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Exploring the cost-effectiveness of HPV vaccination in Vietnam: Insights for evidence-based cervical cancer prevention policy

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ABSTRACT

Using mathematical models of cervical cancer for the northern and southern regions of Vietnam, we assessed the cost-effectiveness of cervical cancer prevention strategies and the tradeoffs between a national and region-based policy in Vietnam. With 70% vaccination and screening coverage, lifetime risk of cancer was reduced by 20.4–76.1% with vaccination of pre-adolescent girls and/or screening of older women. Only when the cost per vaccinated girl was low (i.e., <I$25) was vaccination combined with screening (three times per lifetime or every 5 years) favored in both regions; at high costs per vaccinated girl (i.e., >I$100), screening alone was most cost-effective. When optimal policies differed between regions, implementing a national strategy resulted in health and economic inefficiencies. HPV vaccination appears to be an attractive cervical cancer prevention strategy for Vietnam, provided high coverage can be achieved in young pre-adolescent girls, cost per vaccinated girl is <I$25 (i.e., <$5 per dose), and screening is offered at older ages.

1. Introduction

Cervical cancer incidence in Vietnam is approximately 20.2 cases per 100,000 person-years at risk [1], yet there is substantial variation within the country. In the Northern city of Hanoi, incidence rates are as low as 6.8 per 100,000 women [2], whereas in the Southern city of Ho Chi Minh, rates are as high as 26.0 per 100,000 women [3]. This variation is consistent with the observed five-fold difference between the two regions in prevalence of high-risk "oncogenic" human papillomavirus (HPV), the causal agent of cervical cancer, as well as differences in patterns of sexual behavior that contribute to HPV transmission [4].

Cervical cancer prevention efforts in Vietnam have generally relied on opportunistic screening, with overall low levels of coverage. A population-based screening program in Ho Chi Minh City and a pilot screening project in Hanoi, established by the Viet/American Cervical Cancer Prevention Project, have demonstrated the ability to introduce cytology screening within the context of a 5-year screening program, starting at age 30 [5], although the long-term impact on cancer incidence is not yet known. Research efforts in other low-resource settings have also suggested that alternative strategies utilizing other screening modalities, such as HPV DNA testing, improve the sensitivity of a single screening test, and when used in a one-visit or two-visit strategy, enhance the linkage between screening and treatment and may be cost-effective [6–9].

More recently, vaccines against HPV types 16 and 18, two of the most common high-risk types and responsible for more than 70% of cervical cancer cases [10], create opportunities for primary prevention in areas of the world where organized secondary prevention with screening has been difficult. Decision makers in Vietnam are now faced with multiple options to reduce mortality from cervical cancer, but need to consider which of these are most likely to be effective, affordable, feasible, acceptable, and sustainable. In addition, they need to comparatively evaluate the cost-effectiveness of cervical cancer prevention programs in relation to interventions for other diseases [11]. Since no single study can inform the full spectrum of factors that need to be considered, model-based analyses conducted from a decision science perspective can be employed to synthesize available epidemiological, clinical, and economic data, as well as take into account the uncertainty in those data; these models are then used to project the expected long-term consequences of different choices.

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To inform the decision making process, we assessed the health and economic outcomes associated with cervical cancer prevention strategies in Vietnam and elucidated what factors and uncertainties were most influential on the results. Because of the variations in cervical cancer incidence between North and South Vietnam, we identified and juxtaposed the optimal strategies in each of the regions. Although previous model-based cost-effectiveness analyses have evaluated cervical cancer prevention strategies in countries with known regional variations in risk factors and cervical cancer risk, to date, this analysis is the first to explore and quantify the clinical and economic tradeoffs of establishing a national versus region-based policy for cervical cancer prevention.

2. Methods

2.1. Model

We synthesized available epidemiological, clinical, and economic data from Vietnam and neighboring Asian countries using a previously described individual-based Monte Carlo simulation model [12–14]. This model is comprised of health states that are descriptive of each patient's underlying true health, including HPV infection status, grade of precancerous lesions, and stage of invasive cancer. Individual girls enter the model at age 9, prior to sexual debut and free of HPV infection, and transition between health states throughout their lifetimes. Each month, females face an age-dependent risk of acquiring HPV infection; those with infection can subsequently develop low- or high-grade lesions, categorized as cervical intraepithelial neoplasia, grade 1 (CIN 1) or grade 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, distant stages); all women are subject to mortality from competing causes. 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 categorized as (1) high-risk type 16 (HR-16); (2) high-risk type 18 (HR-18); (3) other high-risk types (HR-other), including 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 82; and (4) low-risk (LR) types, including 6, 11, 26, 32, 34, 40, 42, 44, 53, 54, 55, 57, 61, 62, 64, 67, 69, 70, 71, 72, 81, 83, and 84.

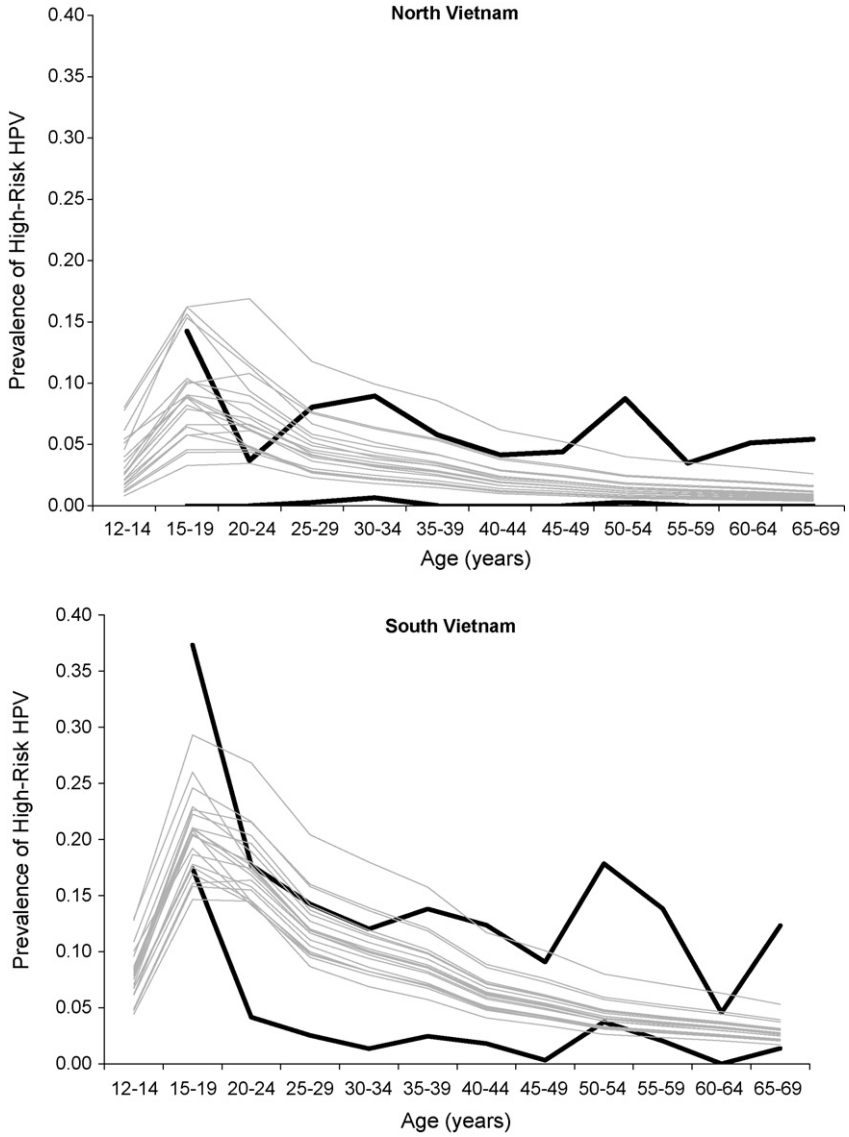

Fig. 1. Model calibration outputs. Prevalence of high-risk HPV from a sample of good-fitting sets from the north (top) and the south (bottom), compared with empirical data. Gray curves represent model output for a sample of 25 good-fitting sets in the north (top) and the south (bottom). Bold lines depict the 95% confidence intervals of the empirical data [4,15].

2.2. Input parameters and costs

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 Vietnamese context by using likelihood-based methods to fit the model to country-specific epidemiological data. Models were tailored to the northern and southern regions separately using data from Hanoi and Ho Chi Minh City, respectively. For this analysis, we elected to calibrate two distinct models to ensure projected outcomes approximated observed epidemiological differences between the northern and southern regions.

Age-specific prevalence of high- and low-risk HPV were from studies that conducted HPV DNA testing of married women with normal cytology aged 15–85 years in both Hanoi ($n = 983$) and Ho Chi Minh City ($n = 914$), collected as part of the IARC HPV prevalence survey [4,15]. In addition, estimates of age-specific cervical cancer incidence were based on data from cancer registries in Hanoi, where 515 cases were reported from 1991 to 1997, and Ho Chi Minh City, where 2289 cases were reported from 1995 to 1998 [16]. Where region-specific estimates either were based on low sample sizes or were lacking, we used additional data from Vietnam to reflect population prevalence at the country level for the calibration exercises. Age-specific prevalence of CIN 1 and CIN 2,3 were obtained from the IARC prevalence study and included women over age 15 with adequate cytology results pooled from both Hanoi and Ho Chi Minh City ($n = 2308$) [17,18]. Although there were no published data on HPV type distribution among Vietnamese women at the time of analysis, we estimated HPV prevalence among women with CIN or invasive cancer using data from neighboring Asian countries, such as Thailand, Malaysia, and the Philippines [10,17–20].

We allowed baseline natural history parameters to vary over plausible ranges. Using a likelihood-based scoring algorithm, we identified unique sets of parameter values that achieved close fit to the empirical data in each of the two regions and proceeded with the analysis using a sample of good-fitting parameter sets. Fig. 1 shows examples of model calibration outputs using 25 good-fitting parameter sets for the model representing the north (top panel) and the model representing the south (bottom panel). The baseline parameter values, plausible ranges, and calibration target data used in this analysis are provided in Supplemental Appendix; details of the model structure and calibration process have been described elsewhere [12,13].

We included health-related costs, such as clinic visits, screening tests, diagnostic work-up, treatment of lesions or cancer, vaccine, administration, and programmatic costs. Also included were non-medical costs, such as transportation required to access care, and the costs of patient time (Table 1). Since the price of the vaccine and cost of delivery in Vietnam are not yet known, we assumed a composite cost per vaccinated girl, which was varied from I$10 (per dose cost of $2) to I$450 (per dose cost of $127); for example, for a composite cost of I$50 per vaccinated girl, we assumed three doses of vaccine at $12.25 each ($36.75 total), wastage of I$5.51, freight, supplies, and supply wastage of I$1.31, administration of I$1.50, and vaccine support and programmatic costs of I$4.94 [13]. In the base case, we assumed costs did not differ between the northern and southern regions, although this assumption was examined in sensitivity analysis. Costs are presented in 2000 international dollars (I$), a currency that takes into account purchasing power of a particular country [21]. Costs of "tradable" goods (e.g., vaccine doses and supplies) were converted from local currency units (LCU) using direct U.S. dollar exchange rates as they carry an international dollar price that is independent of current setting (LCU per U.S. dollar = 14,167.75 in 2000). Costs of "non-tradable" goods (e.g., administration, support and programmatic components), which vary more considerably between countries with different socioeconomic and development profiles, were converted to and from LCU using purchasing power parity (PPP) conversion rates (LCU per I$: 2,789.81 in 2000). Additional assumptions about costs are provided in Supplemental Appendix.

Table 1
Costs[a]

Variable	Base case	Range
Screening, diagnostic, and treatment costs[b]		
HPV DNA test	6.91	1.73–34.55
Cytology	1.11	0.28–22.20
Colposcopy and biopsy	21.73	5.43–43.46
Cryotherapy	14.05	3.51–28.10
Treatment for women ineligible for cryotherapy	123.24	30.81–246.48
Local invasive cancer	1183	296–2365
Regional invasive cancer	1341	335–2683
Distant invasive cancer	1341	335–2683
Cost per vaccinated girl[c] [13]	50	10–450
Vaccine dose (per dose)[d]	12.25	2.00–126.71
Vaccine wastage (15%)	5.51	0.90–57.02
Freight, supplies, and supply wastage	1.31	0.59–4.91
Administration	1.50	0.50–3.00
Immunization support (monitoring, cold chain, injection safety, operational and programmatic services)	2.94	2.00–2.94
Social mobilization and outreach for new adolescent vaccine	2.00	0–2.00

[a] Costs are reported in 2000 international dollars. HPV, Human papillomavirus; DNA, deoxyribonucleic acid.

[b] All screening, diagnostic, and treatment costs include direct medical, direct non-medical, and patient time costs. Direct medical costs for screening include the HPV DNA assay or Papanicolaou test, specimen transport, laboratory processing, staff time, and office visit; for diagnosis, include colposcopy, biopsy, laboratory processing, staff time, and office visit; and for treatment, include the procedure, complications, hospitalization, and facility visit. For women ineligible for immediate cryotherapy, treatment assumes a proportion of cases requiring LEEP (loop electrosurgical excision procedure), cold knife conization, or simple hysterectomy. Direct non-medical costs and patient time costs include all patient time in transport, waiting, receiving treatment, and in hospitalization, as well as actual transport costs. See Supplemental Appendix for details.

[c] Vaccine cost is expressed as a composite estimate of cost per vaccinated girl. Shown are the values for cost per vaccinated girl of I$50, which was varied from I$10 to I$450 in the analysis. See Supplemental Appendix for details.

[d] Vaccine strategies involve full three-dose series, and therefore, the per dose cost is multiplied by 3.

2.3. Analysis

Lifetime costs and life expectancy benefits were projected in each region for strategies including pre-adolescent vaccination alone (before age 12), screening alone using either cytology or HPV DNA testing, and vaccination combined with screening. 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. HPV DNA testing was assumed to occur in two visits, including the initial screen (visit 1), return visit for results (visit 2) plus, for screen-positive women, a gynecologic exam 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., district or regional hospital) for further diagnostic testing, and if necessary,

Table 2
Selected model parameters[a]

Variable	Base case	Range
Vaccine coverage and properties[b]		
Primary vaccination coverage (%)	70	0–100
Efficacy against infection with HPV 16 and 18 (%)	100	50–100
Duration of vaccine-induced protection	Lifelong	10–40 years
Screening coverage and properties (%)[c]		
Primary screening coverage	70	0–100
Loss to follow-up (per visit)[d]	15	5–25
HPV DNA test performance for detection of CIN[e]		
Probability of HR HPV DNA positivity given CIN 1	78	65–95
Probability of HR HPV DNA positivity given CIN 2,3 or worse	88	70–95
Probability of HR HPV DNA negative result given no CIN	93	70–96
Cytology performance for detection of CIN[f]		
Probability of abnormal result given CIN 1	70	50–95
Probability of abnormal result given CIN 2,3 or worse	80	50–95
Probability of normal result given no CIN	95	90–99
Ineligible for cryosurgery, by health state (%)[g]		
Normal	5	0–50
HPV	5	0–50
CIN 1	15	0–50
CIN 2,3	25	0–50
Invasive cancer	90	50–100
Efficacy of cryosurgery (%)[h]		
Treatment effectiveness for CIN 1	85	50–90
Treatment effectiveness for CIN 2,3	75	50–90
Major complications	1	0–3
Minor complications	5	0–15

[a] Parameters represent the values used in the base case. Sensitivity analyses were conducted by varying each parameter over the range of values shown. HR, High-risk; HPV, human papillomavirus; DNA, deoxyribonucleic acid; CIN, cervical intraepithelial neoplasia.

[b] Vaccine strategies assumed three doses were given to girls before age 12, and that the vaccination series was completed before sexual debut.

[c] In the base case, we assumed screening strategies of three-visit cytology (involving the initial screen, colposcopy and possible biopsy for screen-positive women, and treatment of precancerous lesions or invasive cancer), or two-visit HPV DNA testing (involving the initial screen, and return for results plus same-day treatment for screen-positive women who are deemed eligible via colposcopy).

[d] Loss to follow-up was assumed to occur at each clinical contact; for example, within any particular strategy, a woman who required a return visit for further diagnostic testing and/or any necessary treatment had an approximate 15% chance of never receiving that care.

[e] Probability of HR HPV DNA positivity given high-risk HPV is assumed to be 100%; however, the clinically relevant sensitivity of HPV DNA testing is the probability of HR HPV DNA positivity given CIN 1 and CIN 2,3+.

[f] Abnormal cytology is defined as low-grade or high-grade squamous intraepithelial lesions (LSIL or HSIL+) for the base case analysis.

[g] Women ineligible for cryosurgery were referred to a physician at a district or tertiary clinical care site for appropriate work-up, and if necessary, treatment for precancerous lesions or cancer with loop electrosurgical excision procedure, cold knife conization, or simple hysterectomy.

[h] Treatment for high-grade CIN with cryosurgery resulted in 10% immediate failure, an additional 10% recurrence after 6 months, and an additional 5% recurrence after 1 year.

treatment. Loss to follow-up was assumed to be 15% at each clinical contact. Screening frequencies included three times per lifetime at ages 35, 40, and 45, and every 5 years starting at age 35. In the base case, we assumed that both vaccination and screening coverage rates were 70%, but varied both extensively and independently in sensitivity analysis. Base case values for model parameters and ranges used in sensitivity analysis are presented in Table 2.

Our main analysis focused on assessing the comparative benefits and cost-effectiveness of the strategies in each of the regions. We initially assumed that both cytology and HPV DNA testing were equally available screening options, but also evaluated scenarios in which we assumed that only one of the screening tests was a feasible option. Strategies were compared using the incremental cost-effectiveness ratio, measured as the additional cost divided by the additional health benefit of one strategy compared to 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 excluded from the final cost-effectiveness calculations. To explicitly incorporate the effect of parameter uncertainty, cost-effectiveness analyses were conducted with 25 good-fitting calibrated input parameter sets in each region. Results are reported as the mean outcomes, while incremental cost-effectiveness ratios are reported as the ratio of the mean-costs divided by the mean-effects across the good-fitting parameter sets.

As recommended by published guidelines on cost-effectiveness [22,23], we adopted a societal perspective, and discounted future costs and benefits by 3% per year. As no universal cost-effectiveness threshold exists below which a strategy would be considered cost-effective (i.e., good value for money relative to other health investments Vietnam could elect to adopt), we framed our results in the context of several benchmarks. For the base case, we used the per capita GDP from year 2000 (I$2000) as recommended by the Commission on Macroeconomics and Health [24], and in secondary analyses we assessed the implications of using a lower threshold (i.e., 50% per capita GDP, I$1000). We identified the optimal prevention policies in both North and South Vietnam across different assumptions about vaccine price and other uncertainties. When the policies differed in the two regions, we quantified the loss (or gain) in clinical benefits and costs associated with adopting a single national cervical cancer policy based on the optimal strategy for one region versus the other.

3. Results

3.1. If both cytology and HPV DNA testing are equally available as screening tests

Table 3 shows the mean reductions in lifetime risk of cervical cancer and incremental cost-effectiveness ratios for all strategies when varying cost per vaccinated girl under three scenarios of screening test availability in both regions. In the north, screening with cytology alone three times per lifetime reduced lifetime risk of cancer by 21.3% and had an incremental cost-effectiveness ratio of I$290 per year of life saved (YLS), compared to no intervention. In comparison, screening every 5 years reduced cancer risk by 32.5%, with an incremental cost-effectiveness ratio of I$560 per YLS. While screening alone with HPV DNA testing three times per lifetime was more effective than cytology, it was dominated (i.e., less costly but less cost-effective) by a strategy of either vaccination combined with cytology screening (when cost per vaccinated girl was I$25 or less) or screening alone with HPV DNA testing every 5 years (when cost per vaccinated girl was I$50 or more).

Table 3
Mean cancer reductions and incremental cost-effectiveness ratios by cost per vaccinated girl, availability of screening test, and region[a]

	Cancer reduction (%)[b]	Cost per vaccinated girl[c]							
		I$10	I$25	I$50	I$75	I$100	I$150	I$200	I$450
If both cytology and HPV DNA testing are equally available for screening									
North									
Screening alone (cytology, three times)	21.3	I$290	I$290	I$290	I$290	I$290	I$290	I$290	I$290
Screening alone (cytology, 5 years)	32.5	I$560	I$560	I$560	I$560	I$560	I$560	I$560	I$560
Screening alone (HPV test, three times)	33.3	dom	dom	dom	dom	dom	dom	dom	dom
Screening alone (HPV test, 5 years)	48.9	dom	dom	I$3230	I$3230	I$3230	I$3230	I$3230	I$3230
Vaccination alone	51.2	dom	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (cytology, three times)	62.2	I$970	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (cytology, 5 years)	67.7	I$1250	I$2180	dom	dom	dom	dom	dom	dom
Vaccination + screening (HPV test, three times)	68.2	dom	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (HPV test, 5 years)	76.1	I$6620	I$6620	I$7250	I$10,970	I$14,690	I$22,120	I$29,560	I$66,730
South									
Screening alone (cytology, three times)	20.4	cs	cs	cs	cs	cs	cs	cs	cs
Screening alone (cytology, 5 years)	31.1	I$15	I$15	I$15	I$15	I$15	I$15	I$15	I$15
Screening alone (HPV test, three times)	31.9	dom	dom	dom	dom	dom	dom	dom	dom
Screening alone (HPV test, 5 years)	47.3	dom	dom	I$470	I$470	I$470	I$470	I$470	I$470
Vaccination alone	48.4	I$30	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (cytology, three times)	59.3	I$50	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (cytology, 5 years)	65.0	I$140	I$270	dom	dom	dom	dom	dom	dom
Vaccination + screening (HPV test, three times)	65.4	dom	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (HPV test, 5 years)	73.4	I$1030	I$1030	I$1190	I$1870	I$2550	I$3910	I$5260	I$12,050
If only cytology is available for screening									
North									
Screening alone (three times)	21.3	I$290	I$290	I$290	I$290	I$290	I$290	I$290	I$290
Screening alone (5 years)	32.5	I$560	I$560	I$560	I$560	I$560	I$560	I$560	I$560
Vaccination alone	51.2	dom	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (three times)	62.2	I$970	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (5 years)	67.7	I$1250	I$2180	I$5680	I$8600	I$11,520	I$17,350	I$23,190	I$52,370
South									
Screening alone (three times)	20.4	cs	cs	cs	cs	cs	cs	cs	cs
Screening alone (5 years)	31.1	I$15	I$15	I$15	I$15	I$15	I$15	I$15	I$15
Vaccination alone	48.4	I$30	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (three times)	59.3	I$50	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (5 years)	65.1	I$140	I$270	I$900	I$1430	I$1960	I$3020	I$4070	I$9360
If only HPV DNA testing is available for screening									
North									
Screening alone (three times)	33.3	dom	I$880	I$880	I$880	I$880	I$880	I$880	I$880
Screening alone (5 years)	49.0	dom	I$2060	I$2060	I$2060	I$2060	I$2060	I$2060	I$2060
Vaccination alone	51.2	I$650	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (three times)	68.3	I$1830	I$2260	dom	dom	dom	dom	dom	dom
Vaccination + screening (5 years)	76.1	I$4430	I$4430	I$7250	I$10,970	I$14,690	I$22,120	I$29,560	I$66,730
South									
Screening alone (three times)	31.9	dom	I$90	I$90	I$90	I$90	I$90	I$90	I$90
Screening alone (5 years)	47.3	dom	dom	I$290	I$290	I$290	I$290	I$290	I$290
Vaccination alone	48.4	I$20	dom	dom	dom	dom	dom	dom	dom
Vaccination + screening (three times)	65.4	I$240	I$280	dom	dom	dom	dom	dom	dom
Vaccination + screening (5 years)	73.4	I$640	I$640	I$1190	I$1870	I$2550	I$3910	I$5260	I$12,050

[a] Values represent incremental cost-effectiveness ratios (the ratio of the mean-costs divided by the mean-effects of 25 good-fitting parameter sets in each region) expressed as cost per year of life saved (international dollar per YLS); "dom" denotes strategies that were more costly and less effective or less costly and less cost-effective than alternative options, and were thus considered dominated; "cs" denotes strategies that were cost-saving compared to no intervention, because the future costs averted by preventing cancer were greater than the cost of the intervention.

[b] Reductions in lifetime cancer risk for all strategies were calculated against no intervention and then averaged across 25 good-fitting sets.

[c] Cost per vaccinated girl includes three doses, wastage, delivery, and programmatic costs, and is expressed in 2000 international dollars.

Both strategies of screening alone with HPV DNA testing every 5 years and vaccination alone reduced cervical cancer incidence roughly by half; at a cost per vaccinated girl of I$25 or lower, both were also less cost-effective than either combined vaccination and cytology screening three times per lifetime (at cost of I$10 per vaccinated girl) or vaccination and 5-year cytology (at cost of I$25 per vaccinated girl). At these low vaccine costs, vaccination combined with screening every 5 years, which reduced cancer by 67.7–76.1%, ranged from I$1250 to I$2180 per YLS (with cytology) to I$6620 per YLS (with HPV DNA testing). Provided the cost per vaccinated girl was I$50 or higher, screening alone with HPV DNA testing every 5 years cost I$3230 per YLS, compared to screening alone with cytology. As the cost per vaccinated girl increased from I$50 to I$450, vaccination combined with 5-year screening using HPV DNA testing increased from I$7250 per YLS to I$66,730 per YLS.

Results in the south followed a similar trend, but because of its higher cancer risk, cost-effectiveness ratios were more attractive than in the north. Screening alone with cytology three times per lifetime was cost-saving (indicating that the costs averted from cancer prevention outweighed the costs of screening), and screening alone every 5 years was I$15 per YLS, compared to no intervention. When cost per vaccinated girl was I$10, all strategies were less than I$1100 per YLS; as the cost per vaccinated girl increased to I$450, the cost-effectiveness ratio of combined vaccination and

screening every 5 years with HPV DNA testing increased to I$12,050 per YLS.

When using the per capita GDP (i.e., I$2000) as a threshold for cost-effectiveness, the optimal strategy in the north at a cost of I$10 per vaccinated girl was combined vaccination and cytology screening every 5 years; at I$25 per vaccinated girl or higher, strategies involving vaccination were no longer optimal, and cytology screening alone every 5 years was most cost-effective. When we lowered the cost-effectiveness threshold to 50% per capita GDP (i.e., I$1000), the optimal strategy at I$10 per vaccinated girl was combined vaccination and cytology screening three times per lifetime, and the switch to a strategy of screening alone again occurred between I$10 and I$25 per vaccinated girl.

In contrast, in the south, the cost at which the optimal strategies shifted away from vaccination was much higher; provided the cost per vaccinated girl was less than I$100, combined vaccination and HPV DNA testing every 5 years was the optimal strategy; above I$100, HPV DNA testing every 5 years without vaccination was the most cost-effective strategy. At the lower cost-effectiveness threshold of 50% per capita GDP, strategies including vaccination were no longer attractive between I$25 and I$50 per vaccinated girl. Table 20 in Supplemental Appendix shows relevant vaccine cost thresholds.

3.2. If only cytology or HPV DNA testing is available as a screening test

Using per capita GDP as the threshold for cost-effectiveness, vaccination combined with cytology every 5 years was consistently the most cost-effective strategy provided cost per vaccinated girl was I$10 or less in the north and I$100 or less in the south. At 50% per capita GDP, unless cost per vaccinated girl was I$10 or less in the north, and I$50 or less in the south, cytology screening alone every 5 years was the optimal strategy.

When HPV DNA testing was the only screening test considered, the incremental cost-effectiveness ratios were generally higher. For example, when cost per vaccinated girl was I$25 or more in the north, HPV DNA testing alone, either three times per lifetime or every 5 years, had a cost-effectiveness ratio that was over three times greater than the corresponding strategies using cytology. In the south, this trend was similar although more pronounced; at a cost per vaccinated girl of I$50 or higher, HPV DNA testing three times per lifetime cost I$90 per YLS, and HPV DNA testing every 5 years cost I$290 per YLS, compared to the corresponding strategies when only cytology is available, which were cost saving and I$15, respectively. In both regions, when the cost per vaccinated girl was very low (i.e., I$10), vaccination alone was more efficient than HPV DNA testing alone at either interval.

3.3. Tradeoffs in costs and health benefits associated with a national cervical cancer policy

Because of the discordance of optimal strategy between regions, we juxtaposed the results in the north and south to elucidate both qualitatively and quantitatively the tradeoffs of overlooking important heterogeneities within a particular country when making policy decisions. Fig. 2 contrasts the optimal strategies in both regions when the cost per vaccinated girl was varied from I$10 to I$450, assuming a cost-effectiveness threshold of per capita GDP. When cytology and HPV DNA testing were assumed to be equally available in the north (top panel), a threshold existed between I$10 and I$25 per vaccinated girl, at which the optimal strategy switched from vaccination combined with cytology screening every 5 years (represented in yellow) to cytology screening alone every 5 years (green). In the south, however, at lower vaccine costs, the optimal strategy was vaccination combined with HPV DNA testing every 5 years; the switch to an optimal strategy of screening alone (using HPV DNA testing every 5 years) did not occur until the cost per vaccinated girl reached I$100. Therefore, the optimal strategies in both regions were dissimilar at vaccination costs between I$25 and I$75.

We evaluated the gains and losses in total costs and health benefits when implementing a national cervical cancer policy based on one region's optimal policy versus the other's. Fig. 3 depicts this tradeoff of costs and benefits for strategies in both regions,

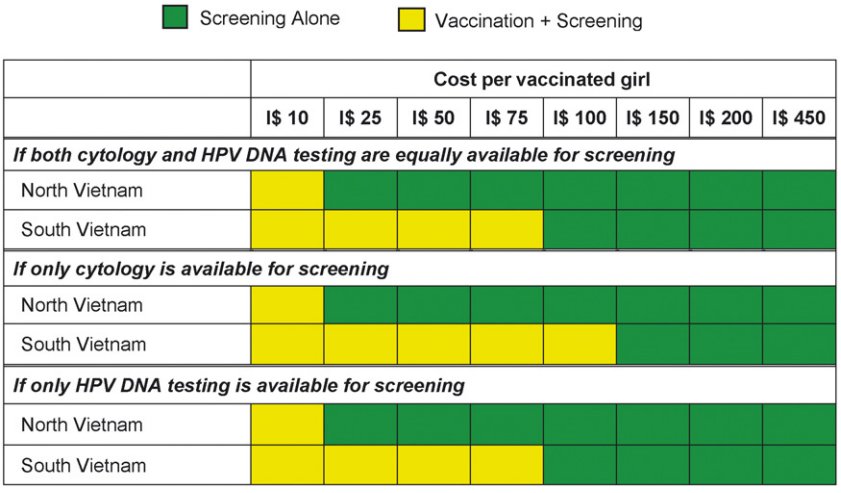

Fig. 2. Optimal strategies in the north and south using a cost-effectiveness threshold of per capita GDP (I$2000). The optimal strategy across a range of costs per vaccinated girl (I$10–I$450) is indicated by the colored boxes for scenarios in which both three-visit cytology and two-visit HPV DNA testing are available for screening (top), only cytology is available (middle panel), and only HPV DNA testing is available (bottom). Green represents screening alone; and yellow, vaccination plus screening. When cytology and HPV DNA testing were assumed to be equally available in the north (top panel), a threshold existed between I$10 and I$25 per vaccinated girl at which the optimal strategy switched from vaccination combined with screening (represented in yellow) to screening alone (green). In the south, however, the switch to screening alone did not occur until cost per vaccinated girl reached I$100. When assuming only cytology was available for screening (middle panel), the vaccine cost threshold was the same as the previous analysis in the north but higher in the south (I$150 or higher). When assuming only HPV DNA testing was available (bottom panel), the optimal strategy was combined vaccination and screening when cost per vaccinated girl was I$10 or less in the north; in the south, the switch in optimal strategy from vaccination plus screening to screening alone occurred between I$75 and I$100 per vaccinated girl.

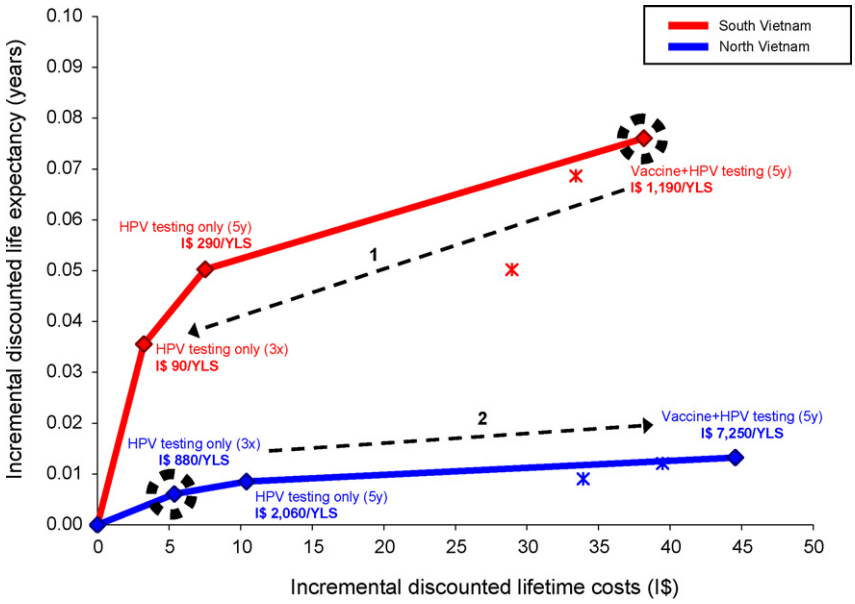

Fig. 3. Gains and losses in outcomes associated with a national cervical cancer prevention policy. The efficiency curves show the discounted lifetime costs (*x*-axis) and discounted life expectancy (*y*-axis) for strategies in each region (blue line, North Vietnam; red line, South Vietnam), when assuming only two-visit HPV DNA testing is available for screening and cost per vaccinated girl is I$50. Costs and benefits represent the mean values of 25 good-fitting parameter sets from each region, incremental to each region's baseline strategy of no intervention. Strategies lying on the curves are considered efficient strategies because they are more cost-effective than a cheaper strategy that falls to the right of the curves (indicated by asterisks; in both regions, vaccination alone and combined vaccination and HPV DNA testing three times per lifetime are inefficient, or "dominated"). At the regional level, vaccination combined with screening every 5 years (vaccine + HPV testing (5*y*)) is optimal in the south, and screening alone (HPV testing only (3*x*)) is optimal in the north, both strategies circled on the graph. At the national level, however, if the north's optimal policy (i.e., screening alone) were implemented in the south, total benefits would decrease by 42% (approximately 1920 fewer cases averted over the lifetime of a cohort of 9-year-old girls) in the south at a cost savings of I$35 per woman (shown by the arrow marked "1"). If, on the other hand, the south's optimal policy (i.e., vaccination plus screening) were implemented in the north, total benefits would increase by 43% (approximately 230 additional cases averted over the lifetime of a cohort of 9-year-old girls) in the north at an increased cost of I$39 per woman (shown by the arrow marked "2").

assuming a cost per vaccinated girl of I$50 and HPV DNA testing for screening. When assuming a cost-effectiveness threshold of per capita GDP, the optimal prevention policy in the north was screening alone three times per lifetime while the optimal policy in the south was vaccination combined with screening every 5 years. Implementing a national strategy based on the north's optimal policy (i.e., HPV DNA testing three times per lifetime without vaccination) would result in approximately 42% less prevented cancer in the south (approximately 1920 fewer cases averted over the lifetime of a cohort of 9-year-old girls) at a cost savings of I$35 per woman. On the other hand, if the optimal strategy in the south (i.e., vaccination plus screening every 5 years) was adopted in the north, total benefits would increase by 43% (approximately 230 additional cases averted over the lifetime of a cohort of 9-year-old girls) in the north at an increased cost of I$39 per woman.

3.4. Sensitivity analysis

We have reported extensive sensitivity analyses with respect to natural history assumptions, vaccine and screening properties, and costs in the context of other settings [9,12–14,25]. Consistent with those findings, our results were most sensitive to assumptions about achievable vaccination and screening coverage, vaccine efficacy, and vaccine and screening costs. Within Vietnam, these variables were more influential in the north than in the south, particularly when the cost per vaccinated girl was assumed to be low; however, although the cost-effectiveness ratios changed, in most scenarios, the optimal strategies remained similar to those identified in the base case. For example, at a cost per vaccinated girl of I$10 or I$25 in the north, when cytology test cost was increased by I$5, approaching the cost of an HPV DNA test, the optimal strategy using a criteria of per capita GDP shifted from vaccination combined with cytology screening every 5 years to vaccination and cytology screening three times per lifetime. In the south, however, the optimal strategy remained vaccination and HPV DNA testing every 5 years, even when the cost of the HPV DNA test was doubled; it was not until the HPV DNA test cost exceeded I$17 that vaccination and HPV DNA testing every 5 years exceeded the per capita GDP of I$2000. Varying the range of cancer costs from 25% to 200% of base case values in the north resulted in only modest changes in cost-effectiveness ratios and no changes in optimal strategies across the range of costs per vaccinated girl. In the south, however, where cancer incidence is greater, variations in cancer costs had a greater impact on ratios, although the optimal strategies remained the same as in the base case. For example, when cancer costs were decreased to 25% of base case values, the cost-effectiveness ratio for vaccination and 5-year HPV DNA testing increased slightly from I$1030 to I$1210 per YLS at a cost per vaccinated girl of I$10; when cancer costs were increased to 200% of base case values, the base case results in the south were only strengthened, with vaccination and 5-year HPV DNA testing decreasing to I$14 per YLS and all other strategies being cost-saving. These changes were blunted at higher costs per vaccinated girl.

When exploring the relationship of vaccination and screening coverage, in general, at lower vaccination coverage rates, screening became more attractive, resulting in lower cost-effectiveness ratios for combined vaccination and screening strategies. In the north, however, even when the cost per vaccinated girl was very low, the optimal strategy remained combined vaccination and cytology. At higher vaccine costs, strategies involving vaccination in the north remained either dominated or too costly (>I$10,000 per YLS). In the south, when vaccination coverage was less than 60%, the cost-effectiveness ratio for combined vaccination and HPV DNA testing every 5 years fell below 50% per capita GDP (i.e., <I$1000) when the

cost per vaccinated girl was I$10. At higher costs per vaccinated girl, the optimal strategy was more sensitive to vaccination coverage; for example, at I$50 per vaccinated girl, combined vaccination and HPV DNA testing every 5 years was less than 50% per capita GDP when vaccination coverage was lower than 40%, but exceeded per capita GDP when coverage increased close to 100%. At I$100 per vaccinated girl, this strategy exceeded the per capita GDP when vaccination coverage was greater than 20%, shifting the optimal strategy to HPV DNA testing alone every 5 years.

When exploring lower estimates of vaccine efficacy or waning vaccine protection, there was an expected shift towards strategies that involve screening alone. Only at low vaccine costs (I$10) did these properties influence the optimal strategy in the north; when vaccine efficacy was below 80%, the optimal strategy switched from combined vaccination and cytology screening every 5 years to cytology screening alone every 5 years. In the south, the optimal strategy remained vaccination combined with HPV DNA testing every 5 years at a cost per vaccinated girl of I$10, even when vaccine efficacy decreased to 20%; at a vaccine cost of I$50 per vaccinated girl, HPV DNA testing alone every 5 years became the optimal strategy when vaccine efficacy decreased to 60% or lower.

When duration of vaccine efficacy was assumed to be only 10 or 20 years, the cost-effectiveness of strategies involving vaccination and screening more frequently (i.e., every 5 years) generally looked more attractive. This trend is understandable since the effects of screening are more apparent when vaccine protection is only temporary. Adding a single booster 10 years after initial vaccination in order to extend vaccine protection over the lifetime led to vaccination strategies becoming less attractive, but had little to no effect in changing the optimal strategy based on a cost-effectiveness threshold of per capita GDP. Results from sensitivity analyses can be found in Supplemental Appendix.

Results were stable across explorations of test characteristics. Even when sensitivity of cytology dropped to 50% or specificity dropped to 90%, there were no changes in optimal strategies based on the two thresholds of cost-effectiveness in either region. Furthermore, when loss to follow-up decreased to 5%, and all other factors were held constant, strategies involving three-visit cytology did improve marginally; for example, in the north, cytology alone three times per lifetime and every 5 years decreased to I$230 per YLS and I$510 per YLS, respectively (compared to I$290 per YLS and I$560 per YLS in the base case). At 25% loss to follow-up per visit, two-visit HPV DNA testing was only marginally more attractive than cytology.

4. Discussion

Assuming 70% vaccination and screening coverage in Vietnam, our model projected that lifetime risk of cancer can be reduced by 20.4–48.9% with cervical cancer screening of older women alone (three times per lifetime or every 5 years using cytology or HPV DNA testing); 48.4–51.2% with vaccination of pre-adolescent girls alone; and 59.3–76.1% with vaccinating pre-adolescent girls and screening older women, depending on region, frequency and test. Although the calculated reductions were quite similar between the north and south, because of the disparate cancer risks between the two regions, the absolute cancer cases averted were much higher in the south. For example, a strategy of vaccination combined with HPV DNA testing every 5 years is projected to avert 3400 cervical cancer cases over the lifetime of a single cohort of 9-year-old girls in the south, whereas in the north, the estimated number of cases averted with this same strategy is 410.

Using a commonly cited cost-effectiveness threshold of per capita GDP in Vietnam (I$2000), we found that when cost per vaccinated girl was low (e.g., I$10, implying a per dose cost of $2), vaccination combined with screening every 5 years with either cytology or HPV DNA testing was the most cost-effective strategy in both the north and south, resulting in reductions in lifetime cervical cancer ranging from 67.7% to 73.4% at 70% coverage. At very high costs per vaccinated girl (e.g., I$100, implying a per dose cost of $26), vaccination was no longer attractive, and strategies of screening alone were most cost-effective in both regions. When cost per vaccinated girl was in between these two thresholds, however, the optimal strategies in each region diverged. In particular, in the north, cytology screening every 5 years without vaccination was the most cost-effective strategy when cost per vaccinated girl was I$25 or higher, whereas in the south, strategies involving both screening and vaccination were preferred until cost per vaccinated girl reached I$100.

There is no consensus on the willingness to pay for a year of life saved (i.e., a “cost-effectiveness threshold”). While we elected to use the per capita GDP criterion as a heuristic for comparative purposes, a more realistic threshold may be 50% per capita GDP or even lower, based on the cost-effectiveness of other vaccine programs that have been adopted in developing countries [26]. Under this lower threshold, cost per vaccinated girl must be below I$10 in the north and I$50 in the south (implying per dose costs of $2 and $12, respectively) in order for the most cost-effective strategy to include vaccination. At even lower thresholds, such as I$500 per YLS suggested for other vaccination strategies in resource-poor settings [26], even in the south, vaccine costs would need to be lower.

Vaccine costs were influential on these results, especially in the north, since the cost of screening is relatively low in Vietnam. In the south, the cancer risk is far higher such that the costs averted by preventing cancer were fairly large compared to the cost of either vaccination or screening. Other influential factors, such as vaccine efficacy, shifted the absolute cost-effectiveness ratios, but rarely changed the optimal strategy in both regions using either cost-effectiveness threshold (i.e., per capita GDP, 50% per capita GDP). As we have found in previous analyses [13,25], provided vaccine-induced immunity was long lasting, the incremental benefit of screening diminished with higher vaccination coverage rates. Based on the recent immunization experience of Vietnam with respect to childhood vaccinations, high vaccination coverage may be indeed achievable [27]. However, vaccination of young adolescents prior to sexual activity may pose greater challenges than childhood vaccination since there are not well-established contacts with the health care system at this age. Moreover, although programs that do not rely solely on traditional health care settings, such as school-based immunization, possess theoretical appeal, many children are not in school at this age (i.e., up to 20% of females) [21]. Finally, a large disparity exists between rural and urban areas of the country, with vaccination coverage 25% lower in rural areas [28]; with 35% of the population in Hanoi and 14% in Ho Chi Minh City living in rural settings [28], a high priority will be to increase accessibility among those who live in remote areas with limited infrastructure.

The regional differences in cost-effectiveness ratios and optimal strategies between the north and south were largely driven by the differences in rates of HPV infection and cervical cancer incidence. A population-based survey of HPV in Vietnam showed that overall prevalence was 2.0% in Hanoi and 10.9% in Ho Chi Minh City [4]. Pham et al. [4] found moderate associations of HPV prevalence with lifetime number of sexual partners (only in Ho Chi Minh City), parity, and oral contraceptive use. A survey of sexual behavior among married people in Vietnam found that there has been an increase in the number of men and women who engage in premarital sex throughout the country, with a disproportionate increase in the north [29]. As the level of sexual activity equalizes throughout the country, the disparity in cancer rates between the northern and

southern regions of Vietnam could potentially dissipate in coming years. This is an important priority for future study.

Cost-effectiveness analysis can provide useful information about the value of investing in different health interventions but is certainly only one of many considerations for decisions about policy, and more specifically, the adoption of a new vaccine. In no particular order, affordability and financial resources required, cultural acceptability, political will, and distributional and equity considerations are all important to consider. Indeed, even the most cost-effective interventions (i.e., economically efficient or good value for money) may not be feasible to implement because they may not be affordable—it may simply be too costly given an annual fixed budget to cover the target population given competing priorities and other relevant health issues. Using a threshold of per capita GDP in our base case analysis, we found that a strategy of pre-adolescent vaccination combined with HPV DNA testing every 5 years was consistently the most cost-effective strategy in the south, up to a cost of I$75 per vaccinated girl (implied dose cost of $19). However, at this cost, the short-term annual financial costs would exceed I$40 million to vaccinate 70% of a single birth cohort of 9-year-old girls in Vietnam. With an annual health budget of I$164 per capita (in 2003) [30], it is unlikely that such a high vaccine cost will be affordable in Vietnam.

Within the context of these financial considerations, we also explored the policy implications of adopting a single national prevention policy in scenarios where the optimal policies diverged between the north and south. We found that basing a national strategy on only one of the regions resulted in inefficiencies in the other. For example, at a vaccine cost of I$50, adopting a national policy favored by the north (i.e., screening three times per lifetime without vaccination) would reduce cancer benefits by 42% and total lifetime costs by I$35 per woman in the south, compared to adopting the south's optimal policy (i.e., vaccination and 5-year screening). At the population level, this reduction in benefit translates to up to 1920 fewer cases prevented over the lifetime of a cohort of 9-year-old girls in the south for a cost reduction of nearly I$6 million. Meanwhile, adopting the south's optimal policy at the national level would prevent an additional 230 cervical cancer cases over the lifetime of a cohort of 9-year-old girls in the north at an additional cost of nearly I$5 million (i.e., I$39 per woman). While not intended to be a comprehensive analysis of all factors associated with national versus region-based policy, these results are meant to provide qualitative insight for decision-makers who are considering the optimal approach to cervical cancer prevention in heterogeneous settings. Decision makers in Vietnam will need to consider other factors, such as achievable vaccination and screening coverage in both regions, acceptability of the strategies, competing priorities vying for the same resources, and other local characteristics.

As with all model-based analyses, our results should be interpreted within the context of our limitations. Although we used regional estimates of HPV prevalence and cancer incidence from Hanoi and Ho Chi Minh City, we did not have regional data for all calibration targets and, therefore, could not reflect all of the epidemiological variation between the two regions. Data were also based on surveys from the mid-1990s, which may not reflect recent changes in sexual behavior in Vietnam over the past decade. To address the uncertainty in the natural history model parameters, we used multiple good-fitting parameter sets (i.e., 25 in each region) for all analyses and reported the mean outcomes. We also assumed that test performance and screening and vaccination coverage were the same between the north and south, but these factors may depend on the relative infrastructure available in each of the regions. Base case estimates of screening and treatment costs were not based on primary sources from Vietnam; instead, we relied on primary cost estimates from a neighboring southeast Asian country, adjusted for differences in economic indicators, such as per capita GDP. For assumptions about vaccine and screening properties, such as efficacy, test performance, and costs, we conducted extensive one- and two-way sensitivity analysis. It is important to underscore that our base case analyses were conducted under the assumptions of lifelong vaccine-induced protection with no cross-protective effects on other high-risk (i.e., non-16/18) HPV types. Longer term data from clinical trials on these two important uncertainties will provide critical information for future analyses. Further limitations of our model assumptions, calibration process, and analyses have been discussed extensively in previous publications [12–14,31].

Despite the inherent limitations of a model-based approach that relies on data of heterogeneous quality and assumptions where data are not yet available, our analysis suggests that HPV vaccination can be an attractive cancer prevention strategy for Vietnam, provided high coverage is achievable in young pre-adolescent girls prior to becoming sexually active, screening is available to women older than age 30, and the cost per vaccinated girl (including the vaccine price, support costs, and programmatic costs) is I$25 or lower. The implied per dose cost of the HPV vaccine would need to be less than a few dollars to be cost-effective, and a fraction of that figure to be affordable. Finally, countries with heterogeneous cervical cancer risk profiles may wish to consider the tradeoffs associated with establishing a national policy versus more local policies tailored for specific regions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2008.05.038.

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