

RESEARCH ARTICLE

The Cost-Effectiveness of Quadrivalent Human Papillomavirus Vaccination in Indonesia

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Abstract

Objective: National cervical cancer prevention program has been initiated in Indonesia since April 2015 and the ministry of health has started efforts to integrate the HPV Vaccine in the national immunization program since Q4 2015. Thus, it becomes important to analyze the cost-effectiveness of HPV vaccine. The objective of this model is to examine the potential long-term epidemiologic and economic impact of quadrivalent HPV(qHPV;6/11/16/18) vaccination program in Indonesia. **Methods:** A previously validated transmission dynamic model was used to estimate the long-term epidemiologic and economic consequences of quadrivalent HPV vaccination by comparing cost-effectiveness of 2 dose qHPV vaccination strategy for girls 11-12 years old (with or without catch up; catch up dose for 12–26 years) versus Screening Only (Pap Smear) for reducing cost related to HPV type 6,11,16,18 (cervical cancer, CIN 1, CIN 2/3, and genital warts). Costs of an HPV disease episode-of-care (diagnosis and treatment) were calculated for base case analysis using local Indonesian cost. **Result:** 2-dose qHPV vaccination strategies without catch up reduce the overall incidence of HPV 16/18-related cervical cancer relative to screening by 54.4% over the 100 year following vaccine introduction. Likewise, vaccination strategies reduce the incidence of HPV type 16/18 CIN 2/3, CIN 1 by 69.1% and 71.8% respectively, also reducing HPV type 6/11 CIN 1, genital warts in female, genital warts in male by 82.9%,84.2%,82.1% respectively, at this time point. From total reduction of health care cost, 67.1% attributable for diseases caused by HPV type 16/18 and 32.9% attributable for diseases caused by HPV type 6/11. Without catch up, cost/QALY would be \$450/year. However catch-up strategy is more cost effective versus vaccinates 12-year-old girls only; with cost/QALYs would be \$390/year. **Conclusion:** HPV 6/11/16/18 vaccination of females in Indonesia are 1) substantially reduce genital warts, CIN, and cervical cancer; 2) improve quality of life, and 3) with the Indonesia GDP of USD 3,531.80 in 2014, Cost/QALYs result with or without catch up is considered very cost-effective when implemented; however with catch up, the cost/QALY can be better.

Keywords: Cervical cancer- prevention- quadrivalent HPV vaccine- cost-effectiveness- Indonesia

Asian Pac J Cancer Prev, 18 (7), 2011-2017

Introduction

Human Papilloma virus (HPV) is a common virus, which results in benign lesions such as wart and papilloma that could progress to malignant lesions such as intraepithelial lesions and neoplasia, if left untreated. (Panatto et al., 2015). The HPV infections are often subclinical and are mainly responsible for malignant and non-malignant lesions of the genital area in both men and women, and head and neck cancers to a lower extent. (Crosignani et al., 2013). Approximately 100 different types of HPV have been identified among which more than 40 are sexually transmitted. Further, HPV types 16, 18 have been termed to be oncogenic, while types 6, 11 are considered non-oncogenic. (Owsianka and Gańczak, 2015). Studies showed that almost 100% cervical cancer

caused by human papilloma virus. (IARC, 2007). And about 70% of all cervical cancers worldwide have been attributed to HPV types 16 and 18. (Bruni et al., 2015). The prevalence and type of distribution of HPV is known to differ substantially between the populations; HPV 18 and HPV 16 are having important role as cervical cancer cause in Indonesian population. (Clifford et al., 2005; Vet et al., 2008), meanwhile the type 6 and 11 are the cause of genital warts, a benign disease even though does not cause mortality but has impactful burden of disease due to its disturbing appearance and recurrence.

According to recent statistics released by the ICO Information Centre on HPV and Cancer, about 20,928 women in Indonesia are diagnosed with HPV related cervical cancers annually, resulting in death of 9,498 women, annually. The incident and mortality rate of

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cervical cancer in Indonesia are the highest in South East Asia. Further, about 89.07 million women (aged ≥ 15 years) in Indonesia are at risk for cervical cancer. (Bruni et al., 2015). Based on data collected from teaching hospitals in Indonesia, genital warts cases is now the highest sexual transmitted infection visit (Indriatmi, et al., 2016).

Bivalent vaccine (HPV2) which targets HPV types 16 and 18 and the quadrivalent vaccine (HPV4) which targets HPV types 6, 11, 16, and 18 are available currently, and are highly efficacious in the prevention of cervical precancerous lesions. They are also known to have long-term immunogenicity and efficacy, and are considered safe and well tolerated. In Indonesia, the bivalent HPV vaccine has approved indication for girls and woman 9-25 years of age, and the quadrivalent HPV vaccine has approved indication for girls and woman 9-45 years of age, also approved indication for man 9-26 years of age. For individuals 9-13 years old, the HPV4 vaccine has approval from local FDA to be given with 2 dose schedule, and for individuals above 13 years old, it should be given with 3 dose schedule. The HPV4 vaccine is also effective against genital warts (from HPV types 6 and 11), vaginal and vulvar precancerous lesions, re-infection, persistent infection, and anal precancerous lesions. (Crosignani et al., 2013)

According to the World Health Organization (WHO) estimates, until September 2016, HPV vaccination as a part of the national immunization program, has been introduced in 67 countries or 34.5% of the world. (WHO, 2016) Further, WHO recommends that routine HPV vaccination should be included in national immunization programs provided that:

- Prevention of cervical cancer and other HPV-related diseases is a public health priority
- Vaccine introduction is programmatically feasible
- Sustainable financing can be secured
- The cost-effectiveness of vaccination strategies in the country or region has been duly considered
- Primary target population is girls prior to onset of sexual activity, in age range of 9-13 years

According to the New Vaccine in MoH decree, HPV has distribution license from Indonesian FDA and available in private market for Bivalent (type 16 and 18) and Quadrivalent (type 6, 11, 16 and 18) vaccines. The HPV Immunization is recommended for girls >10 years old. (Indonesian MoH decree, 2013)

National cervical cancer prevention program has been initiated in Indonesia since April 2015 and the MoH has started for HPV Vaccination integration since Q4 2015, whereas some local province such as Bali and Jakarta already started their HPV Vaccination program. With this background it becomes important to analyze the cost-effectiveness of the quadrivalent vaccine for the prevention of morbidity and mortality associated with HPV in Indonesia. The objective of the study was to evaluate whether the adoption and implementation of the HPV vaccine as part of the national immunisation schedule is a cost-effective option in Indonesia.

Materials and Methods

Methods

Cost effective analysis (CEA) of the HPV vaccines was conducted using available Indonesian data with mathematical modeling. The details of this model and its structure have been previously described (Elbasha, et al., 2007). The CEA involves comparing costs (in terms of monetary units) with outcomes (in term of non-monetary units, such as reduced mortality or morbidity). The costs and the outcomes of costs analyses is said to vary based on the attributes such as comparator, perspective and the time horizon. (Goodman, 2015) The components included were cervical cancer screening rates, treatment rates, and vaccination strategies, as well as epidemiological (e.g., mortality) and economic inputs.

Screening and Vaccination Strategies

A previously validated transmission dynamic model was used to estimate the long-term epidemiologic and economic consequences of quadrivalent HPV vaccination by comparing cost-effectiveness of 2 dose qHPV vaccination strategy for girls 11-12 years old (with or without catch up; catch up dose for 12–26 years) versus Screening Only(Pap Smear) for reducing cost related to HPV type 6,11,16,18 (cervical cancer, CIN 1, CIN 2/3, and genital warts), while the perspective was that of the healthcare payer/government.

Model Parameters and Sources

We determined baseline assumptions and estimates by a comprehensive search of the literature, input from experts, and analysis of clinical trial data (Elbasha, et al.2007). (Table 1) shows baseline demographic parameters, and (Table 2) shows economic parameters and sources that we adopted.

Other data considered during the analysis included the epidemiological data related to cervical cancer and genital warts, screening, staging, and treatment parameters warts (Table 1; Sources: Indonesian Health and Demography Survey 2012; GLOBOCAN 2012 and www.hpvcentre.net August 22nd, 2014; RSCM Cancer Registry and National Cervical Cancer Registry, from 2010-2012).

Screening and Vaccination Program Strategy Parameters

We assumed that the period of protection for the HPV is lifetime in the base case. It was also assumed that vaccination would not have any effect on the natural course of any HPV infection that may have been present at the time of vaccination. The HPV vaccine was assumed to have an efficacy of 90% against cervical cancer caused by HPV 6/11/16/18, 95.2% against all CIN caused by HPV 6/11/16/18, and 98.9% against genital warts caused by HPV6/ 11 (Elbasha, et al.2007). A time frame of 100 years was used in the current study to evaluate the cost-effectiveness of the adoption and implementation of the HPV vaccine as part of the national immunization schedule.

Economic Parameters

All costs are reported in 2014 US dollars (USD or \$;

1 USD = 13,000 Indonesian rupiah or IDR). The direct medical costs for both screening and management of CIN, genital warts, and cervical cancer were based on expert knowledge in their daily practice (Add table economic parameter). Only direct medical costs were considered, therefore the costs associated with work and productivity losses were not included for the analysis (Table 2).

Costs of an episode-of-care (from time of initial diagnosis to time of resolution) of HPV disease including diagnosis and treatment were calculated for base case analysis and sensitivity analysis. Costs calculated included those related to cervical cancer screening and visit, colposcopy, biopsy, CIN1 episode-of-care and related PAP smear routinely/year, CIN2 episode-of-care (including LEETZ), CIN3 episode of care (such as conisation), LCC (Hysterectomy+radiation), RCC (Radiation+Chemo Therapy+Hysterectomy), DCC (Radiation+Chemo Therapy or palliative) and vaccine series plus administration (for base case and sensitivity analysis; for total 2 dose at 25 USD/dose).

Analysis

The CEA was carried out to compare the cost-effectiveness of HPV Quadrivalent 2 dose vaccination Strategy (with or without catch up) versus Screening Only (using Pap Smear Method). The vaccination is targeted for the age of 11–12 years only with no catch up dose later referred to as ‘HPV Quadrivalent 2 Dose Routine Vaccination no catch up’ for analysis purpose and with catch up dose at 12–26 years; referred to as ‘HPV Quadrivalent 2 Dose Routine Vaccination with catch up’ for analysis purpose.

We used parameters to assess the epidemiological impact and cost-effectiveness of both vaccination strategies. The epidemiological outputs included invasive cervical cancer, CIN 2/3, CIN 1, and genital warts cases, as well as cervical cancer deaths. The outputs included total costs quality-adjusted survival and cost per QALY. The incremental cost-effectiveness ratio (ICER) was measured as the incremental cost between two strategies divided by the incremental QALY between the two strategies.

For evaluation purposes, all costs and effectiveness were calculated with respect to the HPV Quadrivalent Vaccine which is known to be effective against 6,11,16,18 types and is widely used. The basic cost of the vaccine was assumed at \$25 for each dose. The cost of vaccine series plus administration for a total of 2 doses at 25 USD was calculated as \$50, accordingly.

Simulation Method

The quadrivalent HPV types 6/11/16/18 mathematical model was developed as a series of differential equations in Mathematica (Wolfram Research, Champaign, IL) and used the NDSolve subroutine in Mathematica version 7.0 to generate numerical solutions for the differential equations of the model. The baseline parameter estimates were used to solve the model for the pre-vaccination state values of the variables. The pre-vaccination status was used as the initial point for the vaccination model. The entire time path of the variables was then considered until the system approached a steady state at approximately

100 years. This solution was used to generate the output described previously for each of the screening and vaccination strategies. The probabilistic sensitivity analysis is not included this time because this model is transmission dynamic model.

Results

Epidemiologic Impact of the Routine HPV Vaccination Strategies without Catch-Up

Reduction of HPV 6/11 and 16/18 infection prevalence

Figures 1 depict the declining projected annual incidence of HPV 6/11 and 16/18 related infection prevalence over time under routine dosage vaccination strategy (without catch up) when compared to screening only strategy. As seen in the figures, screening only strategy will not decrease HPV 6/11/16/18 infection

Table 1. Demographic Parameters

Model Parameters.		
Total Population size		247,041,093
Male		123,242,012
Female		123,799,081
Incidence of HPV related diseases		
Number of new cases of cervical cancer [†]		20,928
Number of cervical cancer deaths [†]		9,498
Genital Warts Incidence [‡]		
Female		108 per 100,000
Male		117 per 100,000 men
Screening, Staging, and Treatment Parameters		
Percent of women with a follow-up screening test following an abnormal PAP result		45%
Cervical Cancer		
*LCC		10.6%
*RCC		84.2%
*DCC		5.2%
Genital warts treated		
Male		25% (75% untreated)
Female		40% (60% untreated)
Female Annual all-cause mortality rate by gender and age		
	Mortality rates (%)	
Age group (y)	Male	Female
<15 years	NA	NA
15-19 years	1.87	1.32
20–24 years	1.79	1.09
25-29 years	2.03	1.55
30–34 years	2.24	1.76
35-39 years	2.45	2.4
40-44 years	4.67	3.54
45-49 years	7.76	6.63
>50 years	NA	NA

HPV (Human Papillomavirus); *, at the given stage who are expected to die over the course of one year; LCC, (Local Cervical Cancer); RCC, (Regional Cervical Cancer); DCC, (Distant Cervical Cancer); [†],GLOBOCAN 2012 Data; [‡], Incidence from Malaysia Proxy

Table 2. Economic Parameters

Parameter	Estimate
Costs of an episode-of-care (from time of initial diagnosis to time of resolution) of HPV disease including diagnosis and treatment (for base case analysis, and sensitivity analysis if any)	
Genital warts-Female	40–80 USD
Genital warts-Male	
Cervical cancer screening and visit	20-125 USD
Colposcopy	62.5 USD
Biopsy	50 USD
CIN1 episode-of-care → pap smear routinely/year	40-125USD
CIN2 episode-of-care → LEETZ	166.7 USD
CIN3 episode of care → conization	750 USD
LCC → Hysterectomy+Radiation	4,200 USD
RCC → Radiation+Chemotherapy+Hysterectomy	8,300 USD
DCC → Radiation+Chemotherapy or Palliatif	3,000 USD
Vaccines series plus administration (for base case and sensitivity analysis)-->for total 2 dose (@25 USD)	50 USD

CIN1,cervical intraepithelial neoplasia grade 1; CIN 2/3,cervical intraepithelial neoplasia grades 2 and 3; DCC, distant cervical cancer;LCC,localized cervical cancer; RCC, regional cervical cancer; *5-y follow-up included.

prevalence; meanwhile vaccination strategy will be effectively decrease HPV 6/11/16/18 infection prevalence over time.

Reduction of Cervical cancer, CIN1 , CIN 2/3 and Genital Warts incidence

Compared with no vaccination, both vaccination strategies (with or without catch-up) significantly reduced the incidence of HPV6/11/16/18 related disease (Figure 2A–D). As genital warts and CIN 1-related HPV type 6/11 have shorter disease development, its decrease happened earlier after the HPV immunization program rather than malignant lesion caused by HPV type 16/18. More than 50% reduction in the incidence of genital warts (in both

Table 3. Cumulative Percent* Reduction in HPV 6/11/16/8-Related Disease Incidence from 2 Dose Routine HPV Quadrivalent Vaccination of Females by Age 11-12 Yo VS Screening Only

	Over 5 Years	Over 25 Years	Over 50 Years	Over 100 Years
Cervical				
Cancer	0	1.2	18.1	54.4
CIN 1	0	13.4	45.3	71.8
CIN 2/3	0	9.6	40.3	69.1
Cervical Cancer Death	0	0.5	14.1	51.2
Genital Warts and HPV 6/11-related CIN 1				
Genital Warts (female)	0.4	38.6	68.5	84.2
Genital Warts (male)	0.1	31.7	64.3	82.1
CIN 1	0.1	33.7	65.7	82.9

*Percentages Rounded to Nearest 0.1

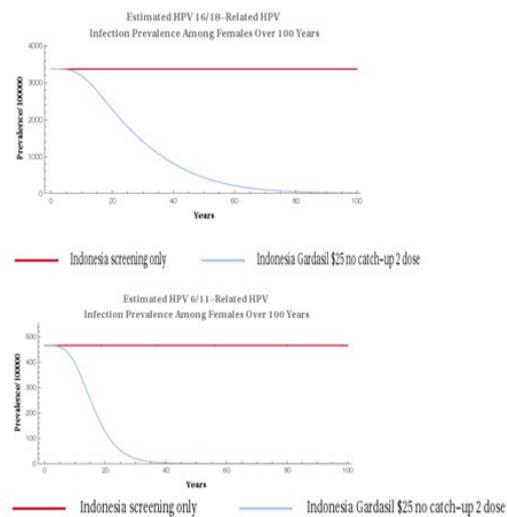


Figure 1. HPV 6/11/16/18 Related Infection Prevalence Reduction by Vaccination Strategy

Table 4. Cost Effectiveness Analysis of HPV Quadrivalent Vaccination Strategies (Without Catch-Up)

Scenario	Discounted Total		Incremental		
	Costs/ Person (USD)*	QALYs/ Person (year)†	Cost/ Person (USD)*	QALYs/ Person (year)†	Costs/ QALYs (USD/ year)‡
Screening Only	34.75	26.810 75	-	-	-
HPV Quadrivalent Vaccination	38.51	26.819 11	3.76	0.008 36	450

*, Costs rounded to 0.01; †, QALYs rounded to 0.00001; ‡, Costs/ QALYs rounded to 1

men and women) could be achieved over a period of 50 years (Tables 3, Figures 2A–D), which could be further reduced to more than 80% over a period of 100 years following the routine vaccine strategy.

2-dose qHPV vaccination strategies without catch up reduce the overall incidence of HPV 16/18–related cervical cancer relative to screening by 54.4% over the 100 year following vaccine introduction. Likewise,

Table 5. Cost Effectiveness Analysis of HPV Quadrivalent Vaccination Strategies (without VS with Catch-Up)

Scenario	Discounted Total		Incremental		
	Costs/ Person (USD)*	QALYs/ Person (year)†	Cost/ Person (USD)*	QALYs/ Person (year)†	Costs/ QALYs (USD/ year)‡
HPV Quadrivalent Vaccination Without Catch Up	38.51	26.819 11	-	-	-
HPV Quadrivalent Vaccination With Catch Up	40.1	26.823 19	1.59	0.004 08	390

*, Costs rounded to 0.01; †, QALYs rounded to 0.00001; ‡, Costs/ QALYs rounded to 1

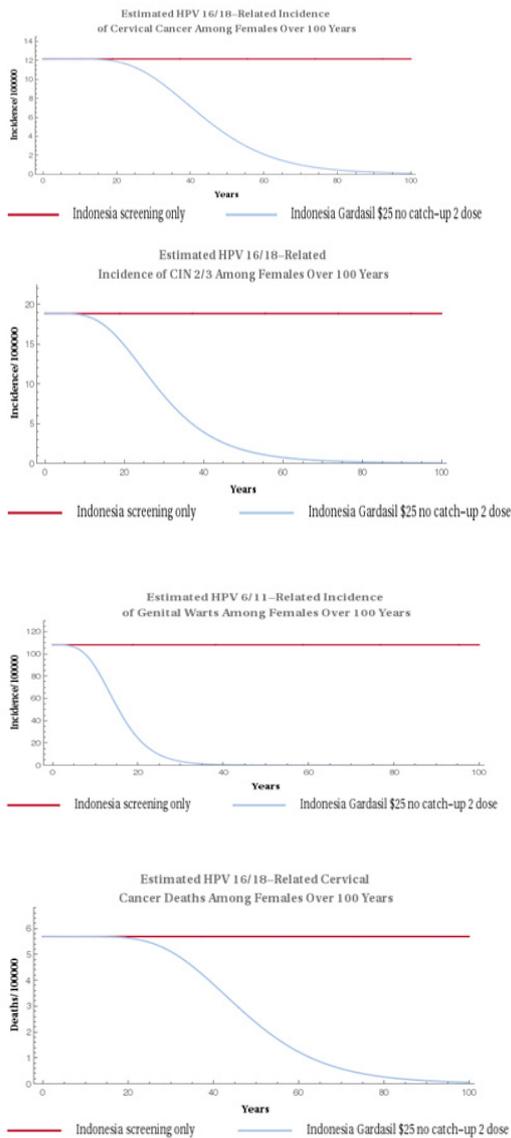


Figure 2. Estimated Annual HPV Related Incidence by Vaccination Strategy in Indonesia

vaccination strategies reduce the incidence of HPV type 16/18 CIN 2/3, CIN 1 by 69.1% and 71.8% respectively, also reducing HPV type 6/11 CIN 1, genital warts in female, genital warts in male by 82.9%, 84.2%, 82.1% respectively, over 100 years.

Reduction of Cervical cancer related deaths

The incidence of deaths related to cervical cancer could be reduced by about 14% by 50 years post initiation of vaccination program and more than 50% reduction could be achieved by year 100. As seen in the model, screening only will not decrease cervical cancer related deaths.

Epidemiologic Impact of the Routine HPV Vaccination Strategies with Catch-up VS without Catch-up

When compared to routine dose strategy, the catch up dose strategy would lead to greater HPV 6/11/16/18 disease reduction. As seen in the Table 3, catch-up strategy would decrease CIN 2/3 33.1% greater over 50 years than without catch-up strategy.

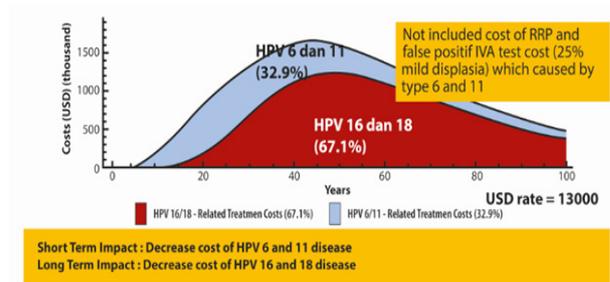


Figure 3. Estimated Healthcare Cost Avoided from 2 Dose Routine HPV Quadrivalent Vaccination of Females by age 11-12 yo VS Screening Only

Economic Impact of HPV Vaccination Strategies

Figure 3 and Table 4 depict the annual, discounted, HPV disease treatment cost prevented in the Indonesian population following a routine only vaccination strategy compared to 'screening only' strategy. While cervical cancer related costs could be reduced by over 24%, costs related to genital warts in women could be reduced by more than 60%. Overall, the total disease costs (direct cost only related to cervical cancer, CIN 1, CIN 2/3, and genital warts) could be reduced by 31.8% by year 100.

Since this model did not include indirect cost such as cervical cancer complication e.g hydronephrosis leading to chronic kidney disease, the actual total cost reduction for cervical cancer patients must have more than 31.8%.

When compared to routine dose strategy, the catch up dose strategy would lead to 19.5% greater disease costs reduction over 100 years.

Tables 4 depict the cost effectiveness analysis of routine only vaccination strategy without catch up. From total reduction of health care cost, 67.1% attributable for diseases caused by HPV type 16/18 and 32.9% attributable for diseases caused by HPV type 6/11 (Figure 3). Without catch up, cost/QALY would be \$450/year (Table 4). With the Indonesia GDP of USD 3,531.80 in 2014, Cost/QALYs result without catch up is considered very cost-effective when implemented.

However catch-up strategy is more cost effective versus vaccinates 12-year-old girls only; with cost/QALYs would be \$390/year (Table 5).

Discussion

In this study, we used a transmission dynamic model to assess the epidemiologic consequences and cost effectiveness of an HPV 6/11/16/18 vaccination program in Indonesia that provides protection against both cervical cancer and genital warts. In this model, as with other models, we assumed that duration of protection was lifelong in the reference case (Goldie et al., 2003; French et al., 2007). Generally, the results from this model demonstrate that a quadrivalent HPV vaccine program with or without catch-up program can be very cost effective, although one important finding generated from this analysis was the role that catch-up vaccination can reduce the burden of disease greater and more cost effective.

The findings also clearly demonstrated the benefits

of a vaccination program that provides protection against HPV types 6 and 11. Given that cervical cancer is a disease that progresses slowly over time, most of the short term benefits from HPV quadrivalent Vaccination program realized in the first 15–25 years following vaccine introduction are projected to result from the prevention of HPV 6/11 infection and genital warts, as seen in real world effectiveness of Australia National HPV Vaccination Program where there were 92% decrease of genital warts after 4 years of program implementation (Ali H et al., 2013) Although genital warts are not life threatening, they are common and can have a negative psychological impact (Maw et al., 1998). Treatment for genital warts can also require multiple patient visits, which have an associated cost (Kodner and Nasraty, 2004; Insinga et al., 2003).

There are some limitations of this model that have been described in detail (Elbasha et al., 2007). Some that are particularly relevant to this study are:

- First, the study have modeled only four HPV disease types (i.e., 6, 11, 16, and 18).

- Second, the model did not account for other potential benefits of vaccination that would have improved the cost effectiveness ratio, such as protection against vulvar and vaginal precancers and cancers (Walboomers et al., 1999), protection against anogenital cancer (Carter et al., 2001), protection against head and neck cancers (Hobbs et al., 2006), protection against recurrent respiratory papillomatosis (Freed and Derkay, 2006), and mortality and productivity costs due to patient and the caregiver inability to have productive live, indirect costs of the treatment e.g : transportation, accommodation while doing intensive radiotherapy and chemotherapy for the patient and caregiver, cost for treating complication such as anemia, hydronephrosis leading to chronic kidney disease.

- Third, given the complexity of the model, it was impractical to conduct probabilistic sensitivity analyses. Hence, we conducted extensive one-way and multivariate sensitivity analyses to identify those parameters which most influenced the results. Based on these sensitivity analyses as well as the many sensitivity analyses conducted by other HPV vaccination costs-effectiveness analyses, we believe we have identified the key parameters and uncertainties which influence results and provide important insights to policy and decision-makers.

In conclusion, HPV 6/11/16/18 vaccination of females in Indonesia are 1) substantially reduce genital warts, CIN, and cervical cancer; 2)improve quality of life, and 3) with the Indonesia GDP of USD 3,531.80 in 2014 , Cost/QALYs result of HPV Vaccination with or without catch up is considered very cost-effective when implemented; however with catch up, the cost/QALY can be better. As based on WHO reference that if the cost/QALYs is less than three times the per capita gross domestic product (GDP), it is considered cost-effective and if the cost/QALYs is less than one time GDP , it is considered very cost effective (World Health Organization, 2008).

Statement conflict of Interest

None declared.

Funding Statement

The views expressed in this article are those of the authors, and approved by Merck and Co., Inc.

Acknowledgements

We would like to acknowledge Amit Sharad Kulkarni, Matthew Pillsbury, Andrew Pavelyev, Anuj Walia, MD Suria Nataatmadja, MD, Vinci Lorensia, MD, Andi Prabowo, Bella Aprilia,MD, Marcillia Rizka Aryadi, MD for their contribution in data analysis and data collection.

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