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Cost-effectiveness of human papillomavirus vaccination and cervical cancer screening in Thailand

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Objective To assess the health and economic outcomes of various screening and vaccination strategies for cervical cancer prevention.

Design Cost-effectiveness analysis from a societal perspective.

Setting Thailand.

Population Females aged 9 years and older.

Methods Using a mathematical model of human papillomavirus (HPV) infection and cervical cancer, calibrated to epidemiological data from Thailand, we estimated the cost-effectiveness of pre-adolescent HPV vaccination, screening [visual inspection with acetic acid (VIA), HPV DNA testing, and cytology] between one and five times per lifetime in adulthood, and combined pre-adolescent vaccination and screening. Vaccine efficacy, coverage, cost, and screening frequency were varied in sensitivity analyses.

Main outcome measures Incremental cost-effectiveness ratios, expressed as cost per year of life saved (YLS).

Results Assuming lifelong efficacy and 80% coverage, pre-adolescent HPV vaccination alone was projected to reduce the lifetime risk of cervical cancer by 55%, which was greater than any strategy of screening alone. When cost per vaccinated girl was I$10 (approximately $2 per dose) or less, HPV vaccination alone was cost saving. Pre-adolescent vaccination and HPV DNA testing five times per lifetime, starting at age 35 years, reduced the lifetime cervical cancer risk by 70%, and had a cost-effectiveness ratio less than Thailand's GDP per capita (I$8100), provided the cost per vaccinated girl was I$200 or less.

Conclusions Low cost pre-adolescent HPV vaccination followed by HPV screening five times per lifetime is an efficient strategy for Thailand. Costs may need to be lower, however, for this strategy to be affordable. If vaccination is not feasible, HPV DNA testing five times per lifetime is efficient.

Keywords Cervical cancer, cost-effectiveness, human papillomavirus, screening, Thailand, vaccination.

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Introduction

Cervical cancer is a leading cause of cancer death among women in Thailand. Over 6000 cases are diagnosed each year, with an age-standardised rate of 19.8 per 100 000 women per year, and both the incidence and mortality rates from cervical cancer are projected to increase in the absence of adequate intervention.[1] Cervical cancer affects women in the prime of their lives, which negatively impacts their families, and shortens their economic and societal contributions, yet the disease is readily preventable. In countries able to support widespread cytology screening at repeated intervals, mortality from cervical cancer has been reduced by up to 80%.[2] However, cytology-based screening has been challenging in Thailand, given the intensive personnel and laboratory requirements, the high financial costs, and the need for up to three or more visits for diagnostic follow-up and any necessary treatment in women with positive test results. A recent study in Thailand found that approximately 40% of women with abnormal cytology results were lost to follow-up.[3] Cytology has been used in Thailand for over 40 years, yet there has been little impact on cervical cancer rates.[3]

The challenges associated with cytology screening have prompted the evaluation of both human papillomavirus (HPV) DNA testing and visual inspection with acetic acid

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(VIA) as alternatives for a primary screening test in low-resource settings.[4] HPV DNA testing has been shown to have a higher sensitivity for detecting significant precancerous lesions, compared with cytology and VIA, which allows for longer screening intervals; furthermore, the processing of results can be automated, making the test more objective and requiring less training of healthcare workers.[5] Most recently, the availability of rapid HPV DNA tests that provide results within a few hours make same-day screening and treatment with cryosurgery possible in selected women.[2] VIA is another strategy that allows for results and treatment in a single visit. However, unlike HPV DNA testing, the performance of VIA has been variable across studies; it is a subjective test that relies heavily on well-trained healthcare workers and adequate quality assurance. The likelihood of a VIA-based screening programme reducing cervical cancer rates has been the source of controversy, with some studies reporting more promising results than others.[6–9]

The Ministry of Health in Thailand recommends a cervical cancer prevention strategy of screening every 5 years with VIA for women aged 30–45 years, and cytology for women aged 50–60 years, with a goal of 80% coverage.[10] Two nationally representative surveys, the Health and Welfare Survey (2003) and the Reproductive Health Survey (2006), both conducted by the National Statistical Office, found the self-reported coverage of cervical cancer screening was 38 and 63%, respectively, with coverage as low as 11% in rural areas.[11] Thailand consists of 76 provinces; as of 2008, 19 of the 76 provinces had implemented single-visit screening programmes with VIA.[11]

In addition to screening, pre-adolescent vaccination against HPV types 16 and 18, which are responsible for 74% of cervical cancer cases in Thailand,[1] offers a primary prevention option for cervical cancer. Unlike many developing countries, the coverage of childhood vaccines such as diphtheria, tetanus, and pertussis (DTP) in Thailand is 98%,[1] indicating that the country has the potential to achieve very high vaccine coverage in infants and young children; whether this will translate to a pre-adolescent age group is uncertain. Two HPV vaccines are licensed in Thailand, and a recent study showed a high degree of acceptability of vaccination among healthcare providers.[12]

In order to make informed decisions regarding cervical cancer prevention strategies, decision makers in Thailand are likely to consider many factors, such as the effectiveness, ability to achieve high coverage, affordability, and 'value for money' (i.e. cost-effectiveness), compared with an alternative use of scarce resources.[13] As no single study can take into account all of the factors that need to be considered, model-based analyses conducted from a decision-analytic perspective can be employed to synthesise epidemiological, clinical, and economic data, as well as to evaluate the consequences of uncertainty in those data. These models can project the expected long-term consequences of various policies and explore the possible synergies between strategies. In order to provide insight to decision makers interested in reducing cervical cancer incidence and mortality in Thailand, we used a decision-analytic approach to evaluate the comparative effectiveness and cost-effectiveness of various cervical cancer prevention strategies.

Methods

Model

We synthesised the available epidemiological, clinical, and economic data from Thailand using a previously described individual-based Monte Carlo simulation model.[14–16] The model comprises health states descriptive of each woman's true underlying health, including HPV infection status, grade of precancerous lesions, and stage of invasive cancer. Individual girls enter the model at age 9 years, prior to sexual debut and free of HPV infection, and transition between health states throughout their lifetime. Each month, females face an age-dependent risk of acquiring HPV infection; those with infection can subsequently develop low- or high-grade lesions, categorised as cervical intraepithelial neoplasia, grades 1 (CIN 1) or 2,3 (CIN 2,3) and those with CIN 2,3 can progress to invasive cancer. Women with cancer can be detected via symptoms or screening, and face stage-specific survival rates (i.e. local, regional, and distant stages); all women are subject to mortality from competing causes. Background mortality was estimated from WHO life tables.[17] Transitions between health states are governed by age, HPV type, and type-specific natural immunity following infection and clearance of HPV infections. HPV type is categorised as: (1) high-risk type 16 (HR-16); (2) high-risk type 18 (HR-18); (3) other high-risk types (HR-other), including types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 82; and (4) low-risk (LR) types, including types 6, 11, 26, 32, 34, 40, 42, 44, 53, 54, 55, 57, 61, 62, 64, 67, 69, 70, 71, 72, 81, 83, and 84.

Model parameters were initially established using the best available information on the natural history of HPV infection and cervical carcinogenesis. The model was then adapted to the Thailand context by using likelihood-based methods to fit the parameters to country-specific epidemiological data. In particular, data on the age-specific prevalence of high-risk and low-risk HPV types, CIN 1 and CIN 2,3 from a study conducted as part of the International Agency for Research on Cancer (IARC) survey were used as calibration target data. The population-based study was conducted in two provinces of Thailand: Lampang and Songkla.[18] We allowed baseline natural history parameters to vary over plausible ranges. Using a likelihood-based scoring algorithm we identified unique sets of parameter

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values that achieved a close fit to the empirical data, and proceeded with the analysis using a sample of 50 close-fitting parameter sets. The baseline parameter values, plausible ranges, and calibration target data used in this analysis are provided in Appendix S1; details of the model structure and calibration process have been described elsewhere.[14,15,19]

The approach we used to estimate costs has been described previously,[14,16,20,21] and further details are provided in Appendix S1. All costs are presented in 2005 international dollars, a currency that provides a means of translating and comparing costs among countries, taking into account differences in purchasing power.[22] For screening, we included direct medical costs (e.g. staff, supplies, and specimen transport), as well as costs associated with women's time and transportation to and from the site of care. For example, in a one-visit VIA screening strategy in which a woman receives cryosurgery, the cost of the test was I$2.47, the patient time was I$2.74, and the cryotherapy procedure was I$51.73. Sources of our screening cost estimates included a previously published analysis in Thailand,[20] WHO CHOICE,[23] and the International Labour Organization.[24]

As both the costs of delivering the HPV vaccine to this age group and the price of the vaccine are not yet known, we considered a composite cost per vaccinated girl, which we varied from I$10 to I$500. We assumed that this composite cost represented the sum of vaccine costs, wastage, freight and supplies, administration, immunization support, and programme costs. For example, for a composite cost of I$25 per vaccinated girl, we assumed three doses of vaccine at I$5 each, with the remaining money allocated to the other component costs. Additional assumptions are provided in Appendix S1.

Strategies and assumptions

Screening strategies differed by the initial screening test (cytology, conventional HPV DNA testing, rapid HPV DNA testing, and VIA), screening frequency (from one to five times per lifetime, beginning at age 35 years and continuing at 5-year intervals), and the number of required clinical visits for screening and any necessary diagnosis or treatment. Similar to assumptions we have made previously,[20,25] cytology was assumed to occur in three visits, including the initial screen (visit 1), colposcopy and possible biopsy for screen-positive women (visit 2), and treatment of precancerous lesions or invasive cancer (visit 3), which included cryosurgery, loop electrosurgical excision procedure, cold-knife conization, or simple hysterectomy, depending on lesion size or cancer stage. Conventional HPV DNA testing was assumed to occur in two visits, including the initial screen (visit 1), a return visit for results (visit 2), plus, for screen-positive women, a gynaecological examination and colposcopy to determine whether they were suitable for same-day treatment with cryosurgery. Those who were not eligible (e.g. with lesions covering over 75% of the cervix or extending to the vaginal wall) were referred to a secondary facility (e.g. a district or regional hospital) for further diagnostic testing and treatment, if necessary. Two strategies were evaluated that included only one visit: VIA and rapid HPV DNA testing incorporated same-day screening and treatment for all women with positive screening results. Loss to follow-up was assumed to be 15% at each clinical contact.

We assumed that vaccination occurs before the age of 12 years (prior to sexual debut), that all girls receive three doses, and that vaccine protection against HPV 16 and 18 is life long. In our initial base-case analysis, we assumed that vaccination coverage was 80%. We assumed coverage with the initial screening test was 60%, but also repeated analyses with a coverage of 40%, to represent the range of reported national coverage rates in Thailand. Both vaccination and screening coverage were varied independently and simultaneously in sensitivity analysis. We also evaluated the Thailand Ministry of Health's current recommendation of screening every 5 years with VIA for women aged 30–45 years and cytology for women aged 50–60 years.

Analysis

Our initial analysis focused on assessing the comparative benefits (life-expectancy gains and reductions in lifetime risk) and costs (lifetime costs) associated with each of the strategies: pre-adolescent HPV vaccination alone, screening alone in adulthood, and combined pre-adolescent vaccination followed by screening. The comparative performance of the strategies was described using the incremental cost-effectiveness ratio, measured as the additional cost divided by the additional health benefit of one strategy compared with the next less costly strategy. Strategies that were more costly and less effective (i.e. 'strongly dominated') or less costly and less cost-effective (i.e. 'weakly dominated') than an alternative strategy were considered inefficient, and as is standard practice, were eliminated from the calculations in that specific analysis. To incorporate the effect of uncertainty in the natural history parameters, cost-effectiveness analyses were conducted with a sample of 50 close-fitting input parameter sets. Results are reported as mean outcomes, whereas incremental cost-effectiveness ratios are reported as the ratio of the mean costs divided by the mean effects across the 50 close-fitting sets.

We conducted an analysis in which we assumed that all screening strategies were possible to implement. We also conducted analyses in which we assumed only one of the screening test approaches was feasible, as the choice about which screening modality to use in Thailand might depend on factors not included in this study, such as existing pilot

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programmes, the human resources available, and cultural preferences.

As recommended by published guidelines on cost-effectiveness,[26–29] we adopted a societal perspective, and discounted future costs and benefits by 3% per year. We identified the optimal prevention policies across different assumptions of vaccine price and other uncertainties.

Results

Reductions in lifetime risk of cancer

Assuming a vaccination coverage of 80% and lifelong vaccine protection, pre-adolescent HPV vaccination alone reduced the lifetime risk of cervical cancer by 55% (range 45–69%), and was more effective than any strategy of screening alone (Figure 1). A combined strategy of vaccination of pre-adolescents followed by screening at age 35 years was more effective than either strategy alone. Strategies involving cytology were associated with lower cancer reductions than those with VIA or HPV DNA testing, although the relative differences were attenuated when vaccination was added. The relative differences among the strategies became more pronounced as the number of screens per lifetime increased.

Cost-effectiveness of screening and vaccination

Table 1 displays the cost-effectiveness results when varying the cost per vaccinated girl under four scenarios of screening test availability.

Assuming that all screening strategies are equally available

Provided the cost per vaccinated girl was equal to, or under, I$25 (approximately I$5 per dose), screening alone was either more costly and less effective, or less costly and less cost-effective, than vaccination alone. At a vaccine cost of I$10 (approximately I$2 per dose), vaccination alone was cost saving compared with no intervention. At vaccine costs of up to I$50, strategies combining pre-adolescent vaccination with screening using a one-visit VIA two, three, or five times per lifetime were <I$3000 per year of life saved (YLS); the combined strategy of vaccination and HPV DNA testing five times per lifetime yielded the highest cancer reductions, costing I$6380 per YLS.

At a cost per vaccinated girl of I$100 (approximately I$20 per dose) and above, vaccination alone was less costly but less cost-effective than (and therefore, dominated by) screening alone with HPV five times per lifetime, which provided a cancer reduction of 32.7% and cost I$3140 per

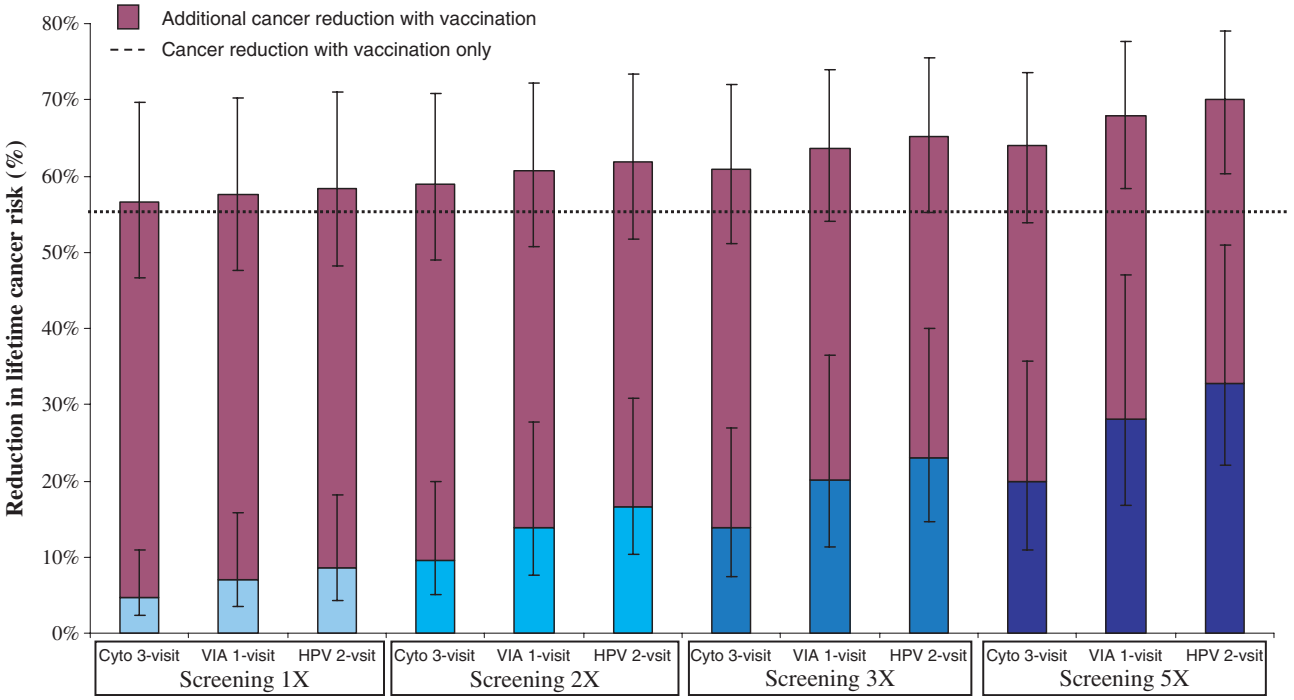

Figure 1. Reductions in lifetime risk of cervical cancer for different screening strategies, with and without HPV vaccination. Screening strategies include: cytology requiring three visits; VIA requiring one visit; and HPV DNA testing requiring two visits; by screening frequency (from one to five times per lifetime). Blue bars represent strategies of screening alone assuming 60% coverage; purple bars represent the additional reductions associated with including pre-adolescent HPV vaccination, assuming 80% coverage. The height of the bars represent the mean reduction in lifetime risk of cervical cancer across the 50 close-fitting parameter sets; the error bars represent the minimum and maximum reductions achieved for each strategy. The dotted line indicates the reduction in cancer risk associated with vaccination at 80% coverage.

Table 1. Mean cancer reductions and incremental cost-effectiveness ratios by cost per vaccinated girl and availability of screening test*

	Mean cancer reduction** (%)	Cost per vaccinated girl (I$)***							
		I$10	I$25	I$50	I$100	I$200	I$250	I$300	I$500
All screening strategies equally available									
Natural history (no screening or vaccination)	–	–	–	–	–	–	–	–	–
Cytology once per lifetime	4.7	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
VIA once per lifetime	7.1	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
HPV once per lifetime	8.6	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Cytology twice per lifetime	9.6	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Cytology three times per lifetime	13.8	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
VIA twice per lifetime	13.9	Dom	Dom	**$750**	**$750**	**$750**	**$750**	**$750**	**$750**
HPV twice per lifetime	16.5	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
VIA three times per lifetime	19.8	Dom	Dom	**$870**	**$870**	**$870**	**$870**	**$870**	**$870**
Cytology five times per lifetime	19.9	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
HPV three times per lifetime	23.1	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
VIA five times per lifetime	28.2	Dom	Dom	Dom	**$1280**	**$1280**	**$1280**	**$1280**	**$1280**
HPV five times per lifetime	32.7	Dom	Dom	Dom	**$3140**	**$3140**	**$3140**	**$3140**	**$3140**
Vaccination alone	54.7	**CS**	**$350**	**$1200**	Dom	Dom	Dom	Dom	Dom
Vaccination and cytology once per lifetime	56.6	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA once per lifetime	57.6	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and HPV once per lifetime	58.3	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and cytology twice per lifetime	58.8	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA twice per lifetime	60.8	**$1990**	**$1990**	**$1990**	Dom	Dom	Dom	Dom	Dom
Vaccination and cytology three times per lifetime	61.0	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and HPV twice per lifetime	61.9	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA three times per lifetime	63.7	**$2040**	**$2040**	**$2040**	Dom	Dom	Dom	Dom	Dom
Vaccination and cytology five times per lifetime	64.1	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and HPV three times per lifetime	65.2	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA five times per lifetime	68.0	**$2850**	**$2850**	**$2850**	**$3490**	Dom	Dom	Dom	Dom
Vaccination and HPV five times per lifetime	70.1	**$6380**	**$6380**	**$6380**	**$6380**	**$7720**	**$9750**	**$11780**	**$19920**
Only one-visit VIA available for screening									
Natural history (no screening or vaccination)	–	–	–	–	–	–	–	–	–
VIA once per lifetime	7.1	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
VIA twice per lifetime	13.9	Dom	Dom	**$750**	**$750**	**$750**	**$750**	**$750**	**$750**
VIA three times per lifetime	19.8	Dom	Dom	**$870**	**$870**	**$870**	**$870**	**$870**	**$870**
VIA five times per lifetime	28.2	Dom	Dom	Dom	**$1280**	**$1280**	**$1280**	**$1280**	**$1280**
Vaccination alone	54.7	**CS**	**$350**	**$1200**	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA once per lifetime	57.6	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA twice per lifetime	60.8	**$1990**	**$1990**	**$1990**	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA three times per lifetime	63.7	**$2040**	**$2040**	**$2040**	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA five times per lifetime	68.0	**$2850**	**$2850**	**$2850**	**$3440**	**$7240**	**$9140**	**$11040**	**$18630**
Only two-visit HPV available for screening									
Natural history (no screening or vaccination)	–	–	–	–	–	–	–	–	–
HPV once per lifetime	8.6	Dom	Dom	**$970**	**$970**	**$970**	**$970**	**$970**	**$970**
HPV twice per lifetime	16.5	Dom	Dom	**$980**	**$980**	**$980**	**$980**	**$980**	**$980**
HPV three times per lifetime	23.1	Dom	Dom	Dom	**$1200**	**$1200**	**$1200**	**$1200**	**$1200**
HPV five times per lifetime	32.7	Dom	Dom	Dom	**$1760**	**$1760**	**$1760**	**$1760**	**$1760**
Vaccination alone	54.7	**CS**	**$350**	**$1030**	Dom	Dom	Dom	Dom	Dom
Vaccination and HPV once per lifetime	58.3	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and HPV twice per lifetime	61.9	**$2380**	**$2380**	**$2380**	Dom	Dom	Dom	Dom	Dom
Vaccination and HPV three times per lifetime	65.2	**$2630**	**$2630**	**$2630**	**$3640**	Dom	Dom	Dom	Dom
Vaccination and HPV five times per lifetime	70.1	**$3790**	**$3790**	**$3790**	**$3790**	**$7720**	**$9750**	**$11780**	**$19920**

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Table 1. (*Continued*)

	Mean cancer reduction** (%)	Cost per vaccinated girl (I$)***							
		I$10	I$25	I$50	I$100	I$200	I$250	I$300	I$500
Only three-visit cytology available for screening									
Natural history (no screening or vaccination)	–	–	–	–	–	–	–	–	–
Cytology once per lifetime	4.7	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Cytology twice per lifetime	9.6	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Cytology three times per lifetime	13.8	Dom	Dom	Dom	**$2150**	**$2150**	**$2150**	**$2150**	**$2150**
Cytology five times per lifetime	19.9	Dom	Dom	Dom	Dom	**$2800**	**$2800**	**$2800**	**$2800**
Vaccination alone	54.7	**CS**	**$350**	**$980**	**$2400**	Dom	Dom	Dom	Dom
Vaccination and cytology once per lifetime	56.6	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and cytology twice per lifetime	58.8	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and cytology three times per lifetime	61.0	**$4830**	**$4830**	**$4830**	**$4830**	Dom	Dom	Dom	Dom
Vaccination and cytology five times per lifetime	64.1	**$5670**	**$5670**	**$5670**	**$5670**	**$6450**	**$8170**	**$9890**	**$16750**

*Values represent incremental cost-effectiveness ratios (the ratio of the mean costs divided by the mean effects of 50 close-fitting parameter sets) expressed as cost per year of life saved; strategies listed in order of increasing effectiveness; Dom, strategies that were more costly and less effective or less costly and less cost-effective than alternative options, and were thus considered dominated; CS, strategies that were cost-saving compared with no intervention, because the future costs averted by preventing cancer were greater than the cost of the intervention. Values in bold represent non-dominated strategies.

**Reductions in lifetime cancer risk for all strategies were calculated against no intervention and then averaged across 50 close-fitting parameter sets.

***Cost per vaccinated girl includes three doses of vaccine, wastage, freight and supplies, administration, immunisation support, and programme costs. Costs are expressed in 2005 international dollars.

YLS. Higher cancer benefits were achieved with a combined strategy of pre-adolescent vaccination followed by HPV screening five times per lifetime, which varied from I$6380 to I$7720, as vaccine costs were varied from I$100 to I$200. At a cost per vaccinated girl of I$250 (approximately I$50 per dose) and above, strategies that included vaccination had cost-effectiveness ratios exceeding Thailand's gross domestic product (GDP) per capita (I$8100),[30] and screening alone with HPV testing five times per lifetime was the most efficient strategy under that threshold. Strategies involving cytology were consistently less effective and more costly or less cost-effective in all analyses.

Assuming screening options are limited

We repeated our analysis assuming that, for reasons other than cost-effectiveness, one particular screening modality was the only realistic option. When only HPV DNA testing was considered, vaccination followed by HPV DNA testing five times per lifetime was I$3790 per YLS at vaccine costs ranging from I$10 to I$100, and I$7720 per YLS when the cost per vaccinated girl was I$200 (approximately I$40 per dose).

When screening was restricted to cytology, the incremental cost-effectiveness ratios of screening alone were twice as high as those of corresponding strategies involving HPV DNA testing alone or VIA alone. The strategy of combined vaccination and cytology screening five times per lifetime was I$5670 per YLS at vaccine costs ranging from I$10 to I$100, and I$6450 per YLS at a vaccine cost of I$200 (I$50 per dose).

Evaluating the Thailand Ministry of Health's recommended screening strategy

We explored scenarios in which screening was available up to seven times per lifetime in order to evaluate Thailand's Ministry of Health's recommendation for screening every 5 years with VIA for women aged 30–45 years and cytology for women aged 50–60 years (Table 2). We found this strategy to be dominated at all vaccine costs. At costs per vaccinated girl ranging from I$10 to I$100, vaccination and VIA seven times per lifetime was I$4250 per YLS, and vaccination and HPV seven times per lifetime was I$9750. At vaccine costs higher than I$200, strategies involving vaccination exceeded Thailand's GDP per capita, and screening alone with HPV seven times per lifetime was cost-effective at a ratio of I$4510 per YLS.

Assuming that HPV vaccination is limited

To explore a scenario in which an organised HPV vaccination programme is not feasible in Thailand, we evaluated the cost-effectiveness of screening alone (assuming an equal availability of all screening tests) (Table 3). Strategies using

Table 2. Thailand's current screening strategy: mean cancer reductions and incremental cost-effectiveness ratios by cost per vaccinated girl and availability of screening test*

	Mean cancer reduction** (%)	Cost per vaccinated girl (I$)***							
		I$10	I$25	I$50	I$100	I$200	I$250	I$300	I$500
All screening strategies equally available									
Natural history (no screening or vaccination)	–	–	–	–	–	–	–	–	–
Cytology once per lifetime	4.7	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
VIA once per lifetime	7.1	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
HPV once per lifetime	8.6	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Cytology twice per lifetime	9.6	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Cytology three times per lifetime	13.8	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
VIA twice per lifetime	13.9	Dom	Dom	**$750**	**$750**	**$750**	**$750**	**$750**	**$750**
HPV twice per lifetime	16.5	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
VIA three times per lifetime	19.8	Dom	Dom	**$870**	**$870**	**$870**	**$870**	**$870**	**$870**
Cytology five times per lifetime	19.9	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
HPV three times per lifetime	23.1	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Cytology seven times per lifetime	23.4	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
VIA five times per lifetime	28.2	Dom	Dom	Dom	**$1280**	**$1280**	**$1280**	**$1280**	**$1280**
VIA switch cytology seven times per lifetime	31.9	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
HPV five times per lifetime	32.7	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
VIA seven times per lifetime	33.2	Dom	Dom	Dom	**$1820**	**$1820**	**$1820**	**$1820**	**$1820**
HPV seven times per lifetime	38.5	Dom	Dom	Dom	Dom	**$4510**	**$4510**	**$4510**	**$4510**
Vaccination alone	54.7	**CS**	**$350**	**$1200**	Dom	Dom	Dom	Dom	Dom
Vaccination and cytology once per lifetime	56.6	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA once per lifetime	57.6	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and HPV once per lifetime	58.3	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and cytology twice per lifetime	58.8	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA twice per lifetime	60.8	**$1990**	**$1990**	**$1990**	Dom	Dom	Dom	Dom	Dom
Vaccination and cytology three times per lifetime	61.0	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and HPV twice per lifetime	61.9	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA three times per lifetime	63.7	**$2040**	**$2040**	**$2040**	Dom	Dom	Dom	Dom	Dom
Vaccination and cytology five times per lifetime	64.1	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and HPV three times per lifetime	65.2	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and cytology seven times per lifetime	65.8	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA five times per lifetime	68.0	**$2850**	**$2850**	**$2850**	**$3920**	Dom	Dom	Dom	Dom
Vaccination and VIA switch cytology seven times per lifetime	69.8	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and HPV five times per lifetime	70.1	Dom	Dom	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination and VIA seven times per lifetime	70.4	**$4250**	**$4250**	**$4250**	**$4250**	**$9050**	Dom	Dom	Dom
Vaccination and HPV seven times per lifetime	72.8	**$9750**	**$9750**	**$9750**	**$9750**	**$9750**	**$11520**	**$13930**	**$23580**

*Values represent incremental cost-effectiveness ratios (the ratio of the mean costs divided by the mean effects of 50 close-fitting parameter sets) expressed as cost per year of life saved; strategies listed in order of increasing effectiveness; Dom, strategies that were more costly and less effective or less costly and less cost-effective than alternative options, and were thus considered dominated; CS, strategies that were cost-saving compared with no intervention, because the future costs averted by preventing cancer were greater than the cost of the intervention. Values in bold represent non-dominated strategies.

**Reductions in lifetime cancer risk for all strategies were calculated against no intervention and then averaged across 50 close-fitting parameter sets.

***Cost per vaccinated girl includes three doses of vaccine, wastage, freight and supplies, administration, immunisation support, and programme costs. Costs are expressed in 2005 international dollars.

VIA had ratios ranging from I$680 to I$1440, depending on the frequency and coverage level of screening. Screening with two-visit HPV DNA testing five times per lifetime was the most effective strategy, and ranged from I$2260 to I$3550 per YLS, as screening coverage varied from 20–80%. Strategies involving cytology were consistently less effective and more costly or less cost-effective (and therefore, dominated) in all analyses.

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Table 3. Screening alone: incremental cost-effectiveness ratios by screening frequency and coverage*

Screening strategy	Screening frequency	Coverage			
		20%	40%	60%	80%
VIA	Once	Dom	Dom	Dom	**$770**
	Twice	Dom	**$720**	**$750**	**$810**
	Three times	**$680**	**$780**	**$870**	**$990**
	Five times	**$1020**	**$1130**	**$1280**	**$1440**
Cytology	Once	Dom	Dom	Dom	Dom
	Twice	Dom	Dom	Dom	Dom
	Three times	Dom	Dom	Dom	Dom
	Five times	Dom	Dom	Dom	Dom
HPV DNA testing	Once	Dom	Dom	Dom	Dom
	Twice	Dom	Dom	Dom	Dom
	Three times	Dom	Dom	Dom	Dom
	Five times	**$2260**	**$2630**	**$3140**	**$3550**

*Values represent incremental cost-effectiveness ratios (the ratio of the mean costs divided by the mean effects of 50 close-fitting parameter sets) expressed as cost per year of life saved; strategies are grouped by screening test; Dom, strategies that were more costly and less effective or less costly and less cost-effective than alternative options, and were thus considered dominated. Values in bold represent non-dominated strategies.

Sensitivity analysis

We have previously reported how the comparative performance of cervical prevention strategies depends on several factors.[15,20,31] In order to explore the impact of important assumptions on our current results, we varied vaccine efficacy and duration, as well as screening and vaccination coverage levels. We also investigated potential reductions in loss to follow-up by using the one-visit rapid HPV test.

When we evaluated the effects of lower vaccine efficacy of 75% (base-case 100%), we found that HPV vaccination alone was no longer cost saving at a vaccine cost of I$10, and rather that it costs I$170 per YLS. In addition, strategies involving HPV vaccination exceeded the threshold of Thailand's per capita GDP at vaccine costs that were half that of the base case (i.e. I$100 versus I$200 in the base case). Screening of adult women using one-visit VIA two, three, or five times per lifetime, as well as two-visit HPV DNA testing five times per lifetime, became more attractive relative to combined strategies of pre-adolescent vaccination and screening.

Consistent with our previous analyses, results were quite sensitive to vaccine waning. For example, when we assumed that the vaccine waned completely after 20 years, all vaccination strategies were more costly and less effective, or were less costly and less cost-effective, than screening alone with VIA two or more times per lifetime or HPV testing five times per lifetime, which was the most efficient strategy.

If rapid HPV testing were available in Thailand, its lower sensitivity and specificity (as compared with two-visit HPV testing) would be compensated for by its reduction in loss to follow-up; strategies using the rapid HPV test were preferable to the two-visit HPV test, even when the costs of both tests were the same. Combined HPV vaccination and rapid HPV testing five times per lifetime cost I$2250 per YLS at vaccine costs ranging from I$10 to I$50, and I$7930 per YLS at a cost per vaccinated girl of I$200.

Two nationally representative surveys, the Health and Welfare Survey (2003) and the Reproductive Health Survey (2006), were conducted in Thailand to determine screening rates for cervical cancer, which were estimated as 38 and 63%, respectively.[11] Although we presented results from the more recent survey as the base screening level in our model (60% coverage), we repeated all analyses with screening coverage at 40%. Results were consistent with those at 60%, with the exception that VIA twice per lifetime in combination with vaccination was less efficient than vaccination and screening with VIA three or more times per lifetime.

We varied vaccination coverage from 25 to 100%, and screening coverage from 20 to 100%, both independently and simultaneously. At low levels of screening and high levels of vaccination coverage, strategies involving vaccination became more attractive, yet even at high levels of screening and low levels of vaccination, strategies involving vaccination remained efficient. Our results were robust across a range of vaccination and screening coverage levels, with strategies involving VIA having low costs per YLS, strategies involving cytology being less effective and more costly or less cost-effective than other strategies, and a strategy of HPV vaccination combined with two-visit HPV testing five times per lifetime providing the highest benefits. Vaccination alone was cost saving under all scenarios provided the cost of vaccine was at or below I$10 per vaccinated girl.

Discussion

Assuming 80% vaccination coverage in Thailand, our model projected that the lifetime risk of cervical cancer can be reduced by 55% (range 45–69%) with pre-adolescent HPV vaccination alone. Adding coverage with HPV testing five times per lifetime in adulthood yielded even higher cancer reductions (70%). However, the health benefits from the vaccine may be lower than projected if the vaccine efficacy is lower than reported in clinical trials (possibly because of prior infections with vaccine-targeted HPV types), or if vaccine-induced immunity wanes while individuals are still at risk for HPV infections. On the other hand, the benefit of the vaccine could be higher if natural immunity is not lifelong (as assumed by our model), or if there are cross-protective benefits against non-16/18 high-risk infections, as suggested by recent studies.[32,33]

There is no consensus on a specific threshold below which an intervention would be considered cost-effective (i.e. good value for money relative with the other health investments that Thailand could adopt). For the purposes of this analysis, we used the suggested threshold of the per capita GDP in Thailand (I$8100)[30], although realistically this may be a relatively high threshold for developing countries. When the cost per vaccinated girl was I$10 or lower, HPV vaccination alone was cost saving compared with no intervention, meaning that the upfront cost of vaccination was completely offset by the downstream savings in cancer treatment. When assuming all screening tests were equally available, a combined strategy of pre-adolescent vaccination and HPV DNA testing five times per lifetime was less than the per capita GDP, provided that the cost per vaccinated girl was I$200 or less. The use of a rapid HPV test that provides same-day results made HPV testing strategies even more attractive. If we elected to adopt a lower threshold of 100 000 baht (approximately I$3340), which has been used by previous studies in Thailand,[11] vaccination combined with VIA screening five times per lifetime would be the most effective strategy with a ratio under this threshold, provided the cost per vaccinated girl was <I$50; at higher vaccine costs, screening alone with HPV testing five times per lifetime would be optimal.

Across various scenarios, strategies that involved three-visit cytology were generally inefficient, that is, they were less effective and less cost-effective than alternative strategies; indeed, the current recommendation for cervical cancer screening in Thailand involving VIA screening in younger women and cytology testing in older women was found to be more costly and less effective than alternative strategies involving either HPV testing or VIA screening at all ages.

We evaluated scenarios in which screening test options were not equally available, to reflect regions of Thailand with varying levels of infrastructure and technical capacity, which may favour one screening modality over another for reasons other than cost-effectiveness; for example, a quarter of Thailand's provinces have already implemented screening with VIA. We therefore evaluated the cost-effectiveness of pre-adolescent vaccination with each screening test alone. Irrespective of screening modality, we found that the cost-effectiveness ratio associated with combined vaccination and screening five times per lifetime was less than the per capita GDP, provided that the vaccine cost per vaccinated girl was I$200 or less. We wish to emphasise, however, that when all screening options were considered together, HPV DNA testing was robustly found to be a more efficient screening strategy than either VIA or cytology.

Our results are consistent with a previous analysis that also found that HPV DNA testing was a cost-effective alternative to cytology screening in Thailand.[20] However, our findings differ from those of an analysis conducted by Thailand's Ministry of Health, which found that HPV vaccination was not cost-effective. In contrast to our analysis, the previous study by the Ministry of Health assumed that the vaccination of girls would begin at older ages, when exposure to HPV is already substantial, and assumed a lower HPV vaccine efficacy of 79%, both assumptions that disadvantage a strategy of HPV vaccination. Furthermore, they concluded that a strategy of screening every 5 years with VIA for women aged 30–45 years and cytology for women aged 50–60 years was most efficient,[11] but did not consider HPV DNA testing as a screening option.

The cost-effectiveness of HPV vaccination will depend largely on the incremental costs of adding a pre-adolescent vaccine to Thailand's existing national vaccination programme, as well as on the negotiated price of the HPV vaccine for Thailand. Other influential factors, such as vaccine efficacy, shifted the absolute cost-effectiveness ratios, but rarely changed the rank order of the strategies or the optimal strategy. As in previous studies, the incremental benefit of screening diminished at higher vaccination coverage rates.[14,16] Based on the high coverage of several three-dose childhood vaccinations achieved in Thailand, a high coverage of HPV vaccination may be feasible; however, pre-adolescent vaccination poses unique challenges compared with infant vaccination, as older children are not as well connected to the healthcare system. In addition, high vaccination coverage may be more difficult to achieve in rural areas. School-based vaccination programmes, which have achieved success in other developing countries, may be a viable strategy for Thailand.

As with all model-based analyses, our results should be interpreted within the context of our limitations. We intended to provide quantitative approximations of the potential benefits of HPV vaccination, as well as insight into the relative value of screening and vaccination strategies. We have previously described the inherent limitations of our modelling approach,[14,15,19] but we briefly summarise the key points here. There is uncertainty with respect to the natural history of HPV, as some transitions in the progression to cancer are unobservable. To address this issue, we averaged results across 50 parameter sets that provide a good model fit to empirical data, and reported the mean outcomes. Although in prior sensitivity analyses we have extensively explored the range of uncertainty in screening test characteristics (i.e. sensitivity/specificity), we did not explore the impact of relative variability of test performance on our results; for example, test performance of VIA has been found to be quite variable across settings, depending on the level of training and quality control, whereas HPV DNA testing results are more automated and therefore less variable. Therefore, the comparative effectiveness and cost-effectiveness among screening strategies may differ by setting. Our base-case analysis assumed complete and

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lifelong vaccine-induced protection against vaccine-targeted HPV types. Long-term efficacy data on this uncertainty will help to inform future analyses. We also did not include potential herd-immunity benefits from the HPV vaccine or prevention of non-cervical HPV-16/18 related diseases, which would make HPV vaccination more attractive.

More generally, cost-effectiveness analyses can provide information about the value of investing in various health interventions, but it is only one of many considerations in the development or adoption of a policy. Such analyses do not provide information on affordability: many strategies that are cost-effective (i.e. provide good value for money) are not affordable in developing countries, because they are too costly given a fixed budget and other competing health issues. Cultural acceptability, political will, and distributional equity are other important considerations that will factor into Thailand's decision on a cervical cancer prevention strategy.

Conclusion

Our analysis suggests that strategies involving HPV vaccination targeted to pre-adolescent girls at 80% coverage, followed by screening women over 30 years of age, could reduce the lifetime risk of cancer by up to 70%, provided screening coverage rates of 60% or greater. Using Thailand's GDP per capita as a metric for cost-effectiveness, we found that pre-adolescent vaccination combined with HPV DNA testing five times per lifetime, starting at age 35 years, was the most cost-effective strategy. From the perspective of our economic evaluation, in regions where HPV testing is not feasible, screening with VIA five times per lifetime combined with vaccination may be a reasonable alternative.

Disclosure of interests

None declared.

Contribution to authorship

All authors have contributed equally to the design, analysis, and writing of this article.

Details of ethics approval

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Supporting information

The following supplementary materials are available for this article:

Appendix S1. Cost-effectiveness of HPV vaccination and cervical cancer screening in Thailand.

Additional Supporting Information may be found in the online version of this article.

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