RESEARCH COMMUNICATION

The Cost-Effectiveness of a Quadrivalent Human Papillomavirus Vaccine in Taiwan

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Abstract

Background: A quadrivalent human papillomavirus (HPV 6/11/16/18) vaccine has recently received regulatory approval in Taiwan for the prevention of cervical carcinoma, high-grade cervical dysplasia (cervical intraepithelial neoplasia 2/3 [CIN 2/3]), low-grade cervical dysplasia (CIN 1), high-grade vulvar and vaginal dysplasia, and external genital warts. Objective: To examine the potential long-term epidemiologic and economic consequences of a quadrivalent HPV (6/11/16/18) vaccination program in Taiwan. Methods: A transmission dynamic model was used to estimate the long-term epidemiologic and economic consequences of quadrivalent HPV vaccination. Two vaccination strategies were evaluated in conjunction with current cervical cancer screening: 1) vaccination of 12-year-old girls and 2) vaccination of 12-year-old girls with a temporary 5-year catch-up vaccination of females aged 12–24 years (catch-up). Results: From an epidemiologic perspective, both vaccination strategies reduce the overall incidence of HPV 16/18–related cervical cancer relative to no vaccination by 91% during year 100 following vaccine introduction. Likewise, both vaccination strategies reduce the incidence of CIN 2/3, CIN 1, and genital warts by ~90%, 86%, and 94%, respectively, at this time point. However, the catch-up program consistently achieves greater benefit earlier than the 12-year-old program. The catch-up strategy is both more effective and efficient than the strategy that vaccinates 12-year-old girls only, with an incremental cost-effectiveness ratio of New Taiwan dollars (NT$) 410,477 per quality-adjusted life-year gained. Conclusions: The results from this model suggest that in Taiwan, prophylactic HPV 6/11/16/18 vaccination of females can 1) substantially reduce genital warts, CIN, and cervical cancer, 2) improve quality of life and survival, and 3) be cost-effective when implemented as a vaccination strategy that includes a temporary catch-up program.

Key Words: Cervical cancer - prevention - quadrivalent HPV vaccine - cost-effectiveness - Taiwan

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Introduction

Cervical cancer is a common malignancy and, as such, is an issue of significant global concern. Approximately half a million women a year develop cervical cancer, and half of those die as a result (World Health Organization, 2007). The cause of cervical cancer is now attributed almost exclusively to persistent human papillomavirus (HPV) infection (Walboomers et al., 1999; Bosch et al., 2002). HPV infections are also associated with anogenital warts (Brown et al., 1999), vaginal and vulvar cancers (Joura et al., 2007), penile cancer (Palefsky, 2007), head and neck cancer (Hobbs et al., 2006), and recurrent respiratory papillomatosis (Freed & Derkay, 2006). To date, more than 100 different HPV types have been identified based on DNA homology, of which 40 are known to infect the anogenital tract (de Villiers et al., 2004). Infection with high-risk oncogenic HPV types (e.g., 16 and 18) can lead to cervical cancer, whereas infection with low-risk types (e.g., 6 and 11) can result in genital warts.

Cervical cancer progresses slowly through specific stages from mild, moderate, and severe dysplasia, to carcinoma in situ, and then to fully invasive carcinoma. Cervical intraepithelial neoplasia (CIN) grades 1, 2, and 3 correspond to mild, moderate, and severe dysplasia, respectively. The implementation of cytologic screening (Papanicolaou smear) has been effective at significantly decreasing invasive cervical cancer morbidity and mortality in the developed world in the last 50 years (Franco et al., 2006); however, it has limitations, related to test sensitivity, specificity, and patient compliance

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(Shingleton et al., 1995; Cuzick, 2001; Coste & Pouchot, 2003). As a result, many countries are considering HPV vaccination as a potential complementary strategy to reduce cervical cancer incidence. However, the extended length of time involved in the development of cervical cancer following HPV infection (Mosciki et al., 1998) poses a challenge for evaluating an HPV vaccine. This is primarily because it will be years before reductions in cancer incidence and mortality rates will be observed within a vaccinated population. Mathematical models can provide supplemental insights to policy makers on the potential long-term health and economic benefits of a prophylactic HPV vaccination program (Dasbach et al., 2006). A number of mathematical models have been developed to evaluate the potential long-term benefits of HPV vaccination (Goldie et al., 2003; Kulasingam & Myers, 2003; Sanders & Taira, 2003; Barnabas et al., 2006). However, the cost-effectiveness of HPV vaccination has not been evaluated for Taiwan.

Among developed countries, Taiwan has a relatively high incidence of cervical cancer (Department of Health, 2002). Even though Taiwan has been conducting mass cervical cancer screening since the initiation of National Health Insurance in 1995, the incidence of cervical cancer remains high (Bureau of Health Promotion, 2007). Taiwan has now approved the quadrivalent HPV vaccine Gardasil® (Merck & Co., Inc., Whitehouse Station, NJ, USA) for the prevention of cervical, vulvar, and vaginal cancer; precancerous or dysplastic lesions; and genital warts.

We have developed a transmission dynamic model to assess the epidemiologic and economic consequences of alternative quadrivalent HPV vaccination strategies (Elbasha et al., 2007). Previously, we found that a quadrivalent HPV vaccination program that targets girls and women 12 to 24 years of age can be cost-effective in the United States (Elbasha et al., 2007), as well as in Mexico (Insinga et al., 2007a). In this study, we have adapted our model to evaluate alternative quadrivalent HPV vaccination strategies in Taiwan and answered the following research questions:

1. What is the potential long-term public health impact of a quadrivalent HPV vaccine on the incidence of CIN, cervical cancer, cervical cancer mortality, and genital warts in the population in Taiwan?

2. What is the cost-effectiveness of a quadrivalent HPV vaccine program when added to the current standard of care (i.e., cervical cancer screening and clinical management of CIN, cervical cancer, and genital warts) from the perspective of the health care system in Taiwan?

Materials and Methods

The following sections describe the screening, treatment, and vaccination strategies evaluated; parameters used in the model; model output; validation analyses; and sensitivity analyses. Details on the model structure and equations have been previously published (Elbasha et al., 2007) and an online Supplementary Appendix is available (www.cdc.gov/ncidod/EID/13/1/28-aap.htm). Together, these resources allow for further critical review of the model.

Screening and Vaccination Strategies

We assumed that the HPV vaccination strategies evaluated would be combined with current cervical cancer screening and HPV disease treatment practices in Taiwan. We modeled current cervical cancer screening rates for Taiwan at the time of vaccine introduction (Bureau of Health Promotion, in press). We assumed that organized screening had been established 10 years prior to vaccine introduction. For vaccination, we evaluated an HPV vaccination program for girls at age 12 years as well as a temporary, 5-year catch-up vaccination program for females 12–24 years of age.

Input Parameters, Estimates, and Sources

The model requires input values for demographic, epidemiologic, screening, vaccine, and economic parameters (Elbasha et al., 2007). To adapt this dynamic model for Taiwan, a comprehensive search of the literature was conducted to obtain baseline values for these parameters. The baseline values and sources for model parameters specifically adapted for Taiwan are summarized in Table 1 (Bureau of Health Promotion, 2007; Chen et al., 1999; Chou & Lee, 2004; Tseng, 2006; Tang et al., 2006). Other parameters, such as the natural history of HPV 6/11/16/18 infections and diagnostic and treatment characteristics, were based on international data as summarized in our previous work (Elbasha et al., 2007).

Screening and Vaccination Program Strategy Parameters

We used data from Taiwan's Pap Registry Annual Report to estimate annual compliance rates for cytology screening (Bureau of Health Promotion, in press). The prophylactic efficacy of the vaccine against incident HPV 6, 11, 16, and 18 infections was assumed to be 90% (Villa et al., 2006). We assumed the prophylactic efficacy of the vaccine against HPV 6/11/16/18–related CIN and genital warts to be 95.2% and 98.9%, respectively (US Food and Drug Administration, 2008). The vaccine was assumed not to affect the natural course of HPV infection or disease prevalent at the time of HPV vaccination.

The duration of immunity conferred by vaccination is currently unknown. We assumed the duration of protection of HPV vaccination to be lifelong for the base case, as was done in other models (Goldie et al., 2003; French et al., 2007). Given that uptake (i.e., coverage) for an HPV vaccination program is presently unknown, we assumed in the base case that 85% of adolescents would receive a 3-dose vaccine at 12 years of age, similar to the coverage rates already observed for other school-based vaccination programs in Taiwan (available at http://www.cdc.gov.tw/file.39315_4934837963). Coverage (i.e., percentage of girls vaccinated) was also assumed to increase linearly from 0% up to 85% during the first 5 years of the program and to then remain at 85% thereafter. For the present purpose we further assumed that vaccine coverage for the catch-up program would increase linearly from 0% up to 85% during the first 5 years and then drop to 0% after 5 years with the conclusion of the temporary 5-year catch-up period.

Economic Parameters

All costs are reported in 2006 New Taiwan dollars (NT$). The direct medical costs for both screening and treatment of CIN, genital warts, and cervical cancer were based on insurance data and other sources (Department of Health, 2008; Tang et al., 2006; Ministry of the Interior, 2006). We assumed the cost of the HPV vaccine for three doses and administration would be NT$11,800. We did not include productivity costs (i.e., indirect costs) in the analyses. To estimate quality-adjusted life-years (QALYs), we used data collected in a study by Myers et al. (Myers et al., 2004; Insinga et al., 2007b). The planning horizon following vaccine introduction used in the analysis was 100 years. We assumed the size of the population at any given point in time over the 100-year horizon to be 100,000. Finally, all costs and health effects were discounted to present value at an annual rate of 3.0%.

Model Output

To assess the epidemiologic impact and cost-effectiveness of each vaccination strategy, we used a number of epidemiologic and economic output measures. Epidemiologic output included cases of HPV 6/11/16/18–related CIN, invasive cervical cancer and genital warts, and cervical cancer deaths. The economic output included total costs, survival, quality-adjusted survival, and incremental cost per QALY ratios. Total costs of each strategy included the cost of vaccination, cost of cytology screening, cost of following false-positive results, and total cost of managing detected CIN, invasive cancer, and genital warts. The quality-adjusted survival time was measured by weighting survival time by the quality-of-life adjustment weights associated with each health state and integrating the sum of all of these adjusted health states over the planning horizon (i.e., 100 years). The cost-

Table 1. Model Parameters Specifically Adapted for Taiwan

Parameter	Parameter estimate
Stage-specific cervical cancer mortality rate	
Localized cervical cancer[‡][a]	
<40 years	3.2
40–59 years	3.5
60–79 years	3.9
≥80 years	20.5
Regional cervical cancer[‡][a]	
<40 years	6.7
40–59 years	8.5
60–79 years	9.1
≥80 years	29.0
Distant cervical cancer[‡][a]	
<40 years	14.8
40–59 years	27.6
60–79 years	35.7
≥80 years	100.0
Costs of diagnosing and treating HPV disease (2003 New Taiwan dollars)	
Genital wart treatment[c]	NT$ 2,145
Conventional cytology screening exam[¶]	NT$ 430
Colposcopy and biopsy[¶]	NT$ 6,406
CIN 1 treatment[¶]	NT$ 3,047
CIN 2 treatment[¶]	NT$ 6,349
CIN 3 treatment[¶]	NT$ 9,436
Localized cervical cancer treatment[¶]	NT$ 182,602
Regional cervical cancer treatment[¶]	NT$ 366,409
Distant cervical cancer treatment[¶]	NT$ 398,565

Parameter	Estimate
Hysterectomy for non-HPV–related conditions, % per year	
15–29 years[b]	0.00%
30–34 years [§]	0.10%
35–39 years [§]	0.35%
40–44 years [§]	0.76%
45–49 years [§]	0.86%
50–54 years [§]	0.55%
55–59 years [§]	0.29%
60–64 years [§]	0.31%
65–69 years [§]	0.32%
70–74 years [§]	0.28%
≥75 years [§]	0.17%

Parameter	Estimate
Routine cervical cytology screening, % per year (excluding those with hysterectomy)	
15–17 years [*,§]	0.3
18–19 years [*,§]	1.2
20–24 years [*,§]	4.1
25–29 years [*,§]	9.9
30–34 years [*,§]	27.4
35–39 years [*,§]	30.6
40–44 years [*,§]	32.6
45–49 years [*,§]	34.1
50–54 years [*,§]	33.6
55–59 years [*,§]	29.6
60–64 years [*,§]	30.4
65–69 years [*,§]	29.5
70–74 years [*,§]	25.5
75–79 years [*,§]	19.6
80–84 years [*,§]	12.6
≥85 years [*,§]	6.0
Women never screened, % per year[†]	19.2
CIN 1 cases treated (versus passively managed), %[‖]	45

[a]Five-year survival rates by age and stage from this paper have been annualized and adjusted to relative survival rates based on female general-population 5-year mortality rates for Taiwan, [b]Assumption, no data available, [c]National Health Insurance Research database (unpublished analyses).HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia.

* Bureau of Health Promotion, Department of Health. Cancer Registry Annual Report 2005. Taiwan, Republic of China: The Executive Yuan, 2007

† Bureau of Health Promotion, Department of Health. Taiwan Pap Registry Annual Report 2005. Taiwan, Republic of China: The Executive Yuan, In press

‡ Chen RJ, Lin YH, Chen CA, et al. Influence of histologic type and age on survival rates for invasive cervical carcinoma in Taiwan. *Gynecol Oncol* 1999, 73: 184-90

§ Chou YC, Lee CH. Analysis of women's health care utilization in Taiwan: Cesarean section, hysterectomy, service-specific and group-specific utilization rate. Final report. Taipei, Republic of China: Department of Health, Bureau of National Health Insurance, 2004

‖ Tseng CJ. The 2003–2005 quality review for cervical cancer. Presented in the Bureau of National Health Insurance. Chia-Yi, Taiwan: Chang Gang Memorial Hospital, 2006

¶ Tang CH, Tsai IC, Pwu RF, et al. Treatment costs of cervical precancerous lesion and cervical cancer in Taiwan. [abstract no. P-542]. 23rd International Papillomavirus Conference and Clinical Workshop; 2006 Sep 1–7; Prague, Czech Republic, 382

per-QALY ratio was measured as the incremental cost difference between two strategies divided by the incremental QALY difference between the two strategies.

Simulation Method

We used Mathematica software (Wolfram Research, Champaign, IL, USA) to program all model equations and inputs. We used the NDSolve subroutine in Mathematica version 5.2 to generate numerical solutions for the differential equations that make up the model. The following strategy for simulations was followed: First, the baseline parameter estimates were used to solve the model for the prevaccination values of the variables in the first 10 years. Next, we used the prevaccination data at year 10 as the initial values for the vaccination model. Third, we solved for the entire time path of the variables until the system approached the steady state (approximately 100 years). Lastly, we used this solution to generate the output described for each of the screening and vaccination strategies.

Validation Analyses

Model inputs and outputs were critically reviewed by a panel of experts from Taiwan. The predictive validity of the model was evaluated by comparing model predictions for the screening strategy to observed epidemiologic data on the incidence of cervical cancer in Taiwan (Bureau of Health Promotion, 2007).

Sensitivity Analyses

Having previously performed extensive sensitivity analyses using this mathematical model as well as smaller models, we identified those parameters that impact the model results the most (Elbasha & Galvani, 2005; Elbasha et al., 2007). We conducted one-way sensitivity analyses by changing, one at a time, the baseline values of the parameters we had already identified, as well as those with the greatest uncertainty. These parameters included duration of vaccine protection, HPV disease costs, quality-of-life weights, and reductions in the incidence of HPV 6– and 11–related genital warts. In addition, we conducted a multivariate sensitivity analysis (i.e., a pessimistic scenario) in which we assumed that the duration of vaccine protection was 10 years, HPV disease costs were 25% less, and the impact of HPV disease on quality of life was less. Finally, it was not practical to conduct probabilistic sensitivity analyses given the complexity of the model and the time required to run one scenario for three strategies (~ 2 hours).

Results

Model Validation

The validity of the model for Taiwan was assessed by comparing the cervical cancer incidence rates obtained from the model with observed data reported in the literature. The model predicted that the overall rate of HPV 16/18–related cervical cancer cases would be 13.6 per 100, 000 females 12 or older with current screening and in the absence of vaccination at baseline. The overall incidence of cervical cancer cases observed in Taiwan in 2002 was

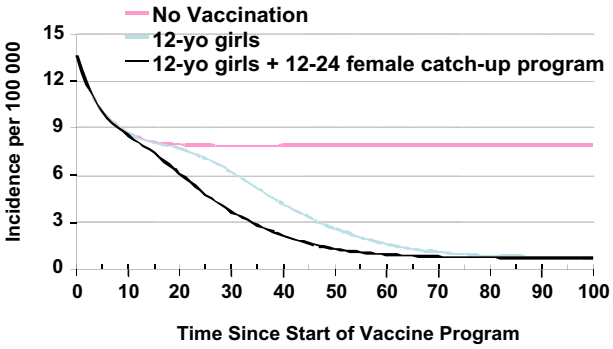

Figure 1. Projected Impact of HPV Vaccination Strategy on HPV 16/18–related Cervical Cancer Incidence

20.2 per 100,000 females across all age groups (Bureau of Health Promotion, 2007). The model predicts that the overall incidence of HPV 6/11–dependent genital warts in women in Taiwan would be 96 per 100,000; however, no data are available on the incidence of genital warts in the Taiwanese population.

Epidemiologic Impact of the HPV Vaccination Strategies

(Reference Case). Figure 1 illustrates the declining projected annual incidence of HPV 16/18–related cervical cancer over time under the two vaccination strategies evaluated. Given that organized screening has only been in place in Taiwan since 1995, the steady-state effect of

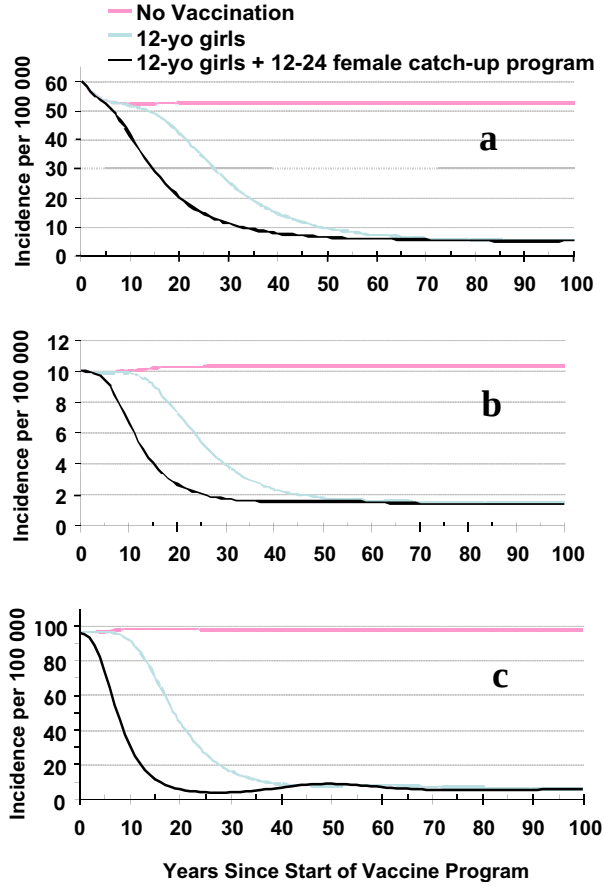

Figure 2. Projected Impact of Alternate Vaccination Strategies on the Incidence of (a) HPV 6/11/16/18–related CIN 2/3, (b) HPV 6/11/16/18–related CIN 1, and (c) HPV 6/11–related Genital Warts

screening has not been fully realized in the population by the tenth year following the introduction of vaccination. As a result, the incidence of cervical cancer continues to decline for the screening strategy until about year 20 following the introduction of vaccination. Both vaccination strategies reduce the overall incidence of HPV 16/18–related cervical cancer relative to no vaccination by 91% during year 100 following vaccine introduction. For the first 10 years, similar declines in HPV-related cervical cancer incidences are expected with screening as well as the two vaccination strategies evaluated, after which time the impact of the various programs diverge. For example, it will take approximately 42 years to see a 50% reduction in HPV 16/18–related cervical cancer incidence rates following vaccination of 12-year-old girls. This is in contrast to the 29 years required with the inclusion of a temporary 5-year catch-up program for females 12 to 24 years of age. Thus, the vaccination strategy that includes a catch-up program achieves greater benefits earlier than the strategy that only routinely vaccinates girls by the age of 12 years. The same type of result, with the catch-up program achieving greater benefit than the 12-year-old only program, is also seen for the changing incidence in HPV 6/11/16/18–related CIN 2/3 (Figure 2a), CIN 1 (Figure 2b), and genital warts (Figure 2c). Additionally, the benefits of the two vaccination programs for CIN 2/3, CIN 1, and genital warts are realized even sooner than for cervical cancer, as the incidence curves for the vaccination strategies are shifted to the left. During year 100 following vaccine introduction, both vaccination strategies will reduce the incidence of CIN 2/3, CIN 1, and genital warts by ~90%, 86%, and 94%, respectively.

Figures 1 and 2 clearly show that a vaccination strategy that includes a catch-up program achieves greater benefits earlier than the strategy that only routinely vaccinates girls by the age of 12 years. In Table 2 we show the cumulative

Table 2. Cumulative Cases of HPV 6/11/16/18 Disease Events Prevented in Taiwan Over the Next 25 Years with Vaccination of 12-year-old Girls Combined with a Temporary 5-year Catch-up program for Females aged 12–24, Relative to No Vaccination

	Years since start of vaccination program				
HPV disease	5	10	15	20	25
Genital warts	5,310	47,607	122,431	209,310	299,608
CIN 1	49	926	3,306	6,693	10,569
CIN 2/3	135	2,694	10,980	24,681	42,003
Cervical cancer	0	20	206	826	2,035
Cancer deaths	0	1	22	122	371

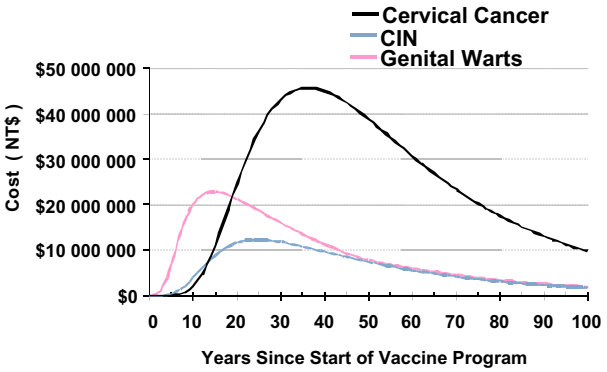

Figure 3. Discounted Annual HPV Disease Treatment Costs Avoided in the Population in Taiwan by a Vaccination Program for 12-year-old Girls that Includes a Temporary Catch-up program for Females aged 12–24, Relative to No Vaccination and Stratified by HPV Disease

cases of HPV 6/11/16/18 disease events that can be prevented over a 25-year time period with the implementation of a catch-up vaccination program. Because cervical cancer is a disease that progresses slowly over time, it will take years before the benefits of any HPV vaccination program will be realized with respect to preventing deaths due to the disease and reducing cervical cancer incidence rates. However, Table 2 does show that the catch-up vaccination strategy can have an early impact on the incidence of genital warts. In the first 5 years, 5,310 cases of genital warts can be prevented. This figures increases ~8.9-fold within 10 years to 47,607 cases. Although the number of cases of genital warts that can be prevented continues to rise over time, at years 15, 20, and 25 there are only 2.5-, 1.7-, and 1.4-fold increases in the number of cases prevented relative to the respective previous 5-year time period. Taken together, this table shows that HPV 6/11/16/18 vaccination of 12-year-old girls with a temporary catch-up program can result in both short-term and long-term reductions in HPV diseases.

Economic Impact of HPV Vaccination Strategies

(Reference Case). For each vaccination strategy, we also measured the costs from the HPV diseases avoided relative to no vaccination. Figure 3 summarizes the annual, discounted, HPV disease treatment costs prevented in the population in Taiwan by the most effective vaccination strategy (i.e., the vaccination program that includes a catch-up program for females 12–24 years of age) relative to the screening program without vaccination, stratified by HPV disease type. For the first 15 years, the majority

Table 3. Cost-effectiveness Analysis of Alternative Vaccination Strategies[a]

	Total		Incremental		
Strategy	Costs	QALYs	Costs	QALYs	Costs NT$/QALY[b]
No vaccination	192,653,749	2,700,559	-	-	-
12-year-old girls	397,358,710	2,701,027	204,704,960	468	Weakly dominated
12-year-old girls + 12–24 female catch-up program	482,947,608	2,701,266	290,293,859	707	410,477

[a]All costs are measured in 2006 New Taiwan (NT) dollars. Assumed cost of vaccination series is NT$11,800 and duration of protection is lifelong. Costs and QALY are discounted at a 3.0% annual rate, [b]Compared with the preceding non-dominated strategy, QALY = quality-adjusted life-year

Table 4. Summary of Incremental Cost-effectiveness Ratios (ICER) for Sensitivity Analyses[a]

Input variable	12-year-old girls + 12–24 female catch-up program (NT$)
Reference case	410,477
No reduction in HPV 6/11 disease	575,437
Less disutility	698,360
Duration of protection = 10 years	1,473,976
Pessimistic scenario	2,467,498

[a]All costs are measured in 2006 New Taiwan (NT) dollars. The 12-year old only vaccination program was weakly dominated by the program including catch-up vaccination for all sensitivity analyses. HPV = human papillomavirus

of costs avoided are attributable to the prevention of genital wart cases. However, after year 15, the majority of costs avoided through vaccination are attributable to the prevention of cervical cancer.

Using the model, the total discounted cost incurred by each strategy over a 100-year period was determined (Table 3). Table 3 also shows how efficient each vaccination strategy is over a 100-year period. The strategies are ordered from least effective (no vaccination) to most effective (vaccination including a catch-up strategy) using the QALY measure. Incremental costs, QALYs, and cost-per-QALY ratios are shown in the last three columns of Table 3. The catch-up vaccination strategy is both more effective and efficient, with an incremental cost-effectiveness ratio (ICER) of NT$410, 477 per QALY gained, than the strategy that only vaccinates girls at the age of 12 years. Hence, the strategy that only vaccinates girls at the age of 12 years is weakly dominated by the strategy that includes a catch-up program.

Sensitivity Analyses

We performed a variety of sensitivity analyses. The most influential parameters for the ICERs were the degree of protection against HPV 6/11 infection and disease, the duration of vaccine protection, and the health utility weights. A summary of the sensitivity analyses is shown in Table 4. The most influential parameter is the duration of protection. In this model, it was assumed that HPV 6/ 11/16/18 vaccination would confer lifelong protection. When the duration of protection is limited to 10 years, the ICER for the catch-up program increased to NT$1, 473,976, a 3.6-fold increase relative to the reference case (NT$410,477). Likewise, the ICER under the pessimistic scenario was high compared with the reference case, increasing to NT$2,467,498.

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 Taiwan that provides protection against both cervical cancer and genital warts. Generally, the results from this model demonstrate that a quadrivalent HPV vaccine program that includes a catch-up program can be cost-effective with an incremental cost-effectiveness ratio (ICER) of NT$410,477 according to criteria established by the World Health Organization (WHO). In particular, the WHO recommends that if the ICER is less than three times the per capita gross domestic product (GDP), it is considered cost-effective (World Health Organization, 2008). In 2007, the per capita GDP in Taiwan was approximately NT$512,000 (Department of Investment Services, 2008). These findings are consistent with other cohort-based cost-effectiveness analyses that have generally shown that vaccination of 12-year-old girls can be cost-effective (Barnabas & Kulasingam, 2007), but they also illustrate the population effects as well as the indirect herd immunity benefits provided by vaccination.

One important finding generated from this analysis was the role that catch-up vaccination can play in significantly reducing the burden of disease early on. Figure 2 demonstrated that a significant amount of disease can be prevented soon after the introduction of HPV vaccination in the population. From a cost-effectiveness perspective, we also found the strategy that vaccinates girls by the age of 12 years is weakly dominated by the strategy that includes a catch-up program.

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 benefits 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. 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 & Nasraty, 2004; Insinga et al., 2003).

Sensitivity analyses were also important for generating insights for developing an HPV vaccination policy. One of the key variables identified in the sensitivity analysis was the importance of duration of vaccine protection. To date, high sustained efficacy of the quadrivalent HPV vaccine has been demonstrated through 5 years of follow-up (Villa et al., 2006). 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). We found that as the duration of protection decreased, the cost-effectiveness ratios increased. Another insight from the sensitivity analysis was the importance that protection against genital warts (HPV 6 and 11) played in reducing the burden of HPV diseases, as well as its importance regarding cost-effectiveness. For example, the cost-effectiveness ratio increased approximately 40% to NT$575,437 per QALY gained in the absence of any reductions in HPV 6- and 11-related genital warts.

Although the limitations of this model have been described in detail (Elbasha et al., 2007), we have briefly listed two that are particularly relevant to this study in Taiwan. First, we have modeled only four HPV disease types (i.e., 6, 11, 16, and 18). However, it is possible that this vaccine may provide cross-protection (i.e., protection against HPV diseases associated with infection with other HPV types not directly targeted by the vaccine) (Merck & Co., Inc., 2007). Additionally, the proportion of invasive cancers

attributable to HPV 16/18 vary between different regions of the world (Walboomers et al., 1999; Smith et al., 2007). Several Taiwanese studies have demonstrated the presence of HPV 16 and/or 18 in neoplastic lesions (Yang et al., 2004; Wu et al., 1994; An et al., 2003; Huang et al., 2006), with values ranging from 41% to 88% reported for women with invasive cervical carcinoma (Huang et al., 2006); however, HPV 58, which is relatively uncommon in Western populations, is also prevalent in Taiwan (Lai et al., 1999).

Second, we 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 & Derkay, 2006), and mortality and productivity costs (i.e., indirect costs).

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, the results from this model suggest that in Taiwan, in a setting of organized cervical cancer screening, a prophylactic quadrivalent HPV (6/11/16/18) vaccine can be beneficial from a public health standpoint by 1) substantially reducing genital warts, CIN, and cervical cancer in the population and 2) improving quality of life and survival. From an economic perspective, vaccination can be cost-effective when implemented as a strategy that includes a temporary catch-up program.

References

An HJ, Cho NH, Lee SY, et al (2003). Correlation of cervical carcinoma and precancerous lesions with human papillomavirus (HPV) genotypes detected with the HPV DNA chip microarray method. *Cancer*, **97**, 1672-80.

Barnabas RV, Kulasingam SL (2007). Economic evaluations of human papillomavirus vaccines. *Expert Rev Pharmacoeconomics Outcomes Res*, **7**, 251-67.

Barnabas RV, Laukkanen P, Koskela P, et al (2006). Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses. *PLoS Med*, **3**, e138.

Bosch FX, Lorincz A, Muñoz N, et al (2002). The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol*, **55**, 244-65.

Brown DR, Schroeder JM, Bryan JT, et al (1999). Detection of multiple human papillomavirus types in Condylomata acuminate lesions from otherwise healthy and immunocompromised patients. *J Clin Microbiol*, **37**, 3316-22.

Bureau of Health Promotion, Department of Health (2007). Cancer Registry Annual Report 2005. Taiwan, Republic of China: The Executive Yuan.

Bureau of Health Promotion, Department of Health (in press). Taiwan Pap Registry Annual Report 2005. Taiwan, Republic of China: The Executive Yuan.

Carter JJ, Madeleine MM, Shera K, et al (2001). Human papillomavirus 16 and 18 L1 serology compared across anogenital cancer sites. *Cancer Res*, **61**, 1934-40.

Central Intelligence Agency. The World Factbook – Hungary. Retrieved in March 2008 from https://www.cia.gov/library/publications/the-world-factbook/geos/tw.html#Econ.

Chen RJ, Lin YH, Chen CA, et al (1999). Influence of histologic type and age on survival rates for invasive cervical carcinoma in Taiwan. *Gynecol Oncol*, **73**, 184-90.

Chou YC, Lee CH (2004). Analysis of women's health care utilization in Taiwan: Cesarean section, hysterectomy, service-specific and group-specific utilization rate. Final report. Taipei, Republic of China: Department of Health, Bureau of National Health Insurance.

Coste J, Pouchot J (2003). A grey zone for quantitative diagnostic and screening tests. *Int J Epidemiol*, **32**, 304-13.

Cuzick J (2001). Time to consider HPV testing in cervical screening. *Ann Oncol*, **12**, 1511-4.

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

Department of Health, National Health Insurance Annual Statistics Information Services, Executive Yuan, Taiwan, Republic of China, 2002. Retrieved in January 2008 from http://www.nhri.org.tw/nhird.

Department of Investment Services, MOEA (2008). http://investintaiwan.nat.gov.tw/em/env/stats/per_capita_gdp.html

de Villiers EM, Fauquet C, Broker TR, et al (2004). Classification of papillomaviruses. *Virology*, **324**, 17-27.

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

Elbasha EH, Galvani AP (2005). Vaccination against multiple HPV types. *Math Biosci*, **197**, 88-117.

Franco EL, Mayrand MH, Trottier H (2006). Cervical cancer prevention. Promises and perils in a changing landscape. *Oncol Exchange*, **5**, 9-13.

Freed GL, Derkay CS (2006). Prevention of recurrent respiratory papillomatosis: role of HPV vaccination. *Int J Pediatr Otorhinolaryngol*, **70**, 1799-803.

French KM, Barnabas RV, Lehtinen M, et al (2007). Strategies for the introduction of human papillomavirus vaccination: modelling the optimum age- and sex-specific pattern of vaccination in Finland. *Br J Cancer*, **96**, 514-8.

Goldie SJ, Grina D, Kohli M, et al (2003). A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. *Int J Cancer*, **106**, 896-904.

Hobbs CG, Sterne JA, Bailey M, et al (2006). Human papillomavirus and head and neck cancer: a systematic review and meta-analysis. *Clin Otolaryngol*, **31**, 259-66.

Huang LW, Hwang JL, Lin YH (2006). Type-specific distribution of human papillomavirus in relation to grades of cervical neoplasia. *Int J Gynecol Obstet*, **92**, 143-4.

Insinga RP, Dasbach EJ, Elbasha EH, et al (2007). Cost-effectiveness of quadrivalent human papillomavirus (HPV) vaccination in Mexico: A transmission dynamic model-based evaluation. *Vaccine*, **26**, 128-39.

Insinga RP, Dasbach EJ, Myers ER (2003). The health and

economic burden of genital warts in a set of private health plans in the United States. *Clin Infect Dis*, **36**, 1397-403.
Insinga RP, Glass AG, Myers ER, et al (2007). Abnormal outcomes following cervical cancer screening: event duration and health utility loss. *Med Decis Making*, **27**, 414-22.
Joura EA, Leodolter S, Hernandez-Avila M, et al (2007). Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet*, **369**, 1693-702.
Kodner CM, Nasraty S (2004). Management of genital warts. *Am Fam Physician*, **70**, 2335-42.
Kulasingam SL, Myers ER (2003). Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *JAMA*, **290**, 781-9.
Lai HC, Sun CA, Yu MH, et al (1999). Favorable clinical outcome of cervical cancers infected with human papilloma virus type 58 and related types. *Int J Cancer*, **84**, 553-7.
Maw RD, Reitano M, Roy M (1998). An international survey of patients with genital warts: perceptions regarding treatment and impact of lifestyle. *Int J STD AIDS*, **9**, 571-8.
Merck & Co., Inc. (2007). Merck submits new cross-protection data for Gardasil® to the FDA and seeks new indications for vaginal and vulvar cancers. Retrieved in November 2007 from http://www.merck.com/newsroom/press_releases/product/2007_0417.html.
Ministry of the Interior, Republic of China (2004). Abridged life table in Taiwan-Fuchien area–female: 2004 [online]. Retrieved in September 2006 from http://sowf.moi.gov.tw/stat/english/elife/te935202.htm.
Mosciki AB, Shiboski S, Broering J, et al (1998). The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *J Pediatr*, **132**, 277-84.
Myers ER, Green S, Lipkus I (2004). Patient preferences for health states related to HPV infection: visual analogue scales vs time trade-off elicitation [abstract no. 390]. Proceedings of the 21st International Papillomavirus Conference; Mexico City, Mexico.
Palefsky JM (2007). HPV infections in men. *Dis Markers*, **23**, 261-72.
Sanders GD, Taira AV (2003). Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerg Infect Dis*, **9**, 37-48.
Shingleton HM, Patrick RL, Johnston WW, et al (1995). The current status of the Papanicolaou smear. *CA Cancer J Clin*, **45**, 305-20.
Smith JS, Lindsay L, Hoots B, et al (2007). Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer*, **121**, 621-32.
Tang CH, Tsai IC, Pwu RF, et al (2006). Treatment costs of cervical precancerous lesion and cervical cancer in Taiwan. [abstract no. P-542]. 23rd International Papillomavirus Conference and Clinical Workshop; Prague, Czech Republic, 382.
Tseng CJ (2006). The 2003–2005 quality review for cervical cancer. Presented in the Bureau of National Health Insurance. Chia-Yi, Taiwan: Chang Gang Memorial Hospital.
US Food and Drug Administration. Gardasil (human papillomavirus vaccine). Retrieved in January 2008 from http://www.fda.gov/cber/products/gardasil.htm/.
Villa LL, Costa RLR, Petta CA, et al (2006). High sustained efficacy of a prophylactic quadrivalent human papillomavirus type 6/11/16/18 L1 virus–like particle vaccine through 5 years of follow-up. *Br J Cancer*, **95**, 1459-66.
Walboomers JM, Jacobs MV, Manos MM, et al (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*, **189**, 12-9.
World Health Organization (2007). Vaccinating against cervical cancer. *Bull World Health Organ*, **85**, 89-90.
World Health Organization (WHO). Threshold values for intervention cost-effectiveness by region. Retrieved in March 2008 from http://www.who.int/choice/costs/CER_levels/en/index.html.
Wu CH, Lee MF, Chang MC, et al (1994). Detection of human papillomavirus types in cervical lesions of patients from Taiwan by the polymerase chain reaction. *Sex Transm Dis*, **21**, 309-14.
Yang YY, Koh LW, Tsai JH, et al (2004). Correlation of viral factors with cervical cancer in Taiwan. *J Microbiol Immunol Infect*, **37**, 282-7.