Cost–Benefit Analysis of Human Papillomavirus Vaccine in Iran

Nasrin Sargazi1 · Amirhossein Takian1,2,3 · Rajabali Daroudi1 · Azin Nahvijou4 · Mehdi Yaseri5 · Ali Ghanbari Motlagh6,7 · Kazem Zendehdel4,8,9

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Abstract

Despite increasing global attention to the national human papillomavirus (HPV) immunization program, this program is controversial in Iran. Evidence indicates that HPV vaccination is not cost-effective in Iran. Using cost-effectiveness analysis for decision-making about public health interventions such as vaccination is controversial because its potential benefits may not fit this framework. This study aimed to evaluate the economic effects of the HPV vaccination by cost–benefit analysis (CBA) using bivalent and quadrivalent in Iran in 2020. We performed a CBA from a societal perspective. We used two approaches of the vaccine’s economic benefits: willingness to pay by discrete choice experiment and cost of illness. Costs only included the vaccine cost. The cost of two doses of bivalent and quadrivalent vaccines were US $29 and the US $151, respectively (US $1 = IRR 42,000). The benefits of bivalent and quadrivalent vaccines were US $−432, US $380 per person using the willingness to pay approach, and they were US $7375 and US $6590 thorough cost-of-illness approach. The cost–benefit ratio (CBR) of bivalent and quadrivalent vaccines was −15.11 and 2.51 by the willingness to pay approach, and 258.12 and 43.51 by the cost of illness approach. This study confirms the benefits of the national bivalent and quadrivalent vaccination programs and provides reliable evidence for policy-makers programming HPV vaccination.

Keywords HPV · Vaccine · Cost–benefit analysis · Discrete choice experiment · Cost-of-illness · Iran


### Background

Human papillomavirus (HPV) infections are the most common sexually transmitted infections worldwide (Serrano et al., 2018). The global prevalence is estimated at 11.7%, and HPV will infect 80% of women in their lifetime (Serrano et al., 2018; World Health Organization, 2020). The HPV prevalence is estimated at 9.3% among women in the East Mediterranean region (EMR) (Farahmand et al., 2019), while its prevalence was 9% in Iranian females (Salavatiha et al., 2021). Persistent HPV infection with high-risk types such as HPV type 6, 11, 16, and 18 causes almost all cases of cervical cancer, genital wart, and some anal, vaginal, penile, and oropharyngeal cancers (De Martel et al., 2017).

Cervical cancer is the fourth most common cancer in women globally, with an estimated 604,127 new cases and 341,831 deaths in 2020 (Sung et al., 2021). The highest number of deaths (33.94%) was in the South-East Asia Region (SEAR) and lowest (2.81%) in EMR (Sargazi et al., 2021). International Agency for Research on Cancer (IARC) estimated the age-standardized incidence rate (ASR) and mortality rate of cervical cancer to be around 2.3 and 1.5 per 100,000 females, respectively, in Iran, 2020 (International Agency for Research on Cancer, 2021). Although these rates are lower than many countries, they are estimated to increase by 2040 (International Agency for Research on Cancer, 2021). 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 (Sargazi et al., 2021).

Cervical cancer is primarily preventable by vaccination to prevent HPV infection or screening to detect and treat cervical precancerous lesions (Reis et al., 2021). HPV immunization can prevent up to almost 70% of cervical cancers (Spayne & Hesketh, 2021). Currently, cervical cancer screening is not organized in Iran (Ghahramani et al., 2020), 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 (Paavonen et al., 2009), and quadrivalent adds type 6 and 11, associated with the development of genital warts (Group FIIS, 2010).

The World Health Organization (WHO) recommends including HPV vaccination in girls aged 9–14 years as a first priority and boys, as appropriate, in the national immunization program (World Health Organization, 2016). 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 (Bruni et al., 2021). In Iran, HPV vaccination has not been cost-effective yet, so the government has not included it in the immunization schedule (Sargazi et al., 2021; Yaghoubi et al., 2018). 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). Nonetheless, intense debates exist about whether CEA captures the entire domain of these public health programmer vaccines (Bärnighausen et al., 2012). Economists have suggested that cost–benefit analysis (CBA) can...
capture a broader range of vaccination benefits compared to CEA (Robinson et al., 2019). 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 (Rudmik & Drummond, 2013). 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 Iran 2020.

Methods

We conducted a CBA to evaluate the impact of the HPV vaccines (in this case, bivalent and quadrivalent) for 9–14-year-old girls compared to no vaccination in Iran in 2020 (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 (Table 1), (Fig. 1). The study had three major 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 mean indirect costs through vaccination. We considered only cervical cancer because robust data about the incidence, prevalence and cost of genital warts and cervical intraepithelial neoplasia was scarce. Nevertheless, the incidence of other forms of HPV-associated cancers was low in Iran (De Martel et al., 2017). We used a prevalence-based and bottom-up approach through adopting societal lenses. We divided the costs into direct (medical and nonmedical) and indirect costs.

We extracted the diagnostic and treatment process from the National Comprehensive Cancer Network (NCCN) guideline (National Comprehensive Cancer Network, 2022) 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 visits, diagnostic procedures, surgery, chemotherapy, radiotherapy,
### Table 1 Input parameters

| Parameters                                                                 | Value  | References                        |
|---------------------------------------------------------------------------|--------|-----------------------------------|
| Percentage of cervical cancer attributable to types 16/18 in Iran         | 66.1   | Serrano et al. (2018)             |
| Percentage of cervical cancer attributable to types 31/33/35/39/45/51/52/56/58/59 in Iran (cross-protection) | 23.6   | Serrano et al. (2018)             |
| Vaccine efficacy to HPV types 16 and 18 (bivalent), %                    | 96     | World Health Organization (2020)  |
| Vaccine efficacy to HPV types 31/33/35/39/45/51/52/56/58/59 (bivalent), % | 68.4   | Farahmand et al. (2019)           |
| Vaccine efficacy to HPV types 16 and 18 (quadrivalent), %                | 96     | World Health Organization (2020)  |
| Vaccine efficacy to HPV types 31/33/35/39/45/51/52/56/58/59 (quadrivalent), % | 32.5   | Salavatia et al. (2021)           |
| Vaccine effectiveness in Iran (bivalent), %                              | 79.59  | Calculated                        |
| Vaccine effectiveness in Iran (quadrivalent), %                           | 71.12  | Calculated                        |
| Cervical cancer incidence in Iran                                         | 1056   | De Martel et al. (2017)           |
| Cervical cancer prevalence in Iran                                        | 2948   | De Martel et al. (2017)           |
| Cervical cancer mortality in Iran                                         | 644    | De Martel et al. (2017)           |
| Surgery probability (stage I, II, III, IV), %                            | 60, 30, 18, 10 | Expert opinion                  |
| Chemotherapy probability (stage I, II, III, IV), %                       | 0, 0, 0, 16 | Expert opinion                  |
| Radiotherapie probability (stage I, II, III, IV), %                      | 0, 0, 0, 16 | Expert opinion                  |
| Brachytherapy probability (stage I, II, III, IV), %                      | 40, 86, 90, 67 | Expert opinion                  |
| Chemoradiation probability (stage I, II, III, IV), %                     | 40, 86, 90, 67 | Expert opinion                  |
| Patients probability (stage I, II, III, IV), %                          | 32, 38, 20, 10 | Expert opinion                  |
| Mean of missed work days                                                 | 17     | Calculated                        |
| Employed rate, %                                                         | 84     | Statistical Centre of Iran (2020) |
| Unemployed rate, %                                                       | 16     | Statistical Centre of Iran (2020) |
| Daily wages for employed, (US $)                                         | 16.02  | Ministry of Cooperatives, Labour, and Social Welfare (2020) |
| Daily wages for unemployed, (US $)                                       | 15.27  | Ministry of Cooperatives, Labour, and Social Welfare (2020) |
| Number mean of transportations                                            | 10     | Calculated                        |
| Parameters                                              | Value    | References                |
|---------------------------------------------------------|----------|---------------------------|
| Mean cost, (US $)                                       |          |                           |
| Direct cervical cancer                                  | 7629     | Calculated                |
| Diagnostic procedures                                   | 146      | Calculated                |
| Surgery                                                 | 1429     | Calculated                |
| Chemotherapy                                            | 23       | Calculated                |
| Radiotherapy                                            | 62       | Calculated                |
| Brachytherapy                                           | 1417     | Calculated                |
| Chemo radiation therapy                                 | 3089     | Calculated                |
| Chemotherapy medications                                | 1228     | Calculated                |
| Follow-up                                               | 234      | Calculated                |
| Direct non-medical cost cervical cancer                 | 190      | Calculated                |
| Transportation cost                                     | 190      | Calculated                |
| Indirect cost cervical cancer                           | 21,934   | Calculated                |
| Loss of productivity due to disability                  | 521      | Calculated                |
| Productivity lost due to premature death                | 21,413   | Calculated                |
| WTP to bivalent vaccine per person                      | −432     | Sargazi et al. (2021)     |
| WTP to quadrivalent vaccine per person                  | 380      | Sargazi et al. (2021)     |
| Bivalent vaccine cost                                   | 29       | Expert opinion            |
| Quadrivalent vaccine cost                               | 151      | Expert opinion            |
| Life expectancy of Iranian women                        | 76       | World Bank (2020)         |
| Discount rate%                                          | 3        | Vahdatimanesh et al. (2017) |
brachytherapy, chemoradiation therapy, chemotherapy medications, and one-year follow-up costs, including the cost of visits, pap smear, and magnetic resonance imaging (MRI). We calculated these costs by reviewing medical records for all patients treated (n = 117) in 2020, at the Imam Khomeini Hospital Complex (IKHC), the largest referral hospital in Iran, with 1000-beds affiliated with the Tehran University of Medical Sciences (TUMS), to which about 40% of cervical cancer patients are referred from across the country (Sadeghi et al., 2017). Since the tariff for public medical service is universal across Iran and the IKHC is a national referral center, 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. We identified the performed chemotherapy regimen through interviews with specialists and the patient’s medical records (i.e., cisplatin + paclitaxel, cisplatin and carboplatin + paclitaxel + cisplatin). We determined the frequency of each regimen based on the information obtained from medical records. Then, we calculated the average cost of each regimen according to the medication’s 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. Our team used the human capital method to calculate indirect and productivity loss costs because of disability and premature death (Daroudi et al., 2015). We used different daily wages for employed and unemployed patients. We used the minimum daily wage approved by the Ministry of Cooperatives Labor and Social Welfare for unemployed patients. As these patients are usually accompanied during visits, we also estimated and added the time costs for the accompanying persons based on the minimum wage rate (Statistical Centre of Iran, 2020; Ministry of Cooperatives, Labour, and Social Welfare, 2020). We determined and categorized the number of deaths based on age groups using the IARC data to estimate the cost of productivity lost due to premature death.

Besides, according to the World Bank report, we obtained the life expectancy of Iranian women in different age groups to estimate life expectancy at the age of death (World Bank, 2020). A 3% discount rate was considered converting the stream of lifetime earnings into a present value (Vahdatimanesh et al., 2017).
We identified vaccine effectiveness and prevalence of HPV types and obtained the lifetime risk of cervical cancer in Iran from IARC (International Agency for Research on Cancer, 2021). Then, we considered a 3% discount rate (Cropper et al., 2019) to convert the expected cost into a present value according to the average cost of cervical cancer estimated expected cost per person. Finally, we estimated the average benefit per person (the present expected costs of cervical cancer * vaccine effectiveness in Iran) (Yaghoubi et al., 2018).

**Vaccine Effectiveness**

We conducted a literature review to identify the HPV vaccine efficacy (Paavonen et al., 2009; Wheeler et al., 2012), and the percentage of cervical cancer attributable to HPV types in Iran (Shoja et al., 2019). We considered the cross-protective effects on other high-risk HPV types (31/33/35/39/45/51/52/56/58/59). Besides, we calculated the HPV vaccine effectiveness in Iran \[\text{\{vaccine efficacy} \times \text{percentage of cervical cancer attributable to type }16/18 \text{in Iran}}\] + \[\text{\{vaccine efficacy} \times \text{percentage of cervical cancer attributable to types }31/33/35/39/45/51/52/56/58/59 \text{in Iran}\}\]. We assumed that two-dose HPV vaccines provided lifelong protection and considered coverage value to be 100%.

**Willingness to Pay (WTP)**

Our major study elicited WTP to HPV vaccines per person in Iran (Sargazi et al., 2021). This study used DCE to elicit mothers’ preferences and WTP for vaccinating 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, interviewed face-to-face in 2019. In our study, participants considered the time when expressing their preferences, so there was no need to use a discount rate.

**Estimating the Cost of Vaccination**

According to Iran’s national vaccination curriculum system, the Ministry of Health and Medical Education (MoHME) pays the annual vaccination costs. Therefore, the only considerable cost during vaccination was the HPV vaccine cost, which we obtained from the MoHME.

**Cost–Benefit Analysis (CBA) and Sensitivity Analysis**

We performed CBA for total costs and vaccination benefits compared with no vaccination. Further, we performed CBA with two economic criteria: net benefit (benefit-cost > 0) and cost–benefit ratio (CBR) (benefit/cost > 1) for the HPV vaccination program (Robinson et al., 2019). We conducted a one-way sensitivity analysis for
both vaccines to investigate possible parameter uncertainty changes influencing the CBA results, i.e. incidence of cervical cancer, percentage of cervical cancer attributable to HPV types, vaccine effectiveness, vaccine cost, cervical cancer cost, and discount rate (Mihajlović et al., 2019).

**Results**

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

**Benefits**

We estimated the percentage of cervical cancer attributable to types (16/18) and types (31/33/35/39/45/51/52/56/58/59) at 66.1% and 23.6%, respectively in women in Iran [31]. We estimated the effectiveness of bivalent and quadrivalent vaccines at 79.59% and 71.12%, respectively, in Iran. The estimated cost of HPV associated with cervical cancer treatment was US $31,419,956 during the study period (Table 2). Besides, the average benefit per person of bivalent and quadrivalent vaccines by COI approach was US $7375 and US $6590, respectively. The average

| Table 2  | Cervical cancer costs in Iran in 2020 |
|----------|--------------------------------------|
| Cost component | Mean cost, (US $) | Total cost, (US $) | Percentage of total cost (%) |
| Direct medical cost | 7629 | 8,056,628 | 25.64 |
| Diagnostic procedure | 146 | 154,609 | 0.49 |
| Surgery | 1429 | 1,508,841 | 4.80 |
| Radiotherapy | 62 | 65,830 | 0.21 |
| Brachytherapy | 1417 | 1,496,617 | 4.76 |
| Chemotherapy | 23 | 24,546 | 0.08 |
| Chemo radiation | 3089 | 3,261,981 | 10.38 |
| Chemotherapy medications | 1228 | 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 |
Table 3  The cost–benefit analysis of the HPV vaccine by the 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                           | 9266                                         | 7375                                              | 29                                 | 7346                           | 258.12                           |
| Quadrivalent   | 0.71                           | 9266                                         | 6590                                              | 151                                | 6439                           | 43.51                            |
The benefit per person of bivalent and quadrivalent vaccines by the WTP approach was US $−432 and US $380, respectively (Table 3, 4).

Costs

The price per dose of the bivalent and quadrivalent vaccines was US $14 and US $76 at the time of this analysis, 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

We estimated the benefit–cost to be positive from the COI approach, the BCR for bivalent vaccine greater than 1, meaning that this vaccine’s benefit was higher than its cost. We also estimated the benefit–cost to be positive for both COI and WTP approach, the BCR for quadrivalent vaccine greater than 1, meaning that this vaccine’s benefit was higher than its cost.

Table 5 shows the results of the one-way sensitivity analysis. When the vaccine cost increases by 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 parameters do not affect the outcomes significantly.

Discussion

The main objective of the present study was to conduct 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 (Park et al., 2018). Our findings reveal that the national bivalent and quadrivalent vaccine with COI approach has been beneficial and illustrative in Iran (CBR bivalent and quadrivalent vaccines 258.12 and 43.51, respectively). Our results are in line with several studies in the United States (US), Germany and Indonesia (Frost et al., 2014; Kotsopoulos et al., 2015; Setiawan et al., 2016).

One study in Lebanon did not include the indirect costs of cancer and showed that it was not cost-beneficial (Bahr et al., 2019). In contrast, our adapted COI approach indicated that bivalent and quadrivalent vaccine was cost-beneficial in Iran.

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

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| Variable                          | Net benefit, (US $) | Cost benefit ratio |
|----------------------------------|---------------------|--------------------|
| **Base-case**                    |                     |                    |
| **Bivalent**                     |                     |                    |
| Willingness to pay               | −460                | −15.11             |
| Cost of illness                  | 7346                | 258.12             |
| **Quadivalent**                  |                     |                    |
| Willingness to pay               | 229                 | 2.51               |
| Cost of illness                  | 6439                | 43.51              |
| **Lower**                        |                     |                    |
| **Upper**                        |                     |                    |
| **Incidence cervical cancer (± 20%)** |                 |                    |
| **Bivalent**                     |                     |                    |
| Willingness to pay               | −460                | −15.11             |
| Cost of illness                  | 8688                | 305.07             |
| **Quadivalent**                  |                     |                    |
| Willingness to pay               | 229                 | 2.51               |
| Cost of illness                  | 7637                | 51.43              |
| **Lower**                        |                     |                    |
| **Upper**                        |                     |                    |
| **Percentage of cervical cancer attributable to HPV types (± 20%)** | | |
| **Bivalent**                     |                     |                    |
| Willingness to pay               | −460                | −15.11             |
| Cost of illness                  | 5872                | 206.52             |
| **Quadivalent**                  |                     |                    |
| Willingness to pay               | 229                 | 2.51               |
| Cost of illness                  | 5121                | 34.81              |
| **Effectiveness HPV vaccine (± 20%)** |               |                    |
| **Bivalent**                     |                     |                    |
| Willingness to pay               | −460                | −15.11             |
| Cost of illness                  | 5871                | 206.49             |
| **Quadivalent**                  |                     |                    |
| Willingness to pay               | 229                 | 2.51               |
| Cost of illness                  | 5121                | 34.81              |
| **Vaccine cost (± 20%)**         |                     |                    |
| **Bivalent**                     |                     |                    |
| Willingness to pay               | −455                | −18.59             |
| Cost of illness                  | 7352                | 322.65             |
| **Quadivalent**                  |                     |                    |
| Willingness to pay               | 259                 | 3.14               |
| Cost of illness                  | 6469                | 54.39              |
| **Cervical cancer cost (± 20%)** |                     |                    |
| **Bivalent**                     |                     |                    |
| Willingness to pay               | −460                | −15.11             |
| Cost of illness                  | 5871                | 206.49             |


WTP approach showed the cost-beneficial of the quadrivalent vaccine (CBR 2.51). 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.

Our calculation estimated the total cost of cervical cancer US $ 31,419,956 (i.e., US $ 8,056,628 direct and US $23,162,186 indirect costs) most which attributed to lost productivity (73.72%). Our findings are similar to another study of gynecological cancers in Iran (Sargazi et al., 2022) and the study conducted in California-USA, confirming the mortality cost as the major part (77%) of the total costs of cervical cancer followed by medical costs (23%) (Max et al., 2003). Our findings also revealed the biggest proportion of direct medical cost were attributed to chemoradiation, which is consistent with another Iranian study (Sargazi et al., 2022).

Although CEA and CBA can lead to similar results (Cheng et al., 2020; Choi et al., 2018), our results indicated that HPV vaccines were cost-beneficial, contrary to previous studies that showed HPV vaccines were not cost-effective (Yaghoubi et al., 2018). We indicated that the two methodologies may not always allocate a limited public health budget to the same ranking allocation. This can happen because preferences and WTP are not well-reflected in cost-effectiveness (Johnson, 2014). On the other hand, they usually focus on the health service benefits and underestimate vaccination’s actual value (Christensen et al., 2020; Park et al., 2018).

Our results were consistent across all sensitivity analyses, and HPV vaccines remained cost-beneficial. Due to the lack of data, we did not consider the cost savings of HPV vaccination, such as protection against genital warts, anal, vaginal, penile, and oropharyngeal cancers. The benefit of protection against cervical cancers is approximately as great as the benefit of protecting against non-cervical cancers in some scenarios (Choi et al., 2018; Jit et al., 2011). We doubled the benefit of HPV vaccines with this assumption, and the results remained unchanged.

The average age of cervical cancer patients was around 52 years at the time of diagnosis in Iran (Bruni et al., 2010). However, the patients are diagnosed in advanced stages and the mortality to incidence ratios (MIRs) is relatively high at about 44% (Khorasanizadeh et al., 2013). Further, with the increase in high-risk sexual behaviors, this cancer is anticipated to increase. Although this paper focuses on women and cervical cancer, men can also be infected with HPV and at risk for other HPV-related cancers including penis, anus and oropharynx cancers (Hendry et al.,

Table 5 (continued)

| Variable               | Net benefit, (US $) | Cost benefit ratio |
|------------------------|---------------------|--------------------|
| Discount rate (5%, 7%) |         |         |
| Bivalent               |         |         |
| Willingness to pay     | –460    | – 15.11 |
| Cost of illness        | 3717    | 2010    | 131.08 | 71.36 |
| Quadrivalent           |         |         |
| Willingness to pay     | 229     |         | 2.51   |
| Cost of illness        | 3195    | 1671    | 22.10  | 12.03 |

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Boys were not the target of our research, nonetheless, HPV vaccination might also contribute to the decrease of HPV-related cancers in male.

**Limitations**

There are several limitations to our study. First, we assumed high effectiveness against HPV 16/18 with two doses and the coverage value was considered being 100% for simplification. Second, we acknowledge our results are bound 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. Third, our model does not consider the indirect effects of vaccination on other non-cervical HPV-related diseases due to insufficient reliable local data, e.g. other anogenital cancers or genital warts.

Furthermore, given the nature of our model, indirect effects of herd protection could not be included, and it may have underestimated the potential benefits of the vaccine. Fourth, this study did not include costs of the vaccination, supply chains, and service delivery, while these might impose a cost on the system. Finally, 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 a model for the EMR countries. 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. Cost-effectiveness evaluation can lead to misleading conclusions about resource allocation towards the HPV vaccination program without such a view.

**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 programs. 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 to the global efforts to eliminate cervical cancer ultimately, along the pathway to reach SDG 3.4.

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

Compliance With Ethical Standards

Conflict of Interest  The authors declare that they have no conflict of interest.

Ethics Approval  The ethical committee approved this research of Tehran University of Medical Sciences (TUMS) by the code of IR.TUMS.SPH.REC.1398.121.

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Authors and Affiliations

Nasrin Sargazi¹ · Amirhossein Takian¹,²,³ · Rajabali Daroudi¹ · Azin Nahvijou⁴ · Mehdi Yaseri⁵ · Ali Ghanbari Motlagh⁶,⁷ · Kazem Zendehdel⁴,⁸,⁹

¹ Department of Health Management, Policy and Economics, School of Public Health, Tehran University of Medical Sciences (TUMS), Tehran, Iran
² Department of Global Health and Public Policy, School of Public Health, Tehran University of Medical Sciences (TUMS), Tehran, Iran
³ Health Equity Research Center (HERC), Tehran University of Medical Sciences (TUMS), Tehran, Iran
⁴ Cancer Research Center of Cancer Institute, Tehran University of Medical Sciences (TUMS), Tehran, Iran
⁵ Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences (TUMS), Tehran, Iran
⁶ Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
⁷ Mortazavi (Jorjiani) Radiation Oncology Center, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
⁸ Cancer Biology Research Center, of Cancer Institute, Tehran University of Medical Sciences (TUMS), Tehran, Iran
⁹ Breast Diseases Research Center, Cancer Institute of Iran, Tehran University of Medical Sciences (TUMS), Tehran, Iran