

SPECIAL ARTICLE

## Cost-Effectiveness of Cervical-Cancer Screening in Five Developing Countries

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### ABSTRACT

#### BACKGROUND

Cervical-cancer screening strategies that involve the use of conventional cytology and require multiple visits have been impractical in developing countries.

#### METHODS

We used computer-based models to assess the cost-effectiveness of a variety of cervical-cancer screening strategies in India, Kenya, Peru, South Africa, and Thailand. Primary data were combined with data from the literature to estimate age-specific incidence and mortality rates for cancer and the effectiveness of screening for and treatment of precancerous lesions. We assessed the direct medical, time, and program-related costs of strategies that differed according to screening test, targeted age and frequency, and number of clinic visits required. Single-visit strategies involved the assumption that screening and treatment could be provided in the same day. Outcomes included the lifetime risk of cancer, years of life saved, lifetime costs, and cost-effectiveness ratios (cost per year of life saved).

#### RESULTS

The most cost-effective strategies were those that required the fewest visits, resulting in improved follow-up testing and treatment. Screening women once in their lifetime, at the age of 35 years, with a one-visit or two-visit screening strategy involving visual inspection of the cervix with acetic acid or DNA testing for human papillomavirus (HPV) in cervical cell samples, reduced the lifetime risk of cancer by approximately 25 to 36 percent, and cost less than \$500 per year of life saved. Relative cancer risk declined by an additional 40 percent with two screenings (at 35 and 40 years of age), resulting in a cost per year of life saved that was less than each country's per capita gross domestic product — a very cost-effective result, according to the Commission on Macroeconomics and Health.

#### CONCLUSIONS

Cervical-cancer screening strategies incorporating visual inspection of the cervix with acetic acid or DNA testing for HPV in one or two clinical visits are cost-effective alternatives to conventional three-visit cytology-based screening programs in resource-poor settings.

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N Engl J Med 2005;353:2158-68.  
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**C**ERVICAL CANCER IS A LEADING CAUSE of death from cancer among women in low-resource settings, affecting women at a time of life when they are critical to social and economic stability.<sup>1</sup> Cervical cancer is highly preventable through cytologic screening programs that facilitate the detection and treatment of precancerous lesions. Such screening, however, requires an established laboratory, highly trained cytotechnologists, and up to three visits for screening, evaluation of cytologic abnormalities, and treatment and is therefore difficult to implement and sustain in settings with limited resources. Alternative methods, such as DNA testing for human papillomavirus (HPV) and simple visual screening, may prove more practical when incorporated into new strategies that are less dependent on existing laboratory infrastructure and require fewer visits.<sup>2-6</sup>

Although recent studies support the potential promise of an effective vaccine against selected high-risk types of HPV, the vaccine is not yet commercially available.<sup>7,8</sup> Since first-generation vaccines will target young adolescents, it will take several decades to determine the effect of these vaccines on the rate of death from cervical cancer. Even then, since current vaccines target only two types of oncogenic HPV, a combination of screening and vaccination will probably be required. Consequently, timely implementation of a cost-effective screening strategy for use in developing countries is particularly critical.

Using primary data from studies in countries with diverse epidemiologic profiles and resources (India, Kenya, Peru, South Africa, and Thailand), we assessed the cost-effectiveness of alternative strategies to reduce the rate of death from cervical cancer (Table 1).<sup>9-11</sup> This approach had considerable advantages over previous analyses, which generally have not included the costs of laboratory equipment and supplies, transportation of specimens, training, administration, and other program-related activities. Moreover, because most studies have involved the assessment of screening options for a single country,<sup>12,13</sup> clinical and economic assumptions have not been standardized, making it difficult to compare results. The analytic approach we have used was designed to permit inferences to be made about policies regarding the control of cervical cancer that would be easily generalizable.

## METHODS

### OVERVIEW

With the use of a computer-based model, we synthesized the best available data and simulated the natural history of HPV-induced cervical neoplasia and the procedures used in the screening, diagnosis, and treatment of cervical cancer. We assessed alternative strategies by determining the incremental cost-effectiveness ratio, which is defined as the additional cost of a specific strategy divided by its additional clinical benefit, as compared with the next-less-expensive strategy. The numerator represents the average lifetime costs per woman (in 2000 international dollars, a currency unit that minimizes the consequences of differences in price levels existing among countries), and the denominator represents the average gain in life expectancy per woman. We discounted costs and benefits by an annual rate of 3 percent, consistent with economic guidelines.<sup>14,15</sup>

### NATURAL-HISTORY MODEL

In our model, which has been described previously,<sup>12</sup> the health states among subjects represent HPV DNA status, the grade of cervical intraepithelial neoplasia (grade 1, grades 2 and 3), and the stage of invasive cancer. Movement through the health states occurs in monthly increments according to probabilities that are dependent on age, HPV status, and disease history. Although we assume that the natural history of cervical cancer is similar across countries, we also assume that patterns of sexual behavior and risk factors for cervical cancer vary; we therefore have incorporated age-specific rates of death due to causes other than cancer, such as those associated with pregnancy and the human immunodeficiency virus (HIV).<sup>16</sup> Calibration methods ensured that the age-specific incidence of cervical cancer and rates of death from the disease as predicted by each model approximated the best available country-specific data<sup>1</sup> (see the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)).

### SCREENING MODEL AND STRATEGIES

We differentiated screening strategies according to number of clinical visits, frequency of screening, and targeted ages. Tests included visual inspection of the cervix with acetic acid (hereafter referred to

**Table 1. Demographic and Economic Characteristics of the Countries.\***

Characteristic	India	Kenya	Peru	South Africa	Thailand
Total population (millions)	1,016	30	26	44	61
Rural population (% of total)	72.34	64.11	27.23	44.51	68.86
Population density (no. of persons/km <sup>2</sup> )	341.69	52.87	20.26	36.03	118.87
Women 35–39 yr of age (% of total population)	3.28	2.18	3.21	3.35	4.10
Literacy rate among women ≥15 yr of age (%)	45.39	76.02	85.24	84.56	90.52
Women employed in informal sector (% of women employed)	86	83	58	58	54
Average hourly wage rate (2000 international dollars)†	0.48	1.94	2.26	9.90	2.59
Female life expectancy at birth (yr)‡	63.56	47.37	71.69	48.97	71.06
Cervical-cancer incidence (age-standardized incidence per 100,000)§	186.50	200.10	238.30	174.80	129.60
HIV prevalence among adults (% of total population)	0.70	14	0.40	19.90	2.20
Per capita gross domestic product (2000 international dollars)†	2,430	1,005	4,747	9,486	6,373

\* Data are from the World Bank,<sup>9</sup> the International Labor Office,<sup>10</sup> and the U.S. Department of Commerce.<sup>11</sup>

† The international dollar is a unit of currency that minimizes the consequences of differences in price levels existing among countries.

‡ The average life expectancy for women who reach 35 to 40 years of age in Kenya is 67.9 years and in South Africa 68.8 years.

§ Age-standardized incidence is computed as a weighted average of age-specific cancer rates, with the population proportions of a global standard age pattern used as weights.

as visual inspection), cytologic examination of cervical cells on a Papanicolaou smear, and DNA testing for HPV in cervical-cell samples with the use of the hybrid-capture method (Hybrid Capture II HPV test, Digene). We also evaluated a combined strategy of HPV and visual inspection testing in which visual inspection followed a positive HPV DNA test. Three-visit strategies included an initial screening test, colposcopy and biopsy in the case of positive results, and treatment of cervical intraepithelial neoplasia. Two-visit strategies consisted of initial screening followed by treatment, without colposcopic evaluation, of all women with positive screening results. One-visit strategies incorporated same-day screening and treatment for women with positive screening results. A single lifetime screening was performed at 35 years of age, with additional screenings performed at five-year intervals. Target ages and screening intervals were varied in sensitivity analyses.

We assumed that screening was performed at a primary-level facility. One-visit and two-visit strategies involved the use of visual inspection to determine whether women with positive results on screening were eligible for cryosurgery; those with lesions that covered more than 75 percent of the cervix or that extended to the vaginal wall or 2 mm beyond the tip of the probe used for cryosurgery and those with anatomical abnormalities of the cer-

vix were ineligible. Women deemed ineligible were referred to a secondary-level facility (e.g., a district or regional hospital) for diagnostic testing (e.g., colposcopy and biopsy) and, if necessary, treatment of precancerous lesions with a loop electrosurgical excision procedure, cold-knife conization, or simple hysterectomy, depending on the size and type of lesion. For three-visit strategies, women with positive screening results were referred for diagnostic testing, with those who required treatment returning for a third visit. Women in whom cancer was detected were referred to secondary or tertiary care hospitals.

#### CLINICAL DATA

Table 2 shows selected variables, based on primary data and published literature,<sup>3-6,17,18</sup> that were used to conduct comparative analyses for all five countries. Methods to derive variables related to natural history, including those used to account for the effect of HIV, have been described previously<sup>12</sup> (see also the Supplementary Appendix).

#### COST DATA

Costs are presented in 2000 international dollars, with differences in purchasing power taken into account.<sup>19</sup> We used a quantity-and-price approach to estimate total costs, with primary data used when available. Details of the procedures used for cost es-

timation are provided in the Supplementary Appendix.

We categorized costs as direct medical costs (e.g., for staff, disposable supplies, equipment, and specimen transport), women’s time costs (time spent traveling and waiting for and receiving care), transportation costs, or program-related costs. Since many women who were eligible for screening were not formally employed, we estimated the value of their time with the use of a weighted average of wages for formal-sector jobs and of minimum wages for informal-sector jobs<sup>9-11,19-21</sup> (see the Supplementary Appendix). We estimated program-related costs that differed according to strategy, such as those for laboratory equipment and supplies, specimen transport, and training for and supervision of particular techniques, assuming an 80 percent use of capacity.<sup>19,22</sup> We assumed that activities related to administration and recruitment would increase the total medical costs by an additional 25 percent and varied this increase from 10 to 75 percent in the sensitivity analysis.

Figure 1 shows the relative consistency of the direct medical costs associated with the screening visits in all five countries. The considerable variation in patient time and transport costs reflects differences among rural populations and population densities, comprehensiveness of coverage by the primary-level clinic, and wages, difficulty of travel, or both.<sup>9-11,19-23</sup>

Table 3 summarizes selected costs associated with diagnosis and treatment, including those for false positive results, referral of women ineligible for cryosurgery to other centers, and treatment complications. The allocation of resources for each stage of cancer treatment was based on clinical protocols used at regional hospitals and cited in other studies.<sup>12,13,24,25</sup>

RESULTS

REDUCTION IN LIFETIME RISK

The country-specific reduction in the lifetime risk of invasive cervical cancer with a single screening at the age of 35 years ranged from 25 to 31 percent with one-visit and two-visit visual inspection, 30 to 36 percent with one-visit and two-visit HPV DNA testing, and 18 to 22 percent with two-visit and three-visit cytologic examination. As compared with a single screening, two screenings (at 35 and 40 years of age) provided an increased relative reduction in lifetime risk of approximately 40 percent.

Table 2. Selected Variables of the Model Used in the Comparative Analysis for the Five Countries.\*

Variable	Base Case	Range
	<i>percent</i>	
<b>Characteristics of screening tests</b>		
Visual inspection with acetic acid		
Sensitivity†	76	60–90
Specificity	81	66–96
HPV DNA		
Sensitivity†	88	65–95
Specificity	93	70–96
Cytology		
Sensitivity†	63	45–85
Specificity	94	80–98
<b>Characteristics of screening program</b>		
Participation‡	100	25–100
Loss to follow-up (per visit)§	15	0–50
<b>Criterion for ineligibility for cryosurgery according to disease status¶</b>		
DNA is normal or positive for HPV, without CIN	5	0–50
CIN, grade 1	15	0–50
CIN, grade 2 or 3	25	0–50
<b>Cryosurgery  </b>		
Effectiveness in women with CIN, grade 1	85	50–90
Effectiveness in women with CIN, grade 2 or 3	75	50–90
Major complications	1	0–3
Minor complications	5	0–15

\* The variables shown represent only those values used in the comparative analysis for all five countries; other variables are shown in the Supplementary Appendix. Each variable used in the baseline analysis (base case) was varied over the range of values shown in the sensitivity analysis. HPV denotes human papillomavirus, and CIN cervical intraepithelial neoplasia.

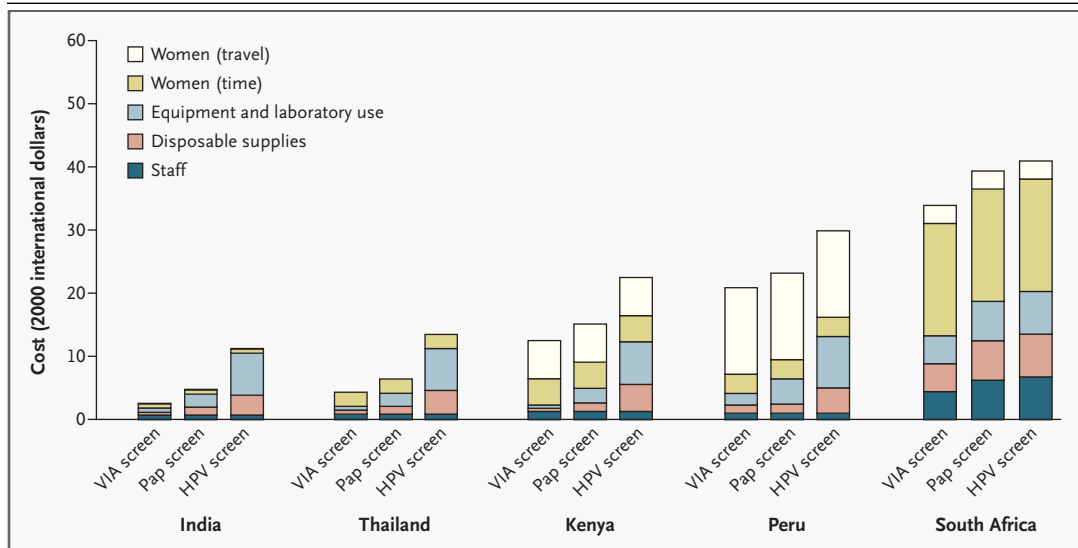
† Sensitivity is defined as the probability of a positive test given the presence of cervical intraepithelial neoplasia of grade 2 or more.

‡ In order to compare our results with those of other published analyses, we assumed that screening participation was 100 percent in the base case. Sensitivity analyses varied coverage according to the assumption that the population has either a homogenous or a heterogeneous risk of cervical cancer (i.e., women who are not screened are at higher risk than women who receive screening) (see the Supplementary Appendix).

§ We assumed that a loss to follow-up occurred for each clinical contact. For example, for a three-visit strategy, there would be an overall loss to follow-up of approximately 45 percent (see the Supplementary Appendix).

¶ The value shown is the proportion of women in each underlying disease category who would be ineligible for cryosurgery on the basis of visual inspection of the cervix and would be referred to a district or tertiary clinical care site for appropriate evaluation. Among those with grade 1 cervical intraepithelial neoplasia, one third would undergo a loop electrosurgical excision procedure, one third a cold-knife conization, and one third a simple hysterectomy; among those with cervical intraepithelial neoplasia of grade 2 or 3, 50 percent would undergo cold-knife conization and 50 percent simple hysterectomy.

|| Treatment for cervical intraepithelial neoplasia of grade 2 or 3 with cryosurgery resulted in a rate of immediate failure of 10 percent; a 10 percent recurrence of cervical intraepithelial neoplasia after six months; and a 5 percent recurrence after one year.



**Figure 1. Components of the Costs Associated with Screening.**

The costs associated with screening, in 2000 international dollars (a unit of currency that minimizes the consequences of differences in price levels existing among countries), are shown for the five countries. The height of each bar represents the total costs associated with the initial screening visit according to strategy — visual inspection of the cervix with acetic acid (VIA), DNA testing for human papillomavirus (HPV), or cytologic examination of Papanicolaou smears (Pap); the colored regions within bars represent categories of costs. Direct medical costs are subdivided into those attributable to staff (dark blue), supplies (pink), and equipment and laboratory use (light blue). Other costs include those associated with travel by the women (yellow) and the time associated with the women’s traveling and waiting for and receiving care (green). Because data regarding all direct medical costs in South Africa were grouped into one category, we attributed one third to staff, one third to laboratory and equipment use, and one third to supplies.

Three screenings (at 35, 40, and 45 years of age) provided an additional 15 percent reduction in risk. With maximized follow-up, through one-visit strategies or other methods, HPV DNA testing was the most effective strategy, followed closely by visual inspection and then cytologic examination. The least effective strategies were two-visit and three-visit cytologic examination and the combination of two-visit visual inspection and HPV DNA testing.

**COST-EFFECTIVENESS OF SCREENING AT DIFFERENT INTERVALS**

Figure 2 shows the lifetime costs and life expectancy associated with eight strategies performed at different intervals for each country. Detailed results for all strategies are available in the Supplementary Appendix.

The total discounted costs for a single lifetime screening strategy (one-visit visual inspection, two-visit HPV DNA testing, or three-visit cytologic examination) were lowest in India (\$24.20, \$26.29, and \$33.56, respectively) and highest in South Africa

(\$78.86, \$82.51, and \$110.95, respectively). The costs for all screening strategies increased only moderately with more frequent screening, since the majority of the lifetime cost per woman is attributable to cancer treatment.

The cost-effectiveness of a change from one screening strategy to a costlier alternative is represented by the difference in cost divided by the difference in life expectancy associated with a competing strategy. Strategies lying on the “efficiency curve” shown in each panel of Figure 2 “dominate” those lying to the right of the curve, because they are more effective and either cost less or have a better cost-effectiveness ratio than the next best strategy.

The cost per year of life saved associated with a single lifetime screening, with the use of either visual inspection or HPV DNA testing as compared with no screening, varied from \$10 to \$467. A strategy of one-visit visual inspection is the least costly nondominated strategy in India (\$10 per year of life saved) and Kenya (\$134 per year of life saved). HPV DNA testing with same-day treatment is the least

**Table 3. Selected Costs Associated with the Diagnosis and Treatment of Cervical Cancer in the Five Countries.\***

Variable	India	Kenya	Peru	South Africa	Thailand
<i>2000 international dollars</i>					
<b>Diagnostic and treatment options for CIN grade 2 or 3†</b>					
Direct medical costs					
Colposcopy and biopsy	36.14	27.71	10.42	107.87	81.10
Cryosurgery	16.55	25.18	13.61	96.11	45.11
Loop electrosurgical excision procedure	95.96	222.33	173.43	378.63	324.39
Cold-knife conization	212.58	291.58	394.17	458.48	486.58
Simple hysterectomy	303.68	601.39	533.64	1,582.73	973.16
Transportation and time costs‡					
Patient's average hourly wage	0.30	0.76	1.81	4.80	1.82
Colposcopy and biopsy	13.90	20.84	28.56	29.60	10.32
Cryosurgery	0.70	10.18	17.17	20.14	2.40
Loop electrosurgical excision procedure	13.95	20.97	28.86	30.40	10.63
Cold-knife conization	14.03	21.16	29.31	31.60	11.08
Simple hysterectomy	14.45	22.23	31.88	38.40	13.66
<b>Staging and treatment of invasive cervical cancer§</b>					
Costs according to cancer stage at diagnosis¶					
Local	1,445.39	1,552.45	3,436.34	4,658.51	2,550.17
Regional	2,104.93	1,925.20	2,894.28	3,043.83	2,892.57
Distant	2,104.93	1,925.20	2,894.28	2,640.16	2,892.57

\* Each value used in the baseline analysis was varied by  $\pm 75$  percent in sensitivity analyses. The international dollar is a unit of currency that minimizes the consequences of differences in price levels existing among countries. CIN denotes cervical intraepithelial neoplasia.

† Diagnostic and treatment costs include those associated with staff time, supplies, and equipment depreciation.

‡ Transportation and time costs include those associated with two-way travel, waiting at the clinical site, and receiving treatment, as well as for round-trip transportation to the clinical site. Estimates do not include recovery time.

§ The costs associated with invasive cancer include both direct medical costs (those associated with staging of cancer severity, hospitalization, stage-appropriate treatment, and follow-up visits) and direct nonmedical costs (those associated with care, including all patient time spent in transport, waiting for and receiving treatment, and hospitalization), as well as actual transportation costs.

¶ Local cancer denotes the classification of invasive cervical cancer as stage 1a1, 1a2, 1b1, 1b2, or 2a, regional as stage 2b, 3a, or 3b, and distant as stage 4a or 4b. For all countries except South Africa, treatment costs associated with regional and distant cancer were derived as a single category.

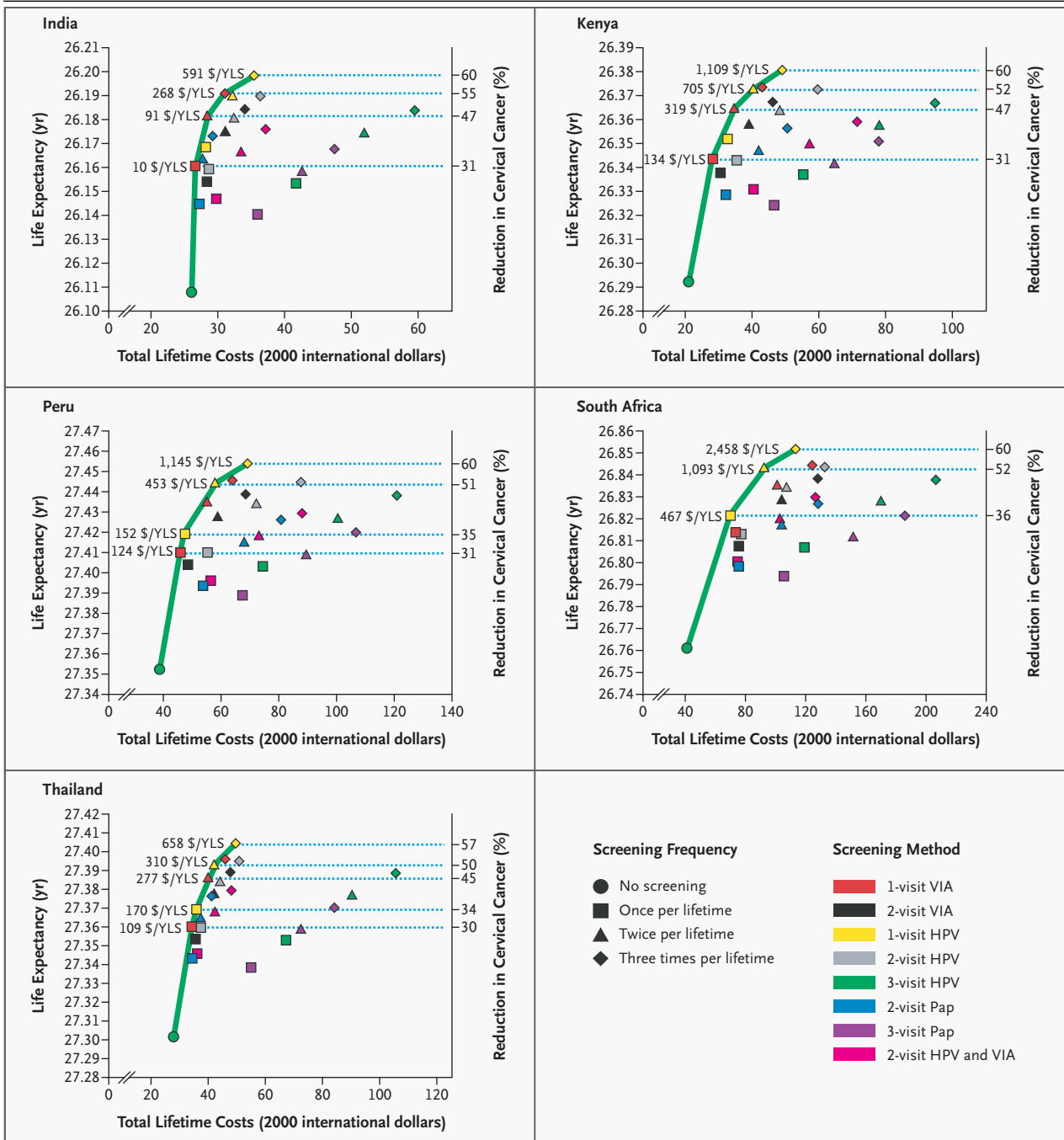
costly nondominated strategy in South Africa (\$467 per year of life saved). In Peru and Thailand, both one-visit visual inspection (\$124 per year of life saved and \$109 per year of life saved, respectively) and HPV DNA testing (\$152 per year of life saved and \$170 per year of life saved, respectively) dominate all other options. In all countries, an increase in screening frequency to two and three times per lifetime is more effective but costlier, as reflected in the increase in the cost-effectiveness ratio by a factor of 5 to 10.

Several strategies lying to the far right of the efficiency curve — including three-visit strategies using cytologic examination or HPV DNA testing — are consistently unattractive because they cost more

but are less effective than one-visit or two-visit strategies involving visual inspection or HPV DNA testing over a wide range of sensitivity analyses. Other strategies lying adjacent to the efficiency curve — notably, two-visit HPV DNA testing, two-visit cytologic examination, and two-visit visual inspection — may be as cost-effective as strategies on the curve, given varying assumptions about medical and program-related costs, follow-up rates, and test performance.

#### SENSITIVITY ANALYSIS

The cost-effectiveness of screening, irrespective of method, was sensitive to the costs associated with the treatment of invasive cancer and the target age



**Figure 2. Cost-Effectiveness of Screening for Cervical Cancer.**

The discounted lifetime costs and life expectancy associated with eight strategies performed at different screening intervals are shown for the five countries. The cost-effectiveness associated with a change from one strategy to a more costly alternative is represented by the difference in cost divided by the difference in life expectancy associated with the two strategies. Strategies that lie on the efficiency curve dominate those to the right of the curve because they are more effective and either cost less (indicating strong dominance) or have a more attractive cost-effectiveness ratio (weak dominance) than the next-best strategy. A cost-effectiveness ratio is shown for each nondominated strategy and is the reciprocal of the slope of the line connecting the two screening strategies under comparison; this slope is steeper when the net gain in life expectancy per dollar is greater. YLS denotes year of life saved, VIA visual inspection of the cervix with acetic acid, HPV human papillomavirus DNA testing, and Pap Papanicolaou smear.

of screening, whereas the choice among strategies was sensitive to test characteristics and screening costs. When the costs associated with invasive cancer were doubled, as was the case when we included the productivity costs of women dying from cervical cancer, screening with a single lifetime visual inspection or HPV DNA test became cost saving in India, Kenya, Peru, and Thailand and was less than \$500 per year of life saved in South Africa. When costs were halved, the cost-effectiveness of once-in-a-lifetime screening increased by 50 to 75 percent in Kenya, Peru, and Thailand, by 25 percent in South Africa, and by a factor of 8 in India. Strategies involving a single lifetime screening when targeted to women younger than 30 or older than 45 years of age were never as cost-effective as was targeting women in their mid-30s (see the Supplementary Appendix).

In India, if the costs of HPV DNA testing were reduced by 50 percent, two-visit HPV DNA testing dominated one-visit visual-inspection strategies and cost \$1 per year of life saved for one screening, \$73 for two screenings, and \$231 for three screenings in a lifetime. In Kenya and Peru, time and transportation accounted for most of the screening costs, and varying these costs had a greater effect than did varying the direct medical costs. Furthermore, these costs influenced the cost-effectiveness of two-visit strategies more than one-visit strategies, owing to a doubling of savings for travel and time. When these costs were lowered by 50 percent, the costs associated with all two-visit strategies were reduced considerably, although visual inspection dominated unless the costs associated with HPV DNA testing were also reduced by 50 percent.

The varying of program-related costs common to all strategies (e.g., those associated with recruitment) did not affect the rank ordering of strategies. Large changes in program-related costs associated with a particular strategy were more influential. If the costs associated with ongoing training for a one-visit visual-inspection strategy increased the total screening costs by a factor of more than five relative to two-visit HPV DNA testing, for example, the latter strategy was preferred. In contrast, two-visit HPV DNA testing became less attractive if the program-related costs of HPV DNA testing relative to a one-visit visual-inspection strategy resulted in a relative increase of more than twice the costs associated with a one-visit visual-inspection strategy.

Results were sensitive to assumptions about follow-up rates and differential screening coverage

among women with different risks of cancer. If the per-visit loss to follow-up was reduced to 5 percent, two-visit strategies became more attractive. In all countries, three-visit strategies were never attractive unless there was a simultaneous reduction in the loss to follow-up, in time and travel costs, and in direct medical costs. A reduction of 50 percent in screening coverage resulted in a near-proportional increase in the expected incidence of cervical cancer, provided that all women were equally compliant. With the assumption that screening was less likely to occur in high-risk women, the expected reduction in incidence was less than proportional, making screening less cost-effective (see the Supplementary Appendix). The results for Kenya and South Africa that incorporated age-specific HIV-related mortality were stable, provided that the target population was women 35 to 40 years of age who did not have symptomatic cases of AIDS.

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## DISCUSSION

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The most clinically effective and cost-effective strategies in the countries we assessed were those that enhanced the linkage between screening and treatment, through either a reduced number of visits or improved follow-up, and that relied on less laboratory infrastructure than did conventional cytologic methods. The screening of women with one-visit or two-visit visual inspection or HPV DNA testing at about 35 years of age would reduce the lifetime risk of cervical cancer by 25 to 36 percent. Two screenings in a lifetime would provide a relative increase in the lifetime reduction of risk of cancer of approximately 40 percent, although the incremental benefits of three screenings are much smaller.

The lifetime costs associated with alternative screening approaches vary among countries, owing to differences in the costs associated with labor and nontradable goods and the relative proportion of direct medical, time, and transportation costs. For similar reasons, cost-effectiveness ratios vary as well. For example, the cost per year of life saved for screening twice in a lifetime with a one-visit visual-inspection strategy is \$91 in India and \$319 in Kenya; this same strategy with the use of HPV DNA testing costs \$310 per year of life saved in Thailand, \$453 in Peru, and \$1,093 in South Africa. Despite considerable differences among absolute cost-effectiveness ratios, the policy implications for these countries are similar once their relative re-

sources (e.g., per capita gross domestic product [GDP]) are considered.

There is no universal criterion that defines a threshold cost-effectiveness ratio, above which an intervention would not be considered cost-effective. We chose to use guidelines specifically intended for international comparisons, as proposed by the Commission on Macroeconomics and Health, which defines interventions with a cost-effectiveness ratio that is less than the per capita GDP as “very cost-effective.”<sup>26</sup> Expressed in international dollars, the per capita GDP ranges from \$1,005 in Kenya to \$9,486 in South Africa, suggesting that screening for cervical cancer twice in a lifetime in Kenya and three times in South Africa, Peru, Thailand, and India would be considered very cost-effective. To place our results in the context of other public health interventions, the cost-effectiveness ratios that are associated with the most efficient strategies are expressed as a percentage of each country’s GDP (Table 4). Strategies that involve a single lifetime screening are as cost-effective as hepatitis B immunization in India, second-line treatment for tuberculosis in Peru, and prevention of malaria with the use of bed nets in Kenya.<sup>27-29</sup>

Our analysis has several limitations. Data were combined from multiple sources with varied study designs, and many variables are uncertain. We could not account for the temporal effects of factors such as sexual behavior, although the effect of these factors on the cost-effectiveness of a strategy involving one or two screenings in a lifetime would probably be minimal. In settings with severe resource constraints, treatment for invasive cervical cancer may be unavailable. That being said, cervical cancer is one of the few cancers with a long preclinical phase, and a successful cancer-control program aimed at detecting and treating precancerous lesions therefore will reduce the number of cases that require treatment. Finally, strategies we have identified as cost-effective may be unaffordable without assistance in the poorest countries; our results can provide guidance for the global community by identifying health investments that are of the highest priority and have the greatest promise.

The cost-effectiveness of an intervention is only one consideration in terms of allocating scarce resources. All screening tests may not be equally available in all settings, and they may be selected for program-related reasons, for qualitative attributes, or

**Table 4. Cost-Effectiveness Ratios, Expressed as a Percentage of per Capita GDP, According to Country.\***

Variable	India	Kenya	Peru	South Africa	Thailand
Per capita GDP — international dollars†	2,430	1,005	4,747	9,486	6,373
Screening strategy — %‡					
Once per lifetime					
VIA	0.41	13.33	2.61	D	1.71
HPV DNA test	D	D	3.2	4.92	2.67
Twice per lifetime					
VIA	3.74	31.74	D	D	4.35
HPV DNA test	D	70.15	9.54	11.52	4.86
Three times per lifetime					
VIA	11.03	D	D	D	D
HPV DNA test	24.32	110.35	24.12	25.91	10.32

\* The screening strategies shown reflect a same-day testing and treatment approach. GDP denotes gross domestic product, VIA visual inspection of the cervix with acetic acid, and HPV human papillomavirus.

† According to criteria proposed by the Commission on Macroeconomics and Health, interventions with cost-effectiveness ratios of less than 100 percent of the per capita GDP are very cost-effective. By comparison, the cost-effectiveness ratio associated with hepatitis B immunization in India, expressed as a percentage of the GDP, is 2 percent; with voluntary counseling and testing for HIV in Kenya, 5 percent; with second-line treatment for tuberculosis in Peru, 10 percent; and with malaria prevention with the use of bed nets in Kenya, 20 percent.

‡ Screening of women once per lifetime occurs at 35 years of age, twice per lifetime at 35 and 40 years, and three times at 35, 40, and 45 years. D denotes strategies that are dominated, meaning that they cost more than and are either less clinically effective or less cost-effective than the next-best strategy.

for their synergy with future public health initiatives. We considered it prudent to provide results for all potentially available strategies, recognizing that country-specific circumstances vary. For example, a strategy that involves one-visit HPV DNA testing requires screening sites to run the test on the day that the sample is received. The currently available diagnostic test for HPV DNA takes several hours to process, and a same-day approach may be impractical for smaller rural settings. On the other hand, two-visit strategies may be more culturally acceptable in certain countries because women may want to discuss treatment options with family members after being screened.

Strategies that involve the use of visual inspection or HPV DNA testing and that require only one or two clinical visits offer cost-effective alternatives to conventional cytology-based screening in low-resource settings. If targeted once or twice in a lifetime to women between the ages of 35 and 45 years,

these strategies would be among the most cost-effective interventions available and could lower the global incidence of cervical cancer by as much as 50 percent.

Supported by the Bill and Melinda Gates Foundation; by grants to EngenderHealth, the International Agency for Research on Cancer, JHPIEGO, the Pan American Health Organization, and the Program for Appropriate Technology in Health; and by a grant (R01 CA93435) from the National Cancer Institute (to Dr. Goldie).

We are indebted to the participants, investigators, and staff members associated with the Alliance for Cervical Cancer Prevention for their outstanding dedication and commitment, including Dr. Graciela Salvador (JHPIEGO, Cervical Cancer Prevention Office), Dr. Pirom Kamolratanakul (dean, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand), Kasturi Jayant and M.K. Chauhan (Nargis Dutt Memorial Cancer Hospital, Barshi, India), Dr. Parthasarathy Basu (Chittaranjan National Cancer Institute, Calcutta, India), Sylla G. Malvi (Tata Memorial Centre, Mumbai, India), Dr. Ramani Wesley (Regional Cancer Center, Trivandrum, India), Dr. Roberto Del Aguila (Pan American Health Organization, World Health Organization [WHO], Lima), and Dr. Miguel Gonzales (Pan American Health Organization, WHO, Tarapoto, Peru); and to Steven Sweet and Jesse Ortendahl of the Harvard University Initiative for Global Health, Cambridge, Mass., for their outstanding technical and computer-programming assistance.

#### APPENDIX

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#### REFERENCES

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: cancer incidence, mortality and prevalence worldwide, version 1.0. IARC Cancerbase no. 5. Lyon, France: IARC Press, 2001.
2. Sankaranarayanan R, Budukh AM, Rajkumar R. Effective screening programmes for cervical cancer in low- and middle-income developing countries. *Bull World Health Organ* 2001;79:954-62.
3. Denny L, Kuhn L, Pollack A, Wainwright H, Wright TC Jr. Evaluation of alternative methods of cervical cancer screening for resource-poor settings. *Cancer* 2000;89:826-33.
4. Visual inspection with acetic acid for cervical-cancer screening: test qualities in a primary care setting: University of Zimbabwe/JHPIEGO Cervical Cancer Project. *Lancet* 1999;353:869-73.
5. Kuhn L, Denny L, Pollack A, Lorincz A, Richart RM, Wright TC. Human papillomavirus DNA testing for cervical cancer screening in low-resource settings. *J Natl Cancer Inst* 2000;92:818-25.
6. Sankaranarayanan R, Shyamalakumary B, Wesley R, Sreedevi Amma N, Parkin DM, Nair MK. Visual inspection with acetic acid in the early detection of cervical cancer and precursors. *Int J Cancer* 1999;80:161-3.
7. Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med* 2002;347:1645-51.
8. Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus type 16 and 18 in young women: a randomised control trial. *Lancet* 2004;364:1757-65.
9. World Bank WDI Online. (Accessed October 24, 2005, at <http://www.worldbank.org/data/countrydata/countrydata.html>.)
10. Women and men in the informal economy: a statistical picture. International Labour Office Report. (Accessed October 24, 2005, at: <http://www.ilo.org/public/english/employment/gems/download/women.pdf>.)
11. Department of Commerce. 1999 Income data. (Accessed October 24, 2005, at <http://ia.ita.doc.gov/wages/99wages/99wages.htm>.)
12. Goldie SJ, Kuhn L, Denny L, Pollack A, Wright TC. Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. *JAMA* 2001;285:3107-15. [Erratum, *JAMA* 2001;286:1026.]
13. Mandelblatt JS, Lawrence WF, Gaffikin L, et al. Costs and benefits of different strategies to screen for cervical cancer in less-developed countries. *J Natl Cancer Inst* 2002;94:1469-83.
14. Disease Control Priorities Project guidelines. (Accessed October 24, 2005, at <http://www.fic.nih.gov/dcpp/authors.html>.)
15. Gold MR, Siegel JE, Russel LB, Weinstein MC, eds. Cost-effectiveness in health and medicine. New York: Oxford University Press, 1996.
16. World Health Organization. Life tables for 191 countries. (Accessed October 24, 2005, at [http://www3.who.int/whosis/life\\_tables/life\\_tables\\_process.cfm?country=tcd&language=en](http://www3.who.int/whosis/life_tables/life_tables_process.cfm?country=tcd&language=en).)
17. Future directions in epidemiologic and preventive research on human papillomavirus and cancer. In: Bosch FX, Schiffman M, Solomon D, eds. National Cancer Institute monograph no. 31. Bethesda, Md.: National Cancer Institute, 2003.
18. Alliance for Cervical Cancer Prevention (ACCP). Effectiveness, safety, and acceptability of cryotherapy: a systematic literature review.

- (Accessed October 24, 2005, at <http://www.alliance-cxca.org/english/publications.html#presentations>.)
19. World Health Organization statistical information system: CHOICE (CHOosing Interventions that are Cost Effective). (Accessed October 24, 2005, at <http://www3.who.int/whosis/>.)
20. Department of Labor. Wages, benefits, poverty line, and meeting workers' needs in the apparel and footwear industries of selected countries. (Accessed October 24, 2005, at <http://www.dol.gov/ilab/media/reports/oiea/wagestudy/wagestudy.pdf>.)
21. Nominal interbank exchange rates (year averages). (Accessed October 24, 2005, at <http://www.oanda.com/convert/fxhistory>.)
22. Johns B, Baltussen R, Hutubessy R. Programme costs in the economic evaluation of health interventions. *Cost Effectiveness and Resource Allocation* 2003;1:1. (Accessed October 24, 2005, at <http://www.resource-allocation.com/content/1/1/1>.)
23. International Center for Tropical Agriculture. Accessibility, transport and travel time information. (Accessed October 24, 2005, at [http://gisweb.ciat.cgiar.org/cross\\_scale/download/2.5\\_web.pdf](http://gisweb.ciat.cgiar.org/cross_scale/download/2.5_web.pdf).)
24. Waggoner SE. Cervical cancer. *Lancet* 2003;361:2217-25.
25. van Ballegooijen M, Koopmanschap M, Tjokkrowardojo AJ, van Oortmarsen GJ. Care and costs of advanced cervical cancer. *Eur J Cancer* 1992;28A:1703-8.
26. World Health Organization. Macroeconomics and health: investing in health for economic development: report of the Commission on Macroeconomics and Health. Geneva: World Health Organization, 2001.
27. Aggarwal R, Ghoshal UC, Naik SR. Assessment of cost-effectiveness of universal hepatitis B immunization in a low-income country with intermediate endemicity using a Markov model. *J Hepatol* 2003;38:215-22.
28. Wiseman V, Hawley WA, ter Kuile F, et al. The cost-effectiveness of permethrin-treated bed nets in an area of intense malaria transmission in western Kenya. *Am J Trop Med Hyg* 2003;68:Suppl 4:161-7.
29. Suarez PG, Floyd K, Portocarrero J, et al. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet* 2002;359:1980-9.

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