

RESEARCH ARTICLE

Cost-Effectiveness Analysis of HPV Vaccination: Comparing the General Population with Socially Vulnerable Individuals**Kyu-Tae Han^{1,2}, Sun Jung Kim^{1,2&}, Seo Yoon Lee^{2,3}, Eun-Cheol Park^{1,2*}****Abstract**

Background: After the WHO recommended HPV vaccination of the general population in 2009, government support of HPV vaccination programs was increased in many countries. However, this policy was not implemented in Korea due to perceived low cost-effectiveness. Thus, the aim of this study was to analyze the cost-utility of HPV vaccination programs targeted to high risk populations as compared to vaccination programs for the general population. **Materials and Methods:** Each study population was set to 100,000 people in a simulation study to determine the incremental cost-utility ratio (ICUR), then standard prevalence rates, cost, vaccination rates, vaccine efficacy, and the Quality-Adjusted Life-Years (QALYs) were applied to the analysis. In addition, sensitivity analysis was performed by assuming discounted vaccination cost. **Results:** In the socially vulnerable population, QALYs gained through HPV vaccination were higher than that of the general population (General population: 1,019, Socially vulnerable population: 5,582). The results of ICUR showed that the cost of HPV vaccination was higher for the general population than the socially vulnerable population. (General population: 52,279,255 KRW, Socially vulnerable population: 9,547,347 KRW). Compared with 24 million KRW/QALYs as the social threshold, vaccination of the general population was not cost-effective. In contrast, vaccination of the socially vulnerable population was strongly cost-effective. **Conclusions:** The results suggest the importance and necessity of government support of HPV vaccination programs targeted to socially vulnerable populations because a targeted approach is much more cost-effective. The implementation of government support for such vaccination programs is a critical strategy for decreasing the burden of HPV infection in Korea.

Keywords: HPV vaccination - cost-effectiveness analysis - cost-utility analysis - cervical cancer

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Introduction

HPV (human papillomavirus) infection is the main cause of cervical cancer, and infection typically occurs through sexual behavior. The prevalence of cervical cancer is associated primarily with early sexual experience, low income, the number of sexual partners, and sexual activity with high-risk men (Deacon et al., 2000); thus, the highest prevalence of HPV infection is in individuals in their 20s (Dunne et al., 2007). Most HPV infections spontaneously resolve within a few months, and 90% of infections disappear within 2 years. However, some cases of persistent HPV infection result in cervical cancer (Koshiol et al., 2008). According to the annual report of cancer statistics in Korea, the age-standardized prevalence of cervical cancer was reported as 12.3 per 100,000 people in 2010, which was a decreasing trend from 18.6 per 100,000 people in 1999 (The Korea Central Cancer Registry, 2010). However, the economic burden of HPV

infection-related diseases was reported to be 280 billion KRW in 2005 (Shin, 2007).

Gardasil and Cervarix have been used to prevent cervical cancer caused by HPV infection. Gardasil is a quadrivalent vaccine that is effective against HPV types 6, 11, 16, and 18. Cervarix is a bivalent vaccine that is effective against HPV types 16, and 18. The efficacy of these vaccines is 99% and 95%, respectively. However, efficacy is significantly reduced in women with pre-existing HPV infection (Mao et al., 2006; Villa et al., 2006; Ozgul et al., 2011). After the WHO recommended HPV vaccination of the general population in 2009, government support of HPV vaccination programs was instituted in many countries (WHO, 2008; Do et al., 2009; Karadag et al., 2014; Yilmazel and Duman, 2014). However, programs for the general population were not implemented in Korea due to less cost-effective. Due to various limitations, previous studies on the cost-effectiveness of HPV vaccination in Korea had low accuracy (Shin, 2007;

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Marra et al., 2009; Armstrong, 2010). In contrast, other studies on the cost-effectiveness of HPV vaccination in some countries showed high cost-effectiveness for the specific population (Techakehakij and Feldman, 2008; Jeurissen and Makar, 2009).

According to a study by Wilkinson, the home environment was among environmental risk factors that most influenced to the problem behavior of adolescents. In particular, the structural aspects such as the absence of one or both parents instead, low socio-economic status, etc., and functional aspects such as psychological distance between parent and child, and poor parenting attitudes were reported as major factors for problem behaviors in adolescents (Wilkinson, 1973). In addition, the results of previous studies showed that the population most vulnerable to HPV infection had been exposed to many risk factors including low income, and low education level (Bambra, 1999; Nyari et al., 2001; Frohlich and Potvin, 2008; Zhang et al., 2012). Thus, the aim of this study was to include these additional factors in our analysis of the cost-effectiveness for an HPV vaccination program targeted to high risk populations, as compared to the general population.

Materials and Methods

Study population

This study used a novel approach of focusing on adolescents from broken families and low-income families as the socially vulnerable population. These subjects were chosen because of the high probability of problem and risky behavior that could lead to HPV infection.

Standardized prevalence rate

The standardized prevalence of HPV infection in the total population was calculated using the disease statistics provided by the HIRA (Health Insurance Review and Assessment Service). Subsequently, we calculated the odds ratio by adjusting for age, economic status, academic records, and survey year in the Korea Youth Risk Behavior Web-based Survey (KYRBWS). These data then were used to calculate the standardized prevalence in the general and socially vulnerable populations (Health Insurance Review & Assessment Service, 2010-2012; Korea Centers for Disease Control and Prevention, 2010-2012).

Cost

The medical costs of HPV-infected patients included the vaccine cost as well as the costs imposed by those not vaccinated. Health insurance claims data provided by the National Evidence-based Healthcare Collaborating Agency were used to calculate the non-medical costs of HPV-infected patients. These costs included administration costs and transportation costs (National Evidence-based Healthcare Collaborating Agency, 2012).

Vaccination rates

It is inevitable that incomplete vaccination occurs at a certain rate because complete HPV vaccination consists of a series of three vaccinations. Thus, the data were stratified according to each stage of vaccination; the

data used were provided by the National Evidence-based Healthcare Collaborating Agency (National Evidence-based Healthcare Collaborating Agency, 2012).

Vaccine efficacy

Within the group of sexually active individuals, we included in the definition of incomplete vaccination individuals who engaged in potentially risky sexual activity before vaccination. Then, the calculation for vaccine efficacy was stratified by age (Korea Centers for Disease Control and Prevention, 2010-2012).

QALYs

Because the data from the Korea National Health and Nutrition Examination Survey appeared to be an overestimation of the QALY in Korea, we used the U.S. estimation of QALYs for analysis. QALYs for the economic evaluation of HPV vaccination were determined for both the general population and the social vulnerable population (Elbasha et al., 2007; Basu et al., 2008).

Incremental cost-utility ratio (ICUR)

In order to determine the ICUR, we set the study population to 100,000 individuals for the simulation study, then standard prevalence rates, cost, vaccination rates, vaccine efficacy, and QALYs were applied to the analysis (Hassan et al., 2008).

In performing the analysis, the following assumptions were made. First, vaccination was assumed all members of each population. Second, vaccination efficacy was evaluated according to vaccine type, incomplete vaccination, and whether individuals were sexually active. Third, the ratio of vaccine type administered was assumed to be 1:1. Fourth, the income threshold was set to 24 million KRW. If the ICUR of vaccination was lower than 24 million KRW, the results indicated cost-effective for vaccination of that population. Finally, a 3% discount rate for vaccine cost was applied to the analysis for each year.

Sensitivity analysis

We wanted to determine if providing vaccines at a discounted cost would affect the cost-effectiveness of vaccinating the general and the target populations. Incremental discounted costs for vaccination (33%, 55%, and 66%) were applied to the analysis. From these data, the incremental cost-utility ratio was determined (Figure 1).

Results

The odds ratio for sexual activity was calculated by adjusting age, economic status, academic records, and survey year for the data from the Korea Youth Risk Behavior Web-based Survey. The socially vulnerable population had a higher odds ratio than the general population (OR of the socially vulnerable population: 4.264, Ref=general population).

Applying the odds ratio to the statistics of disease from the HIRA, the standardized prevalence of HPV infection in the general and socially vulnerable populations was calculated (Table 1).

The analysis of vaccination efficacy (see Table 2),

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taking into account age at first sexual experience, showed that the vaccination efficacy in the general population was higher than in the socially vulnerable population. (General population: 88.0%, Socially vulnerable population: 84.0%).

The cost for vaccination was calculated by applying the costs reported in study of the National Evidence-based Healthcare Collaborating Agency to vaccination rates. Costs were calculated for the target population of 100,000 people (Medical cost: 48,716,167,500 KRW, Non-medical cost: 4,577,017,680 KRW). To evaluate the efficacy of HPV vaccination, QALYs for each population were calculated using the QALYs of HPV-related disease. In the socially vulnerable population, QALYs gained through HPV vaccination were higher than that of general population (General population: 1,019, Socially vulnerable population: 5,582; Table 3).

ICUR was determined by adjusting for standardized prevalence rates, vaccination efficacy, QALYs, and cost. The results showed that the cost of HPV vaccination was higher for the general population than the socially vulnerable population. (General population: 52,279,255

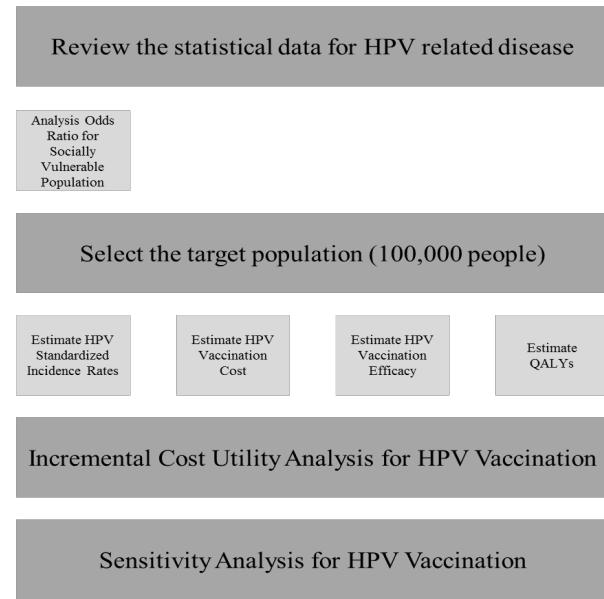


Figure 1. Flow Chart of Study

KRW, Socially vulnerable population: 9,547,347 KRW; Table 4). Compared with 24 million KRW/QALYs as the social threshold, vaccination of the general population had no cost-effective. In contrast, vaccination of the socially vulnerable population had strong cost-effective.

After assuming discounted the vaccination cost, the result of study analyzed by applying discounted vaccination cost to the sensitivity analysis. In the sensitivity analysis, vaccination of the general population had cost-effective only at the 66% discounted vaccination cost level. In the case of the socially vulnerable population, discounted vaccination costs had cost-effective at all discount levels evaluated (Figure 2).

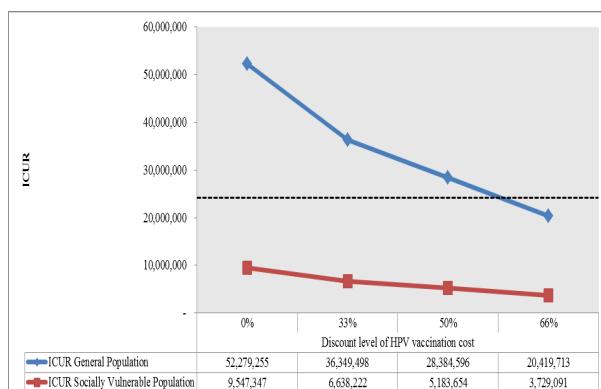


Figure 2. Sensitivity Analysis for HPV Vaccination Cost by Discounted Level (Unit: KRW/QALYs)

Table 2. Vaccination Efficacy by Population

Vaccination timing (Age)	Percentages of general population	Percentages of socially vulnerable population
11	99.03%	98.78%
12	97.74%	97.09%
13	97.81%	97.11%
14	97.91%	97.19%
15	98.31%	97.68%
16	98.85%	98.39%
17	99.03%	98.63%
18	99.37%	99.11%
Vaccination Efficacy	88.04%	83.99%

Table 1. Standardized Prevalence Rates of Disease Associated with HPV (Unit: Patients Per 100,000 People)

Study Population	Age	Cervical Cancer	CIN I	CIN II	CIN III	Carcinoma in situ of cervix uteri
			Mild Cervical dysplasia	Moderate Cervical dysplasia	Severe Cervical dysplasia	
General Population	10-19	0.2	5.3	1.2	0.6	0.3
	20-29	12.8	216.8	63.3	37.6	62.1
	30-39	72	296.6	97.2	74.4	188.3
	40-49	160.5	304.9	92.7	67	208.4
	50-59	230.8	206.9	61	44.8	144.1
	60-69	256.9	102.9	38.2	31.4	106.5
	70-79	193	36.9	17.7	16.9	57.6
	80-	65.2	4.1	3	3	8
Socially vulnerable population	10-19	0.82	17.32	3.93	1.86	0.88
	20-29	52.75	704.09	205.57	122.03	201.84
	30-39	297.78	963.6	315.64	241.65	611.59
	40-49	663.54	990.5	301.11	217.64	677.06
	50-59	954.13	672.13	198.06	145.45	468.15
	60-69	1,061.90	334.4	123.99	101.97	345.8
	70-79	797.85	119.78	57.44	54.76	186.97
	80-	269.55	13.16	9.65	9.65	25.83

Table 3. The Costs of HPV Vaccination and QALYs for Economic Evaluation (Unit: KRW, QALYs)

Cost	Medical Cost	Vaccine Cost	Vaccination Rates	Vaccinated People	Total Vaccination Cost	Total Cost
	165,000	1/3 dose schedule of vaccination 2/3 dose schedule of vaccination 3/3 dose schedule of vaccination Total Loss of Cost (5%)	5.14% 8.53% 86.33% 100%	5,140 8,530 86,330 100,000	848,100,000 2,814,900,000 42,733,350,000 46,396,350,000 2,319,817,500	48,716,167,500
Non-medical cost	Details					Total Cost
	Administration Cost Transportation costs	Personnel expenses Average cost*1.5 (Subjects and their parents)				4,577,017,680
QALYs	Disease		General population		Socially vulnerable population	
	Cervical Cancer		240		1,380	
	CIN I		108		620	
	CIN II		276		1,581	
	CIN III		534		3,065	
	QALYs Increase for Vaccination (A)		1,158		6,646	
	Non-immunization among vaccinated people (B)		138		1,064	
	Total QALYs Increase (A-B)		1,019		5,582	

*QALYs: CINI(0.910), CINII/III(0.870), Cervical Cancer(0.700)

Table 4. Increment Cost-Utility Ratio for HPV Vaccination by Population (Unit: KRW, KRW/QALYs)

Target Population	Medical Cost	Non-medical Cost	Total Cost	QALYs		A-B	ICUR	
				Not Vaccination (B)	Vaccination (A)			
General Population			48,716,167,500	3,121,300	3,122,319	1,019	52,279,255	
Socially Vulnerable Population			4,577,017,680	53,293,185,180	3,115,811	3,121,393	5,582	9,547,347

Discussion

Many previous studies for HPV-related disease measured the cost-effectiveness of vaccine programs targeted to the general population, and those studies found that vaccination programs for the general population had not cost-effective. However, the studies were limited by the expensive vaccination cost and limits of efficacy. The present study analyzed the cost-effectiveness of vaccination programs targeted to a socially vulnerable population versus the general population.

The result of our analysis showed that HPV vaccination programs targeted to the socially vulnerable population had high cost-effective, unlike the lack of cost-effective for the general population. By sensitivity analysis, the general population had cost-utility only at a 66% discounted vaccination cost. The socially vulnerable population had absolute cost-effective at all discount levels tested.

Of course, some studies about HPV vaccination of targeted groups have demonstrated economic value (Aponte-Gonzalez et al., 2013; Demarteau et al., 2013; Drolet et al., 2013; Elbasha et al., 2009; English et al., 2013; Fesenfeld et al., 2013; Kim et al., 2007; Natunen et al., 2013; Turner et al., 2013; Woertman and van der Wilt, 2013). However, the present study also considered the home environment when defining the socially vulnerable group. Thus, our findings include another important factor for the target group when evaluating the economic value of HPV vaccination.

This study has some limitations. First, we used estimated data for the simulation study because we did not have access to actual numbers. Therefore, the results

of this study can provide only trends about the economic value of HPV vaccination. Next, we did not consider medical costs incurred because of disease related to HPV infection. However, we applied the same assumptions to each population that was evaluated. Our approach provides a method to determine a reasonable estimate of the economic burden of HPV vaccination. In addition, this study had to use U.S. QALYs because exact data about QALYs in Korea is lacking.

In spite of these limitations, our results suggest the importance and cost-effectiveness for national support of HPV vaccination of socially vulnerable populations. Through the implementation of a national policy to support vaccination of socially vulnerable populations rather than the general population, we expect to see a decrease in the economic burden caused by HPV infections (Liao et al., 2009; Demarteau et al., 2012; da Fonseca et al., 2013). Of course, it is difficult to determine the actual economic value of HPV vaccination from the results of this study; thus, further studies should be undertaken. Targeting vaccination programs to specific populations at high risk is a new alternative for reducing the economic burden due to HPV infection.

In conclusion, the results of this study suggest the importance and necessity of government support of HPV vaccination programs targeted to socially vulnerable populations because a targeted approach is much more cost-effective than vaccinating the general population. The implementation of government support for such vaccination programs is a critical strategy for decreasing the burden of HPV infection in Korea.

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