Costs and Benefits of Different Strategies to Screen for Cervical Cancer in Less-Developed Countries

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Background: **About 80% of cervical cancers occur in less-developed countries. This disproportionate burden of cervical cancer in such countries is due mainly to the lack of well-organized screening programs. Several cervical cancer screening strategies have been proposed as more cost-effective than cytology screening. We compared the costs and benefits of different strategies and their effectiveness in saving lives in a less-developed country.** ***Methods:*** **We used a population-based simulation model to evaluate the incremental societal costs and benefits in Thailand of seven screening techniques, including visual inspection of the cervix after applying acetic acid (VIA), human papillomavirus (HPV) testing, Pap smear, and combinations of screening tests, and examined the discounted costs per year of life saved (LYS).** ***Results:*** **Compared with no (i.e., not well-organized) screening, all strategies saved lives, at costs ranging from $121 to $6720 per LYS, and reduced mortality, by up to 58%. Comparing each strategy with the next least expensive alternative, VIA performed at 5-year intervals in women of ages 35–55 with immediate treatment if abnormalities are found was the least expensive option and saved the greatest number of lives, with a cost of $517 per LYS. HPV screening resulted in similar costs and benefits, if the test cost is $5 and if 90% of women undergo follow-up after an abnormal screen. Cytology (Pap smear) was a reasonable alternative if sensitivity exceeds 80% and if 90% of women undergo follow-up. Compared with no screening, use of a combination of Pap smear and HPV testing at 5-year intervals in women of ages 20–70 could achieve greater than 90% reduction in cervical cancer mortality at a cost of $1683 per LYS, and VIA could achieve 83% reduction at $524 per LYS.** ***Conclusions:*** **Well-organized screening programs can reduce cervical cancer mortality in less-developed countries at low costs. These cost-effectiveness data can enhance decision-making about optimal policies for a given setting.** **[J Natl Cancer Inst 2002;94:1469–83]**

Although the incidence of and mortality from cervical cancer have declined substantially over the last four decades worldwide *(1),* cervical cancer continues to be a leading cause of cancer death in women *(2,3).* Cervical cancer rates are highest in less-developed countries, including those of Latin America, sub-Saharan Africa, and Southeast Asia *(4–7),* and lowest in industrialized nations *(8).* About 80% of all cervical cancer cases and deaths occur in less-developed countries *(4–6);* this disproportionate burden of cervical cancer is due largely to the absence of well-organized screening programs *(9,10).*

Unfortunately, in many less-developed countries, health care resources for cytology screening programs may be low and difficult to organize, are often of suboptimal quality, and must compete with other pressing health problems for funding *(11).* Recently, human papillomavirus (HPV) DNA testing *(10,12–18)* and visual inspection of the cervix after applying acetic acid (VIA) *(19–22)* have been proposed as reasonable screening strategies in low-resource settings.

In this study, we used a population-based model to simulate the natural history of cervical neoplasia and compared the benefits and costs of using VIA, HPV DNA testing, and Pap smears to screen for cervical cancer in Thailand. We chose Thailand as an example of a less-developed country because it has high rates of cervical cancer incidence and mortality *(3,23,24),* has a largely rural population, and has minimal infrastructure for cytologic testing. Thailand has also identified cervical cancer as a key public health problem *(7)* and is implementing a pilot program for alternative screening strategies. Our results are intended to inform public health debate about the most efficient use of limited resources to eradicate cervical cancer worldwide.

Methods

Simulation Model

We developed a semi-Markov model that incorporates 17 health states and used first-order Monte Carlo stochastic simulations *(25)* to portray the dynamic processes of cervical neoplasia, screening, diagnosis, and treatment (Fig. 1). Each simulation represents a cohort of one million women. All health states represent histopathologic states; women move through health states on a 1-year cycle. Women may transition between health states as a result of being screened, developing symptoms, or dying from cervical cancer or other causes (competing mortality; *see* "Life Expectancy" section for the source of competing mortality data). The model has the ability to "remember" prior states only after women are diagnosed with cancer and treated.

We used this model to evaluate 42 combinations of seven different screening strategies performed at varying intervals

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See "Notes" following "References."

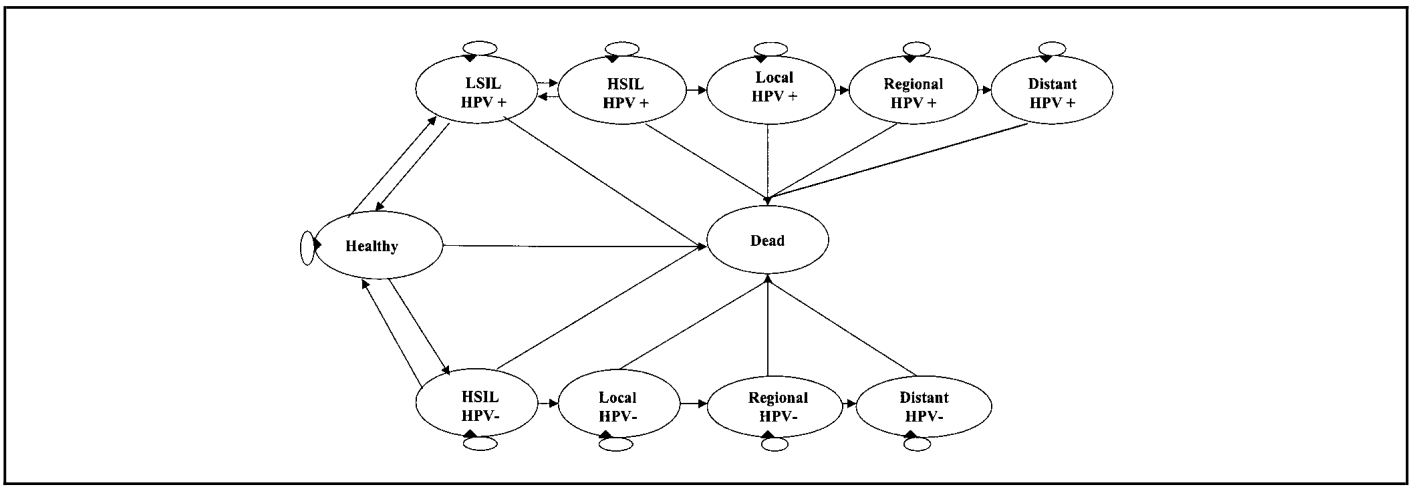

Fig. 1. Representation of model health states. Each circle represents a health state. The figure shows 11 health states. Health states depicting cancer (local, regional, and distant) represent undiagnosed disease. Not shown are six additional health states (local, regional, and distant cancers for both human papillomavirus [HPV]+ and HPV–) that are diagnosed and treated. Therefore, a total of 17 health states are incorporated in this model. At the start of the model, women are in one of these health states. A woman may transition from her current health state to another health state (designated transitions are indicated by arrows between different states) or remain in the same health state (designated by **circular arrows** on top of each circle). After a women dies from cervical cancer or any other cause, she remains in the health state denoted as "dead." Women may develop HPV-dependent neoplasia (**top row** of health states); a small proportion (about 5%) may develop high-grade squamous intra-epithelial lesions (HSIL) or invasive cancers that have no detectable HPV (**bottom row** of health states). The HSIL/HPV+ state can regresses to the healthy state only via the LSIL/HPV+ state. Local = local stage invasive cancer; Regional = regional stage invasive cancer; Distant = distant stage invasive cancer.

(e.g., 5 or 10 years) for cohorts of rural nonpregnant women (note that prevalence of contraceptive use is approximately 75% in this setting). The overall rate of human immunodeficiency virus (HIV) infection is very low in Thailand (<2%) *(26),* so we modeled natural history in women without HIV, because HIV and HPV interact in their effects on natural history of cervical cancer *(27–29).* The details of model parameters for the base case are described in Table 1. The cost is determined by using base-case parameters followed by cost comparisons after incremental changes.

Screening Strategies

The seven screening strategies (with six different screening frequencies in each—a total of 42 combinations) that we evaluated included 1) VIA and immediate offer of cryotherapy treatment of abnormal lesions; 2) VIA with referral of women with abnormal results to a regional hospital; 3) HPV DNA testing (with hybrid capture II or polymerase chain reaction [PCR]); 4) Pap smear screening; 5) Pap smear screening with HPV DNA testing, followed by evaluation of women with an abnormal result from either test; 6) VIA followed by HPV DNA testing, with women who are found to have VIA-detected lesions that are not appropriate for immediate treatment being referred for appropriate care (work-up of lesion), regardless of HPV test result; and 7) no screening (but treatment of symptomatic disease). We calculated incremental cost-effectiveness ratios, in which the additional cost of a strategy divided by the added savings in life-year(s) saved (LYS) is compared with the cost of the next least expensive strategy *(30).* We also calculated cervical cancer incidence and reductions in mortality associated with each strategy. All costs and effects were discounted at 3% *(30).* Investments in screening programs yield future savings in costs and lives. Discounting adjusts these future costs and outcomes to current values.

Screening, diagnostic, and treatment procedures were based on current practice conventions. Briefly, VIA is performed at a community site; other screening examinations are offered at existing centers in the closest district hospital. In strategy 1, VIA with immediate treatment, women with an abnormal examination are offered immediate treatment with cryotherapy. However, if VIA reveals a suspected invasive cancer [a lesion that occupies 75% or more of the cervical surface, that extends into the os, or that extends more than 2 mm beyond the diameter of the cryotherapy probe *(31)*], women are referred for further hospital evaluation. Among women undergoing HPV DNA or Pap smear testing, those with oncogenic types of HPV or Pap smears showing low-grade squamous intra-epithelial lesions (LSILs) or more severe lesions (denoted as >LSILs) are referred to a regional hospital for diagnostic evaluation. Women with confirmed disease (>LSIL) undergo regional hospital treatment and surveillance and a return to periodic screening *(3,24).* The alternative of treating only those women with histologically confirmed high-grade squamous intra-epithelial lesions (HSILs) or more severe lesions is considered in sensitivity analyses. Women with false-negative results will undergo screening in the next time period; women who are not screened will be diagnosed and treated if they present with symptoms.

Model Assumptions

There are several underlying assumptions in our model. The key assumption is that cervical neoplasia reflects the natural history of human papillomavirus infection and rarely (in up to 5% of cases) occurs in the absence of HPV infection *(32–36).*

To produce a model that faithfully reflects the underlying events in cervical neoplasia yet is parsimonious, we also make several simplifying assumptions. One is that all health states represent histopathologic states. We have combined the health states for newly acquired HPV infection (without cytologic or histologic abnormalities) and LSIL (cytologic and pathologic

evidence of HPV infection) in one state for two reasons. First, the transition between both of these health states and the healthy state is rapid and frequent, and there are limited reliable primary data to quantify the probabilities of these transitions. Second, the reproducibility of interpretations of these states is only fair, leading to high potential for misclassification *(37)*.

The second assumption is that the baseline risk of HPV infection varies among countries but that the underlying disease process is the same in developed and less-developed countries. Third, atypical squamous cells of uncertain significance (ASCUS) is a cytologic finding, not a pathologic state. Although in developed countries ASCUS is often considered a result requiring evaluation, it is not routinely evaluated or treated in Thailand. Consequently, we combined women who have ASCUS with women who have negative tests; all model sensitivity and specificity values reflect this cut point.

Fourth, while women treated for LSIL may have either a higher or lower probability of redeveloping LSIL after first treatment, the Markov model health states do not have the ability to remember prior events except cancer *(38)*. Thus, we assume that women who are treated for HPV/LSIL and are cured return to the healthy state and acquire new HPV infection at similar rates to those seen in women without prior HPV/LSIL; women who are treated and not cured remain in the HPV/LSIL state in the model.

Finally, we assume, based on current patterns of medical care in Thailand (where hysterectomies are uncommon for reasons other than cancer) that women without cancer retain their cervix and continue to be at risk for neoplasia.

Model Parameters

To estimate the probability of all events in the model, we reviewed the literature for the best quality, least biased studies applicable to Thailand *(39)*. If Thailand-specific data were unavailable, we used data from areas with similar cervical cancer mortality rates (e.g., India, Costa Rica, South Africa). For parameters for which no published data existed, we used estimates from clinicians and health ministry staff. All parameters are summarized in Tables 1 and 2.

Natural History of Disease

Our general approach to modeling the course of the disease was to begin with the observed HPV prevalence rates in Thailand. We then used longitudinal data from developed countries on the rates of progression, regression, and persistence of HPV infection to develop transition probabilities between different health states and to calculate incidence rates *(24,70)*.

Age-specific prevalence rates. There is a paucity of HPV data from Thailand. To improve the precision of our estimates, we estimated the prevalence of HPV infection/LSIL by pooling weighted data from Thailand, Costa Rica, and Honduras, because the latter two countries 1) have good quality data available and 2) have cervical cancer rates and populations similar to those of Thailand (e.g., largely rural, poor, large agricultural economy) *(14,15,40,41)*. Because the current rate of HPV screening is extremely low in Thailand, age-specific invasive cancer incidence rates were used to approximate prevalence in unscreened populations *(24)*.

Transition probabilities. Transition rates for oncogenic types of HPV were calculated using pooled, weighted data from studies published between 1990 and 2000 using standard fixed effects meta-analysis methods (SAS, SAS Institute, Cary, NC). Pooled rates were converted to annual transition probabilities, calibrated across the model to predict intermediate events and constrained so that the sum of the probabilities of regression, progression, persistence, and noncervical cancer death equaled 1. As in other models, to accurately predict observed cancer rates we used age-dependent transition probabilities (e.g., regression of HPV infection and neoplasia is less likely in older women than in young women) *(46–52,57,71–73)*. Finally, once women develop invasive cancer, disease does not regress. In the absence of screening, based on observed incidence data that are published *(42)*, it is assumed that women present with clinical symptoms (10% symptomatic at local disease, 50% at regional, and 70% at distant).

Test Characteristics

We included data on sensitivity and specificity under current field conditions from studies in less-developed countries with colposcopy and/or histologic confirmation of disease status for all testing positive for each test and for a reasonable proportion of those testing negative *(18,74–77)*. In sensitivity analyses, we assumed that test performance varies by age *(78,79)*, and we evaluated results at wide ranges of sensitivity. We assumed that results of repeated tests are independent.

VIA. The sensitivity of VIA for LSIL and HSIL or more severe lesions was 57.5% and 76.9%, respectively, with specificity of 65.4% *(22,60)*. We assumed that sensitivity of VIA was not affected by cryosurgery, because field experience in Thailand demonstrates that, 1 year after cryotherapy, the squamocolumnar junction is visible in almost all women.

Pap smears. Based on Pap smear performance data from several less-developed countries, we estimated sensitivity of 19.6% for LSIL and 46.2% for HSIL or more severe lesions; we estimated specificity to be 94.5% *(17,22,60,61)*. However, because these test characteristics were noted in unstructured screening programs, and test performance is likely to be better in an organized program, we also tested a range of values in sensitivity analyses *(80)*.

HPV DNA testing. HPV sensitivity was estimated to be 55.6%, 78.7%, and 78.7% for LSIL, HSIL, and invasive cancer, respectively, based on weighted pooled estimates from studies in less-developed countries from 1990 through 2000 that used polymerase chain reaction (PCR) or Hybrid Capture II (Digene, Inc., Gaithersburg, MD) *(35,81,82)* to detect moderate or high oncogenic HPV types. Specificity was estimated to be 79% *(10, 12,60)*.

Diagnostic Evaluation

Because many rural hospitals do not have trained colposcopists or colposcopy equipment, we assume that diagnostic evaluations are done using biopsy under VIA; use of colposcopy is evaluated in sensitivity analyses. If women are diagnosed with cancer, they undergo a staging evaluation.

Compliance

In the base case, we assume that all women attend screening because it is offered locally but that only 50% of women follow through with referrals to a district hospital for diagnostic evaluation. We assume that 95% of women who have an abnormal VIA not requiring referral will agree to immediate cryotherapy *(31)*. Finally, we assume that all women who complete a diagnostic evaluation and have HSIL or cancer will complete treatment. Alternative assumptions are evaluated in sensitivity analyses.

Table 1. Parameters used in the simulation model to estimate the effects of screening

Parameter	Base case (range)	References
Natural history of disease		
Prevalence of HPV/LSIL %*		*(14,15,40,41)*
20–24 years	21.0	
25–29 years	18.0	
30–34 years	15.0	
35–39 years	12.0	
40–44 years	8.4	
45–49 years	8.2	
50–54 years	8.2	
55–59 years	6.3	
60–64 years	6.3	
⩾65 years	2.7	
Transition probabilities†		
Progression from healthy to HPV/LSIL‡		*(42)*
20 years	0.088	
25 years	0.059	
35 years	0.050	
50 years	0.034	
65 years	0.0053	
Regression from HPV/LSIL to healthy§	0.284	Imputed
Persistence of HPV/LSIL	[(1 − [regression + progression]) × (1 − competing mortality)]	*(43–49)*
Progression from HPV/LSIL to HSIL‡		*(43,45,47–58)*
20 years	0.005	
25 years	0.005	
35 years	0.015	
50 years	0.03	
65 years	0.04	
Regression from HSIL to HPV/LSIL		*(48,57–59)*
20–39 years	0.25	
⩾40 years	0.23	
Persistence of HSIL	[(1 − [regression + progression]) × (1 − competing mortality)]	*(52,59)*
Progression from HSIL to invasive cancer‡		*(48,57–59)*
20 years	0.011	
25 years	0.025	
35 years	0.025	
50 years	0.041	
65 years	0.053	
Screening and diagnostic test characteristics		
VIA‖		*(22,60)*, clinical estimates for age-specific rates
Sensitivity LSIL	57.5% (95% CI = 44.4% to 70.6%)	
>55 years	37.5%	
Sensitivity ⩾HSIL	76.9% (95% CI = 75.9% to 77.8%)	
>55 years	60.0%	
Specificity ⩾LSIL	65.4% (95% CI = 56.3% to 74.6%)	
>55 years	55%	
Pap smear		*(17,22,60,61)*, clinical estimates for age-specific rates
Sensitivity LSIL	19.6% (95% CI = 11.6% to 27.5%)	
>55 years	17.1%	
Sensitivity ⩾HSIL	46.2% (95% CI = 35.4% to 56.9%)	
>55 years	40.2%	
Specificity ⩾LSIL	94.5% (95% CI = 92.1% to 96.8%)	
>55 years	82.2%	
HPV DNA testing—Hybrid Capture II or PCR		*(10,12,60)*
Sensitivity LSIL	55.6% (95% CI = 45.6% to 65.5%)	
Sensitivity ⩾HSIL	78.7% (95% CI = 71.9% to 85.5%)	
Specificity ⩾LSIL	79.2% (95% CI = 57.4% to 100%)	
Biopsy under visual inspection		*(62,63)*
Sensitivity ⩾LSIL	87% (95% CI = 75% to 95%)	
Specificity ⩾LSIL	100%	
Biopsy under colposcopic visualization		*(62,63)*
Sensitivity ⩾LSIL	95% (95% CI = 80% to 100%)	
Specificity ⩾LSIL	100%	
Cure rates for preinvasive disease		*(64–66)*
LSIL		
Immediate cryotherapy	90% (95% CI = 83% to 98%)	
Referral cryotherapy or LEEP	95% (95% CI = 88% to 99%)	
HSIL		
Immediate cryotherapy	75% (95% CI = 68% to 83%)	
Referral TAH or cone	98% (95% CI = 95% to 99%)	

(Table continues)

Table 1 (continued). Parameters used in the simulation model to estimate the effects of screening

Parameter	Base case (range)	References
Compliance		*(67,68)*
Screening	100% (95% CI = 30% to 100%)	
Diagnosis		
VIA and immediate cryotherapy	95% (95% CI = 90% to 100%)	
Evaluation at hospital	50% (95% CI = 40% to 100%)	
Treatment	100%	
Age-specific 5-year relative survival, %		Sankaranarayanan R: unpublished data
Local invasive		
19–24 years	86.3	
25–29 years	93.9	
30–34 years	97.1	
35–39 years	94.7	
40–44 years	86.8	
45–49 years	91.8	
50–54 years	85.3	
55–59 years	83.2	
60–64 years	52.2	
⩾65 years	81.8	
All ages	89.2	
Regional invasive, %		
19–24 years	100.00	
25–29 years	61.6	
30–34 years	62.3	
35–39 years	65.7	
40–44 years	63.0	
45–49 years	59.4	
50–54 years	65.9	
55–59 years	57.1	
60–64 years	56.8	
⩾65 years	58.5	
All ages	61.6	
Distant invasive, %		
19–24 years	50.4	
25–29 years	67.2	
30–34 years	21.5	
35–39 years	20.9	
40–44 years	47.8	
45–49 years	42.7	
50–54 years	38.6	
55–59 years	39.9	
60–64 years	23.8	
⩾65 years	29.7	
All ages	35.7	
Age- and sex-specific average annual all-cause mortality		*(69)*
20–24 years	1.3 per 1000	
25–29 years	1.6	
30–34 years	1.6	
35–39 years	1.9	
40–44 years	2.5	
45–49 years	3.6	
50–54 years	2.5	
55–59 years	7.2	
60–64 years	11.6	
65–69 years	17.5	
⩾70	69.5	

*Because there has been no well-organized screening in Thailand, we assumed that published incidence rates were equivalent to prevalence rates. Prevalence rates of oncogenic HPV/LSIL and annual transition probabilities were used to calculate the incidence of HSIL and invasive cancer. Incidence of invasive cancer reported to the Thailand Ministry of Health was compared with model projections to assess model validity. HPV = human papillomavirus; LSIL = low-grade squamous intraepithelial lesion (and ⩾LSIL = more severe lesions than LSIL); HSIL = high-grade squamous intraepithelial lesion (and ⩾HSIL = more severe lesions than HSIL); VIA = visual inspection of the cervix after applying acetic acid; HSIL = Federation Internationale de Gynecologie et d'Obstetrique (FIGO) *in situ* stage; local = FIGO stage 1a, 1b, and 2a; regional = FIGO stage 2b, 3; distant = FIGO stage 4; TAH = total abdominal hysterectomy.

†In the model, all transition probabilities noted in the table are multiplied by (1 – annual probability of death), so that total probability of movement between possible states is always equal to 1. Probabilities are based on observed data for oncogenic HPV and then calibrated to produce observed cancer incidence rates.

‡Progression rates vary by age. Rates vary by year for women ages 20–24, then vary by 5-year age groupings beginning at age 25. Probabilities are presented for exemplar ages.

§For simplification purposes, we assume that regression probabilities are equal at all ages and that progression and persistence rates vary to produce overall model age-dependent transition probabilities. This approach yields results that are mathematically equivalent to the observed higher regression at younger ages and increased probability of progression at older ages.

‖These VIA test characteristics are based on a dichotomous outcome (normal/abnormal). To reflect the three possible outcomes depicted in the model (normal, abnormal allowing immediate treatment, and abnormal requiring referral for treatment), we used additional data to revise the sensitivities and specificities. To estimate the probability of having an abnormal VIA that required referral, we assumed that 5% of LSIL lesions, 35% of HSIL, and 90% of invasive cervical cancer would require referral in the VIA and immediate treatment scenario.

Table 2. Medical and nonmedical care costs associated with screening, diagnosis, and treatment*

Parameter	Personnel and supply cost, U.S. $	Patient time cost, U.S. $†	Total, U.S. $
Screening/diagnosis			
VIA screening‡	0.92	1.13	2.05 per patient
Pap smear	7.50	1.88	9.38
HPV screening	30.00	1.88	31.88
Biopsy (without colposcopy)	8.50	2.41	10.91
Treatment			
Cryotherapy after VIA§	2.17	1.01	3.18
LSIL	7.50	1.88	9.38
HSIL	78.75	28.94	107.69
Local ICC	275.00	56.00	331.00
Regional ICC	395.00	35.20	430.20
Distant ICC	425.00	30.00	455.00

*In year 2000 constant U.S. dollars, the exchange rate is 40 bahts per U.S. dollar. Costs are based on the estimated costs of providing care in a government hospital, which provides the majority of care on a sliding fee schedule. Cost estimates include personnel, equipment, supplies, overhead, and operating room time. Cost data were obtained in 2000 from the Thailand Ministry of Health and from personal communication with Dr. Pisake Lumbiganon, Thailand. VIA = visual inspection of the cervix after applying acetic acid; Pap = Pap smear screening; HPV = human papillomavirus; LSIL = low-grade squamoous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; ICC = invasive cervical cancer.

†Patient time costs include travel time to a local clinic or hospital for screening, diagnosis or treatment, waiting time, and time to undergo the procedure. Patient time is valued at a minimum wage rate of 20 bahts per hour.

‡The wage rate for a nurse who performs VIA is 80 000 bahts (U.S. $2000). We assume that the nurse works 6 hours/day, 40 weeks/year, and sees one patient every 15 minutes, or 4800 patients per year.

§These costs include costs of minor complications after cryotherapy, such as bleeding, spotting, or discharge and cervicitis, requiring a clinic visit (4% of patients at a total cost of $12.50 per patient) and major complications, such as pelvic inflammatory disease or major bleeding, requiring hospitalization (0.5% of patients at a total of $75.00 per patient).

Treatment and Treatment Effectiveness

Cryotherapy. In the United States and Canada, cryotherapy cure rates for pre-invasive neoplasia range from 88% to 99% and often decrease with increasing grade and size of the lesion *(64–66)*. For this analysis, where cryotherapy is being performed in the field by trained nurses or health care workers, we conservatively estimate that 90% of women with LSIL and 75% of those with HSIL treated with immediate cryotherapy will be cured. To the extent that we are underestimating cure rates, we bias the results against VIA and immediate treatment strategies (i.e., a conservative assumption). Based on clinical field experience, we assume that 10% of women with invasive cancers will be misdiagnosed on VIA and treated with cryotherapy; 15% (range = 0%–20%) of the women with invasive cancers may be cured if they have very small lesions, but none of those with regional and distant disease will be cured *(64,83,84)*.

The side effects of cryosurgery have been well documented *(85)*. For our model, we assume that among women who undergo immediate cryotherapy (with post-treatment counseling about management of sequelae), 4% will have minor complications or side effects (e.g., vaginal discharge, cervicitis, minor bleeding, or abdominal cramps) that require a return clinic visit, and 0.5% will have a major complication requiring hospital treatment (e.g., blood transfusion, surgery, or antibiotics for pelvic inflammatory disease) *(86)*. Alternative rates are tested in sensitivity analyses.

Therapy for invasive disease. Treatment algorithms reflect guidelines established by the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) system *(87)* as well as by standard practice in Thailand *(88–91)*. For instance, we assumed that women with HSIL could have cone biopsy, laser excision electrical procedures (LEEP), or simple hysterectomy; that women with localized invasive disease (stages 1a, 1b, or 2a) would undergo radical hysterectomy; and that women with regional and distant disease would have radiation therapy. We assumed that, because resources are limited, chemotherapy would not be used. Operative mortality rates (i.e., mortality rates during and immediately after surgery) are between 0.1% and 1%, depending on age (Lumbiganon P: personal communication). After treatment, surveillance occurs via routine practice. Alternative algorithms are tested in sensitivity analyses.

Life Expectancy

Thailand's age- and stage-specific relative 5-year cervical cancer survival rates (Sankaranarayanan R: personal communication) are used to calculate life expectancy among cancer cases *(89–94)*. Age- and sex-specific mortality rates in Thailand are used to estimate risk of noncervical cancer death (competing mortality) *(69)*.

There are limited data on the disutility of gynecologic cancers (i.e., quality of life associated with different stages of cancer) in the United States *(95)*. Because we did not have any data on the preferences for health outcomes following screening for women in developing countries, we do not include quality-adjusted life expectancy. We also did not consider the short-term decrements in quality of life caused by a false-positive result. Potential effects of infertility following cryotherapy were also not included, because cryotherapy does not impair subsequent fertility or childbirth *(96,97)*.

Costs

Costs were estimated using the best quality data from Thailand. All costs are converted to year 2000 bahts; bahts are converted to U.S. dollars using an exchange rate of 40 bahts per dollar *(98)*. We include direct costs for medical care (consumable supplies, personnel, and laboratory and procedure costs) and nonmedical care (patient time costs) (Table 2). Costs for procedures and supplies were provided by the Thailand Ministry of Health, Government Health Service. The cost of performing VIA is based on the wage rate of a nurse with moderate expe-

rience. Patient time costs include time spent traveling to screening, receiving screening, undergoing diagnostic evaluation, being treated, and traveling to receive cancer care. Women's time is valued at the Thailand minimum wage rate of 20 bahts per hour ($0.50 U.S. per hour) *(99)*. We evaluated the effect of varying travel time in sensitivity analyses.

Sensitivity Analyses

We varied individual parameters (e.g., test sensitivity, test cost, prevalence rates) (one-way sensitivity analysis) and combinations of parameters (e.g., two- or three-way sensitivity analysis) over reasonable ranges to examine the robustness of the model results (e.g., low cost and high test sensitivity) under a variety of conditions (*see* additional details in the "Results" section). We varied one parameter, holding all other parameters constant to see if changes in that parameter changed the results. Fig. 2 shows the bounds of a range. If we were testing the sensitivity from 50% to 100%, for example, one end of the bar on the figure would show a cost-effectiveness ratio at 50% sensitivity and the other end the ratio at 100% sensitivity.

Model Validation and Statistical Testing

Model face validity and clinical validity were reviewed by our scientific advisors. Using transition probabilities originally developed to reflect U.S. cancer incidence rates and rates of HPV infection observed in Thailand, we evaluated the ability of our model to generate observed incidence rates for Thailand (predictive validity). We also used a second-order Monte Carlo simulation *(25)* to examine uncertainty in parameters. Confidence intervals around each result were determined by using bootstrap simulation *(100)* of 1000 replications of a 10% cohort sample; this method was also used to estimate the probability that strategies are cost-effective *(101)*.

Role of Funding Source

The funding agencies had no role in data analysis or the decision to publish these results. To reflect the field situation in Thailand, collaborators on the Thailand SAFE project reviewed the model and participated in the interpretation of results.

Results

Compared with not having a well-organized screening program (hereinafter referred to as "no screening"), under baseline assumptions, all screening strategies and intervals reduce incidence and mortality at low cost (Table 3). Screening with any strategy could save between almost 2 and 14 discounted days of life per woman (7–56 undiscounted days). Over a lifetime, screening can avoid up to 735 invasive cancers per 100 000 women screened, compared with no screening. Among women destined to develop cancer in the absence of screening, screening saves up to 2.7 discounted years of life per woman (1.3–10.9 undiscounted years). The model predicts a 1.4% lifetime risk that a woman in Thailand will develop invasive cervical cancer.

Maximal reductions in population mortality from current levels could be achieved by screening every 5 years from ages 20 to 70 by using one of three strategies: VIA followed by immediate treatment if abnormalities are found, HPV testing combined with VIA or Pap smear, or VIA and immediate treatment at the same interval but restricted to women aged 35–55 years. For instance, if all women received VIA with immediate treatment every 5 years from age 35 to 55, there would be a reduction in mortality of approximately 35%—84% of that achieved by screening from ages 20 to 70. Strategies that involve regular interval screening were more effective than those that involve screening only once or twice in a woman's lifetime.

Overall, under baseline assumptions, comparing each strategy with the next least expensive option, we found that the best strategies are VIA and immediate treatment every 5 years from ages 35 to 55 or from ages 20 to 70 (Table 4). However, because the sensitivity and specificity of VIA decrease with age (because of involution of the transformation zone after menopause), and because younger women are already attending some screening or family planning services, restricting screening to women in the 35- to 55-year-old age group appears to be the optimal strategy (for life years for a given cost). Cytology- and HPV-based strategies were "dominated" (i.e., they cost more and saved somewhat fewer lives due to losses to follow-up after an abnormal screen) by VIA.

Sensitivity Analyses

The results of our analysis are most sensitive to assumptions about rates of participation in screening, costs, compliance with follow-up of abnormal results, test characteristics, and assumptions about progression and/or regression rates (Fig. 2). The results are less affected by assumptions about the proportion of HPV-negative cancers, restricting treatment to women with HSIL or greater lesions versus treating all women with LSIL and beyond, overall disease prevalence, patient time costs, cryosurgery cure and complication rates, mode of diagnostic biopsy (i.e., use of colposcopy), or post-cancer surveillance algorithms.

In our base case, we assumed that all women would present for screening. While costs decrease as fewer women use screening, LYS decreases even more dramatically. Mortality reductions of 25% or more could be expected only if 70% of women attend screening with VIA in any given cycle. Results showing the effects of compliance with screening attendance on the cost-effectiveness of other strategies are comparable and do not affect the ranking of strategies.

If 100% of women comply with post-screening follow-up, more lives would be saved than were saved in the base case. However, after evaluating screening every 5 years from age 35 to 55 years using VIA and immediate treatment with HPV testing, or with Pap smear combined with HPV testing, we noted that VIA and immediate treatment remains the most cost-effective approach ($263 per LYS). The HPV-based strategies result in the greatest mortality reductions if all women complete follow-up of abnormal tests, but these strategies cost substantially more. For instance, the cost of using both HPV testing and Pap smears is $13 646 per LYS, compared with VIA and immediate treatment (*see* Fig. 2 for the results of the sensitivity analysis).

The cost-effectiveness results are a linear function of the cost of the HPV test. If HPV test costs are reduced theoretically from $30 to $5, then the cost per LYS saved by screening with HPV (compared with no screening) drops from $3004 to $672 for screening every 5 years from age 35 to 55 years (*see* Fig. 2 for details). However, even at $5, HPV screening is more costly and less effective than VIA with immediate treatment every 5 years from age 35 to 55 because of losses to follow-up that occur after an abnormal HPV test. If low HPV cost could be combined with 90% compliance and with follow-up of abnormal results (two-way sensitivity analysis), then HPV screening yields results similar to VIA and immediate treatment (data not shown).

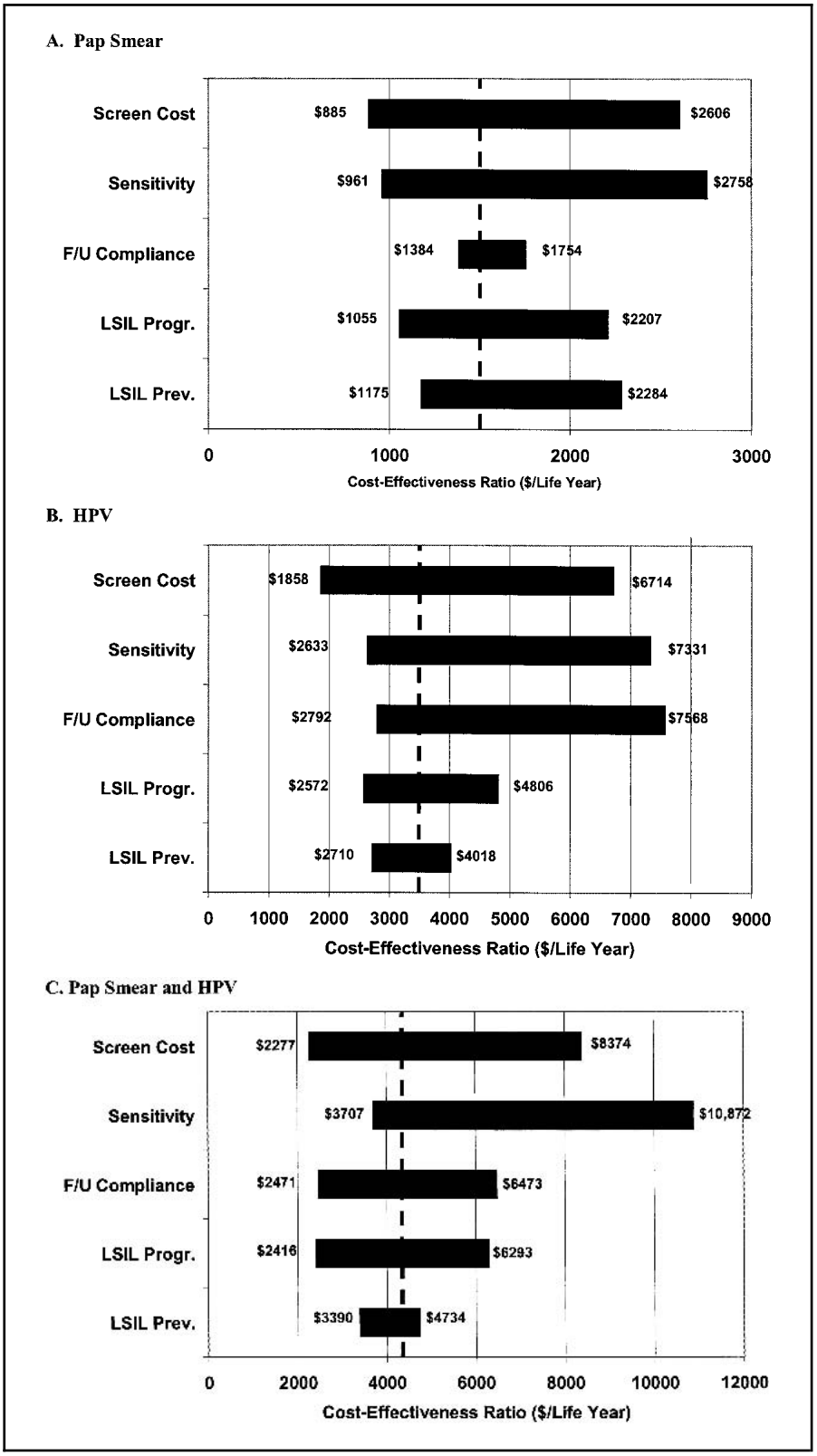

Fig. 2. One-way sensitivity analyses for each screening strategy. **A–F**) Change in cost-effectiveness ratios for one-way changes (i.e., varying one parameter at a time) in different assumptions about relevant parameters. Dashed lines represent the base case cost-effectiveness ratios. In each panel, parameters are arrayed from those having the highest to those having the lowest impact on the base case results. (For details of the parameters describing the base case in the model, *see* Table 1.) Numbers to the left and right of each bar represent lowest and highest bounds of the range of costs per life-year saved, respectively, over the range of the parameter varied. Parameters include screening costs (0.5× to 2× the baseline cost), sensitivity (from 100% to 10%) of each screening test to detect disease (i.e., detection of low-grade squamous intra-epithelial lesion [LSIL] or more severe lesions), follow-up compliance (100%–20%) after an abnormal screen, LSIL progression (3× to 0.5× the baseline progression rate to high-grade squamous intra-epithelial lesion [HSIL]), and LSIL prevalence (2× to 0.5× the baseline prevalence and incidence rate). HPV = human papillomavirus DNA testing; VIA = visual inspection of the cervix after applying acetic acid; F/U = follow-up; Progr = progression; Prev = prevalence. (Continued on facing page).

Cost-effectiveness of HPV testing improves when applied in areas with a higher prevalence of HPV infection, greater rate of progression of LSIL to HSIL, or where all HSIL and cancers have detectable HPV.

If cytology sensitivity could be improved to a minimum of 80% (which would involve including ASCUS as an abnormal cytology), then the cost-effectiveness ratio drops to below $1000 per life-year saved (compared with no screening). If both cytology sensitivity of 80% and follow-up compliance of 90% were achieved, then Pap smear screening every 5 years from age 35 to 55 would also be considered cost-effective.

Under ideal conditions (e.g., 85% sensitivity for Pap smear test and 95% sensitivity for HPV testing, 100% follow-up after an abnormal test, 100% accuracy of biopsy, 99% treatment ef-

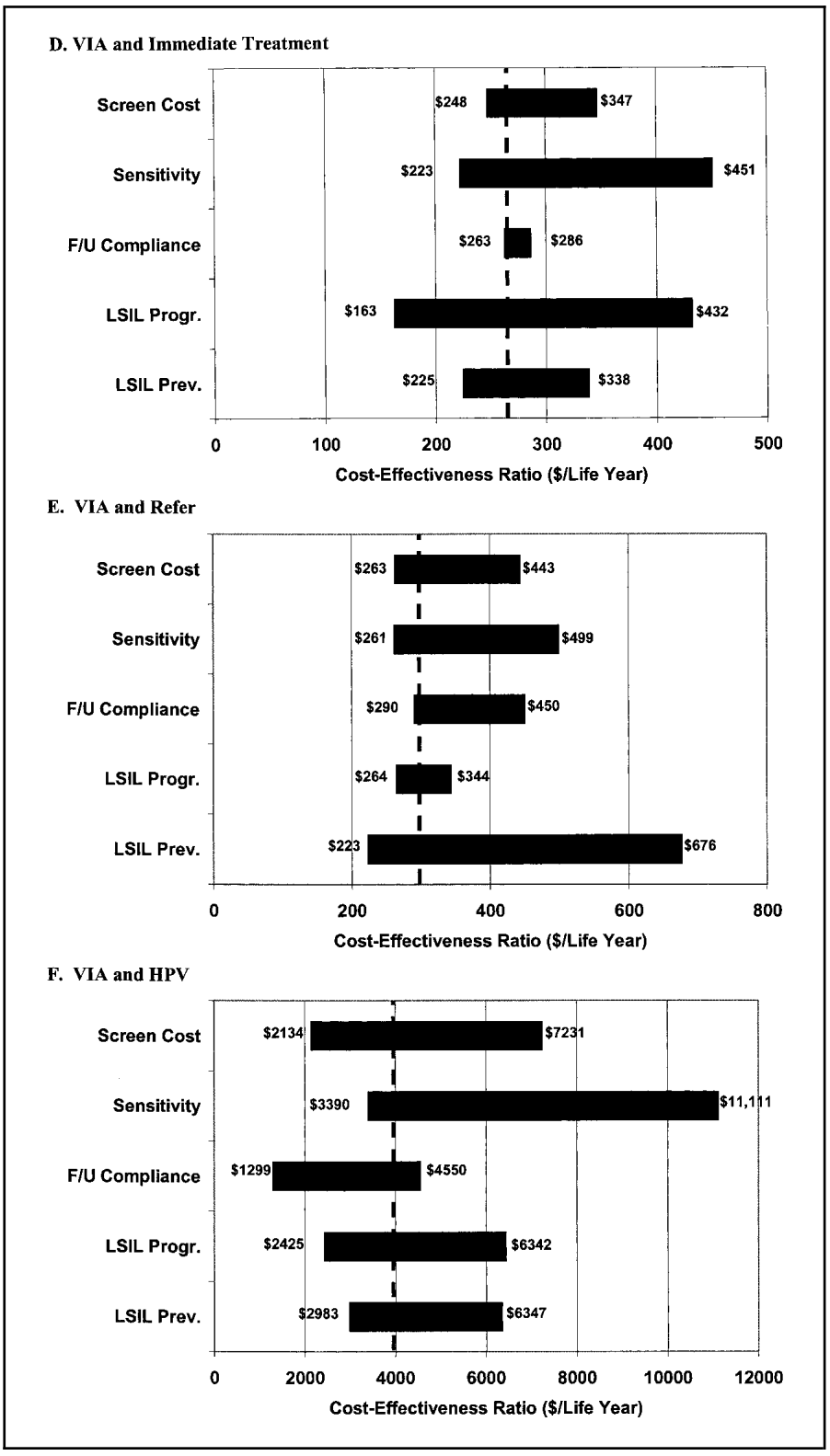

Fig. 2. (Continued from facing page).

fectiveness for pre-invasive lesions, and $5 test cost for HPV), the screening of women aged 20–70 every 5 years with a combination of Pap smear and HPV testing could achieve a 92% reduction in cervical cancer mortality at a cost of $1683 per LYS, compared with no screening. In these ideal circumstances, the use of HPV testing as the sole screening test achieves a 90% reduction in mortality at a cost of $1001 per LYS. Optimal performance of VIA with immediate treatment (85% sensitivity, 98% cryotherapy treatment effectiveness for LSIL, and 83% cryotherapy treatment effectiveness for HSIL) achieves only an 83% mortality reduction, but at a lower cost—$524 per LYS.

Model Validation and Statistical Testing

We compared our model prediction of cervical cancer incidence in unscreened women with incidence rates seen in Thailand *(24)*. As can be seen in Fig. 3, model predictions accurately

Table 3. Costs and benefits of cervical cancer screening compared with having no well-organized screening program*

Strategy	Frequency or age at screening q*X* (*Y*–*Z*)	Cost, U.S. $	LY	Incremental cost, U.S. $	Incremental LY	Incremental C-E ratio ($/LY)	ICC incidence reduction, %	ICC mortality reduction, %
No screening		2	27.024					
Pap	q5 (20–70)	55	27.0408	53	0.0168	$3,168	18.8	23.2
HPV	q5 (20–70)	182	27.0523	180	0.0283	$6,359	32.9	37.6
Pap and HPV	q5 (20–70)	224	27.0618	222	0.0378	$5,876	38.3	43.5
VIA Tx	q5 (20–70)	23	27.0625	21	0.0385	$548	52.4	58.2
VIA Ref	q5 (20–70)	14	27.0423	12	0.0183	$668	16.1	24.1
VIA and HPV	q5 (20–70)	196	27.0528	194	0.0288	$6,720	39.6	46.0
Pap	q10 (20–70)	32	27.0352	30	0.0112	$2,634	10.2	12.0
HPV	q10 (20–70)	102	27.0498	100	0.0258	$3,868	18.5	21.5
Pap and HPV	q10 (20–70)	125	27.0504	123	0.0264	$4,665	23.4	26.5
VIA Tx	q10 (20–70)	14	27.0505	12	0.0265	$454	32.1	36.8
VIA Ref	q10 (20–70)	9	27.043	7	0.019	$357	9.5	14.1
VIA and HPV	q10 (20–70)	110	27.0435	108	0.0195	$5,507	23.7	28.1
Pap	q5 (35–55)	25	27.0393	23	0.0153	$1,459	10.8	13.5
HPV	q5 (35–55)	78	27.0457	76	0.0217	$3,477	20.0	22.0
Pap and HPV	q5 (35–55)	95	27.0456	93	0.0216	$4,309	23.2	26.2
VIA Tx	q5 (35–55)	11	27.0565	9	0.0325	$263	30.8	34.9
VIA Ref	q5 (35–55)	7	27.0418	5	0.0178	$290	8.3	12.3
VIA and HPV	q5 (35–55)	83	27.0453	81	0.0213	$3,805	23.6	28.5
Pap	q10 (35–55)	16	27.0373	14	0.0133	$1,016	5.2	6.3
HPV	q10 (35–55)	48	27.0366	46	0.0126	$3,616	12.7	14.4
Pap and HPV	q10 (35–55)	58	27.0462	56	0.0222	$2,535	14.2	16.2
VIA Tx	q10 (35–55)	7	27.0433	5	0.0193	$272	21.3	24.1
VIA Ref	q10 (35–55)	5	27.0424	3	0.0184	$170	5.2	7.5
VIA and HPV	q10 (35–55)	51	27.0371	49	0.0131	$3,742	15.6	19.0
Pap	Once (35 y.o.)	8	27.0351	6	0.0111	$548	1.3	1.0
HPV	Once (35 y.o.)	23	27.0412	21	0.0172	$1,191	2.1	1.6
Pap and HPV	Once (35 y.o.)	27	27.0413	25	0.0173	$1,462	2.4	2.2
VIA Tx	Once (35 y.o.)	5	27.0449	3	0.0209	$121	4.4	4.5
VIA Ref	Once (35 y.o.)	4	27.0289	2	0.0049	$295	1	1
VIA and HPV	Once (35 y.o.)	24	27.0297	22	0.0057	$3,864	3.5	3.7
Pap	Once (45 y.o.)	7	27.0316	5	0.0076	$578	1.0	0.7
HPV	Once (45 y.o.)	17	27.0365	15	0.0125	$1,181	2.8	3.9
Pap and HPV	Once (45 y.o.)	20	27.0398	18	0.0158	$1,156	2.0	2.7
VIA Tx	Once (45 y.o.)	4	27.0353	2	0.0113	$143	6.1	8.0
VIA Ref	Once (45 y.o.)	3	27.0322	1	0.0082	$127	1	1
VIA and HPV	Once (45 y.o.)	18	27.0327	16	0.0087	$1,827	2.1	3.6
Pap	Twice (35 y.o./45 y.o.)	13	27.0327	11	0.0087	$1,201	2.7	3.6
HPV	Twice (35 y.o./45 y.o.)	37	27.0359	35	0.0119	$2,958	6.2	7.1
Pap and HPV	Twice (35 y.o./45 y.o.)	46	27.0374	44	0.0134	$3,241	8.6	9.2
VIA Tx	Twice (35 y.o./45 y.o.)	6	27.0444	4	0.0204	$202	11.0	12.3
VIA Ref	Twice (35 y.o./45 y.o.)	5	27.0369	3	0.0129	$189	2.1	2.6
VIA and HPV	Twice (35 y.o./45 y.o.)	40	27.0369	38	0.0129	$2,937	7.1	9.0

*Pap = Pap smear screening; HPV = human papillomavirus screening; VIA Tx = visual inspection of the cervix with acetic acid, followed by immediate cryotherapy if positive; VIA Ref = visual inspection of the cervix with acetic acid, followed by referral for evaluation and treatment if positive; q*X*(*Y*–*Z*) = screen every *X* years, starting at age *Y* and continuing until age *Z*; y.o. = years old; 35 y.o./45 y.o. = at age 35 and 45 (twice); LY = life years calculated by cost-effectiveness model; C-E ratio = cost-effectiveness ratio; ICC = invasive cervical cancer.

predicted observed incidence. To the extent that incidence rates assumed for unscreened women actually include some screened women, our model may underestimate the true burden of disease. Finally, confidence areas for cost-effectiveness results indicated that VIA and immediate treatment was the most consistently cost-effective strategy, with a 99.1% probability of having an incremental cost-effectiveness ratio of less than $1000 per LYS, compared with no screening.

Discussion

Using Thailand as a case study, we applied a comprehensive simulation model of cervical carcinogenesis and found that, compared with having no organized screening, all 42 combinations of screening strategies and screening frequencies that we evaluated reduce incidence and mortality at costs ranging from $121 to $6720 per life-year saved. By comparing the strategies with each other, we found that, under current conditions, the most cost-effective strategy is VIA with immediate treatment ($517 per life-year saved for women aged 35–55 years), but several other options would be viable alternatives depending on resources, test performance, and compliance with screening and follow-up. To put these costs in perspective, after development of the screening infrastructure our model projects the total (undiscounted) annual cost of a VIA screening program with immediate treatment for the entire Thailand female population aged 35–55 years every 5 years to be $0.79 per woman, or $4.7 million annually. Such a screening program would increase the

Table 4. Incremental cost-effectiveness ratios of screening strategies compared with the next most expensive strategy*

Strategy	Frequency or age at screening, q*X*(*Y*–*Z*)	Cost, U.S. $	LY	Incremental cost, U.S. $	Incremental LY	Incremental C-E ratio ($/LY)
No screening		2.21	27.024			
VIA Ref	45 y.o.	3.26	27.0322	1.04	0.0082	$127
VIA Ref	35 y.o.	3.66	27.0289	0.40	–	(D)
VIA Tx	45 y.o.	3.83	27.0353	0.57	0.0031	$185
VIA Ref	35 y.o./45 y.o.	4.65	27.0369	0.82	0.0016	$512
VIA Tx	35 y.o.	4.75	27.0449	0.10	0.0080	$12
VIA Ref	q10 (35–55)	5.34	27.0424	0.59	–	(D)
VIA Tx	35 y.o./45 y.o.	6.33	27.0444	1.58	–	(D)
Pap	45 y.o.	6.61	27.0316	1.86	–	(D)
VIA Ref	q5 (35–55)	7.38	27.0418	2.63	–	(D)
VIA Tx	q10 (35–55)	7.46	27.0433	2.71	–	(D)
Pap	35 y.o.	8.29	27.0351	3.54	–	(D)
VIA Ref	q10 (20–70)	9.00	27.043	4.25	–	(D)
VIA Tx	q5 (35–55)	10.75	27.0565	6.00	0.0116	$517
Pap	35 y.o./45 y.o.	12.66	27.0327	1.91	–	(D)
VIA Tx	q10 (20–70)	14.25	27.0505	3.51	–	(D)
VIA Ref	q5 (20–70)	14.44	27.0423	3.69	–	(D)
Pap	q10 (35–55)	15.73	27.0373	4.98	–	(D)
HPV	45 y.o.	16.98	27.0365	6.23	–	(D)
VIA and HPV	45 y.o.	18.11	27.0327	7.36	–	(D)
Pap and HPV	45 y.o.	20.47	27.0398	9.72	–	(D)
HPV	35 y.o.	22.69	27.0412	11.94	–	(D)
VIA Tx	q5 (20–70)	23.31	27.0625	12.56	0.0060	$2,093†

*(D) = Strategy is dominant, i.e., the screening strategy is more expensive and less effective than another strategy. Pap = Pap smear screening; HPV = human papillomavirus screening; VIA Tx = visual inspection of the cervix with acetic acid, followed by immediate cryotherapy if positive; VIA Ref = visual inspection of the cervix with acetic acid, followed by referral for evaluation and treatment if positive; q*X*(*Y*–*Z*) = screen every *X* years, starting at age *Y* and continuing until age *Z*; y.o. = years old; LY = life years; C-E ratio = cost-effectiveness ratio; – = incremental LY less than 0.

†All screening strategies from Table 3 not shown on this table are more expensive than the VIA Tx q5 (20–70) strategy and are less effective than this strategy.

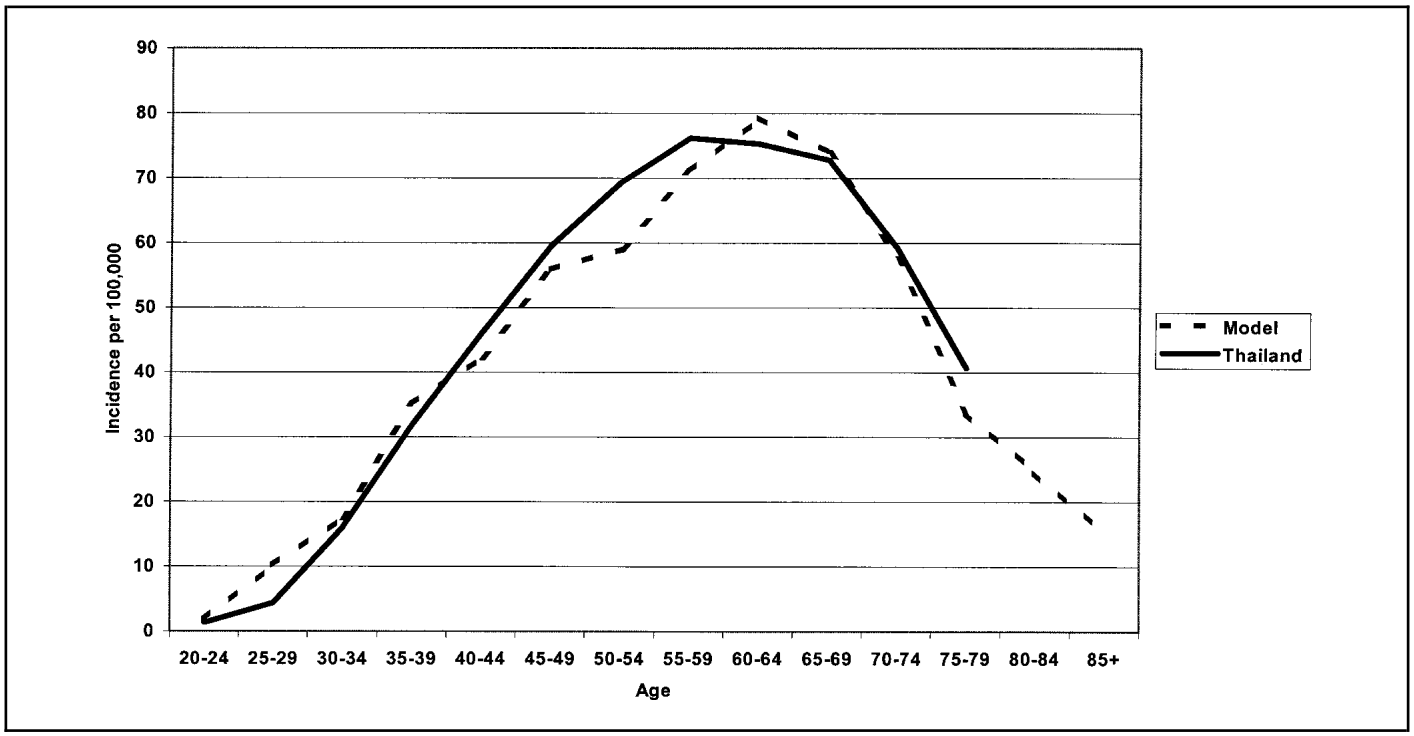

Fig. 3. Comparison of model-predicted age-specific invasive cervical cancer incidence rate and the observed rate (Thailand). The **dashed line** represents the model prediction of invasive cervical cancer incidence in Thailand (per 100 000 women). The **solid line** represents observed Thailand incidence data obtained from the Thailand tumor registry *(24)*.

overall national per capita health expenditure for Thailand of $112 by 0.08% *(99)*.

Screening women aged 35–55 years every 5 years with VIA and immediate treatment currently saves more lives and costs less than other strategies. In other less-developed countries, VIA has also been noted to be the most cost-effective approach *(102)*. This result is largely a function of good field performance, low cost, and the fact that, unlike cytology- or virology-based ser-

vices, results are available immediately. If, in the future, new technologies arise that combine high accuracy and immediate results at low cost, these technologies could be a cost-effective alternative to VIA followed by immediate treatment. Such options mean that management decisions, such as offering immediate treatment to women with the highest probability of disease, can be made and implemented in the field without losses to follow-up when women have to return or travel long distances for diagnosis and/or treatment *(20,103,104).* Thus, VIA or other tests offering immediate results are likely to be most useful in countries with large rural populations and long distances between primary and tertiary health care services. VIA has the drawback of generating an offer of treatment for some women who either do not have neoplasia or have low-grade disease that might otherwise regress; this "over-treatment" has been factored into our analysis. The ultimate cost-effectiveness of VIA will depend on several factors, such as the training of health care workers who conduct the examinations, acceptability in the population, and effectiveness after cryotherapy. Although there are currently no data on the sensitivity of VIA post cryotherapy, the squamocolumnar junction remains visible, and VIA and immediate treatment remains the best strategy until its sensitivity for HSIL or more severe lesions falls to below about 60%.

HPV DNA testing could have several advantages as a primary screening strategy in resource-poor countries, including sensitivity and specificity that are equivalent to or higher than those of Pap smears and VIA, a high positive predictive value in areas with high prevalence, the ability to predict women at high risk for future disease, a requirement for technicians who are less skilled than cytology or VIA technicians, and the potential for self-collection of specimens *(12,17,105).* However, in our study, although HPV DNA testing saved nearly as many lives as VIA with immediate treatment, even at $5 per test it was not cost-effective compared with VIA with immediate treatment. If follow-up of abnormal HPV tests is 90% and tests cost $5 each, then HPV-based strategies approach the cost-effectiveness of VIA with immediate treatment. These results are similar to the findings of other studies that model the use of HPV as a primary screening test, in which results depend on the relative costs of HPV and Pap smears or VIA, sensitivity, and natural history of HPV *(11,16,36,102,106,107).*

In a recent report that estimated the costs of screening in southern Vietnam, Suba and colleagues *(108)* suggest that cytology would be a reasonable investment relative to current spending. In our study, however, cytology-based approaches were more costly and less effective than other screening modalities, largely as a function of the 20% sensitivity of Pap smears noted in fairly unstructured screening programs. Pap smear test performance is likely to be better in an organized national screening program, and if the overall sensitivity could be increased to at least 80%, and if almost all women were to receive a follow-up evaluation after an abnormal smear, then Pap screening would become a plausible alternative to VIA-based strategies *(108–110).* A Pap smear screening program that couples high sensitivity with education and immediate interpretation and treatment (e.g., using a mobile screening and laboratory facility) *(104,111)* could be as cost-effective as VIA. However, the ability to maintain the technical requirements and predict the costs of a high-quality mobile program has not yet been fully demonstrated.

Regardless of modality adopted, screening benefits accrue in direct proportion to compliance with screening *(112).* Furthermore, if women with abnormal tests do not receive diagnosis (and treatment), costs are incurred without benefits, decreasing cost-effectiveness *(113).* Thus, regardless of the strategy chosen, community education will be key to ensuring compliance with screening and follow-up recommendations; these costs will need to be considered when evaluating initial costs of building and maintaining any screening infrastructure.

Our analysis has several important strengths, including use of current standards for conduct of cost-effective analyses *(30),* use of data specific to less-developed countries, a comprehensive validated model, comparison of multiple strategies, and an assessment of the role of uncertainty on conclusions. Despite these important strengths, several caveats should be considered when interpreting our results, including considerations of infrastructure costs, model assumptions, impact of new technologies, lack of primary quality-of-life data, use of modeling, and generalizability of our results.

Our model assumes that screening occurs in the setting of an existing system and does not include infrastructure development costs (e.g., costs of training cytology technologists, HPV laboratory staff, and health care workers, and fixed equipment). For example, Suba and colleagues *(108)* estimated that Pap smear screening of one million women per year would require 104 examiners, 73 cytology technologists, and 3.2 gynecologists to perform diagnostic evaluations. If the costs of initiating and maintaining one strategy differed markedly from the others, this could affect the ranking of the cost-effectiveness of the different screening modalities. For example, if training laboratory staff to conduct high-quality HPV tests were substantially less costly than training health care workers to conduct sensitive VIA then under certain circumstances (e.g., low HPV test costs and complete follow-up of women with abnormal screening), HPV could be more cost-effective than VIA with immediate treatment. In future work, it will be important to collect primary data to understand infrastructure start-up and maintenance costs.

A key assumption in our model is that the natural history of cervical neoplasia in less-developed countries is similar to that in developed countries. To the extent that cofactors such as nicotine use *(16)* or dietary components *(114,115)* vary among countries and affect HPV progression, it is possible that we have over- or underestimated the effectiveness of screening. Our model also combines HPV infection and LSIL into one health state. This simplification allows us to use the natural history data available as generally reported in the literature, but biases the results so as to make HPV screening appear slightly more favorable (due to lower rates of work-up of transient HPV infection) than it might be relative to the other strategies.

We did not evaluate the effect on costs and case detection of new technologies, such as liquid-based methods to improve cytology sensitivity *(116,117)* and tests for HPV, nor did we assess serial screening approaches, such as using HPV to triage women for evaluation after an abnormal screen. At present, these technologies would be considered too expensive in low-resource settings.

Our model also did not capture the effects of distress associated with a false-positive screening result or with the knowledge of having a sexually transmitted viral infection, because the short-term impact of these outcomes has not been quantified *(118,119).*

Models such as the one used in this study are useful in combining the best data available and in projecting events over a sufficiently long time horizon to "observe" incidence and mortality endpoints *(39,118)*. To the extent that the data are of poor quality or the assumptions are incorrect, our results could be inconclusive. However, reliable data are available on the natural history of cervical neoplasia, and our results were very robust over wide ranges of multiple parameters. Our estimate of the lifetime risk of invasive cancer of 1.4% in Thailand with higher rates of cervical cancer than the United States is consistent with Eddy's estimate of a 0.7% lifetime risk for U.S. women *(120)*. Finally, our results are generalizable only to less-developed countries with low rates of HIV infection. In countries with endemic HIV infection, additional modeling would be necessary to portray the interactions between HIV and HPV and competing risks of mortality *(27)*.

Prevention of cervical cancer mortality will be achieved only through an expenditure of health care resources. To achieve the greatest success in eradicating cervical cancer worldwide, less-developed countries need to use the most sensitive tools possible within their fiscal constraints and infrastructure resources. The promise of cervical cancer screening will be realized only with clinical and financial investments in start-up and maintenance programs to deliver the most accurate tests available, train staff, establish quality control, promote compliance with screening and follow-up, and ensure access to diagnostic and/or treatment services *(12,107,110,112,121)*. Cost-effectiveness analyses, such as the one presented here, can therefore be considered important adjuncts to policy decision-making about important public health objectives.

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