Cost-effectiveness of cervical-cancer screening in five developing countries

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Several screening strategies for cervical cancer were studied. The strategies were differentiated according to the number of clinical visits, the frequency of screening, and targeted ages. The three testing strategies were:

- visual inspection of the cervix with acetic acid (VIA),
- cytologic examination of cervical cells on a Papanicolaou smear (PAP), and
- DNA testing for human papillomavirus (HPV) in cervical-cell samples using the hybrid-capture method (HPV-DNA).

Three-visit strategies included an initial screening test, colposcopy and biopsy in the case of positive results, and the 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 5-year intervals. Details of all screening strategies were provided. Screening of women once per lifetime occurred at age 35 years, twice per lifetime at age 35 and 40, and three times at age 35, 40 and 45.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women eligible for cervical cancer screening.

Setting
The setting was primary care. The economic study was carried out in the five countries under examination.

Dates to which data relate
The clinical data appear to have been derived from studies published between 1999 and 2005. No dates for the resource use data were explicitly reported. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

Modelling
A computer-based, state-transition, decision model was constructed to simulate the natural history of cervical cancer and the clinical and economic impact of the alternative screening strategies in hypothetical cohorts of women in the five countries. The time horizon of the model was lifetime and monthly cycles were considered. The health states of the model represented HPV DNA status, the grade of cervical intraepithelial neoplasia (CIN; Grades 1, 2 and 3) and the stage of invasive cancer (local, regional, distant). All probabilities were dependent on age, HPV status and disease history. The natural history was the same for all countries. However, since patterns of sexual behaviour and risk factors for cervical cancer might vary, age-specific rates of death due to causes other than cancer, such as those associated with pregnancy and the human immunodeficiency virus (HIV), were incorporated. A simplified version of the model was reported in an appendix.

**Outcomes assessed in the review**
The outcomes estimated from the literature were the age-specific incidence of cervical cancer, the sensitivity and specificity of the screening tests, and variables associated with cryosurgery. Other demographic characteristics of the five countries were also reported. For example, the total population, population density, percentage of women aged 35 to 39 years; female life expectancy at birth, HIV prevalence among adults, and gross domestic product. Such data were derived from the World Bank, the International Labor Office and the US Department of Commerce.

**Study designs and other criteria for inclusion in the review**
It was unclear whether a systematic review of the literature was undertaken to identify the primary estimates. The designs of the primary studies were not reported.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
At least 9 primary studies provided data.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The age-specific incidence of cervical cancer was reported graphically. Only key model inputs are reported here.

With VIA, the sensitivity was 76% (range: 60 - 90) and the specificity was 81% (range: 66 - 96).

With HPV-DNA, the sensitivity was 88% (range: 65 - 95) and the specificity was 93% (range: 70 - 96).
With cytology, the sensitivity was 63% (range: 45 - 85) and the specificity was 94% (range: 80 - 98).

The proportion of women ineligible for cryosurgery according to disease status was:

- 5% (range: 0 - 50) if DNA is normal or positive for HPV without CIN;
- 15% (range: 0 - 50) with CIN Grade 1; and
- 25% (range: 0 - 50) with CIN Grade 2 or 3.

Cryosurgery was 85% effective (range: 50 - 90) in women with CIN Grade 1 and 75% effective (range: 50 - 90) in women with CIN Grade 2 or 3.

The rate of major complications associated with cryosurgery was 1% (range: 0 - 3), while that of minor complications was 5% (range: 0 - 15).

**Methods used to derive estimates of effectiveness**

Some assumptions were made in the decision model.

**Estimates of effectiveness and key assumptions**

Participation in screening was assumed to have been 100% (range: 25 - 100). The rate of loss to follow-up (per visit) was 15% (range: 0 - 50).

**Measure of benefits used in the economic analysis**

The summary benefit measure used was the life-years (LYs). These were estimated using a modelling approach. An annual discount rate of 3% was applied. The reduction in lifetime risk of invasive cervical cancer was also reported.

**Direct costs**

The health services included in the economic evaluation were the direct medical costs (e.g. staff, disposable supplies, equipment and specimen transport), transportation costs, programme-related costs and costs of cancer care. The cost/resource boundary of the service payer and the patient appears to have been adopted. The unit costs were presented separately for most categories of costs. The resource use data was estimated from country-specific data whenever possible, supplemented with published literature when necessary. Some standardised assumptions, using consensus meetings involving representatives from all five countries, were also made for supplies and equipment needs, clinician time and protocols of care. For example, the programme-related costs were estimated assuming an 80% use of capacity. The costs came mainly from country-specific civil services as well as international data. Discounting was relevant, as the lifetime costs were estimated, and an annual rate of 3% was used. The price year was 2000.

**Statistical analysis of costs**

The costs were treated deterministically in the base-case.

**Indirect Costs**

The indirect costs were estimated. These comprised patient time spent travelling to and from the site of care, her waiting time, her time receiving care, and hospitalisation time post treatment. The estimates of wage rate were derived using a weighted average of wages for formal sector jobs and minimum wage rates for informal sector jobs. The data came from the US Department of Commerce, the World Bank and the Economic Research Institute. The minimum wage rates were derived from US Department of Labor wage rate studies and World Bank estimates, while average yearly hours worked were ascertained from the World Bank. The unit costs were presented separately for most items. Discounting was relevant and was performed. The price year was 2000.
Currency
International dollars ($). Costs in local currency units were converted into international dollars using purchasing power parity exchange rates rather than official exchange rates.

Sensitivity analysis
Univariate sensitivity analyses were performed. These assessed the robustness of the estimated cost-effectiveness ratios to variations in several model inputs, such as age or cost variables.

Estimated benefits used in the economic analysis
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% with one-visit and two-visit VIA,
- 30 to 36% with one-visit and two-visit HPV DNA testing, and
- 18 to 22% with two-visit and three-visit PAP.

Compared with a single screening, two screenings (at age 35 and 40 years) provided an increased relative reduction in lifetime risk of approximately 40%. Three screenings (at age 35, 40 and 45) provided an additional 15% reduction in risk. With maximised follow-up, through one-visit strategies or other methods, HPV-DNA testing was the most effective strategy, followed closely by VIA and then PAP. The least effective strategies were two-visit and three-visit PAP and the combination of two-visit VIA and HPV-DNA testing.

The estimated LYs were reported only in the technical appendix.

The LYs ranged from:

- 26.710 with no screening to 26.8520 with 1-visit HPV-DNA three times in South Africa;
- from 27.3002 with no screening to 27.4033 with 1-visit HPV-DNA three times in Thailand;
- from 26.1079 with screening to 26.1979 with 1-visit HPV-DNA three times in India;
- from 26.2919 with no screening to 26.3804 with 1-visit HPV-DNA three times in Kenya; and
- from 27.3518 with no screening to 27.4531 with 1-visit HPV-DNA three times in Peru.

The strategy of 1-visit HPV-DNA was thus associated with the highest LYs in all countries.

Cost results
The estimated costs were reported only in the technical appendix.

The costs ranged from:

- $46.65 with no screening to $211.85 with 3-visit HPV-DNA three times in South Africa;
- from $30.40 with no screening to $107.97 with 3-visit HPV-DNA three times in Thailand;
- from $23.67 with screening to $56.98 with 3-visit HPV-DNA three times in India;
- from $23.31 with no screening to $96.67 with 3-visit HPV-DNA three times in Kenya; and
- from $41.29 with no screening to $123.24 with 3-visit HPV-DNA three times in Peru.
The strategy of 3-visit HPV-DNA was thus the most expensive in all countries.

**Synthesis of costs and benefits**

Incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative screening strategies. Each strategy was compared with the next less expensive option. Dominated strategies (those that were both more expensive and less effective than at least another option) were excluded.

In South Africa, the incremental cost per LY gained was $467 with 1-visit HPV-DNA once, $1,093 with 1-visit HPV-DNA twice and $2,458 with 1-visit HPV-DNA three times, compared with the next less expensive options.

In Thailand, the incremental cost per LY gained was $170 with 1-visit HPV-DNA once, $277 with 1-visit VIA twice, $310 with 1-visit HPV-DNA twice and $658 with 1-visit HPV-DNA three times.

In India, the incremental cost per LY gained was $10 with 1-visit VIA once, $91 with 1-visit VIA twice, $268 with 1-visit VIA three times and $591 with 1-visit HPV-DNA three times.

In Kenya, the incremental cost per LY gained was $134 with 1-visit VIA once, $319 with 1-visit VIA twice, $705 with 1-visit HPV-DNA twice and $1,109 with 1-visit HPV-DNA three times.

In Peru, the incremental cost per LY gained was $124 with 1-visit VIA once, $152 with 1-visit HPV-DNA once, $453 with 1-visit HPV-DNA twice and $1,145 with 1-visit HPV-DNA three times.

The results reported above were achieved under the assumption that all screening strategies were equally available.

Thus, the most cost-effective strategies were those that required the fewest visits, resulting in improved follow-up testing and treatment. Using each country's per capita gross domestic product as a threshold for cost-effectiveness, screening for cervical cancer twice per lifetime in Kenya and three times per lifetime in South Africa, Peru, Thailand and India would be considered very cost-effective.

The sensitivity analysis showed that the cost-effectiveness ratios were sensitive to the costs associated with the treatment of invasive cancer and the target age of screening. The choice among strategies was sensitive to test characteristics and screening costs. For example, when the costs associated with invasive cancer were doubled, screening with a single lifetime VIA or HPV-DNA test became cost-saving in India, Kenya, Peru and Thailand, and was less than $500 per LY saved in South Africa. Strategies involving a single lifetime screening were never as cost-effective when targeted at women younger than 30 years or older than 45 years as those that targeted women in their mid-30s. Variations in programme-related costs common to all strategies did not affect the rank ordering of the strategies. The results were also sensitive to assumptions about follow-up rates and differential screening coverage among women with different risks of cancer.

**Authors' conclusions**

Screening strategies for cervical cancer that incorporate visual inspection of the cervix with acetic acid (VIA) or DNA testing for human papillomavirus (HPV) in one or two clinical visits were cost-effective alternatives to conventional three-visit cytology-based screening programmes in resource-poor settings.

**CRD COMMENTARY - Selection of comparators**

The rationale for the selection of the comparators was clear. All relevant screening options were considered and described. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness evidence came from a synthesis of published studies. No details on the designs and characteristics of the primary studies were reported. Thus, it was not possible to assess the validity of the primary studies. Some assumptions were also made to derive clinical data that were not available from the literature. The issue of uncertainty...
was not extensively addressed in the sensitivity analysis and very few clinical parameters were varied.

Validity of estimate of measure of benefit
The benefit measure used in the analysis was appropriate as it captured the impact of the interventions on the most relevant dimension of care (i.e. survival). It also enables comparisons with the benefits of other health care interventions. Discounting was appropriately applied.

Validity of estimate of costs
The cost analysis was performed from a societal perspective. This was appropriate as all the relevant categories of costs were considered within the context of poor-resource settings. Extensive information on the methods used to calculate the costs was reported in an appendix. The unit costs were presented for most items. The approaches used to calculate the indirect costs were described and discussed. The source of the data was clear. Statistical analyses of the costs were not performed, but the impact of using alternative cost estimates was investigated in the sensitivity analysis. The price year was reported, which aids reflation exercises in other time periods.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. However, the use of a sensitivity analysis enhances the external validity of the analysis. The authors noted some limitations of their analysis. First, the data came from multiple sources and several variables were uncertain. Second, the impact of specific factors such as sexual behaviour was not explicitly considered in the model. Third, some treatment options might be unavailable in settings with severe resource constraints. The authors stated that a standardised approach was used for all five countries and this ensured the comparability of the results.

Implications of the study
The study results support the implementation of strategies involving visual inspection or HPV-DNA testing and requiring only one or two clinical visits for the reduction of cervical cancer in low-resource settings. The authors noted that their results could provide guidance for the global community by identifying health investments that are of the highest priority and have the greatest promise.

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