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Economic Evaluation of Policy Options for Prevention and Control of Cervical Cancer in Thailand

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Abstract

Background: The Thai healthcare setting has seen patients with cervical cancer experience an increasing burden of morbidity and mortality, a stagnation in the performance of cervical screening programmes and the introduction of a vaccine for the prevention of human papillomavirus (HPV) infection.

Objective: This study aims to identify the optimum mix of interventions that are cost effective, from societal and healthcare provider perspectives, for the prevention and control of cervical cancer.

Methods: A computer-based Markov model of the natural history of cervical cancer was used to simulate an age-stratified cohort of women in Thailand. The strategy comparators, including both control and prevention programmes, were (i) conventional cytology screening (Pap smears); (ii) screening by visual inspection with acetic acid (VIA); and (iii) HPV-16, -18 vaccination. Input parameters (e.g. age-specific incidence of HPV infection, progression and regression of the infection, test performance of screening methods and efficacy of vaccine) were synthesized from a systematic review and meta-analysis. Costs (year 2007 values) and outcomes were evaluated separately, and compared for each combination. The screening strategies were started from the age of 30–40 years and repeated at 5- and 10-year intervals. In addition, HPV vaccines were introduced at age 15–60 years.

Results: All of the screening strategies showed certain benefits due to a decreased number of women developing cervical cancer versus 'no intervention'. Moreover, the most cost-effective strategy from the societal perspective was the combination of VIA and sequential Pap smear (i.e. VIA every 5 years

for women aged 30–45 years, followed by Pap smear every 5 years for women aged 50–60 years). This strategy was dominant, with a QALY gain of 0.01 and a total cost saving of Baht (Bt)800, compared with doing nothing. From the societal perspective, universal HPV vaccination for girls aged 15 years without screening resulted in a QALY gain of 0.06 at an additional cost of Bt8800, based on the cost of Bt15 000 for a full immunization schedule. The incremental cost-effectiveness ratio, comparing HPV vaccinations for girls aged 15 years with the current national policy of Pap smears for women aged 35–60 years every 5 years, was approximately Bt181 000 per QALY gained. This figure was relatively high for the Thai setting.

Conclusions: The results suggest that controlling cervical cancer by increasing the numbers of women accepting the VIA and Pap smear screening as routine and by improving the performance of the existing screening programmes is the most cost-effective policy option in Thailand.

Background

Cervical cancer has been identified as a major cause of morbidity and mortality among Thai women, similar to in other developing countries. Despite effective screening and subsequent treatment options being available through publicly funded programmes for all Thai women for more than 40 years, the cervical cancer-related mortality remains high.[1-3] It was reported that only 5% of women in Thailand were screened for cervical cancer at any point in the previous 5 years,[4] compared with up to 70% in industrialized countries. Cervical cancer is the leading cause of female cancer deaths in Thailand.[1,2]

The establishment of a strong link between high-risk persistent human papillomavirus (HPV) infections[5,6] and the occurrence of cervical cancer resulted in the recent development of HPV-related technologies for the prevention and control of cervical cancer. These include HPV DNA testing and prophylactic HPV vaccines, which were approved by the Thai Food and Drug Administration, and are now available to the public. Although the vaccines appear to be a new hope for bringing cervical cancer under control, they are still very expensive and there is no clear national policy or plan regarding the use of these technologies.[7]

Our aim was, therefore, to conduct a comprehensive assessment of health technology related to the screening and prevention of cervical cancer in Thailand. The study aims to explore the value for money of each health technology, and their combinations, with the hope that the findings will be used for guiding policy decisions regarding resource allocation for cervical cancer at both national and sub-national levels. It is expected that this study would also be useful for decision makers in other developing settings in making the most efficient use of healthcare resources to overcome cervical cancer problems.

Objective

This study aims to determine the optimal strategy for the prevention and control of cervical cancer in Thailand using the efficiency criteria underpinning economic evaluation.

Specifically, a cost-utility analysis, which allows for a direct comparison between interventions with different health outcomes, was conducted for this purpose. We compared the additional costs and benefits of moving from a 'do nothing' scenario to a number of alternative policy options for the prevention and control of cervical cancer, including Pap smears every 5 and 10 years, visual inspection with acetic acid (VIA) every 5 and 10 years and HPV vaccination for women aged 15, 16, 17, …, 60 years and various combinations of these policies. The low specificity in excluding

the absence of high-grade cervical intraepithelial neoplasia (CIN) compared with cytology screening (Pap smears) has discouraged the use of HPV DNA testing as a source of primary screening for cervical cancer and pre-cancer.[8] However, in conjunction with cytology screening, the HPV test may have a higher probability of detecting high-grade lesions. The HPV DNA test is not widely used in Thailand and so is not yet included in the clinical practice guidelines recommended by the Royal Thai College of Obstetricians and Gynecologists.[9] For this reason it was excluded from this study.

Methods

A model-based cost-utility analysis was carried out within the Thai healthcare setting, and both societal and healthcare provider (or third-party payer) perspectives were adopted. The outcomes were measured in terms of both life-years (LYs) and QALYs gained from the interventions. The lifetime time horizon was used.

Overview of Competing Strategies

Pap Smear

Pap smears (cytology-based screening) have been a standard test for the early detection of cervical cancer in Thailand for more than 40 years. The service is planned and supervised by the Ministry of Public Health (MOPH), and is widely available at every health centre and hospital throughout the country, although the cytologists and pathologists who make the diagnoses are available only at secondary or tertiary hospitals or private laboratories. Women identified as having pre-cancerous lesions should have the lesions treated before these lesions progress to an invasive cancer.

Visual Inspection with Acetic Acid (VIA)

VIA was first introduced in Thailand in 2001 as one of the alternatives for cervical cancer screening.[10] The technique involves an examination of the cervix with the naked eye, using a bright light source, after 1 minute of 3–5% diluted acetic acid being applied using a cotton swab or spray. The technique eliminates the need for cytologists and colposcopies. Detection of well defined aceto-white areas close to the squamocolumnar junction indicates a positive test and this allows treatment to be performed immediately, during the same screening visit. In 2006, VIA was available in 15 of 76 provinces, mostly at the district health system level in rural areas (a total of 186 districts).[11]

Human Papillomavirus Vaccines

The Thai Food and Drug Administration recently approved the two currently available vaccines for the prevention of high-risk HPV types 16 and 18: Gardasil® (Merck Sharpe and Dohme) and Cervarix® (GlaxoSmithKline). The vaccines have the potential to greatly reduce the burden of cervical cancer. It is recommended that the prophylactic vaccines be given in three doses at 0, 1–2 and 6 months for women aged 9–26 years.[12,13] The vaccines are only available for those who can afford them, at a total cost of Bt15 000. However, to achieve health benefits across the population, HPV vaccination needs to be part of a publicly funded, universal vaccination programme.

Analyses and Model

We used a Microsoft® Excel 2003 spreadsheet (Microsoft Corp., Redmond, WA, USA) to construct a semi-Markov model, where the transitional probability of moving from one health state to another depends on the amount of time that has elapsed since entry into the current state. This is in contrast to the traditional Markov model, where the transitional probability of moving to another health state is equal regardless of timing or directions of earlier transitions.[14] The model was used to predict the costs and consequences of each policy strategy, following the same female cohort (starting at age 15 years) for all strategies. The lifetime time horizon was used, with a cycle length of 1 year.

The model structure is illustrated in figure 1. The states of health are denoted in square boxes, while an arrow indicates that movement from one state to another is possible. Women who start with no infection (healthy state) can get an HPV infection or remain in the same state for the next

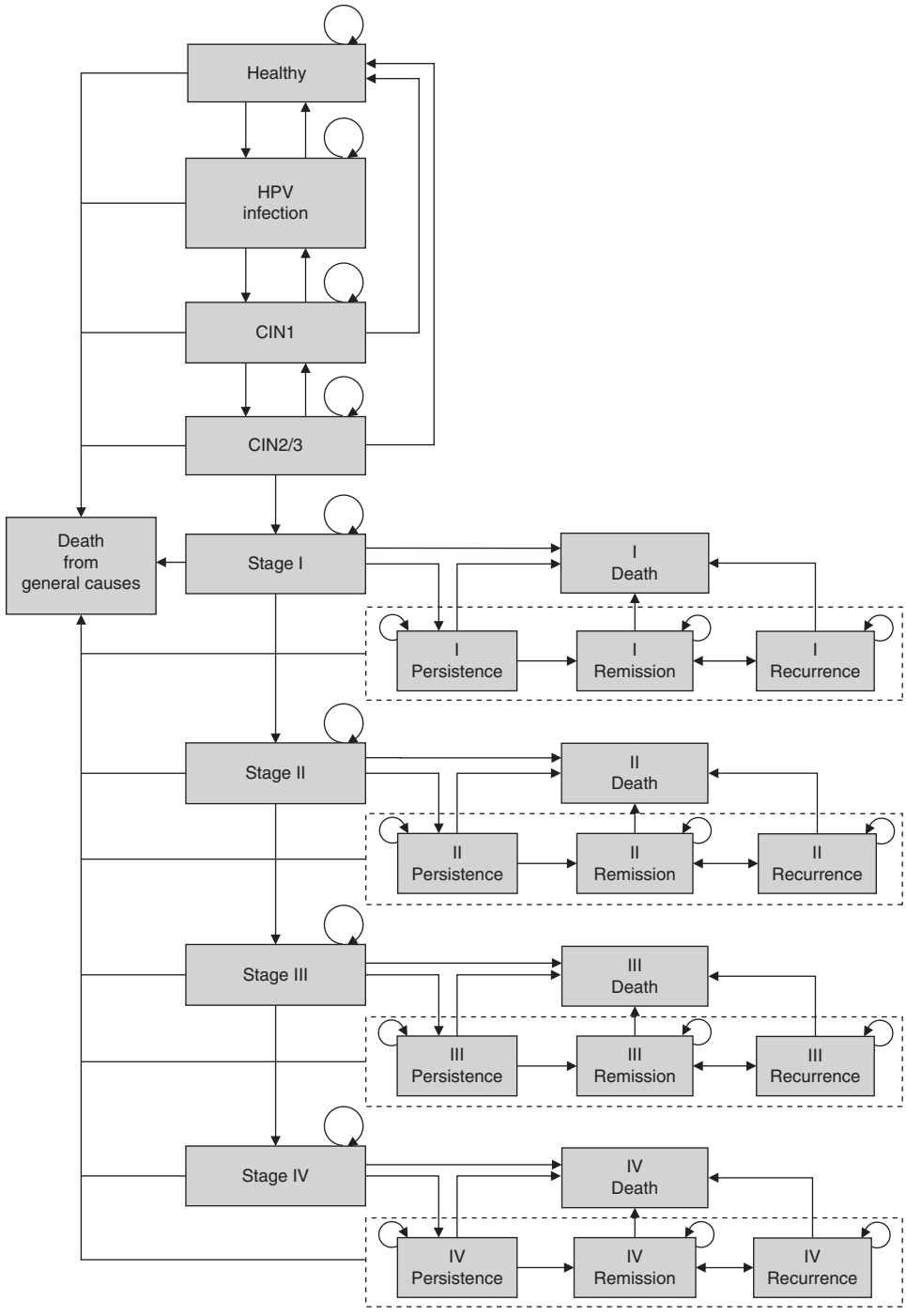

Fig. 1. Schematic diagram of the semi-Markov model. **CIN** = cervical intraepithelial neoplasia; **HPV** = human papillomavirus.

cycle. Women with HPV can move to the precancerous states, CIN1 and CIN2 or CIN3, accordingly, and they can also move back to the previous states or to a healthy state for the next cycle. However, if a woman enters into a cancerous stage, as described by the International Federation of Gynecology and Obstetrics (FIGO) staging system[15] (stage I, II, III or IV), she can not return to the previous states or a healthy state. For each of the cancerous states, the patients can enter into the persistence, remission or recurrence states, or may die from cervical cancer. All women in the hypothetical cohort can also die from other causes, such as accidents, diabetes or breast cancer, at the end of each cycle.

The Monte Carlo simulation was used to model costs and events over a 100-year period to cover the total period over which the whole cohort would be expected to survive. All costs and outcomes were discounted at the rate of 3%, as per health technology assessment guidelines in Thailand.[16] However, we also explored results with discount rates of 0%, 5% and 10%.

Model Parameters

Health State Transitional Probabilities

The probability of transitions between health states for the unscreened population were mainly taken from the work of Myers et al.,[17] who developed a Markov model of the natural history of HPV infections and cervical cancer based on their previous works and published data (table I). These parameters are not specific for HPV-16, -18 types and must be applied for all high-risk HPV types. As a result, the model constructed for this study was not HPV-type specific but accounted for all HPV infections. The transitional probabilities used in the model were validated using observed data from a community survey in Thailand[22] and data reported by the Thai MOPH.[23] Figure 2 illustrates that the predicted age-specific annual prevalence of HPV infection obtained from the baseline model (no intervention, treatment only) was similar to the observed data. This was true for all groups except the young age group (15–24 years), in which the survey data was very limited. Figure 3 shows a common agreement of incidence in all stages of cervical cancer derived from the model and the MOPH official report.[23]

The baseline mortality for the general population and the mortality for patients with cervical cancer were derived from Thai cohorts. First, vital registration data, which had been verified by a verbal autopsy study, were used to obtain the number of deaths by age and sex among the general population for the year 2004.[2] Second, the survival rates of cervical cancer patients with particular disease staging (i.e. I, II, III and IV) were derived from the tumour registry database of the Thai Gynecologic Oncology Collaborative Group (TGOC).[24] This database comprised 799 patients observed over a 5-year period (2000–4). Using the statistical software package STATA (Stata Corp, College Station, TX, USA), the survival rate of each patient group was obtained by parametric analysis. To fit Kaplan-Meier survival curves, graphs of log[–log[$S(t)$]] against log(time) were plotted, where $S(t)$ is survival time, which were generally linear, indicating that a Weibull survival model would adequately fit the data.[25]

For the Weibull distribution, the survival function, which describes the probability of survival as a function of age, is as shown in equations 1 and 2:

$$S(t) = \exp[-H(t)] \quad \text{(Eq. 1)}$$

and

$$H(t) = \lambda t^{\gamma} \quad \text{(Eq. 2)}$$

where $H(t)$ is cumulative hazard; λ is the scale parameter; t is time in days; and γ is the shape parameter that describes the instantaneous death rate, which increases with age if $\gamma > 1$. λ depends on the co-variate, age (years), according to equation 3:

$$\lambda = \exp[(age\_coefficient \times Age) + cons] \quad \text{(Eq. 3)}$$

The transitional probability of dying during the cycle, $tp(c)$, is therefore estimated from the formula (equation 4):

$$tp(c) = 1 - \exp[H(t-c) - H(t)] \quad \text{(Eq. 4)}$$

where c is the number of cycles.

Table I. Model parameters

Parameters	Mean (SE)	Distribution	Reference
Baseline parameters			
Discount rate for both costs and outcomes	0.03		
Epidemiological parameters			
Prevalence of HPV infection; age 15 y	0.100 (0.064)	Beta	17
Prevalence of CIN1; age 15 y	0.010 (0.010)	Beta	17
Age-specific (y) incidence of HPV infection			
15	0.100 (0.038)	Beta	17
16	0.100 (0.038)	Beta	17
17	0.120 (0.046)	Beta	17
18	0.150 (0.057)	Beta	17
19	0.170 (0.065)	Beta	17
20	0.150 (0.057)	Beta	17
21	0.120 (0.046)	Beta	17
22	0.100 (0.038)	Beta	17
23	0.100 (0.038)	Beta	17
24	0.050 (0.019)	Beta	17
30	0.010 (0.004)	Beta	17
50	0.005 (0.002)	Beta	17
Progression rates			
HPV infection to CIN1	0.072 (0.015)	Beta	17
CIN1 to CIN2/3 (age [y])			
15	0.017 (0.010)	Beta	17
35	0.069 (0.013)	Beta	17
CIN2/3 to invasive cancer	0.050 (0.008)	Beta	17
stage I to stage II	0.438 (0.351)	Beta	17
stage II to stage III	0.536 (0.351)	Beta	17
stage III to stage IV	0.684 (0.140)	Beta	17
Age-specific (y) probability of regression:[a] HPV infection to healthy			
15	0.552 (0.084)	Beta	17
25	0.370 (0.033)	Beta	17
30	0.103 (0.018)	Beta	17
Age-specific (y) regression rate:[a] CIN1 to HPV infection or healthy			
15	0.161 (0.024)	Beta	17
35	0.082 (0.021)	Beta	17
Regression rate from CIN2/3 to CIN1 or healthy	0.069 (0.013)	Beta	17
Proportion of CIN1 reverting to healthy	0.900 (0.128)	Beta	17
Proportion of CIN2/3 reverting to healthy	0.500 (0.128)	Beta	17
Proportion having symptoms			
stage I	0.150 (0.150)	Beta	17
stage II	0.225 (0.225)	Beta	17
stage III	0.600 (0.600)	Beta	17
stage IV	0.900 (0.900)	Beta	17

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Table I. Contd

Parameters	Mean (SE)	Distribution	Reference
Weibull survival by cancer stage and patient age (y)			
stage I			
constant	−8.749 (1.259)	Log-Normal	[b]
age coefficient	0.041 (0.020)	Log-Normal	[b]
Gamma	0.589 (1.139)	Log-Normal	[b]
stage II			
constant	−7.066 (0.934)	Log-Normal	[b]
age coefficient	−0.014 (0.011)	Log-Normal	[b]
Gamma	0.919 (1.120)	Log-Normal	[b]
stage III			
constant	−6.778 (0.891)	Log-Normal	[b]
age coefficient	0.023 (0.011)	Log-Normal	[b]
Gamma	0.675 (1.098)	Log-Normal	[b]
stage IV			
constant	−3.863 (1.217)	Log-Normal	[b]
age coefficient	−0.055 (0.022)	Log-Normal	[b]
Gamma	1.004 (1.226)	Log-Normal	[b]
Programme effectiveness parameters			
Pap smear			
Sensitivity for pre-invasive	0.552 (0.070)	Beta	18
Sensitivity for stage I	0.800		[c]
Sensitivity for stage II, III, IV	1.000		[c]
Specificity	0.915 (0.013)	Beta	18
VIA			
Sensitivity for pre-invasive	0.716 (0.025)	Beta	18
Sensitivity for stage I	0.900		[c]
Sensitivity for stage II, III, IV	1.000		[c]
Specificity	0.793 (0.011)	Beta	18
HPV vaccine			
Relative risk of HPV infection[d]	0.213 (0.318)	Beta	19
Programme acceptability			
pap smear[e]	0.200		20
VIA[e]	0.200		20
HPV vaccine[f]	1.000		[c]
Proportion of patients with CIN2/3			
receiving cryosurgery	1.000 (1.000)	Beta	21
receiving cold knife conisation	0.125 (0.125)	Beta	21
receiving simple hysterectomy	0.125 (0.125)	Beta	21
Incidence of OP visit for treating minor complications from cryosurgery	0.05 (0.05)	Beta	21
Incidence of IP visit for treating major complications from cryosurgery	0.01 (0.01)	Beta	21
Probability of patient being treated at OPD			
with initial stage	0.856 (0.017)	Beta	[b]
with remission stage	0.993 (0.004)	Beta	[b]
with persistence stage	0.786 (0.063)	Beta	[b]
with recurrence stage	0.715 (0.041)	Beta	[b]

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Table I. Contd

Parameters	Mean (SE)	Distribution	Reference
Annual rate of OP visits			
initial stage	25.48 (1.41)	Gamma	[b]
remission stage	7.14 (0.59)	Gamma	[b]
persistence stage	38.53 (7.77)	Gamma	[b]
recurrence stage	13.37 (2.02)	Gamma	[b]
Annual rate of IP visits			
initial stage	0.77 (0.10)	Gamma	[b]
remission stage	0.15 (0.04)	Gamma	[b]
persistence stage	0.87 (0.43)	Gamma	[b]
recurrence stage	1.64 (0.31)	Gamma	[b]
Annual hospitalization (d)			
initial stage	5.44 (0.85)	Gamma	[b]
remission stage	1.17 (0.33)	Gamma	[b]
persistence stage	3.60 (1.81)	Gamma	[b]
recurrence stage	6.64 (1.25)	Gamma	[b]
Costing parameters of screening and vaccination[g]			
Direct medical costs of screening (Bt per visit)			
PAP smear	60 (60)	Gamma	21
VIA	30 (30)	Gamma	21
cost of follow-up for Pap screening	32 (32)	Gamma	21
Patient time spent for Pap/VIA (min)	15 (15)	Gamma	21
Cost of HPV vaccination (three doses)	15 000 (1500)	Gamma	[b]
Cost of HPV booster dose	5000 (500)	Gamma	[c]
Cost of vaccine delivery and administration (Bt per dose)	250 (25)	Gamma	[b]
Patient time spent receiving vaccine (min)	5 (5)	Gamma	[b]
Unit cost of colposcopy/biopsy	1169 (1169)	Gamma	21
Patient time spent for colposcopy/biopsy (min)	20 (20)	Gamma	21
Patient travel cost (Bt per visit)			
primary facility	7 (7)	Gamma	21
secondary facility	40 (40)	Gamma	21
tertiary facility	146 (146)	Gamma	21
Patient wage rate (Bt per h)	26 (26)	Gamma	21
Patient waiting time (min)			
primary facility	30 (30)	Gamma	21
secondary facility	35 (35)	Gamma	21
tertiary facility	50 (50)	Gamma	21
Patient one-way travel time (min)			
primary facility	15 (15)	Gamma	21
secondary facility	44 (44)	Gamma	21
tertiary facility	53 (53)	Gamma	21
Unit costs (Bt)			
cryotherapy	650 (650)	Gamma	21
LEEP	4677 (4677)	Gamma	21
cold knife conisation	7015 (7015)	Gamma	21

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Table I. Contd

Parameters	Mean (SE)	Distribution	Reference
simple hysterectomy	14 030 (14 030)	Gamma	21
Cost of hospitalization day (Bt per d)	351 (351)	Gamma	21
Hospitalization days			
cold knife conisation	4 (4)	Gamma	21
simple hysterectomy	7 (7)	Gamma	21
Medical cost of follow-up			
cryosurgery (Bt/y)	32 (32)	Gamma	21
LEEP/cold knife conisation/simple hysterectomy (Bt/y)	1201 (1201)	Gamma	21
Patient time spent for receiving treatment (min)			
cryosurgery	20 (20)	Gamma	21
LEEP	30 (30)	Gamma	21
cold knife conisation	45 (45)	Gamma	21
simple hysterectomy	130 (130)	Gamma	21
Unit cost			
cervical cancer staging	4801 (4801)	Gamma	21
treating complications from cryosurgery (minor)	585 (585)	Gamma	21
treating complications from cryosurgery (major)	3509 (3509)	Gamma	21
Annual costs for treatment of invasive cervical cancer[g]			
Direct medical costs occurred at public hospitals for treatment			
Initial stage			
stage I	26 816 (2233)	Gamma	[b]
stage II	27 610 (2199)	Gamma	[b]
stage III	29 163 (2332)	Gamma	[b]
stage IV	22 268 (2686)	Gamma	[b]
Remission stage			
stage I	5690 (565)	Gamma	[b]
stage II	5714 (564)	Gamma	[b]
stage III	5652 (563)	Gamma	[b]
stage IV	5716 (564)	Gamma	[b]
Persistence stage			
stage I	38 600 (14 286)	Gamma	[b]
stage II	33 064 (11 757)	Gamma	[b]
stage III	32 441 (11 367)	Gamma	[b]
stage IV	24 656 (11 825)	Gamma	[b]
Recurrence stage			
stage I	22 665 (8388)	Gamma	[b]
stage II	22 602 (8500)	Gamma	[b]
stage III	22 892 (7461)	Gamma	[b]
stage IV	23 281 (6490)	Gamma	[b]
Direct medical costs occurred outside public hospitals for treatment			
Initial stage			
stage I	2073 (446)	Gamma	[b]
stage II	2101 (460)	Gamma	[b]
stage III	2157 (491)	Gamma	[b]
stage IV	1910 (382)	Gamma	[b]

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Table I. Contd

Parameters	Mean (SE)	Distribution	Reference
Remission stage			
stage I	2193 (525)	Gamma	[b]
stage II	2197 (527)	Gamma	[b]
stage III	2187 (522)	Gamma	[b]
stage IV	2197 (527)	Gamma	[b]
Persistence stage			
stage I	14 493 (10 251)	Gamma	[b]
stage II	11 979 (8380)	Gamma	[b]
stage III	11 697 (8111)	Gamma	[b]
stage IV	8162 (6865)	Gamma	[b]
Recurrence stage			
stage I	3466 (1149)	Gamma	[b]
stage II	3418 (1099)	Gamma	[b]
stage III	3640 (1197)	Gamma	[b]
stage IV	3939 (1547)	Gamma	[b]
Direct non-medical costs for treatment			
Initial stage			
stage I	30 036 (2319)	Gamma	[b]
stage II	30 905 (2361)	Gamma	[b]
stage III	32 605 (2460)	Gamma	[b]
stage IV	25 055 (2776)	Gamma	[b]
Remission stage			
stage I	7492 (667)	Gamma	[b]
stage II	7514 (668)	Gamma	[b]
stage III	7457 (664)	Gamma	[b]
stage IV	7516 (668)	Gamma	[b]
Persistence stage			
stage I	47 314 (10 252)	Gamma	[b]
stage II	38 881 (8894)	Gamma	[b]
stage III	37 932 (8706)	Gamma	[b]
stage IV	26 071 (13 506)	Gamma	[b]
Recurrence stage			
stage I	15 151 (2441)	Gamma	[b]
stage II	15 297 (2415)	Gamma	[b]
stage III	14 621 (2597)	Gamma	[b]
stage IV	13 714 (3215)	Gamma	[b]
Utility parameters			
Healthy stage or CIN1–3 without complication	*1.00 (1.00)*	*Beta*	[b]
Initial stage			
stage I	0.74 (0.01)	Beta	[b]
stage II	0.76 (0.01)	Beta	[b]
stage III	0.72 (0.02)	Beta	[b]
stage IV	0.63 (0.03)	Beta	[b]

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Table I. Contd

Parameters	Mean (SE)	Distribution	Reference
Remission stage			
stage I	0.79 (0.01)	Beta	b
stage II	0.79 (0.01)	Beta	b
stage III	0.81 (0.01)	Beta	b
stage IV	0.85 (0.05)	Beta	b
Persistence stage			
stage I	0.80 (0.20)	Beta	b
stage II	0.80 (0.04)	Beta	b
stage III	0.65 (0.05)	Beta	b
stage IV	0.45 (0.05)	Beta	b
Recurrence stage			
stage I	0.80 (0.03)	Beta	b
stage II	0.68 (0.02)	Beta	b
stage III	0.66 (0.04)	Beta	b
stage IV	0.81 (0.08)	Beta	b

a Rates from references are converted to annual probabilities in model.

b Analysis of primary data collected by the authors.

c Assumption used in the model.

d The relative risk was calculated using inverse variance method.

e Coverage of 50, 80 and 100% was used in the uncertainty analysis.

f Coverage of 20, 50 and 80% was used in the uncertainty analysis.

g All costs are presented in Bt, year 2007 values.

Bt = Thai Baht; **CIN** = cervical intraepithelial neoplasia; **HPV** = human papillomavirus; **IP** = inpatient; **LEEP** = loop electrosurgical excision procedure; **OP** = outpatient; **OPD** = OP department; **SE** = standard error of mean; **VIA** = visual inspection with acetic acid.

Intervention Effectiveness

Because a more precise estimate can be attained by combining outcome data from a number of studies and also to avoid bias from the selective use of information, the model parameters relating to the effectiveness of the screening interventions were derived only from systematic reviews and meta-analyses of clinical trials. Detailed information about the systematic reviews and meta-analyses are reported elsewhere.[18] The MEDLINE database was searched using the following keywords:

1. 'uterine cervical neoplasms [Mesh]' with subheading 'diagnosis';
2. 'Pap smear' or 'visual inspection with acetic acid';
3. 'sensitivity' or 'specificity'.

The search strategy was (#1 OR #2) AND #3. Only journal articles published in the English language between 1 January 1996 and 28 February 2007 were included.

The title and abstract of each article were initially assessed and, if they appeared to be relevant, full texts were retrieved, reviewed and extracted by

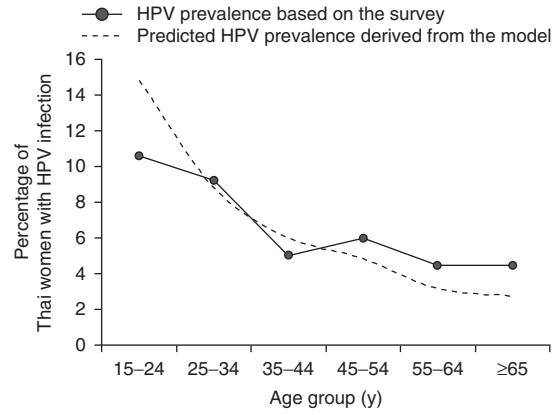

Fig. 2. Observed[22] and predicted prevalence of human papillomavirus (HPV) infection among Thai women.

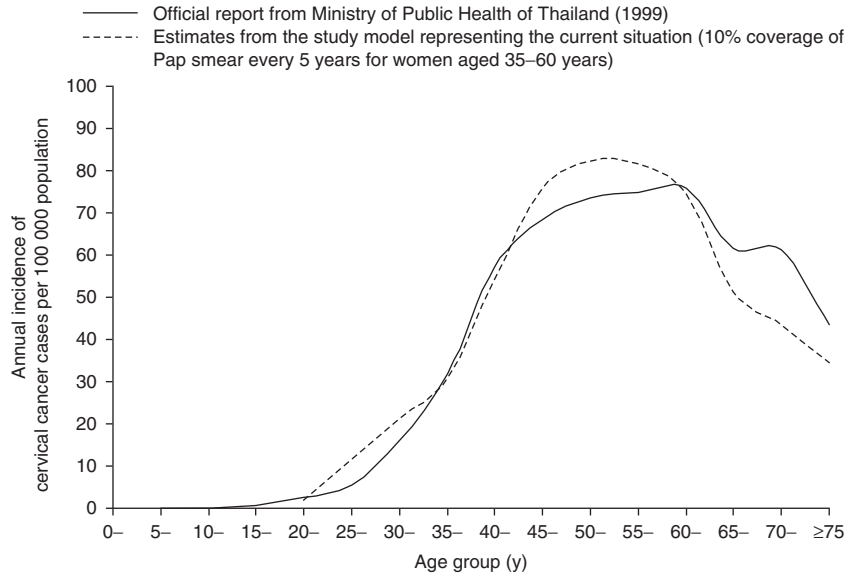

Fig. 3. Cervical cancer incidence estimated from the model and the Ministry of Public Health's official report.[23]

two independent reviewers (Pasakorn Sritipsukho, MD, PhD, and Naiyana Praditsitthikorn, PhD). The studies were included if they compared the sensitivity and specificity of Pap smears or VIA with one of the reference standards (namely, histological pathology and colposcopy) on the same patient. We excluded studies that did not provide information about true or false positives or true or false negatives.

An abnormal Pap smear result was defined as high-grade squamous intraepithelial lesion (HSIL) or worse, or equivalent by other classifications. However, atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL), or equivalent categories by other classifications, could be used as the threshold if HSIL data were not available. Abnormal VIA or VIA with magnifying device (VIAM) was defined as white plaques, ulcer or cancerous-like lesions by naked-eye visual inspection of the cervix after applying 3–5% acetic acid with a cotton swab and by using a magnifying device, respectively. The histology threshold for a positive outcome from screening tests was CIN2 or worse (or equivalent categories by other classifications). Histological confirmation by tissues obtained from colposcopy-directed biopsy, loop excision or endocervical curettage was used to determine abnormalities of the colposcopy results.

Table I shows results from random effects meta-analyses of 12 studies regarding the accuracy of VIA and 15 studies concerning the accuracy of Pap smears. The sensitivity and specificity of Pap smears at the pre-invasive stage were 0.552 (SE = 0.070) and 0.915 (SE = 0.013), respectively. Based on opinion from experts of the TGOC, we assumed a sensitivity of 0.8 and 1.0 for Pap smears in detecting invasive cervical cancer stages I, and II or higher, respectively. We also assumed that all false-positive cases would be detected eventually after undertaking a colposcopy with tissue biopsy. The sensitivity of VIA at the pre-invasive stage was relatively higher than that of Pap smears (0.716, SE = 0.025), but its specificity was lower (0.793, SE = 0.011). We assumed a sensitivity of 0.9 and 1.0 for VIA in detecting invasive cervical cancer stages I, and II or higher, respectively.

Efficacy of the HPV vaccine was obtained from a recent systematic review and meta-analysis by Rambout et al.[19] They reported a 79%

vaccine efficacy (relative risk = 0.213, SE = 0.318) against all types of persistent HPV infections.

The target population coverage of cervical cancer screenings, by either Pap smear or VIA, was derived from two national representative surveys, both conducted by the National Statistical Office: the Health and Welfare Survey (2003)[26] and the Reproductive Health Survey (2006).[4] They revealed that the self-reported coverage of cervical cancer screening was approximately 38–63%. However, coverage of the target population estimated from reported cases screened by healthcare facilities versus the preset target was unacceptably low: 9% for Pap smears and 19% for VIA (which was mostly confined to rural provincial areas).[20] As a result, we assumed an equal coverage of 20% for both Pap smears and VIA to ensure that the difference in terms of cost effectiveness between these interventions resulted from screening accuracy and costs. In the uncertainty analysis, programme coverage of 50%, 80% and 100% were assigned to both Pap smears and VIA.

We derived data from Goldie et al.,[21] who indicated that all patients with CIN2/3 were receiving cryosurgery, and 25% of these patients needed further treatment, i.e. cold knife conisation or simple hysterectomy within 1 year. Hospital utilization data for those diagnosed with cervical cancer, such as the annual rate of ambulatory care, the annual rate of hospital admissions and annual hospitalization days, were classified by disease staging, i.e. initial, remission, persistence and recurrence, and were obtained from the TGOC database.[24]

Because HPV vaccination is not standard practice in Thailand, there was no information about coverage for the target population who were included in a basic health service package. We assumed 100% coverage of the HPV vaccine among eligible groups. If HPV vaccination was not cost effective under these assumptions, then we could clearly discard its value for money. However, if the HPV vaccine was cost effective with 100% coverage, then we would further explore, using threshold analysis, the level of coverage at which it stopped being cost effective. Vaccine efficacy differences across different age groups were as a result of differences in age-specific HPV prevalence. These resulted in differences in the number of HPV infections, cervical cancer cases and cervical cancer deaths averted.

Utility Estimates

The health state values used in this study were derived from a Thai cohort of 1035 patients with invasive cervical cancer who had sought healthcare at four university hospitals and eight regional cancer centres throughout the country.[27] Two types of preference measurement were applied for the patient survey conducted between 1 May 2007 and 29 February 2008. First, a visual analogue scale (VAS; a vertical line scaled from 0 to 1, where 1 represents 'perfect health' and 0 represents 'worst health') was presented to the cohort, who were asked to mark the point on the line that they felt represented their perception of their current health state. The value for the utility was then estimated as the measured distance between 0 and the respondent's mark.

Second, the cohort completed the Thai version of the EQ-5D,[28-30] a multi-attribute utility measure. This instrument includes five dimensions (morbidity, self-care, usual activity, pain/discomfort and anxiety/depression) and three levels ('no health problems', 'moderate health problems' and 'extreme health problems'). A scoring algorithm based on the preference of the UK general population was used to translate EQ-5D scales to the utility weight for each health state.[31] The weight can range from –0.59 to 1.00, with 1.00 indicating 'full health', 0 representing 'death' and negative values indicating states 'worse than death'.

We applied the VAS utility values in the analysis because the EQ-5D values were derived from UK residents rather than those of the Thai population. The remission of every cancer stage yielded the highest utility, and the persistence of cancer stage IV produced the lowest value. Detailed information about means and standard errors of each health state are presented in table I, and the illustration of health state values using different preference elicitation methods is shown in Appendices A and B, available as Supplemental Digital Content 1, http://links.adisonline.com/PCZ/A121.

Costs

The costs employed in the societal perspective included direct medical costs and non-medical costs, including all resources used for vaccination, screening and treatments and real and opportunity costs incurred by patients (e.g. patient time spent for visits to healthcare facilities). The cost of productivity loss was excluded in order to avoid double-counting since the effectiveness outcome or QALYs has already measured morbidity and mortality effects.[32] Briefly, screening costs for Pap smears and VIA were identified from the published literature, mainly that of Goldie et al.[21] It was assumed that VIA requires a single visit, while Pap smears need two visits (one for the procedure, one for the results) if there is no abnormal finding. The current study included the vaccine delivery cost, which accounts for around 5% of vaccine costs based on the information from the National Vaccine Committee Office[33] in Thailand. The costs from the literature were converted to year 2007 values using the Thai consumer price index (table I).[34] For inter-country comparisons, costs can be converted into international dollars (I$) using the purchasing power parity exchange rate of I$1 = Bt12.615 (year 2007 values).[35]

Data regarding the costs for the treatment of cervical cancer were collected using a structured questionnaire from the same patient cohort at four university hospitals and eight regional cancer centres. Table I reports the annual treatment costs for each health state of cervical cancer, provides disaggregate information on direct medical costs occurring at both public and other hospitals (e.g. private clinics, drug stores and traditional healers) and reports direct non-medical costs. This information allows estimation of both the healthcare provider and the societal perspective. Using the provider's perspective, costs for persistence states were the highest, and higher for lower cancer staging (see Appendix C in the Supplemental Digital Content). The treatment costs of the initial stage were the second highest, followed by the costs of the recurrence and remission stages. These costs did not differ much between different cancer stages.

Uncertainty Analyses

Two types of uncertainty were extensively explored in this study.

First, parameter uncertainty refers to the variability inherent in the input variables or in the measurements, e.g. the imprecision surrounding the estimations of a particular transitional probability, mean cost or mean utility. This uncertainty is because input parameters are estimated for the target population on the basis of limited available information, e.g. selected samples.[14] This type of uncertainty can be overcome using probabilistic sensitivity analysis (PSA), where input parameters are assigned a probability distribution to reflect the feasible range of values that each input parameter can attain.[36] A Beta distribution was the choice of distribution for probability and utility parameters, which is bounded by zero and one. A Gamma distribution, which ensures positive values, was modelled for all rate and unit cost parameters. Normality on a log-odds scale with co-variance matrix and Cholesky decomposition[37] was applied for survival parameters.

Based on the PSA, the simulation drew one value from each parameter distribution simultaneously and calculated cost and effectiveness pairs. This process was repeated 10 000 times to provide a range of possible values given the specified probability distributions. Cost-effectiveness acceptability curves based on the net benefit approach were provided to illustrate the relationship between the values of the ceiling ratio (willingness to pay [WTP] for a unit of outcome, i.e. LY gained or QALY gained) and the probability of favouring each policy option.[38,39]

Second, generalizability describes the extent to which research findings can be applied to situations other than that of the original setting. A threshold analysis was performed to determine the level of selected input parameters required to render a particular policy option cost effective. For example, if the HPV vaccine is not cost effective at the current price, a threshold analysis is applied to determine the price at which the vaccine becomes cost effective, given the ceiling threshold of Bt100 000 per QALY; this threshold is indicated by the Subcommittee for Development

of the Health Benefit Package and Service Delivery of the National Health Security Office and the Subcommittee for Development of the National List of Essential Medicines in Thailand.[40] Another uncertainty analysis determined the cost effectiveness of the cervical cancer screening programmes given the different levels of programme coverage. This particular information is useful for policy decision makers or programme managers when considering whether, or under which situations, the results can be applicable to their own settings.

Results

The baseline or 'no intervention' scenario incurred no costs for cervical cancer prevention but it had the highest treatment costs for invasive cancer (table II). The costs of cervical cancer prevention were relatively low for strategies with VIA and/or Pap smears. However, the costs were significantly higher if the strategy involved HPV vaccination. In contrast, the treatment costs for invasive cervical cancer were lowest for strategies including HPV vaccination. In comparison with the healthcare provider's perspective, the societal perspective had slightly higher costs for cervical cancer prevention but more than double the costs for treating invasive cancer. This could reflect the substantial costs incurred by households with patients with invasive cervical cancer. Table II also shows the incremental LYs and QALYs gained with different cervical cancer prevention programmes. Note that the incremental QALYs gained from interventions were slightly greater than the incremental LYs gained, because the interventions averted the future incidences of cervical cancer that results in a worsened health state preference.

Table III presents the incremental cost-effectiveness ratio (ICER) of each policy option, from the societal perspective, by listing all strategies in order of increasing cost and each ICER was calculated in comparison with the next best non-dominated option. Providing VIA for women aged ≤45 years and Pap smears for women aged ≥50 years was the cheapest policy option, with an average lifetime cost of Bt8834 and 28.075 QALYs. This option dominated all other cervical screening strategies. The next best alternative was HPV vaccination at the age of 25 years, with an ICER of Bt317 008 per QALY, which is higher than the current ceiling threshold in Thailand. It is interesting to note that HPV vaccination at the age of 15 years alone was the most expensive option and was dominated by the combination of HPV vaccination at the age of 15 years, followed by VIA for women aged ≤45 years and Pap smear for women aged ≥50 years. The results from the healthcare provider's viewpoint are presented in Appendix D in the Supplemental Digital Content.

Figure 4 presents cost-effectiveness acceptability curves and a summary of the robustness of the model regarding the uncertainty surrounding the model input parameters for each policy option. We plotted only the best strategy for each screening option, i.e. Pap smears every 5 years (age 30–60 years), VIA every 5 years (age 30–45 years) and VIA every 5 years (age 30–45 years) plus sequential Pap smears every 5 years (age 50–60 years). The analysis also included the best strategy for HPV vaccination, i.e. vaccination at the age of 15 years, and combination of HPV vaccination and different screening strategies.

Figure 4a illustrates the results of a base-case scenario with 20% coverage for Pap smear, VIA and VIA plus sequential Pap smear, and 100% coverage for HPV vaccine. The different thresholds of the screening coverage, i.e. 50%, 80% and 100%, were also analyzed (figure 4b–d, respectively). In the base-case scenario, it can be seen that, if decision makers are willing to pay less than Bt300 000 per QALY, VIA plus sequential Pap smear is the best policy option. With increased coverage, VIA plus sequential Pap smears becomes even more likely to be cost effective than other screening options (figures 4b–d). The vaccines become a cost-effective option only if the WTP threshold is higher than Bt300 000 per QALY at the screening coverage of 20% (figure 4a) and Bt780 000 per QALY at the screening coverage of 100% (figure 4d).

Figures 4e–g show results from uncertainty analyses using different thresholds of HPV vaccine coverage. They reveal that, at the lower HPV vaccine coverage, the combination of HPV vaccination

Table II. Lifetime costs (Thai Baht, year 2007 values) and health outcomes of each policy option for cervical cancer prevention and control[a]

Options	Healthcare provider's perspective			Societal perspective			LY	QALYs
	costs of cervical cancer prevention	treatment costs of invasive cancer	total	costs of cervical cancer prevention	treatment costs of invasive cancer	total		
Baseline (no intervention, treatment only)	NA	3820	3820	NA	9610	9610	28.103	28.064
Pap smear every 5 y (age 30–60 y)	140	3510	3650	200	8840	9030	28.108	28.073
Pap smear every 5 y (age 35–60 y)	110	3550	3650	150	8930	9090	28.108	28.072
Pap smear every 5 y (age 40–60 y)	80	3590	3680	120	9050	9170	28.107	28.071
Pap smear every 10 y (age 30–60 y)	80	3640	3720	120	9160	9280	28.106	28.069
Pap smear every 10 y (age 40–60 y)	50	3680	3730	70	9270	9340	28.105	28.068
VIA every 5 y (age 30–45 y)	100	3530	3620	120	8880	9000	28.108	28.072
VIA every 5 y (age 35–45 y)	70	3580	3650	80	9010	9090	28.107	28.071
VIA every 5 y (age 40–45 y)	40	3640	3680	50	9170	9220	28.106	28.069
VIA every 10 y (age 30–40 y)	50	3670	3720	60	9230	9290	28.105	28.068
VIA at the age of 40 y	20	3720	3740	30	9370	9390	28.104	28.066
HPV vaccination at the age of 15 y	15750	1010	16760	15860	2550	18410	28.134	28.124
HPV vaccination at the age of 16 y	15280	1110	16400	15380	2810	18190	28.133	28.121
HPV vaccination at the age of 17 y	14830	1200	16030	14930	3030	17960	28.132	28.119
HPV vaccination at the age of 18 y	14380	1310	15690	14480	3290	17770	28.130	28.117
HPV vaccination at the age of 19 y	13950	1430	15380	14050	3590	17640	28.129	28.114
HPV vaccination at the age of 20 y	13540	1560	15090	13630	3930	17550	28.127	28.111
HPV vaccination at the age of 21 y	13130	1670	14800	13220	4210	17430	28.126	28.108
HPV vaccination at the age of 22 y	12730	1770	14500	12820	4460	17280	28.125	28.106
HPV vaccination at the age of 23 y	12350	1860	14210	12430	4680	17110	28.124	28.104
HPV vaccination at the age of 24 y	11980	1970	13940	12060	4950	17010	28.122	28.102
HPV vaccination at the age of 25 y	11610	2040	13650	11690	5130	16820	28.122	28.100
HPV vaccination at the age of 30 y	9920	2840	12760	9990	7140	17130	28.113	28.083
HPV vaccination at the age of 40 y	7210	3380	10590	7250	8510	15760	28.107	28.072
HPV vaccination at the age of 50 y	5150	3710	8860	5190	9320	14510	28.104	28.066
HPV vaccination at the age of 60 y	3540	3790	7330	3560	9520	13080	28.103	28.064
VIA every 5 y (age 30–40 y) + Pap smear every 5 y (age 45–60 y)	140	3460	3590	180	8710	8890	28.109	28.075
VIA every 5 y (age 30–45 y) + Pap smear every 5 y (age 50–60 y)	130	3440	3570	170	8660	8830	28.109	28.075

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Table II. Contd

Options	Healthcare provider's perspective			Societal perspective			LY	QALYs
	costs of cervical cancer prevention	treatment costs of invasive cancer	total	costs of cervical cancer prevention	treatment costs of invasive cancer	total		
VIA every 5 y (age 35–45 y) + Pap smear every 5 y (age 50–60 y)	110	3490	3590	140	8790	8930	28.108	28.073
VIA every 5 y (age 40–45 y) + Pap smear every 5 y (age 50–60 y)	80	3550	3630	110	8940	9050	28.107	28.072
VIA every 10 y (age 30–40 y) + Pap smear every 10 y (age 50–60 y)	80	3600	3680	100	9070	9170	28.107	28.070
VIA at the age of 40 y + Pap smear every 10 y (age 50–60 y)	50	3660	3710	70	9210	9270	28.106	28.069
HPV vaccination at the age of 15 y + Pap smear every 5 y (age 30–60 y)	15850	930	16790	16010	2350	18370	28.135	28.126
HPV vaccination at the age of 15 y + Pap smear every 5 y (age 35–60 y)	15830	940	16770	15980	2380	18360	28.135	28.126
HPV vaccination at the age of 15 y + Pap smear every 5 y (age 40–60 y)	15810	960	16770	15950	2410	18360	28.135	28.125
HPV vaccination at the age of 15 y + Pap smear every 10 y (age 30–60 y)	15810	970	16780	15950	2440	18380	28.135	28.125
HPV vaccination at the age of 15 y + Pap smear every 10 y (age 40–60 y)	15790	980	16770	15910	2470	18380	28.135	28.125
HPV vaccination at the age of 15 y + VIA every 5 y (age 30–45 y)	15830	940	16760	15950	2360	18310	28.135	28.126
HPV vaccination at the age of 15 y + VIA every 5 y (age 35–45 y)	15800	950	16750	15920	2400	18320	28.135	28.125
HPV vaccination at the age of 15 y + VIA every 5 y (age 40–45 y)	15780	970	16750	15900	2440	18340	28.135	28.125
HPV vaccination at the age of 15 y + VIA every 10 y (age 30–40 y)	15790	970	16760	15910	2450	18360	28.135	28.125
HPV vaccination at the age of 15 y + VIA at the age of 40 y	15770	990	16760	15880	2490	18370	28.134	28.124
HPV vaccination at the age of 15 y + VIA every 5 y (age 30–40 y) + Pap smear every 5 y (age 45–60 y)	15860	920	16780	16000	2320	18320	28.136	28.126
HPV vaccination at the age of 15 y + VIA every 5 y (age 30–45 y) + Pap smear every 5 y (age 50–60 y)	15860	920	16770	16000	2310	18310	28.136	28.126

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Table II. Contd

Options	Healthcare provider's perspective			Societal perspective			LY	QALYs
	costs of cervical cancer prevention	treatment costs of invasive cancer	total	costs of cervical cancer prevention	treatment costs of invasive cancer	total		
HPV vaccination at the age of 15 y + VIA every 5 y (age 35–45 y) + Pap smear every 5 y (age 50–60 y)	15 830	930	16 760	15 970	2340	18 310	28.135	28.126
HPV vaccination at the age of 15 y + VIA every 5 y (age 40–45 y) + Pap smear every 5 y (age 50–60 y)	15 810	950	16 760	15 940	2390	18 330	28.135	28.126
HPV vaccination at the age of 15 y + VIA every 10 y (age 30–40 y) + Pap smear every 10 y (age 50–60 y)	15 810	960	16 770	15 940	2410	18 350	28.135	28.125
HPV vaccination at the age of 15 y + VIA at the age of 40 y + Pap smear every 10 y (age 50–60 y)	15 790	970	16 760	15 910	2450	18 360	28.135	28.125

a Costs presented in this table were rounded to the nearest ten.

HPV = human papillomavirus; **LY** = life-years; **NA** = not applicable; **VIA** = visual inspection with acetic acid.

and cervical cancer screening is a better choice than providing HPV vaccination alone.

Furthermore, this study assessed the impact of alternative discount rates on the overall conclusions. Table IV shows that ICERs of cervical cancer screening and HPV vaccine versus the 'do nothing' scenario were all affected by the discounting rate, although the greater impact was on the HPV vaccination because the real effectiveness of the vaccines, e.g. cancer cases averted, can only be observed in the remote future.

Figure 5 illustrates findings from the threshold analysis under the base-case scenario. It can be seen that, at the current price (Bt15 000 for three doses), the HPV vaccine was not cost effective for any particular age groups. The vaccine price needs to be reduced to Bt8650 for an assumption of lifetime vaccine protection, Bt5360 for 10-year protection and Bt3530 for 5-year protection so that it can become cost effective for girls aged 15 years at the ceiling threshold of Bt100 000 per QALY gained. The price needs to be further reduced if the vaccine is to cover women at the older age groups because the vaccine was less efficacious among the older populations.

Discussion

With the availability of newly developed interventions for the prevention and control of cervical cancer, several countries in both the developed and the developing world are currently reviewing their strategies and are planning to strengthen systems for cervical cancer control.[21,41-45] This study indicates that the currently available cervical cancer screening, i.e. Pap smears, VIA and the combination of VIA plus sequential Pap smears are all cost-saving interventions.

Our analyses also highlight that HPV vaccines, which are only effective against two oncogenic subtypes of HPV infection (16 and 18), have good potential to avert incidences, and save the treatment costs of cervical cancer; although at the current price they are unlikely to be cost effective relative to the recommended threshold of Bt100 000 per QALY, as set by the Subcommittee for Development of the Health Benefit Package and Service Delivery of the National Health

Table III. Incremental cost-effectiveness ratio (ICER) of each policy option for cervical cancer prevention and control using the societal perspective

Options	Costs (Bt)	QALYs	Incremental costs (Bt)	Incremental QALYs	ICER
VIA every 5 y (age 30–45 y) + Pap smear every 5 y (age 50–60 y)	8 834	28.0750			
VIA every 5 y (age 30–40 y) + Pap smear every 5 y (age 45–60 y)	8 887	28.0745	53	–0.0004	Dom
VIA every 5 y (age 35–45 y) + Pap smear every 5 y (age 50–60 y)	8 927	28.0734	93	–0.0016	Dom
VIA every 5 y (age 30–45 y)	9 000	28.0721	167	–0.0028	Dom
Pap smear every 5 y (age 30–60 y)	9 035	28.0733	201	–0.0016	Dom
VIA every 5 y (age 40–45 y) + Pap smear every 5 y (age 50–60 y)	9 051	28.0717	217	–0.0033	Dom
Pap smear every 5 y (age 35–60 y)	9 088	28.0721	254	–0.0029	Dom
VIA every 5 y (age 35–45 y)	9 094	28.0705	260	–0.0044	Dom
Pap smear every 5 y (age 40–60 y)	9 169	28.0707	335	–0.0043	Dom
VIA every 10 y (age 30–40 y) + Pap smear every 10 y (age 50–60 y)	9 170	28.0703	336	–0.0047	Dom
VIA every 5 y (age 40–45 y)	9 220	28.0688	386	–0.0062	Dom
VIA at the age of 40 y + Pap smear every 10 y (age 50–60 y)	9 272	28.0686	438	–0.0064	Dom
Pap smear every 10 y (age 30–60 y)	9 279	28.0694	445	–0.0056	Dom
VIA every 10 y (age 30–40 y)	9 293	28.0682	459	–0.0067	Dom
Pap smear every 10 y (age 40–60 y)	9 337	28.0680	503	–0.0069	Dom
VIA at the age of 40 y	9 395	28.0665	561	–0.0085	Dom
Baseline (no intervention, treatment only)	9 606	28.0638	772	–0.0112	Dom
HPV vaccination at the age of 60 y	13 080	28.0644	4246	–0.0106	Dom
HPV vaccination at the age of 50 y	14 511	28.0658	5677	–0.0092	Dom
HPV vaccination at the age of 40 y	15 762	28.0720	6928	–0.0030	Dom
HPV vaccination at the age of 25 y	16 823	28.1002	7989	0.0252	317 008
HPV vaccination at the age of 24 y	17 008	28.1018	185	0.0016	113 843
HPV vaccination at the age of 23 y	17 112	28.1042	104	0.0024	43 932
HPV vaccination at the age of 30 y	17 125	28.0832	13	–0.0210	Dom

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Table III. Contd

Options	Costs (Bt)	QALYs	Incremental costs (Bt)	Incremental QALYs	ICER
HPV vaccination at the age of 22 y	17 276	28.1061	163	0.0020	82 693
HPV vaccination at the age of 21 y	17 433	28.1083	157	0.0022	72 614
HPV vaccination at the age of 20 y	17 554	28.1109	121	0.0026	46 328
HPV vaccination at the age of 19 y	17 642	28.1139	89	0.0030	29 197
HPV vaccination at the age of 18 y	17 769	28.1167	126	0.0028	45 089
HPV vaccination at the age of 17 y	17 958	28.1191	189	0.0024	80 294
HPV vaccination at the age of 16 y	18 192	28.1212	233	0.0021	111 656
HPV vaccination at the age of 15 y + VIA every 5 y (age 30–45 y) + Pap smear every 5 y (age 50–60 y)	18 306	28.1265	115	0.0053	21 731
HPV vaccination at the age of 15 y + VIA every 5 y (age 35–45 y) + Pap smear every 5 y (age 50–60 y)	18 313	28.1260	7	–0.0005	Dom
HPV vaccination at the age of 15 y + VIA every 5 y (age 30–45 y)	18 315	28.1258	8	–0.0007	Dom
HPV vaccination at the age of 15 y + VIA every 5 y (age 30–40 y) + Pap smear every 5 y (age 45–60 y)	18 321	28.1264	15	–0.0001	Dom
HPV vaccination at the age of 15 y + VIA every 5 y (age 35–45 y)	18 322	28.1253	15	–0.0011	Dom
HPV vaccination at the age of 15 y + VIA every 5 y (age 40–45 y) + Pap smear every 5 y (age 50–60 y)	18 329	28.1256	22	–0.0009	Dom
HPV vaccination at the age of 15 y + VIA every 5 y (age 40–45 y)	18 337	28.1249	31	–0.0016	Dom
HPV vaccination at the age of 15 y + VIA every 10 y (age 30–40 y) + Pap smear every 10 y (age 50–60 y)	18 350	28.1253	43	–0.0012	Dom
HPV vaccination at the age of 15 y + VIA every 10 y (age 30–40 y)	18 358	28.1248	52	–0.0017	Dom
HPV vaccination at the age of 15 y + VIA at the age of 40 y + Pap smear every 10 y (age 50–60 y)	18 359	28.1248	53	–0.0017	Dom

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Table III. Contd

Options	Costs (Bt)	QALYs	Incremental costs (Bt)	Incremental QALYs	ICER
HPV vaccination at the age of 15 y + Pap smear every 5 y (age 35–60 y)	18 360	28.1257	54	−0.0008	Dom
HPV vaccination at the age of 15 y + Pap smear every 5 y (age 40–60 y)	18 362	28.1253	55	−0.0012	Dom
HPV vaccination at the age of 15 y + Pap smear every 5 y (age 30–60 y)	18 367	28.1261	60	−0.0004	Dom
HPV vaccination at the age of 15 y + VIA at the age of 40 y	18 368	28.1243	61	−0.0022	Dom
HPV vaccination at the age of 15 y + Pap smear every 10 y (age 40–60 y)	18 378	28.1247	71	−0.0018	Dom
HPV vaccination at the age of 15 y + Pap smear every 10 y (age 30–60 y)	18 383	28.1251	77	−0.0014	Dom
HPV vaccination at the age of 15 y	18 406	28.1236	99	−0.0029	Dom

Bt = Thai Baht; **Dom** = dominated; **HPV** = human papillomavirus; **VIA** = visual inspection with acetic acid.

Security Office and the Subcommittee for Development of the National List of Essential Medicines in Thailand.

Although Pap smears and VIA are currently offered free to all Thai women, the programmes suffer a lack of effective coordination as they are managed separately by two Departments of the MOPH. At present, Pap smears are overseen by the Department of Medical Services, offered for women at 5-yearly intervals between the ages of 35 and 60 years (i.e. at 35, 40, 45, 50, 55 and 60 years); while, VIA is run by the Department of Health, recommended every 5 years for women aged 30–44 years. The VIA services can be given to women starting from the age of 30 years with the exception of services for women aged 35 and 40 years as they can receive Pap smear services. Nevertheless, women who are concerned about the disease are able to undertake both a Pap smear test and VIA screening at less than the recommended interval (5 years). From a broad public health perspective, this leads to an inefficient use of resources because the additional benefits from the annual or biannual screenings are unlikely to outweigh their costs.[46] Meanwhile, this will also lead to a scarcity of resources needed for improving access to cervical cancer screening among the poor or marginal groups who are likely to be left out from the present prevention programme. Based on the performance assessment in Thailand,[20] the target population coverage of cervical cancer screenings, either by Pap smears or VIA, fell well short of the desirable target of 80% coverage. It estimated a coverage of 9% for Pap smears and 19% for VIA (which is mostly confined to rural provincial areas).

The poor performance of the current cervical cancer screening, and findings from this study, prompt us to recommend that the capacity to provide appropriate screening and improve levels of coverage should be urgently reviewed in the Thai healthcare setting. A policy to provide VIA for women aged 30–45 years and sequential Pap smears for women aged 50–60 years should be adopted because this option is superior in terms of value for money compared with Pap smear- or VIA-only options, especially with a high level of screening coverage (figure 4). The HPV vaccine should only be introduced to the public health

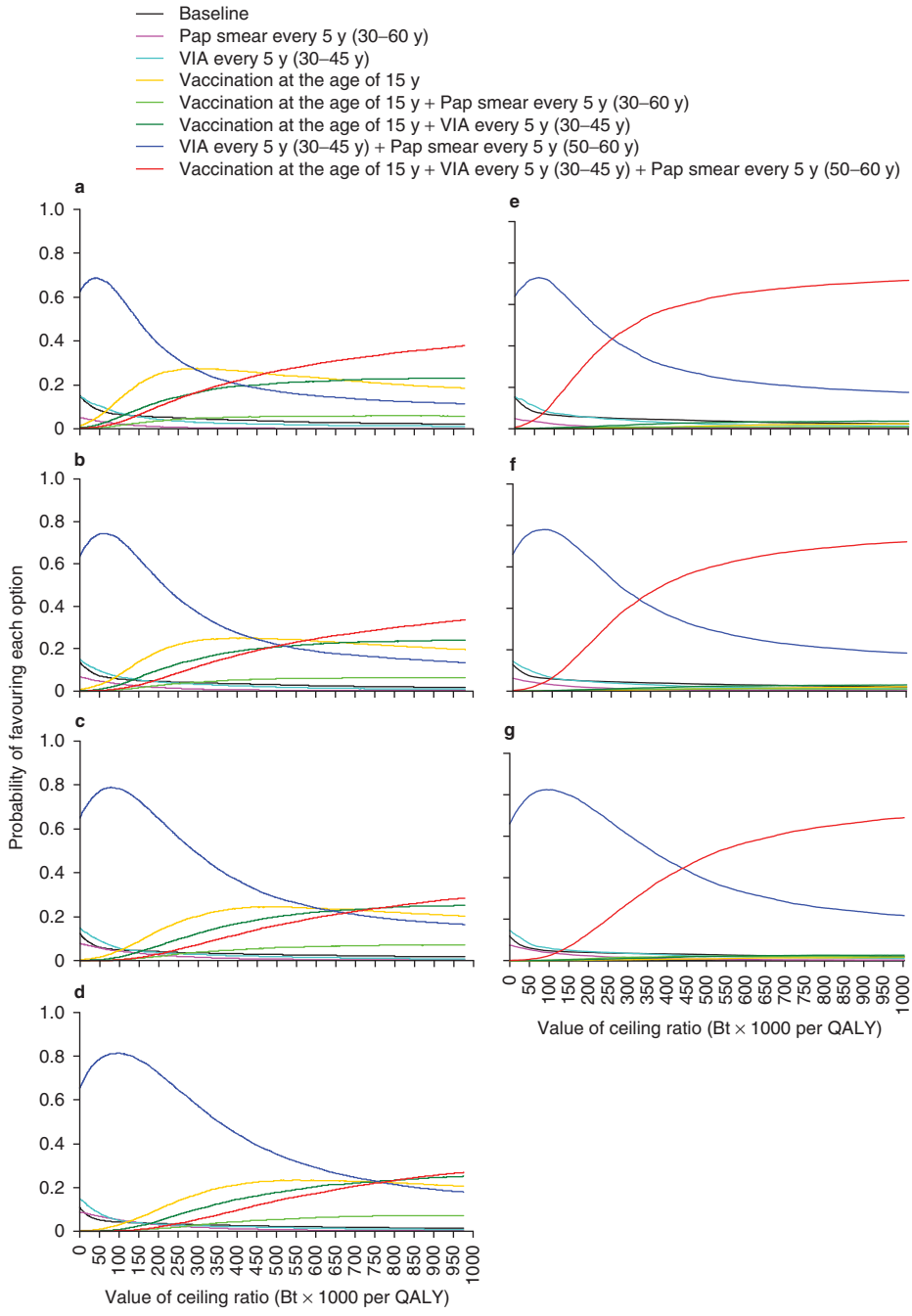

Fig. 4. Cost-effectiveness acceptability curves (baseline: no screening and treatment-only option). (**a**) 20% coverage of screening interventions, 100% coverage of human papillomavirus (HPV) vaccine (base-case scenario). (**b**) 50% coverage of screening interventions, 100% coverage of HPV vaccine. (**c**) 80% coverage of screening interventions, 100% coverage of HPV vaccine. (**d**) 100% coverage of screening interventions and HPV vaccine. (**e**) 20% coverage of screening interventions and HPV vaccine. (**f**) 50% coverage of screening interventions and HPV vaccine. (**g**) 80% coverage of screening interventions and HPV vaccine. **Bt** = Thai Baht; **VIA** = visual inspection with acetic acid.

Table IV. Incremental cost-effectiveness ratio (cost[a] per QALY gained) for each option using different discount rates

Options (baseline as reference)	Discount rate			
	0%	3%	5%	10%
Pap smear every 5 y (age 30–60 y)	–68 000	–60 000	–48 000	12 000
VIA every 5 y (age 30–45 y)	–74 000	–72 000	–66 000	–26 000
VIA every 5 y (age 30–45 y) + Pap smear every 5 y (age 50–60 y)	–73 000	–69 000	–59 000	–18 000
HPV vaccination at the age of 15 y	–44 000	147 000	502 000	3 554 000
HPV vaccination at the age of 15 y + Pap smear every 5 y (age 30–60 y)	–44 000	141 000	485 000	3 455 000
HPV vaccination at the age of 15 y + VIA every 5 y (age 30–45 y)	–45 000	140 000	484 000	3 447 000
HPV vaccination at the age of 15 y + VIA every 5 y (age 30–45 y) + Pap smear every 5 y (age 50–60 y)	–45 000	139 000	480 000	3 433 000

a Figures are presented as Bt and are rounded to the nearest thousand.

Bt = Thai Baht; **HPV** = human papillomavirus; **VIA** = visual inspection with acetic acid.

benefit package if its cost is reduced to the point where its ICERs are within an agreeable threshold and its budget impact is at an affordable level. This study estimates that the vaccine becomes a cost-effective option under the Thai healthcare system at 25% of the current price. Furthermore, this study reveals that the vaccines will be less favourable at a higher coverage of cervical cancer screening (figure 4a–d). At the lower level of vaccine coverage, the study suggests that providing HPV vaccine to girls aged 15 years plus VIA screening for women aged 30–45 years and Pap smears for women aged 50–60 years is more attractive than providing HPV vaccination alone (figure 4e–g).

The results of this study are in agreement with other previous studies, which indicated that VIA and Pap smears are cost effective, and should be widely supported in both developed and developing settings.[46] However, to our knowledge, this study is the first to incorporate the combination of VIA and Pap smear (VIA plus sequential Pap smear) in the economic analysis, and we have found the results promising. This study

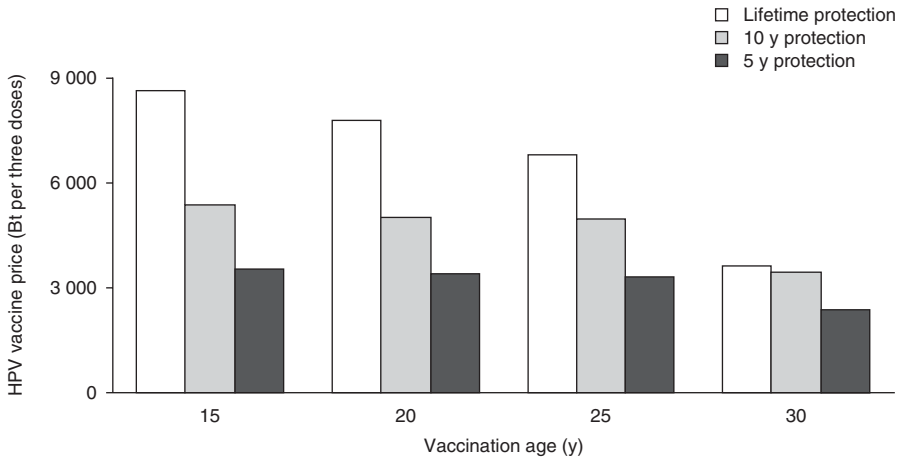

Fig. 5. Threshold analysis for human papillomavirus (HPV) vaccine price at a willingness to pay of Thai Baht (Bt)100 000 per QALY classified by vaccine protection duration.

also extensively assessed the potential use of HPV vaccine alone or in combination with other screening options. Kulasingam et al.[41] found that adding a school-based HPV vaccination programme for girls aged 12 years to the current practice of cervical cancer screening (i.e. liquid-based cytology or Pap smears) represents good value for money under the UK healthcare system. The differences in the conclusions between the UK study and this study are not because of the differences in the estimated costs or benefits of the vaccines but the ceiling thresholds used to decide how much the government should pay for a QALY gained. A much higher ceiling threshold of £20 000–30 000 or Bt1.26–1.89 million was referred to as a threshold to determine whether health interventions are worthwhile in the UK.[47]

Because there is a lack of a comprehensive assessment in other middle-income settings, the results of this study can be used to guide discussions or policy dialogue, as well as to inform further exploration if decision makers in these settings share similar concerns regarding the prevention and control of cervical cancer. The use of systematic reviews and meta-analyses for estimating the effectiveness of all screening interventions and HPV vaccines makes the results of this study applicable to other settings because the costs of screening, HPV vaccination and staging and treatment of invasive cancer are very similar in many developing countries.[21]

This study is limited by a lack of data concerning HPV-type-specific infection, protection duration of the vaccines against HPV infection, and whether, and how many, booster doses are required in the future after the initial three doses. This study used a crucial assumption that the vaccines offer a lifetime protective effect, which would have enormous implications on the estimations of cost and effectiveness of the vaccine. If this assumption is not valid, then the vaccines would be a less favourable choice.

This study is also limited by the exclusion of the HPV DNA test because there were uncertain practice guidelines in Thailand. In addition, this study was conducted using a Markov model so the transmission of HPV infection was assumed to be linear and some potential benefits of the vaccine were excluded (e.g. cross-protection against other HPV types, herd-immunity effects among the non-vaccinated population, prevention of genital warts and reduction of adenocarcinoma, vulvar and vaginal intraepithelial neoplasia).[48] The model constructed in this study was based entirely on knowledge obtained from separate studies that did not account for the effects that one intervention can have on another, e.g. VIA on Pap smears, screening interventions on HPV vaccines.

Lastly, because of limitations in the Thai data, most input parameters related to the natural history of HPV infection and intervention effectiveness were derived from international sources.

Conclusion

The results of this study suggest that controlling cervical cancer by increasing the numbers of women accepting VIA and Pap smear screening as routine and by improving the performance of the existing screening programmes is the most cost-effective policy option in Thailand.

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References

1. Bundhamcharoen K, Teerawattananon Y, Vos T, et al. Burden of disease and injuries in Thailand, priority setting for policy. Nonthaburi: Bureau of Health Policy and Planning, Ministry of Public Health, 2002
2. Working group of Burden of Disease Project. Burden of disease and injuries in Thailand, 2004 (interim report). Nonthaburi: International Health Policy Program, Ministry of Public Health, 2007

3. Sriplung H, Wiangnon S, Sontipong S, et al. Cancer incidence trends in Thailand, 1989-2000. Asian Pac J Cancer Prev 2006 Apr-Jun; 7 (2): 239-44
4. Report of 2006 reproductive health survey. Bangkok: National Statistical Office, Ministry of Information and Communication Technology, 2006
5. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon: International Agency for Research on Cancer, 2005
6. Schiffman M, Kjaer SK. Chapter 2: natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst Monogr 2003; 31: 14-9
7. Yothasamut J, Putchong C, Sirisamutr T, et al. Scaling up cervical cancer screening in the midst of human papillomavirus vaccination advocacy in Thailand. Health Serv Res 2010; 10 Suppl. 1: S5
8. Arbyn M, Sasieni P, Meijer CJ, et al. Chapter 9: clinical applications of HPV testing. A summary of meta-analyses. Vaccine 2006 Aug 21; 24 Suppl. 3: S78-89
9. The Committee of Gynecologic Oncology. Clinical practice guidelines for cervical cancer screening. Bangkok: The Royal Thai College of Obstetricians and Gynecologists, 2006
10. Gaffikin L, Blumenthal PD, Emerson M, et al. Safety, acceptability, and feasibility of a single-visit approach to cervical-cancer prevention in rural Thailand: a demonstration project. Lancet 2003 Mar 8; 361 (9360): 814-20
11. Limwattananon S. Current performance of the Cervical Cancer Prevention and Control Program in Thailand. Bangkok: International Health Policy Program, Health Intervention and Technology Assessment Program, Population and Reproductive Health Capacity Building Program, The World Bank, 2007 Aug 20
12. Eliav B, Heather LS. Prophylactic HPV vaccines: new interventions for cancer control. Vaccine 2008 Nov 18; 26 (49): 6244-57
13. US National Institutes of Health, National Cancer Institute. National Cancer Institute FactSheet. Human papillomavirus (HPV) vaccines [online]. Available from URL: http://www.cancer.gov/cancertopics/factsheet/Prevention/HPV-vaccine [Accessed 2009 Nov 30]
14. Briggs AH, Sculpher MJ, Claxton K. Decision modelling for health economic evaluation. New York: Oxford University Press, 2006
15. Benedet J, Bender H, Jones HI, et al. FIGO staging classifications and clinical practice guidelines in the management of gynaecologic cancers. Int J Gynaecol Obstet 2000; 70 (2): 209-62
16. Permsuwan U, Guntawongwan K, Buddhawongsa P. Handling time in economic evaluation studies. J Med Assoc Thai 2008; 91 Suppl. 2: S53-8
17. Myers ER, McCrory DC, Nanda K, et al. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am J Epidemiol 2000 Jun 15; 151 (12): 1158-71
18. Sritipsukho P. The systematic review of the operating characteristics of screening tests including VIA, PAP smear, and HPV DNA testing. Bangkok: International Health Policy Program, Health Intervention and Technology Assessment Program, Population and Reproductive Health Capacity Building Program, The World Bank, 2007 Aug 20
19. Rambout L, Hopkins L, Hutton B, et al. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. CMAJ 2007 Aug 28; 177 (5): 469-79
20. Limwattananon S. The determination of the performance of the current programs for prevention and control of cervical cancer in Thailand. Bangkok: International Health Policy Program, Health Intervention and Technology Assessment Program, Population and Reproductive Health Capacity Building Program, The World Bank, 2007 Aug 20
21. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, et al. Cost-effectiveness of cervical-cancer screening in five developing countries. N Engl J Med 2005 Nov 17; 353 (20): 2158-68
22. Sukvirach S, Smith JS, Tunsakul S, et al. Population-based human papillomavirus prevalence in Lampang and Songkla, Thailand. J Infect Dis 2003 Apr 15; 187 (8): 1246-56
23. Khuhaprema T, Srivatanakul P, Sriplung H, et al. Cancer in Thailand. Vol. IV, 1998-2000. Bangkok: National Cancer Institute of Thailand, Ministry of Public Health, 2007
24. Tumour Registry Database: Cervical Cancer. 2000-4. Bangkok: The Thai Gynecologic Oncology Collaborative Group (TGOC), 2007
25. Bradburn MJ, Clark TG, Love SB, et al. Survival analysis part III: multivariate data analysis – choosing a model and assessing its adequacy and fit. Br J Cancer 2003; 89: 605-11
26. Report of 2003 health and welfare survey. Bangkok: National Statistical Office, Ministry of Information and Communication Technology, Thailand, 2003. Report No. S2-021
27. Chichareon S. Economic burden of life-time treatment cost, and quality of life among invasive cervical cancer patients treated at university hospitals and cancer centers in Thailand. In: Clinical Research Collaboration Network, The Thai Gynecologic Oncology Collaborative Group, editors. Nonthaburi, 2008 (Data on file; accessed 2008 Mar 30)
28. The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990; 16 (3): 199-208
29. Brooks R. EuroQol: the current state of play. Health Policy 1996; 37 (1): 53-72
30. Tongsiri S. The Thai population based preference scores for EQ5D health states. Thailand: Health Intervention and Technology Assessment Program (HITAP), 2009
31. Szende A, Oppe M, Devlin N, editors. EQ-5D value sets: inventory, comparative review and user guide. EuroQol Group Monographs, Vol. 2. New York (NY): Springer, 2006
32. Brouwer W, Rutten F, Koopmanschap M. Costing in economic evaluations. In: Drummond M, McGuire A, editors. Economic evaluation in health care: merging theory with practice. New York: Oxford University Press, 2001: 68-93
33. Ut-Ang K, Riewpaiboon A. Cost of logistics of vaccines in the expanded programme on immunization in Thailand. Bangkok: Mahidol University, 2009
34. Bureau of Trade and Economic Indices. Consumer price index database. Bangkok: Ministry of Commerce, 2008 April 2 [online]. Available from URL: http://www.price.moc.go.th/price/cpi/index_new_e.asp [Accessed 2008 Jun 7]
35. International Monetary Fund. World economic and financial surveys, world economic outlook database: October 2007 edition [online]. Available from URL: http://

www.imf.org/external/pubs/ft/weo/2007/02/weodata/index.aspx [Accessed 2007 Dec 10]

36. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000; 17 (5): 479-500
37. Daniels MJ, Zhao YD. Modelling the random effects covariance matrix in longitudinal data. Stat Med 2003 May 30; 22 (10): 1631-47
38. Zethraeus N, Johannesson M, Jönsson B, et al. Advantages of using the net-benefit approach for analysing uncertainty in economic evaluation studies. Pharmacoeconomics 2003; 21 (1): 39-48
39. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. Br J Psychiatry 2005; 187: 106-8
40. Wibulpolprasert S. The need for guidelines and the use of economic evidence in decision-making in Thailand: lessons learnt from the development of the National List of Essential Drugs. J Med Assoc Thai 2008; 91 Suppl. 2: S1-3
41. Kulasingam SL, Benard S, Barnabas RV, et al. Adding a quadrivalent human papillomavirus vaccine to the UK cervical cancer screening programme: a cost-effectiveness analysis. Cost Eff Resour Alloc 2008 Feb 15; 6: 4
42. de Kok IM, van Ballegooijen M, Habbema JD. Cost-effectiveness analysis of human papillomavirus vaccination in the Netherlands. J Natl Cancer Inst 2009; 101 (15): 1083-92
43. Sanders GD, Taira AV. Cost effectiveness of a potential vaccine for human papillomavirus. Emerg Infect Dis 2003; 9 (1): 37-48
44. Brisson M, Van de Velde N, De Wals P, et al. The potential cost-effectiveness of prophylactic human papillomavirus vaccines in Canada. Vaccine 2007; 25 (29): 5399-408
45. Diaz M, Kim JJ, Albero G, et al. Health and economic impact of HPV 16 and 18 vaccination and cervical cancer screening in India. Br J Cancer 2008; 99 (2): 230-8
46. Goldie SJ, Kim JJ, Myers E. Chapter 19: cost-effectiveness of cervical cancer screening. Vaccine 2006 Aug 21; 24 Suppl. 3: S164-70
47. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. Health Econ 2004 May; 13 (5): 437-52
48. Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. Vaccine 2006 Aug 21; 24 Suppl. 3: S11-25

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