per year in Iran[9].

Cervical cancer is primarily preventable by vaccination to prevent HPV infection or by screening to detect and treat cervical precancerous lesions [10]. HPV immunization can prevent up to almost 70% of cervical cancers[11]. Currently, in Iran, cervical cancer screening are not organized[12] and among three available ways of HPV vaccination, there are two accessible types, including bivalent and quadrivalent. The bivalent vaccine

protects against HPV type 16, 18[13], and quadrivalent adds type 6 and 11, associated with the development of genital warts[14] .

The World Health Organization (WHO) recommends inclusion of HPV vaccination in girls aged 9–14 years in the national immunization program [15]. The HPV vaccine is cost-effective in many parts of the world, where 107 countries apply this vaccination into their national immunization schedule; nevertheless, most EMR countries have not incorporated HPV into their vaccination program [16]. In Iran, HPV vaccination has not been cost-effective yet, so it is not included in the government's immunization schedule[7, 9].People can seek these two HPV vaccines (bivalent and quadrivalent) in the private sector.

The most popular form of health economic evaluation is cost-effectiveness analysis (CEA). Nevertheless, intense debates exist about whether CEA captures the entire domain of these public health programmer vaccines [17]. Economists have suggested that cost-benefit analysis (CBA) can capture a broader range of vaccination benefits compared to CEA[18]. Unlike CEA, which employs different health metrics such as quality-adjusted life years (QALY) to capture benefits, CBA captures monetary units' benefits, therefore it can provide more comparability and easier comprehension and assess the effects of policies on social welfare rather than only on health [19, 20]. CBA can help policymakers face tight healthcare budget constraints to determine whether the HPV vaccine should be added to the national immunization programs. Using CBA, this study aimed to evaluate the broader economic consequences associated with HPV vaccination from the social perspective in the year 2020 in Iran.

Methods

We conducted a CBA to evaluate the impact of the HPV vaccines (in this case, bivalent and quadrivalent) for 9-14-year- girls compared to no vaccination in 2020 in Iran (societal perspective). CBA is the extensive economic evaluation method that measures all the costs and benefits in monetary units. We applied two approaches, willingness to pay (WTP) by discrete choice experiment (DCE) technique and cost-of-illness (COI) averted to estimate the economic benefits of vaccines. The economic costs only included the price of the vaccines (Fig. 1). The study had three main steps: 1- estimating the benefits of vaccination, 2- estimating the cost of vaccination and 3- cost-benefit analysis.

Estimating the benefits of vaccination

We used two definitions of economic benefits. First, the COI approach evaluates costs of cervical cancer prevented through vaccination; and second, the economic benefits based on the WTP approach by DCE technique.

Cost of illness (COI)

We used the COI method to estimate the economic burden of cervical cancer prevention by averting direct and indirect costs through vaccination. We considered only cervical cancer because we could not acquire robust data about genital warts incidence, whereas the incidence of other forms of HPV-associated cancers was low

in Iran. Through adopting a societal lenses, we used a prevalence-based and bottom-up approach. We divided the costs into direct (medical and nonmedical) and indirect costs.

the diagnostic and treatment process extracted from the National Comprehensive Cancer Network (NCCN) guideline[21] in order to estimate the direct costs of cervical cancer based on the early (stages I and II) and advanced (III and IV) stages. The direct medical costs included the cost of visits, diagnostic procedures, surgery, chemotherapy, radiotherapy, brachytherapy, chemo radiation therapy, chemotherapy medications, and one-year follow-up costs included the cost of visits, Pap smear, and Magnetic resonance imaging (MRI). We calculated these costs by reviewing medical records for all patients who were treated (n=117) at Imam Khomeini Hospital in 2020. With 1000-beds, the Imam Khomeini Hospital is affiliated with the Tehran University of Medical Sciences (TUMS) and is the largest referral hospital in Iran. Since the tariff for public medical service is universal across Iran and this hospital admits patients form across the country, our results can be generalized nationwide. Since the costs of chemotherapy medications were not recorded in patients' records, we calculated these costs according to the type of chemotherapy regimen. In this regard, we identified the performed chemotherapy regimen through interviews with specialists and from patient's medical records (cisplatin + paclitaxel, cisplatin and carboplatin + paclitaxel + cisplatin). The frequency of each regimen was determined based on the information obtained from medical records. Then, the average cost of each regimen was calculated according to the medications' price and the prescription dose. We only calculated the transportation cost by using the clinical practice guidelines, literature review and expert's opinions to estimate the direct non-medical costs. To calculate the indirect costs, we used the human capital method and also calculated the costs of productivity loss because of disability and premature death [22]. A 3% discount rate was considered to convert the stream of lifetime earnings into a present value[23].

The HPV vaccine effectiveness[24] and prevalence of HPV types in Iran [25]were identified through literature review. We calculated the HPV vaccine effectiveness in Iran (vaccine effectiveness * prevalence of HPV types in Iran). We were obtained the lifetime risk of cervical cancer in Iran from IARC. Then, according to the average cost of cervical cancer estimated expected cost per person, We considered a 3% discount rate[26] to convert the expected cost into a present value and Finally, we estimated the average

benefit per person (the present expected costs cervical cancer * vaccine effectiveness in Iran)[7].

Willingness to pay (WTP)

Our main study elicited WTP to HPV vaccines per person in Iran[9]. This study used DCE to elicit mothers' preferences and WTP for vaccinating in their 9–14-year-old daughters against HPV. Commonly used in health economics, DCE is a method to elicit individuals' preferences and WTP by observing their selections within hypothetical choice scenarios. The study participants were 327 mothers who had at least one 9–14-year-old daughter and were referred to five hospitals affiliated with TUMS in the megacity of Tehran, whom were interviewed face-to-face in 2019. In our study, participants when express their preferences, considered time, so there was no need to use a discount rate.

Estimating the Cost of vaccination

According to the structured vaccination system in Iran and annual vaccination costs calculated in the health system, the cost of new vaccines can be overlooked. Therefore, we did not include HPV vaccination cost and only included the vaccine cost. We obtained the cost per dose HPV vaccines from the Ministry of Health and Medical Education (MoHME).

Cost-benefit analysis (CBA) and sensitivity analysis

We performed CBA for total costs and vaccination benefits compared with no vaccination. CBA was performed with two economic criteria: Net benefit and cost-benefit ratio (CBR) for the HPV vaccination program[27] (table1).

Table 1

Cost - benefit analysis criteria; B: Benefit vaccine, C: Cost vaccine.

Criteria	Formula
Cost benefit ratio (CBR)	B/C>1
Net benefit	B-C>0

We conducted one-way sensitivity analysis for both vaccines to investigate possible parameter uncertainty changes influencing the CBA results: (1) Double and a half incidence cervical cancer rates to 2040 according to the IARC reports[9]; (2) changing price of HPV vaccines (±20% of their base-case values) [28] [29].

Results

This study calculated CBA to the HPV vaccines (bivalent and quadrivalent) in Iran. CBR bivalent vaccine by WTP and COI approach were -15.11 and 258.12, respectively. The CBR quadrivalent vaccine by WTP and COI approach were also 2.51 and 43.51, respectively. This section presents vaccines benefits, vaccines cost, and finally, CBA for HPV vaccines.

Benefits

The prevalence of HPV (16, 18) type is estimated at 66.1% in Iran[25]. The effectiveness of bivalent and quadrivalent vaccines is estimated at 79.59% and 71.12%, respectively in Iran. The estimated economic costs of HPV associated with cervical cancer treatment was US $ 31,419,956 during the study period (table 2). The average benefit per person of bivalent and quadrivalent vaccines by COI approach was US $ 7,375 and US $ 6,590, respectively. The average benefit per person of bivalent and quadrivalent vaccines by WTP approach was US $ -432 and US $ 380, respectively (table3, 4).

Table 2

cervical cancer costs in Iran in 2020.

Cost component	Mean cost, (US $)	Total cost, (US $)	Percentage of total cost (%)
Direct medical cost	7,629	8,056,628	25.64
Diagnostic procedure	146	154,609	0.49
Surgery	1,429	1,508,841	4.80
Radiotherapy	62	65,830	0.21
Brachytherapy	1,417	1,496,617	4.76
Chemotherapy	23	24,546	0.08
Chemo radiation	3,089	3,261,981	10.38
Chemotherapy medications	1,228	1,297,001	4.13
Follow-up	234	247,203	0.79
Direct non-medical cost	190	201,143	0.64
Transportation cost	190	201,143	0.64
Indirect cost	21,934	23,162,186	73.72
Loss of productivity due to disability	521	550,524	1.75
Productivity lost due to premature death	21,413	22,611,662	71.97
Total	29,754	31,419,956	100

Costs

The price per dose of the bivalent and quadrivalent vaccines at the time of this analysis was US $ 14 and US $ 76, and it was US $ 29 and US $ 151 for a two-dose Bivalent and quadrivalent vaccination program in Iran.

Cost -benefit analysis and Sensitivity analysis

The BCR for bivalent vaccine greater than 1, the benefit cost was estimated to be positive from the COI approach, meaning that the benefit of this vaccine was high than it's a cost. The BCR for quadrivalent vaccine greater than 1, the benefit cost was estimated to be positive from both COI and WTP approach, meaning that the benefit of this vaccine was high than its cost.

Table 3

Cost- benefit analysis of HPV vaccine by cost of illness approach.

Cost of illness	Vaccine effectiveness population	Cost Cervical cancer per person, discounted at 3%	Vaccination benefit per person, (US $), discounted at 3%	Vaccination costs per person, (US $)	Net benefit discounted at 3 %, (US $)	Cost benefit ratio discounted at 3%
Bivalent	0.79	9,266	7,375	29	7,346	258.12
Quadrivalent	0.71	9,266	6,590	151	6,439	43.51

Table 4

Cost- benefit analysis of HPV vaccines by willingness to pay approach.

willingness to pay	Vaccination benefit per person, (US $)	Vaccination costs per person, (US $)	Net benefit,	Cost benefit ratio,
Bivalent	-432	29	-460	-15.11
Quadrivalent	380	151	229	2.51

Table 5 shows the results of the one-way sensitivity analysis. When the vaccine cost increases %20, CBR bivalent and quadrivalent vaccines will change from 258.12 to 215.10 and 43.51 to 36.26 by COI approach. CBR bivalent and quadrivalent vaccines change from -15.11 to -12.59 and 2.51 to 2.09 by the WTP approach. Generally, changes in two parameters, including the incidence of cervical cancer and cost vaccines, do not affect the outcomes significantly.

Table 5

One-way sensitivity analysis of vaccine HPV.

	Net benefit, (US $)	Cost benefit ratio, (US $)
Base-case		
Bivalent		
willingness to pay	-460	-15.11
Cost of illness	7,346	258.12
Quadrivalent		
willingness to pay	229	2.51
Cost of illness	6,439	43.51
Double and a half incidence cervical cancer rates		
Bivalent		
willingness to pay	-460	-15.11
Cost of illness	18,409	645.31
Quadrivalent		
willingness to pay	229	2.51
Cost of illness	16,324	108.79
Cost+20%		
Bivalent		
willingness to pay	-466	-12.59
Cost of illness	7,341	215.10
Quadrivalent		
willingness to pay	198	2.09
Cost of illness	6,408	36.26
Cost-20%		
Bivalent		
willingness to pay	-455	-18.89
Cost of illness	7,352	322.65
Quadrivalent		
willingness to pay	259	3.14
Cost of illness	6,469	54.39

Discussion

We conducted CBA (in terms of social perspective) of HPV vaccination in Iran's national immunization program. Our estimated CBA is based on two approaches: COI and WTP. Utilizing different approaches to monetize CBA benefits can lead to widely varying outcomes on public health interventions such as vaccination[30]. Our findings that both the national bivalent and quadrivalent vaccine with COI approach in Iran have been beneficial and illustrative. Our results are in line with several studies in the United States (US), Germany and Indonesia [31–33].

One study in Lebanon did not include the indirect costs of cancer and showed that it was not cost-beneficial[34]. In contrast, our adapted COI approach indicated that bivalent and quadrivalent vaccine was cost-beneficial in Iran. The WTP approach indicated cost-beneficial of the quadrivalent vaccine. WTP for the quadrivalent vaccine was US $ 380, which suggests that protection against genital warts is essential, and people on average, had WTP for the additional protection.

Although CEA and CBA can lead to similar results[35, 36], our results indicated that HPV vaccines were cost-beneficial, in contrary to previous studies that showed HPV vaccines were not cost-effective[7, 29] We indicated that the two methodologies may not always give the same ranking allocation of a limited public health budget. This can happen because preferences and WTP are not well-reflected in cost-effectiveness[37]. On the other hand, they usually focus on the health service benefits and underestimate vaccination's actual value[30, 38].

Our results were consistent across all sensitivity analyses, and HPV vaccines remained cost-beneficial. We did not consider the cost savings of HPV vaccination, such as protection against genital warts, anal, vaginal, penile, and oropharyngeal cancers, due to the lack of data. The benefit of protection against cervical cancers is approximately as great as the benefit of protecting against non-cervical cancers in some scenarios[36, 39]. We doubled the benefit of HPV vaccines with this assumption and the results remained unchanged.

There are several limitations to our study. First, we acknowledge that our results are bounded to only one hospital, albeit the main referral hospital in Iran. The direct and indirect costs used for our calculations are hospital and provincial-specific. Second, the structures and inputs of the cost-benefit model in this study were focused on our national health care. Thus, the results might not be perfectly accurate for other countries' strategies. However, we believe that this could be probably used as a model for the EMR countries. Third, this study did not include costs of the vaccination, supply chains, and service delivery based, while these might impose a cost to the system. Despite these limitations, we believe that this economic evaluation enables policymakers to gain a broad understanding of potential economic effects related to the HPV vaccine program. Without such a view, cost-effectiveness evaluation can lead to misleading conclusions about resource allocation towards the HPV vaccination program.

Conclusions

Our findings provide reliable evidence for policy-makers when programming HPV vaccination. This study confirms the benefit of both the national bivalent and quadrivalent vaccination program. This evidence might shed some light on revising the policies for prevention and control of cervical cancer in Iran and Similar

countries, which will contribute, we envisage, to the global efforts to eliminate cervical cancer ultimately, along the pathway to SDG 3.4.

Declarations

Acknowledgements

We are grateful to Somaye Jalilvand (TUMS) and Farnaz Amouzegar Hashemi (Center of Cancer Institute, TUMS) for their insightful advice and assistance during data collection.

Authors' contribution

AT and NS conceived the study. AT supervised all phases of evaluation and critically revised the manuscript; he is the guarantor. RAD, AN, MY, AGM, and KZ were advisors in methodology, analysis, and interpretation of data and equally contributed to the manuscript's development. NS collected and conducted primary data analysis. All authors contributed to the development and approved the final manuscript.

Funding:

This research is a part of an MSc thesis in health economics at the Tehran University of Medical Sciences (TUMS), which benefited from the TUMS, Iran. In Iran and Similar countries Registration code: IR.TUMS.SPH.REC.1398.121.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This research was approved by the ethical committee of Tehran University of Medical Sciences (TUMS) by the code of IR.TUMS.SPH.REC.1398.121. Also informed consent was obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

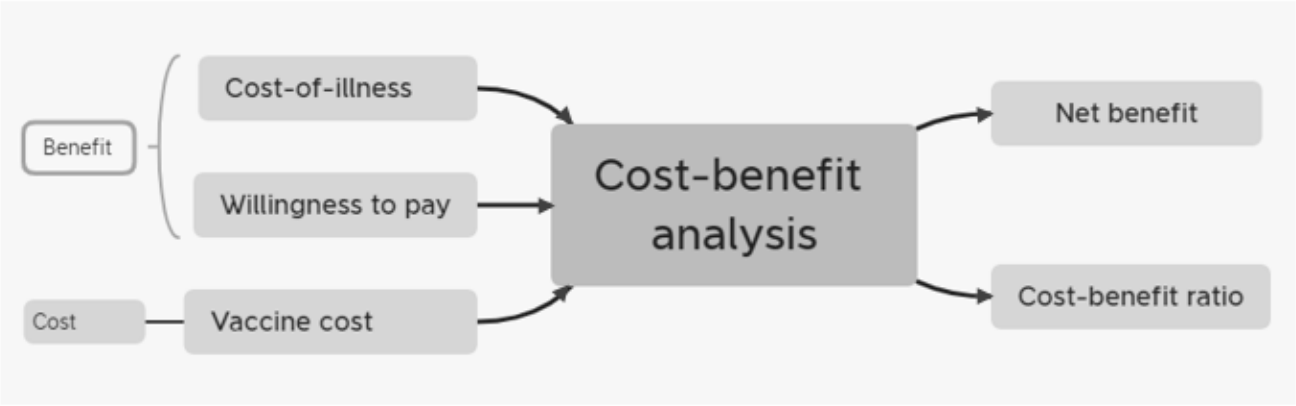

Figure 1

The Analytical Framework.