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Original Article

Applying a Simple Model of Cost Effectiveness Study of HPV Vaccine for Iran

Mohsen Khatibi and Hamid Reza Rasekh*

Department of Pharmacoeconomics and Pharmaceutical Administration, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

HPV vaccine has been recently added to the Iran Drug List, so decision makers need information beyond that available from RCTs to recommend funding for this vaccination. Modeling and economic studies have addressed some of those information needs. We reviewed cost effectiveness studies to find a suitable model for Iranian population to determine the potential cost effectiveness of HPV vaccine program based on domestic available epidemiologic data. Articles were obtained from an extensive literature search to determine the cost effectiveness of implementing an HPV vaccination program with routine cervical cancer screening. A total of 64 studies were included in this review. Although the studies used different model structures, baseline parameters and assumptions (either a Markov, Hybrid, or Dynamic model). Most of the proposed cost effectiveness models need to model the probability of HPV acquisition, the possible progression from HPV infection to CIN I, CIN II, CIN III and cervical cancer, the probability of HPV transmission which are not available in Iranian epidemiologic data. Based on the available epidemiologic data in Iran, the simplified and it requires substantially fewer assumptions than the other more complex Markov and hybrid models, therefore we decided to use this model for the evaluation of cost effectiveness of HPV vaccine in Iran.

Keywords: Cost effectiveness; Simple model; HPV vaccine; Iran.

Introduction

The human papilloma virus (HPV) is among the most common sexually transmitted viruses. Chronic infection with certain subtypes of the HPV is the primary cause of cervical cancer and its precancerous lesions. At least 50% of the adult population is infected with this virus during their lifetime. Despite screening programs for cervical cancer, it remains the second most common cause of cancer-related death among women worldwide (1, 2).

Gardasil is a quadrivalent vaccine of subtypes 6, 11, 16 and 18 of the HPV. On the average, 70% of cervical cancers are caused by infection with subtypes 16 and 18, and 90% of genital wards are caused by subtypes 6 and 11 of the HPV (3, 4). Vaccines are essential tools for preventing the diseases. They will protect the vaccinated individual and help to protect the community by reducing the spread of infectious agents (5). There is no completely secure way for protecting sexually active adults against genital warts, and the current therapy modalities are often painful, time-consuming and with high risk of recurrence. Therefore, Gardasil vaccine may be quite helpful with its protective properties. Gardasil is administered for women aged 9-26 years for preventing diseases caused

* Corresponding author:
E-mail: heli@sums.ac.ir

by the HPV subtypes 6, 11, 16 and 18, including cervical cancer, genital warts, and precancerous or dysplastic lesions (6).

Gardasil vaccine is part of the national immunization program in the United States, Canada and Australia, among others. It is covered by insurance in Canada and Australia. Gardasil has been registered and is in use in 124 countries. Moreover, it is part of the national immunization program in 19 countries of the world which means it is administered to all girls aged 11-12 years (7).

In June 2006, the American Food and Drug Administration (FDA) approved Gardasil vaccine (produced by Merck & Co.) for girls aged 9-26 years (8).

The efficiency of Gardasil is 100% if administered prior to the first sexual contact (8). Numerous studies have been conducted to evaluate its cost-effectiveness by calculating the cost necessary for one quality-adjusted life year. None of them were cost saving for quadrivalent HPV vaccine (9). These include various models such as Markov model, decision model, dynamic model, transmission or a combination (9).

Studies conducted so far have mostly addressed its impact on cervical cancer and cervical intraepithelial neoplasia (CIN) (10). Few studies have dealt with the cost-effectiveness of Gardasil regarding other malignancies caused by the HPV (11).

The national immunization program of girls prior to sexual activity has been shown to reduce HPV-related mortality and morbidity and to be cost-effective (12-16). Since HPV infection is asymptomatic, it is growing silently (17). This vaccine is also recommended for 13-26-year-old females even if the female is already sexually active and could have contracted HPV infection (8).

Vaccination can cause immunity both directly and indirectly through herd immunity (18). For the HPV vaccine, the exact total duration of protection is not known yet, because the current maximum length of clinical trials is around 6 years. Consequently, it could be argued that base-case analysis on the cost-effectiveness of the HPV vaccine should not use durations of protection beyond 6 years, let alone lifelong protection (19)

In order to determine the long term benefit of this vaccine and impact of vaccine program on the future rate of cervical cancer, many pharmacoeconomists used mathematical model. Some models focused on cost effectiveness of different strategies (20-23).

Our objective is to review these cost effectiveness studies to find a suitable model for Iranian population to determine the potential cost effectiveness of HPV vaccine (Gardasil) program based on domestic available epidemiologic data.

Experimental

Methods of literature review

Search strategy development

In order to have a complete review of all cost-effectiveness models for HPV vaccine, we developed a search strategy. In this step "the content-related keywords" were defined and combined it with "AND" or "OR". To assure the quality of the review and increasing the search sensitivity, we didn't use "AND" frequently.

As many diseases are related to HPV, in our search query we mentioned the following keywords based on PICO[1] model: Papillomavirus, HPV and Human Papilloma Virus.

For searching the intervention part "vaccine", "prevention" and "prophylactic" combined with "OR".

The C-CERG[2] strategy was used to search the title, abstract and keyword fields within records of both cost-effectiveness Studies and HTA reports. This method is the most documented search strategy in this field (24).

Search in electronic database for economic evidences

The search query was" ("human papilloma virus″ OR papillomavirus OR HPV OR (papilloma AND viru*)) AND (vaccin* OR preven*)" without any limitations. NHSEED, HTA, DARE, CEA Registry, PEDE, Econlit and EURONHEED were our search databases.

Inclusion criteria and quality assurance

All published English-Language studies were

1 PICO model (Patient/problem/population, Intervention, Comparison, Outcome)

2 Campbell and Cochrane Economics Methods Group

included in the review that assessed the ICER of HPV vaccine compared with other alternative strategy like cervical cancer screening. To find directly related studies, all obtained studies were categorized based on below criteria:

- *Directly relevant (R1):* containing the full economic evaluation studies, considering the cost of quadrivalent HPV vaccine as a main intervention compared to other alternatives.
- *Indirectly Relevant (R2):* Quadrivalent HPV vaccine was not evaluated as main intervention, using different target group (different age or gender), focused on diagnosis, treatment of cervical cancer or screening only, and other vaccines as a main alternative.
- *Irrelevant (R3):* Focus on other viral infection.

Results

Through literature review, 39 studies in NHSEED database, 26 studies in HTA, and 10 studies in DARE were found. These three databases are related to CRD. Moreover, 46 studies in CEA Registry, 35 studies in PEDE, 2 studies in Econlit, and 26 studies in EURONHEED were addressed during the review of the literature.

Overall, a total number of 241 studies were found of which, only 148 remained in second step after omitting duplicate studies among databases. For the next step and based on the inclusion criteria and relevancy criteria, 64 studies were categorized in R1, 81 studies in R2, and 3 studies in R3. After this step we had three expert panels to find the best and suitable model for Iran.

In our study we defined an expert panel consists of 6 members; two gynecologists, two onco-gynecologists, one expert of systematic review and one expert of pharmacoeconomy. In the first expert panel and after reviewing 64 studies, 20 studies were defined as exactly related, which used defined models for their studies (Table 1). The result and summary of these studies categorized based on the used technologies, kind of economic study, effectiveness and cost data, kind of model, time horizon, and discount rate. After summarizing 20 studies, the second expert panel discussed the methods and needed data of the selected studies. Based on the feedback of this panel, 6 studies were selected for modeling which is appraised and summarized in the discussion section. Finally, in third expert panel and based on the available epidemiologic data in Iran and experts' opinion, we defined one of these models as a basic model for Iranian cohort model.

Discussion

In this section, five major articles including Elbasha *et al*., 2007, Brisson *et al*., 2007, Kulasingam *et al.,* 2007, Bergeron *et al*., 2008, Kulasingam *et al.,* 2008 and Chesson *et al*., 2008 have been addressed in a thematic order as follows:

Choice of Interventions or alternative interventions

Elbasha et al., 2007:

The rationale for choosing alternatives is clear and precise in terms of addressing the current status of care (no vaccination strategy) alongside all possible vaccination options. Different conditions must be considered when applying the results.

Brisson et al., 2007:

This study compares vaccination of young girls with anti HPV 16/18 and anti HPV 6/11/16/18 versus no vaccination plan. The latter represents the "do nothing" option, which is the current practice in the study site (Canada). Evidently, the status quo of service provision in the country must be assessed before trying to universalize the results.

Kulasingam et al., 2007 (Australia):

The rationale for selecting alternative interventions is clear and appropriate. The new approach to population-based immunization has been compared to the current standard practice in Australia. Nevertheless, it must be noted that the base strategy of cervical cancer screening alone may not be a suitable representative of the routine care practice in countries, which have already begun HPV vaccination. In sensitivity analysis, different vaccination programs (in different populations) have been considered,

Table 1. Summary of result.

#	Bibliographic information of the study	Technologies studied	Economic study	Effectiveness data	Cost data	Model	Time period	Discount rate
1	Elbasha *et al.* [25]	- Routine vaccination of girls until 12 years of age (F-12) - Routine vaccination of girls and boys until 12 years of age (FM-12) - Routine vaccination of girls until 12 years of age and compensatory vaccination for girls aged 12-24 years (F-12/CU-F) - Routine vaccination of girls and boys until 12 years of age and compensatory vaccination for girls aged 12-24 years (FM-12/CU-F) - Routine vaccination of girls and boys until 12 years of age and compensatory vaccination for girls and boys aged 12-24 years (FM-12/CU-FM) - Current screening and treatment program for HPV-associated diseases (no vaccination strategy)	Desirability cost analysis	Behavioral parameters related to sexually active population Biologic parameters of HPV-associated diseases, such as disease progress or regress and acute HPV infection All-cause death rate Cervical cancer-related death rates Hysterectomy rates Rates of screening and other therapy parameters	Costs of screening, cytology, treatment and vaccination Indirect costs are not included.	Dynamic model including demographic model and epidemiologic model	100 years	3%
2	Brisson *et al.* [26] (Canada)	- Prophylactic anti HPV vaccination (HPV 16/18) - Anti HPV vaccination (6/11/16/18) - Cervical cancer screening program	Desirability cost analysis	Vaccine effectiveness, duration of immunity and vaccine coverage Parameters related to the incidence and natural course of HPV	Costs of vaccine and its administration, screening, and studies addressing treatment of genital warts and cervical cancer. Indirect costs are not included.	Markov model	Lifelong	3% per QALY 5% for costs
3	Kulasingam *et al.* [27] (Australi)	- Integrating the national immunization program with the school health program by vaccinating 12-year old girls alongside the current cervical cancer screening program in Australia - Screening alone, consisting of biennial screening of women aged 18-21 years until 70 years of age (in case of normal Pap smears)	Cost-effectiveness analysis; Desirability cost analysis	Epidemiologic data Vaccine effectiveness Accuracy and coverage of screening Odds of transmission in different health states Mortality data associated with causes other than cervical cancer	Screening (Pap smear, colposcopy or biopsy) Vaccine (cost of vaccine and its inoculation) Cancer treatment (at different stages of cancer) and terminal life services	Published Markov model for simulating natural course of HPV and the impact of two strategies studied was updated.	Lifelong	5% per QALY % for costs

Table 1. (Continued).

4	Bergeron *et al*. [28] (France)	- Using recombinant quadrivalent prophylactic vaccine for HPV (6/11/16/18) for preventing cervical cancer, precancerous lesions, genital warts, and other HPV-associated malignancies alongside the cervical cancer screening program consisting of screening from 25-65 years of age every three years - Cervical cancer screening program alone	Cost-effectiveness analysis; Desirability cost analysis	Effectiveness, including the effectiveness of quadrivalent HPV vaccine	Screening costs including Pap smear, HPV DNA tests, colposcopy and biopsy Treatment for cervical intraepithelial neoplasia and genital warts Costs of vaccine and its inoculation	Published Markov model simulating natural course of HPV infection, cervical cancer and economical outcomes of HPV vaccination	Lifelong	1.5% per QALY and LY 3.5% for costs
5	Kulasingam *et al*. [29] (UK)	- Quadrivalent HPV vaccine (6/11/16/18) for 12-year old school girls and a booster at 22 years of age alongside the current cervical cancer screening program - Screening alone consisting of cervical cancer screening every three years from 25 to 49 years of age, and then every 5 years for women aged 50-64 years	Cost-effectiveness analysis; Desirability cost analysis	Lifelong risk of cancer Mortality Number of cervical cancer, genital warts and cervical intraepithelial neoplasia events	Direct costs of vaccine and its inoculation Screening, diagnosis and treatment of cervical cancer and genital warts	Markov model including a 100,000 person cohort of female residents of England aged 12-85 years	Lifelong	3.5% per QALY and LY 3.5% for costs
6	Jit *et al*. [30] (UK)	- Anti HPV (6/11/16/18) vaccination for 12-year old girls - Vaccination of 13-14-year old girls - Vaccination of 12-year old girls and boys - Compensatory vaccination in the first year for 12-year old girls until 14,16, 18, or 25 years of age in order to achieve a coverage of 70%-90% for 3 doses of vaccine - Vaccination with bivalent vaccine against HPV 16/18	Desirability cost analysis	Vaccine effectiveness Quality of life associated with different health states, including screening, cancer and genital warts	Direct costs including: costs of screening, treatment of cancer and genital warts, and cost of vaccine including its price and inoculation expenses	Dynamic transmission model for predicting HPV-associated diseases	100 years	3.5% for costs
7	Szucs *et al*. [31] (Switzerland)	- Recombinant quadrivalent prophylactic HPV (Gardasil) in 3 doses - Cervical cancer screening program with Pap smear or liquid-based cytology biennially	Cost-effectiveness analysis; Desirability cost analysis	Effectiveness of quadrivalent HPV vaccine Rate of precancerous lesions, aggressive cancers, genital warts attributable to HPV subtypes 6, 11, 16 and 18 Incidence rate of CIN grades 1, 2, and 3; cervical cancer and genital warts	Diagnosis costs (gynecologist visits, Pap smear, HPV DNA tests, colposcopy and colposcopy-biopsy) Treatment of CIN (grades 1,2 , and 3), cervical cancer, and genital warts Vaccine preparation and inoculation	Markov model including a cohort of 41,200 girls aged 11 years with a one-year cycle	Lifelong	1.5% per QALY and LYG 3% for costs

Table 1. (Continued).

8	Kim *et al.* [32] (US)	- screening alone - routine vaccination of 12-year old girls - routine vaccination of 12-year old girls with compensatory vaccination for girls aged 13-26 years	Desirability cost analysis	Vaccine effectiveness Quality of life associated with different health states, including screening, cancer and genital warts	Direct medical costs including costs of screening, diagnosis and treatment (diagnostic tests, procedures and hospital admission) Vaccination costs (3 doses of vaccine, wasted vaccines, vaccine preservation and inoculation)	Economic evaluation with two dynamic and stochastic models	Lifelong	3% per QALY 3% for costs
9	Dasbach *et al.* [33] (UK)	- Routine vaccination of 12-year old girls - Routine vaccination of 12-year old girls with compensatory vaccination program for girls aged 12-14 years - Routine vaccination of 12-year old girls with compensatory vaccination program for girls aged 12-17 years - Routine vaccination of 12-year old girls with compensatory vaccination program for girls aged 12-24 years (All programs above are presented alongside the current cervical cancer screening program and routine treatment for HPV-associated diseases)	Desirability cost analysis	Vaccine effectiveness Quality of life associated with different health states, including screening, cancer and genital warts Data on individual behaviors Data on screening results	Costs related to health service including screening with cytology, vaccination, diagnosis and treatment of aggressive cancer, CIN or genital warts, follow up of false positive cases of screening tests	Transmission model published in literature for determining the clinical and economical impacts of different strategies used	100 years	3.5% for costs
10	Dasbach *et al.* [34] (Norway)	- Routine vaccination of girls under 12 years of age with 3 doses of vaccine (base strategy) - Routine vaccination of girls under 12 years of age with a 55-year temporary compensatory program for girls aged 12-24 years - No vaccination strategy	Desirability cost analysis	Data on natural course of disease Data on screening and vaccination coverage Epidemiologic data Data on vaccine effectiveness	Costs of vaccination (preparation and administration) Costs of cytology screening Costs of follow up for false positive cases of screening tests Medical costs of screening and treatment of HPV-associated infection	Economical evaluation based on dynamic transmission model addressing the direct and indirect impacts of vaccination (herd immunity)	100 years	3.5% per QALY 3.5%for costs

Table 1. (Continued).

11	Mennini *et al*. [35] (Italy)	- Vaccination with quadrivalent HPV vaccine - Screening program consisting of screening women aged 25-64 years every 3 years	Cost-effectiveness analysis; Desirability cost analysis	Screening effectiveness Vaccination effectiveness Clinical parameters including screening and vaccination coverage, incidence and prevalence of HPV infection, cervical cancer and genital warts; odds of transmission between different states; sensitivity and specificity of screening tests; vaccine effectiveness and duration of immunity	Direct medical costs including physician visits, examination, medications and admissions Costs of treatment for cervical cancer, CIN and screening Costs of diagnosing and treating genital warts	Markov model including 280,000 girls aged 12 years under Italian conditions	Lifelong	1.5% per QALY and LYG 3% for costs
12	Hillemanns *et al.* [36] (Germany)	- Recombinant quadrivalent HPV vaccine for 12-year old girls in 3 doses alongside cervical cancer screening program - Cervical cancer screening program alone consisting of annual Pap smears for women aged above 20 years	Cost-effectiveness analysis; Desirability cost analysis	Screening effectiveness Age-specific HPV rates Natural course of disease Screening and vaccination coverage Prevalence and incidence of HPV infection, cervical cancer and genital warts Odds of transmission between different health states Sensitivity and specificity of screening tests Vaccine effectiveness and duration of immunity	Vaccination costs including preparation and administration Screening costs including Pap smear, colposcopy and biopsy Treatment of cervical cancer and genital warts	<Markov model for simulating HPV infection and cervical cancer, including a cohort of 400,000 girls aged 12 years	Lifelong	1.5% per QALY and LYG 3% for costs

Table 1. Continue.

13	Annemans *et al.* [37] (Belgium)	- Vaccination program with quadrivalent HPV vaccine for 12-year old girls alongside cervical cancer screening program based on cytology - Screening program alone	Cost-effectiveness analysis; Desirability cost analysis	Vaccine effectiveness for preventing cervical cancer, CIN (grades 1, 2, and 3) and genital warts Natural course of HPV infection towards aggressive disease Survival and mortality	Screening costs including Pap smear, HPV tests, biopsies, visits y gynecologists' and general practitioners, cost of vaccine preparation and inoculation by general practitioner Treatment of precancerous lesions, hospital treatment of cervical cancer and genital warts	Markov model published and assessed in previous studies	Lifelong (until 85 years of age)	1.5% per QALY and LYG 3% for costs
14	Thiry *et al.* [38] (Belgium)	- HPV vaccination for 12-year old girls in 3 doses and a booster after 10 years alongside cervical cancer screening program - Cervical cancer screening program every three years for women aged 25-64 years	Cost-effectiveness analysis; Desirability cost analysis	Epidemiologic data including incidence and mortality of cervical cancer, vaccine effectiveness, and screening and vaccination coverage	Costs of vaccination, screening and treating cervical cancer	Markov model including a cohort of 586,000 girls aged 12 years	Lifelong	1.5% per QALY and LYG 3% for costs
15	Olsen *et al.* [39] (Denmark)	- Routine vaccination of 12-year old girls with current screening program for cervical cancer in Denmark addressing women aged 23-59 years every three years - Screening alone (no vaccination strategy) - Routine vaccination of 12-year old girls with compensatory vaccination until 15 or 26 years of age - Routine vaccination of 12-year old girls and boys	Cost-effectiveness analysis; Desirability cost analysis	Vaccine effectiveness Duration of immunity Natural course of HPV infection Remission or progression rate of CIN and risk of HPV infection Participation rate of screening program Epidemiologic data such as incidence and prevalence of HPV subtypes 6, 11, 16, and 18, genital warts and cervical cancer	Healthcare costs including vaccine preparation and administration, treatment of genital warts, CIN and cervical cancer	Dynamic transmission model of Denmark, considering herd immunity, as well	62 years	3% per QALY and LYG 3% for costs

Table 1. Continue.

16	Accetta *et al.* [40]	18 preventive strategies for cervical cancer : different combinations of HPV DNA tests, Pap smear, triage test, screening at different frequencies (3 or 5 years) and HPV vaccination	Desirability cost analysis	Clinical effectiveness estimations including incidence and lifelong risk of cervical cancer and prevalence of high-risk HPV infection	Direct medical costs including HPV vaccine, booster doses, invitations for screening, Pap smear, HPV DNA tests, colposcopy, treatment costs of CIN grades 2 and 3, cervical cancer (different stages), distant metastases and terminal stages of the disease	Small-scale Markov model for combining evidence from published studies, epidemiologic data and experts' opinions	Lifelong	3% per QALE 3% for costs
17	Capri *et al.* [41] (Italy)	- Vaccination strategy with bivalent HPV vaccine - Vaccination strategy with quadrivalent HPV vaccine	Cost-effectiveness analysis	Vaccine effectiveness against CIN (grades 1, 2, and 3), cervical cancer, and genital warts associated with HPV subtypes preventable by vaccination Incidence rate of each of the HPV-associated diseases	Direct treatment costs including treatment of all HPV-associated lesions, The costs of both vaccines are considered equal.	A prevalence-based strategy is used to estimate the absolute difference in HPV-associated lesions and their costs between two strategies.	1 year	Not mentioned
18	Lee *et al*. [42] (Singapore)	- Bivalent HPV vaccination alongside screening program - Quadrivalent HPV vaccination alongside screening program - Screening alone (Pap smear every three years for women aged 25-69 years)	Cost-effectiveness analysis; Desirability cost analysis; Cost-benefits analysis	Major clinical parameters including vaccine effectiveness for preventing infection, incidence and prevalence of genital warts, CIN and cervical cancer and survival rate, vaccination coverage and duration of immunity	Direct medical costs including vaccination (design, implementation and support), screening and treating patients with HPV infection, CIN or cervical cancer	Markov model of state transmission including a cohort of 25,000 girls aged 12 years	Lifelong	3% per QALY 3% for costs
19	Demarteau *et al.* [43]	- vaccination program for 12-year old girls alongside routine screening program of France - Screening program alone	Desirability cost analysis	Vaccine effectiveness Screening effectiveness	Direct costs including costs of screening, treatment of CIN grades 1, 2, and 3, cervical cancer and vaccination costs	Markov model	Lifelong	1.5% per QALY 3% for costs

Table 1. Continue.

20	Chesson *et al.* [44] (US)	- 12-year old -	vaccination program for No vaccination	Cost-utility analysis	Vaccine effectiveness against CIN (grades 1, 2, and 3), cervical cancer, and genital warts associated with HPV subtypes preventable by vaccination	Direct medical costs including vaccination (design, implementation and support)	A prevalence-based strategy is used to estimate the absolute difference in HPV-associated lesions and their costs between two strategies	Lifelong	3% per QALY 3% for costs

which may be logical and acceptable for other countries.

Bergeron et al., 2008:

Both interventions are reported clearly and elaborately enough. In addition, the choice of alternative strategy is very well justified. This strategy consists of screening from 25 to 65 years of age every three years in France.

Kulasingam et al., 2008 (UK):

Two options selected for prevention of cervical cancer are completely described. The profile of the population study, vaccination program and screening tests are mentioned.

Chesson et al., 2008:

No vaccination scenario as the second strategy was appropriate.

Validity of effectiveness and Benefit index estimation

Elbasha et al., 2007:

Parameters of effectiveness have been adopted from published studies. However, the authors do not mention their search strategy or inclusion criteria. Also, the reason for selecting these particular estimates is not mentioned. The study mentions a review of literature but fails to indicate its strategies and methodology for review. Also, the information of the initial studies is not mentioned, making it impossible to assess validity of data from the initial studies. QALY estimation uses a decision-making tree model. The methods used for estimating desirability weights are not mentioned and are simply said to have been derived from published studies. Interest has been conducted appropriately. QALY is a good choice since it considers the most important health aspects (survival and quality of life) and provides a basis for comparison with other healthcare interventions.

Brisson et al., 2007:

Model parameters are derived from published studies. However, the authors do not mention the search strategies or inclusion criteria for selecting the initial studies. In addition, the study design is not specified. In general, it is difficult to evaluate the quality of effectiveness data in these studies. Using QALY as an index of benefits makes it possible to compare the findings of this study with others addressing vaccination programs and other interventions. The desirability coefficients for adjusted life expectancy based on quality of life are derived from published literature, but the study does not mention the method used for evaluating different health states. The interest rate of health benefits in the future is appropriate.

Kulasingam et al., 2007 (Australia):

Clinical data, for the most part, adopted from published studies, which are not mentioned, except in the case of data derived from the national database. Therefore, it is impossible to evaluate the validity of these estimations objectively without information regarding the scope, sample size, and follow-up procedures of the original studies, which served as source. However, extensive sensitivity analysis and choice of the most acceptable analysis value improve the power of clinical estimations. Using

two benefit indices, with expected QALY values smaller than LY values, suggests the importance of evaluating quality of life in women with cancer.

Bergeron et al., 2008:

The authors do not mention using a systematic review of the literature for finding all relevant effectiveness and clinical data. An explanation on the method of integrating and summarizing data obtained from studies has not been provided. Nevertheless, a summary about all parameters used in the model and their sources has been mentioned in the study. In addition, sources of desirability estimations are clearly mentioned.

Kulasingam et al., 2008 (UK):

Effectiveness data are obtained from a spectrum of published studies. However, the selection strategy is not mentioned. Clinical outcomes used for evaluating the advantages of two preventive strategies were selected in favor of vaccination and screening strategy. Some health benefits were excluded from the study. Desirability coefficients were adopted from a published and an unpublished study under supervision of experts and authors, which may cause some degree of bias. The reported data do not allow for evaluating methods of desirability assessment. The model structure is not presented visually. Nevertheless, a comprehensive description of different health states and possible transmissions has been provided.

Chesson et al., 2008:

The databases were relevant and valid. The treatment effects were based on trials, which characterized by high internal validity. The clinical and the utility valuations derived from the literature. The use of QALYs was appropriate because they capture the impact of the disease on patients' health.

Validity of cost estimation

Elbasha et al., 2007:

It appears that cost analysis is performed from the payer's point of view. All cost groups have been included in the analysis. Different cost groups are reported, although details of costs are not mentioned. The authors maintain that including indirect costs would reduce the desirability cost and thus improve the appeal of vaccination strategies. No specific source has been provided for this information. Mentioning the reference year of reported costs makes it easy to convert the costs for different time periods. Costs have not been statistically analyzed, but the changes in estimation of major costs have been included in sensitivity analysis.

Brisson et al., 2007:

Economical analysis is performed from the payer's point of view, and all major cost items seem to have been included in the analysis. Uncertainty of cost data and consumed resources are addressed in sensitivity analysis. Future costs are interested appropriately. These factors improve the applicability of the findings. Moreover, the reference year of cost estimations are mentioned clearly, which makes it easier for future calculations.

Kulasingam et al., 2007 (Australia):

The cost groups considered in the study appear to be appropriate for the approach taken to analysis. Details of cost items are not given and some expenses are mentioned generally. Costs are obtained from national health care services, which reflect the local accounting systems. Consumed resources are obtained from published studies. Key assumptions of the study are addressed in sensitivity analysis.

Bergeron et al., 2008:

The economical viewpoints used are clearly expressed. It seems that all cost items are considered based on their relation to the two viewpoints adopted. Sources of cost data (mainly from official French sources or articles published in France) are well presented. In addition, the authors have appropriately reported the time period of the study, interest rate, reference year of prices and currencies.

Kulasingam et al., 2008 (UK):

The costs considered in the model are an appropriate reflection of the viewpoint adopted (NHS). Methods of cost-assessment, modifications, sources of cost data and cost-service unit are presented appropriately and

elaborately. Costs are modified for inflation rate. Nevertheless, the cost results of each strategy are not reported. Moreover, cost information is not mentioned for values consumed from each source.

Chesson *et al*., 2008:

The perspective was societal. The analysis of costs followed a similar approach to the clinical analysis, in that macro-categories were presented without a detailed breakdown of items. The cost estimates varied in the sensitivity analysis.

Analysis and findings

Elbasha *et al.,* 2007:

The authors state that their findings generally agree with those of previous studies. Nevertheless, the study yields considerable discrepancies with findings of other economic evaluations, which the authors attempt to account for. The study deals briefly with the issue of applicability of its findings in the section of sensitivity analysis. Alternative scenarios are considered in this section. The authors have also highlighted some strengths of their analysis, including use of reliable data, clarity and flexibility. Also, certain limitations of the study have been mentioned, including the fact that the model deals mainly with HPV transmission from the opposite sex. Nevertheless, many assumptions of the study are biased towards different vaccination strategies.

Brisson et al., 2007:

The authors do not seem to be biased in presenting their findings. Furthermore, the conclusion is a good reflection of the scope of analysis. The authors compare their findings with those from other countries and to some extent have managed to justify the discrepancies in desirability cost ratios.

Kulasingam et al., 2007 (Australia):

Cost and benefits are appropriately integrated. However, the overall sum of costs and benefits are only presented graphically and only the cost-effectiveness ratios are mentioned. Sensitivity analysis has been conducted and reported appropriately. A wide range of possible scenarios and alternative assumptions are addressed in sensitivity analysis, which indicates the power of the study.

Bergeron et al., 2008:

Details of the Markov model, which was used for modeling costs and outcomes of each intervention, are presented, but relevant diagrams are lacking in the text. The model was previously designed for the United States and then modified for the European status. Although a series of univariate sensitivity analyses were included to measure uncertainty of model findings, using a probabilistic sensitivity analysis may have provided a more comprehensive understanding of the model's overall uncertainty. Methods and results are sufficiently explained. The limitations of the study are mentioned in the discussion section.

Kulasingam et al., 2008 (UK):

Crude costs and health outcomes are integrated as cost-effectiveness ratios. Observational epidemiologic data in England confirm the validity of parameters related to cervical cancer risk. Univariate sensitivity analyses are comprehensive and address all key parameters in an acceptable spectrum. While accepting the limitations of the study, the authors have attempted to justify them. These include the lack of powerful data on desirability coefficients of the health states in questions, lack of a probabilistic sensitivity analysis, and possibility of underestimating health benefits. The authors have compared their findings with those or other studies and discussed the possible applicability of their results.

In general, appropriate methods are used for the study. However, the study has limitations in estimating desirability, cost reports and lack of probabilistic sensitivity analysis. It appears that the authors have provided a correct discussion of their analysis.

Chesson et al., 2008:

The ICERs were presented in this study. The method of this study was mentioned online. The sensitivity analysis investigated the issue of uncertainty, using a deterministic approach, which was useful in terms of identifying the most influential model inputs.

Based on the modeling of cost effectiveness,

six studies have been selected and categorized as follows:

- Brisson *et al*., 2007, Kulasingam *et al.,* 2007, Bergeron *et al*., 2008, and Kulasingam *et al*., 2008 made use Morkov Models
- Elbasha *et al*., 2007, and Chesson *et al*., 2008 made use of Dynamic Models

A number of limitations are included in all discussed models. The studies, which used Markov models, did not take into account the herd immunity, which may result in underestimating the cost effectiveness of vaccination. The studies that used dynamic transmission models did not consider the homosexual and bisexual effect of vaccination, which is not very important in Iran.

Among these six models and based on the available epidemiologic data in Iran, Chesson *et al.* 2008, is simplified and it requires substantially fewer assumptions than the other more complex Markov and hybrid models do. Therefore, we decided to use this model for the evaluation of cost effectiveness of Gardasil in Iran. On the other hand, this simplified model was compared to previous complicated Markov, hybrid and dynamic models like the Markov model of Goldie et al (45), the Markov model of Sanders and Taira (46), the hybrid model of Taira *et al.* (47), and the dynamic model of Elbasha *et al.* (25). The findings were consistent with those from other published cost-effectiveness models (48).

Another advantage of this model is that there is no need to model the probability of HPV acquisition, the possible progression from HPV infection to CIN I, CIN II, CIN III and cervical cancer, and the probability of HPV transmission, which are not available in Iranian epidemiologic data. Age-specific incidence rates of cervical cancer (ASIR CC) is available in Iran. It is mentioned in 2008 population-based cancer registries in Iran. This model needs the following data which are available in Iran:

- Age-specific incidence rates of cervical cancer
- Treatment cost of HPV adverse health outcomes
- Costs Averted by vaccination
- QALYs Saved by vaccination

Conclusion

Cervical Cancer would be considered as a preventable cancer by vaccination. Generally HPV vaccine will have an influential impact on prevention of Cervical Cancer and finally on the epidemiology of HPV related Cancers. The most important note for using HPV vaccine is the age of individuals and their history of sexual activities. Most of the models compared the screening with vaccination and all included studies showed that adding this vaccine to the national vaccination program will be cost- effective based on the cost-effectiveness threshold of 50,000 USD per QALY. As most of these studies were done in the United States, mentioned cost per QALY is suitable for USA. For developing countries like Iran, World Health Organization (WHO) has recommended a cost-effectiveness threshold indicating that a healthcare technology is cost effective if the ICER is less than three times the GDP (Gross Domestic Production) per capita WHO's recommendation about threshold of developing countries considers ICER less than triplet of GDP of Iran for 2012 is 5,810 $. Based on WHO recommendation, ICER less than 17,430 USD per QALYs could be considered cost-effective. The Chesson *et al.,* 2008 model is simple and could be applicable in different countries with limited data. On the other hand, the results of this model were consistent with published studies based on the more complex models whereas key assumptions have been similar. The authors stated and demonstrated that their findings were consistent with those from other published cost-effectiveness studies. The main advantage of this model was its simplicity, which required fewer assumptions compared with more complex models. The biggest drawback of their analysis, as the authors stated, was the limited understanding of the impact of changes in screening strategies on the cost-effectiveness of HPV vaccination.

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References

(1) Smith JS, Lindsay L and Hoots B. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int. J. Cancer* (2007) 121: 621-632.

(2) Parkin DM and Bray F. Chapter 2: the burden of HPV-related cancers. *Vaccine* (2006) 24: 11-25.

(3) Lacey CJ, Lowndes CM and Shah KV. Chapter 4: burden and management of non-cancerous HPV-related conditions. HPV-6/11 disease. *Vaccine* (2006) 24: 35-41.

(4) Wiley D and Masongsong E. Human papillomavirus: the burden of infection. *Obstet. Gynecol. Surv.* (2006) 61: 3-14.

(5) Tavajohi S, Rastegar H, Ostad SN, Rezayat SM and Ghahramani MH. Evaluation of potency of measles vaccine used in iran: comparison of WHO and NIBSC method in cell culture. *Iran. J. Pharm. Res.* (2005) 3: 155-160.

(6) Merck Frosst. Gardasil: quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine. [Accessed 2010 Nov 9]. Available from: URL: http://www.merck.ca/mfcl/en/corporate/products/gardasil.html

(7) Koulova A, Tsui J and Irwin K. Country recommendations on the inclusion of HPV vaccines in national immunization programmes among high – income countries. *Vaccine* (2008) 26: 6529-6541.

(8) Markowitz LE, Dunne EF and Saraiya M. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm. Rep.* (2007) 56: 1-24.

(9) Insinga RP, Dasbach EJ and Elbasha EH. Assessing the annual economic burden of preventing and treating anogenital human papillomavirus-related disease in the US: analytic framework and review of the literature. *Pharm.* (2005) 23: 1107-1122.

(10) Fleurence RL, Dixon JM and Milanova TF. Review of the economic and quality-of-life burden of cervical human papillomavirus disease. *Am. J. Obstet. Gynecol.* (2007) 196: 206-212.

(11) Hu D and Goldie S. The economic burden of noncervical human papillomavirus disease in the United States. *Am. J. Obstet. Gynecol.* (2008) 198: 1-7.

(12) Sanders GD and Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerg. Infect. Dis.* (2003) 9: 37-48.

(13) Kulasingam SL and Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *JAMA* (2003) 290: 781-789.

(14) Goldie SJ, Kohli M and Grima D. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *J. Natl. Cancer Inst.* (2004) 96: 604-615.

(15) Brisson M, Van de Velde N and De Wals P. The potential cost-effectiveness of prophylactic human papillomavirus vaccines in Canada. *Vaccine* (2007) 25: 5399-5408.

(16) Kulasingam S, Connelly L and Conway E. A costeffectiveness analysis of adding a human papillomavirus vaccine to the Australian national cervical cancer screening program. *Sex. Health* (2007) 4: 165-175.

(17) Giuliano AR. Human papillomavirus vaccination in males. *Gynecol. Oncol.* (2007) 107: 24-26.

(18) Garnett GP. Role of herd immunity in determining the effect of vaccines against sexually transmitted disease. *J. Infect. Dis.* (2005) 191: 97-106.

(19) Khatibi M, Rasekh HR, Shahverdi Z and Jamshidi HR. Cost-effectiveness evaluation of quadrivalent human papilloma virus vaccine for hpv-related disease in iran. *Iran. J. Pharm. Res.* (2014) 13: 225-234.

(20) Garnett GP, Kim JJ and French K. Chapter 21: modeling the impact of HPV vaccines on cervical cancer and screening programmes. *Vaccine* (2006) 24: 178-186.

(21) Dasbach EJ, Elbasha EH and Insinga RP. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. *Epidemiol. Rev.* (2006) 28: 88-100.

(22) Newall AT, Beutels P and Wood JG. Cost-effectiveness analyses of human papillomavirus vaccination. *Lancet Infect. Dis.* (2007) 7: 289-296.

(23) Goldie S, Goldhaber-Fiebert JD and Garnett GP. Chapter 18: public health policy for cervical cancer prevention. The role of decision science, economic evaluation, and mathematical modeling. *Vaccine* (2006) 24: 155-163.

(24) Higgins J and Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane Book Series, A John Wiley & Sons publication. Version 5.1.0 [accessed 2011 March]. Available from: URL: http://www.cochrane-handbook.org/

(25) Elbasha EH, Dasbach EJ and Insinga RP. Model for assessing human Papillomavirus vaccination strategies. *Emerg. Infect. Dis.* (2007) 13: 28-41.

(26) Brisson M, Van de Velde N, De Wals P and Boily MC. The potential cost-effectiveness of prophylactic human Papillomavirus vaccines in Canada. *Vaccine* (2007) 25: 5399-5408.

(27) Kulasingam S, Connelly L, Conway E, Hocking J S, Myers E, Regan D G, Roder D, Ross J and Wain G. A cost-effectiveness analysis of adding a human papillomavirus vaccine to the australian national cervical cancer screening program. *Sexual Health* (2007) 4: 165-175.

(28) Bergeron C, Largeron N, McAllister R, Mathevet P and Remy V. Cost-effectiveness analysis of the introduction of a quadrivalent human Papillomavirus vaccine in France. *Int. J. Technol. Assess. Health Care* (2008) 24: 10-19.

(29) Kulasingam SL, Benard S, Barnabas RV, Largeron N and Myers ER. Adding a quadrivalent human

papillomavirus vaccine to the UK cervical cancer screening programme: a cost-effectiveness analysis. *Cost Effectiveness and Resource Allocation* (2008) 6: 4.
(30) Jit M, Choi YH and Edmunds WJ. Economic evaluation of human papillomavirus vaccination in the United Kingdom. *BMJ* (2008) 337: 769.
(31) Szucs TD, Largeron N, Dedes KJ, Rafia R and Benard S. Cost-effectiveness analysis of adding a quadrivalent HPV vaccine to the cervical cancer screening programme in Switzerland. *Cur. Med. Res. Opin.* (2008) 24: 1473-1483.
(32) Kim JJ and Goldie SJ. Health and economic implications of HPV vaccination in the United States. *NEJM* (2008) 359: 821-832.
(33) Dasbach EJ, Insinga RP and Elbasha EH. The epidemiological and economic impact of a quadrivalent human papillomavirus vaccine (6/11/16/18) in the UK BJOG. *Int. J. Obst. Gynaecol.* (2008) 115: 947-956.
(34) Dasbach EJ, Largeron N and Elbasha EH. Assessment of the cost effectiveness of a quadrivalent HPV vaccine in Norway using a dynamic transmission model. *Exp. Rev. Pharmaco. Outcomes Res.* (2008) 8: 491-500.
(35) Mennini FS, Giorgi Rossi P, Palazzo F and Largeron N. Health and economic impact associated with a quadrivalent HPV vaccine in Italy. *Gynecol. Oncol.* (2009) 112: 370-376.
(36) Hillemanns P, Petry KU, Largeron N, McAllister R, Tolley K and Busch K. Cost-effectiveness of a tetravalent human papillomavirus vaccine in Germany. *J. Public Health* (2009) 17: 77-86.
(37) Annemans L, Remy V, Oyee J and Largeron N. Cost-effectiveness evaluation of a quadrivalent human papillomavirus vaccine in Belgium. *Pharmaco.* (2009) 27: 231-245.
(38) Thiry N, De Laet C, Hulstaert F, Neyt M, Huybrechts M and Cleemput I. Cost-effectiveness of human Papillomavirus vaccination in Belgium: do not forget about cervical cancer screening. *Int. J. Technol. Assess. Health Care* (2009) 25: 161-170.
(39) Olsen J and Jepsen MR. Human papillomavirus transmission and cost-effectiveness of introducing quadrivalent HPV vaccination in Denmark. *Int. J. Technol. Assess. Health Care* (2010) 26: 183-191.
(40) Accetta G, Biggeri A, Carreras G, Lippi G, Carozzi FM, Confortini M, Zappa M and Paci E. Is human papillomavirus screening preferable to current policies in vaccinated and unvaccinated women? A cost-effectiveness analysis. *J. Med. Screen.* (2010) 17: 181-189.
(41) Capri S, Gasparini R, Panatto D and Demarteau N. Cost-consequences evaluation between bivalent and quadrivalent HPV vaccines in Italy: the potential impact of different cross protection profiles. *Gynecol. Oncol.* (2011) 121: 514-521.
(42) Lee VJ, Tay SK, Teoh YL and Tok MY. Cost effectiveness of different human papillomavirus vaccines in Singapore. *BMC Public Health* (2011) 11: 203.
(43) Demarteau N, Detournay B, Tehard B, El Hasnaoui A and Standaert B. A generally applicable cost effectiveness model for the evaluation of vaccines against cervical cancer. *Int. J. Public Health* (2011) 56: 153-162.
(44) Chesson HL, Ekwueme DU and Mona Saraiya. Cost-effectiveness of human papillomavirus vaccination in the united states. *Emerg. Infect. Dis.* (2008) 14: 244-250.
(45) Goldie SJ, Kohli M and Grima D. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *J. Nat. Cancer Inst.* (2004) 96: 604-615.
(46) Sanders GD and Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerg. Infect. Dis.* (2003) 9: 37-48.
(47) Taira AV, Neukermans CP and Sanders GD. Evaluating human papillomavirus vaccination programs. *Emerg. Infect. Dis.* (2004) 10: 1915-1923.
(48) Elbasha EH, Dasbach EJ and Insinga RP. A multi-type HPV transmission model. *Bull. Math. Biol.* (2008) 70: 2126-2176.

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