Cost-effectiveness analysis of liquid-based cytology and human papillomavirus testing in cervical cancer screening


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
The study examined cervical cancer screening strategies. Specifically, liquid-based cytology (LBC) with testing for human papillomavirus (HPV) irrespective of cytologic results (DNA/Pap) was compared with LBC with HPV detection for cytologic results of atypical cells of undetermined significance (reflex HPV). These screening strategies were evaluated separately as well as in combination (LBC and reflex HPV before age 30 years and DNA/Pap every 3 years thereafter) and at different frequencies (yearly, every 2 years and every 3 years). In total, nine screening strategies were considered.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of active-duty army service women.

Setting
The setting was the military. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 2002 and 2005. Some data on resource use were derived from sources published in 2002. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and authors’ opinions.

Modelling
A published Markov model was used to simulate the natural history of cervical cancer in a hypothetical cohort of 100,000 active-duty army service women. Women entered the simulation at age 18 years and ended at age 85. The health states of the model were healthy, infected with HPV, low-grade squamous intraepithelial lesion (SIL), high-grade SIL, invasive cervical cancer and death. It was assumed that all women with biopsy-proven cervical intraepithelial neoplasia (CIN) 1 were followed with repeat cytology, while those with persistent CIN 1 were treated using a loop electrosurgical excision procedure. It was also assumed that women with CIN 2 to 3 were referred for immediate treatment. Other details of the decision model were not reported.
Outcomes assessed in the review
The outcomes estimated from the literature were:

the prevalence of HPV infection;

the prevalence of low- and high-grade SIL;

the age-specific incidence of HPV infection;

the age-specific regression rate of HPV (from HPV to well);

the progression rate from HPV to low-grade SIL;

the proportion of infections progressing directly to high-grade SIL;

the regression rate from low-grade SIL to HPV or well;

the proportion of low-grade SIL reverting to well;

the progression rate from low-grade SIL to high-grade SIL;

the regression rate from high-grade SIL to low-grade SIL;

the proportion of high-grade SIL reverting to well;

the progression rate from high-grade SIL to Stage I cancer;

the progression rates by stage in unscreened patients with cancer;

5-year survival probability by stage; and

screening test performance.

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 studies. Most of the clinical data came from a published economic evaluation carried out by the US Army (in which indirect costs were not accounted for). Other data were obtained from a large population-based study carried out in Washington State. Details of the other sources 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
Five primary studies provided the clinical data.
Methods of combining primary studies
A narrative approach appears to have been used to combine the primary estimates.

Investigation of differences between primary studies
Not reported.

Results of the review
The prevalence of HVP infection was 0.10 (range: 0 to 0.20) at 18 years. It ranged from 0.016 to 0.236 depending on enlisted rank (which depended on skill level, job expertise and leadership abilities).

The prevalence of low-grade SIL (CIN 1) was 0.01 at 18 years (range: 0 to 0.20). It ranged from 0.009 to 0.049 depending on the enlisted rank.

The prevalence of high-grade SIL (CIN 2 to 3) ranged from 0.007 to 0.021 depending on the enlisted rank.

The age-specific incidence of HPV infection was reported for different ages (from 0.15 at 18 years to 0.005 for more than 50 years).

The regression rate of HPV (from HPV to well) was 0.7/18 months in women aged 15 to 24 years, 0.5/18 months in women aged 25 to 29 years, and 0.15/28 months in women aged 30 years or older.

The progression rate from HPV to low-grade SIL was 0.2/36 months.

The proportion of infections progressing directly to high-grade SIL was 0.1.

The regression rate from low-grade SIL to HPV or well was 0.65/72 months in women aged 15 to 34 years and 0.4/72 months in women aged 35 years or older.

The proportion of low-grade SIL reverting to well was 0.9.

The progression rate from low-grade SIL to high-grade SIL was 0.1/72 months in women aged 15 to 24 years and 0.35/72 months in women aged 35 years or older.

The regression rate from high-grade SIL to low-grade SIL was 0.35/72 months.

The proportion of high-grade SIL reverting to well was 0.5.

The progression rate from high-grade SIL to Stage I cancer was 0.4/120 months.

The progression rate in unscreened patients with cancer was 0.9/4 years in Stages I-II, 0.9/3 years in Stages II-III, and 0.9/2 years in Stages III-IV.

The 5-year survival probability was 0.85 in Stage I, 0.6766 in Stage II, 0.3987 in Stage III, and 0.1127 in Stage IV.

The sensitivity of LBC plus reflex HPV was 80% and the specificity was 95%.

The sensitivity of the DNA/Pap test was 89% and the specificity 90% for women aged 30 years or older, and 93% (sensitivity) and 80% (specificity), respectively, for women aged younger than 30 years.

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.
Estimates of effectiveness and key assumptions
As all patients were active-duty military personnel, full compliance with screening, diagnosis and treatment was assumed. The sensitivity and specificity of colposcopy were both 100%.

Measure of benefits used in the economic analysis
The summary benefit measure was the life expectancy associated with each screening strategy. This was obtained using a modelling approach. An annual discount rate of 3% was used.

Direct costs
The analysis of the costs was carried out from a societal perspective. The direct medical costs included were for LBC (including office visit), HPV (with no office visit), colposcopy with biopsy and endocervical curettage, loop electrosurgical excision procedure for CIN 2-3, and cancer treatment (by stage). Some unit costs were presented but few details of resource consumption were provided. Some costs were reported as macro-categories. The costs were derived from the US Army and health insurance reimbursements. When costs were not directly available, the military literature was searched. Most data on resource use were derived from published guidelines. For example, all women undergoing colposcopy underwent endocervical curettage. Women with biopsy-proven CIN 1 were followed with repeat cytology, while women with persistent CIN 1 were treated with loop electrosurgical excision procedure. Women with CIN 2-3 were referred for immediate treatment. Discounting was relevant, as the long-term costs were evaluated, and an annual discount rate of 3% was used. The price year was 2004.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
Indirect costs, in terms of the cost of time away from work to undergo screening, diagnosis and treatment, were included in the analysis by applying salaries from the Department of Defence pay tables in 2004, which represented the price year. Only limited information on the unit costs and quantities of resources used was provided. The source of resource use was not clearly reported and appears to have been based on experts' opinion. Fringe benefits (allowance for sustenance and allowable housing costs) were not considered in the calculation of indirect costs in the base-case analysis. An annual discount rate of 3% was used.

Currency
US dollars ($).

Sensitivity analysis
A univariate sensitivity analysis was performed to assess the robustness of cost-effectiveness ratios to variations in model inputs. Such inputs included the prevalence of CIN and HPV, the sensitivity of LBC, the specificity of combined HPV and LBC, the inclusion of fringe benefits, and the cost of the HPV test. Alternative data were based on authors' opinions.

Estimated benefits used in the economic analysis
The estimated mean life expectancy was:

- 25.8770 with no screening;
- 25.9282 with LBC + reflex HPV every 3 years;
- 25.9312 with LBC + reflex HPV every 2 years;
25.9296 with LBC + reflex HPV every 3 years before age 30 and then DNA/PAP every 3 years thereafter;
25.9304 with LBC + reflex HPV every 2 years before age 30 years and then DNA/PAP every 3 years thereafter;
25.9307 with DNA/PAP every 3 years;
25.9315 with LBC + reflex HPV every year before age 30 years and then DNA/PAP every 3 years thereafter;
25.9342 with LBC + reflex HPV every year;
25.9329 with DNA/PAP every 2 years; and
25.9351 with DNA/PAP every year.

Cost results
The expected mean costs per woman were:

- $402 with no screening;
- $665 with LBC + reflex HPV every 3 years;
- $832 with LBC + reflex HPV every 2 years;
- $1,032 with LBC + reflex HPV every 3 years before age 30 and then DNA/PAP every 3 years thereafter;
- $1,072 with LBC + reflex HPV every 2 years before age 30 years and then DNA/PAP every 3 years thereafter;
- $1,130 with DNA/PAP every 3 years;
- $1,224 with LBC + reflex HPV every year before age 30 years and then DNA/PAP every 3 years thereafter;
- $1,355 with LBC + reflex HPV every year;
- $1,515 with DNA/PAP every 2 years; and
- $2,675 with DNA/PAP every year.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios (ICERs; i.e. the incremental cost per life-year gained) were calculated in order to combine the costs and benefits of the alternative strategies.

After excluding dominated strategies (i.e. those that were both less effective and more expensive than at least another option), or extended dominated strategies (ICER higher than an adjacent strategy), the ICER was:

- $5,140 with LBC + reflex HPV every 3 years (over no screening);
- $56,728 with LBC + reflex HPV every 2 years (over LBC + reflex HPV every 3 years);
- $171,224 with LBC + reflex HPV every year (over LBC + reflex HPV every 2 years); and
- $1,472,416 with DNA/PAP every year (over LBC + reflex HPV every year).

The sensitivity analysis showed that the base-case results were quite robust to variations in clinical and economic inputs. The ranking of the alternative screening strategies did not change in most scenarios. A higher prevalence of disease resulted in a lower ICER. The results of the analysis were also sensitive to the sensitivity and specificity of the
alternative options, but the most cost-effective alternative remained LBC with reflex HPV conducted every 2 to 3 years.

**Authors’ conclusions**
A strategy of cervical cancer screening performed with liquid-based cytology (LBC) and reflex human papillamovirus (HPV) testing of atypical squamous cells of undetermined significance performed every 2 (or 3) years was a cost-effective strategy in the USA, especially when the indirect costs were considered.

**CRD COMMENTARY - Selection of comparators**
A range of possible screening strategies based on the inclusion of individual or combined tests was considered in the analysis. Therefore, the choice of the comparators was appropriate. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness data used to populate the decision model were derived mainly from published studies. The authors did not report the methods and conduct of a systematic review of the literature, thus the primary studies might have been identified selectively. There was some information on a small number of studies but, in general, few details were provided. Therefore, it was difficult to assess the validity of the primary estimates. The authors did not report the approach used to combine and extract data from the primary studies. Moreover, the issue of heterogeneity among the primary studies was not addressed. Some assumptions were also made, but sensitivity analyses were conducted to address the impact of uncertainty on key clinical and epidemiological data.

**Validity of estimate of measure of benefit**
The use of life expectancy as the summary benefit measure was appropriate as it captures the impact of the interventions on survival, which is a relevant dimension of health for women who might develop cervical cancer. A further advantage of survival is that it can be compared with the benefits of other health care interventions. Discounting was performed, as recommended by US guidelines. The impact of the intervention on quality of life was not addressed.

**Validity of estimate of costs**
The economic analysis was carried out using a broad perspective. The inclusion of the indirect costs was a positive feature of the study, since their inclusion was intended to overcome the limitations of previous economic evaluations on cervical cancer screening strategies. A detailed breakdown of cost items was not reported for the direct costs, and there was limited information on the unit costs and quantities of resources used for some items. This may limit the possibility of replicating the analysis in other settings. However, the costs of cancer care by stage were often presented as macro-categories. The sources of most costs were reported and appear to have been appropriate. The price year was reported, thus simplifying reflation exercises in other time periods. Statistical analyses of the costs were not carried out, but the impact of variations in key cost estimates was investigated in the deterministic sensitivity analysis.

**Other issues**
The authors reported the results from other published studies and stated the strengths of their economic evaluation in comparison with other analyses, in particular concerning the inclusion of the indirect costs. An advantage of the study was the use of military salary data, which are not only robust because of the rigorous source of data but also correct as they do not distinguish individuals by gender. Previous analyses based on civilian data reported female wages lower than male ones, which could have led to an underestimation of the true costs associated with time away from work. With respect to the generalisability of the study results, the authors stated that their findings could be generalised to other health care systems that not only provide health care but also have to face the economic impact of continuing to provide salary benefits to employees consuming health care resources.

**Implications of the study**
The authors stated that their analysis would change the cervical cancer screening policy of the US Army, which would move from an annual screening strategy to less frequent testing using LBC + reflex HPV.

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None stated.

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