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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 health interventions examined in the study were screening strategies for cervical cancer: direct visual inspection (DVI), human papillomavirus (HPV) testing using a high-risk HPV probe, and cervical cytology using a conventional Papanicolau smear. The strategies were grouped on the basis of the number of visits performed over a life span, thus the alternative screening strategies being evaluated were DVI and HPV testing when one visit was performed; self-collected HPV, DVI followed by HPV, clinician-collected HPV, and cervical cytology when two visits were performed; and cervical cytology when women underwent three visits. Three-visit strategies included an initial screening examination, a second visit for a diagnostic work-up incorporating colposcopy and biopsy in women with positive results, and third visit for treatment of women with confirmed disease; two-visit strategies included a first visit for screening and a second visit for treatment of women with positive results without colposcopy or biopsy; one-visit strategies consisted of immediate treatment in all screening-positive women.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised the general population of 30-year-old black South African women.

Setting
The setting was community in developing countries. The economic study was conducted in South Africa.

Dates to which data relate
Effectiveness data were estimated using data published between 1984 and 2000, while resource use data referred to studies published between 1992 and 2000. The price year was 1999.

Source of effectiveness data
Data on effectiveness were derived from a review of the literature and authors’ assumptions.

Modelling
A state-transition decision model, based on Markov cycles, was constructed to simulate the natural history of human papillomavirus (HPV) infection-induced cervical neoplasia and cervical cancer screening, diagnosis, and treatment in a hypothetical cohort of 30-year-old black South African women. Lifetime costs and benefits were estimated within monthly cycles. The main health states of the model were cervical disease status (normal, low-grade, and high-grade...
squamous intraepithelial lesions (SILs), and local, regional, and distant invasive cervical cancer), HPV infection status, and immunodeficiency virus (HIV) infection status. Mortality was due to acquired immunodeficiency syndrome (AIDS), cervical cancer, and other causes.

Outcomes assessed in the review
The outcomes assessed from published studies and used as model inputs were:

- prevalence data on HPV DNA detected, low-grade SIL, high-grade SIL, local invasive cancer, regional invasive cancer, distant invasive cancer, and HIV;
- in the overall population (HPV status unknown);
- progression rates from normal to low-grade SIL, from low-grade to high-grade SIL, from high-grade SIL to cancer;
- regression rates from low-grade SIL to normal and from high-grade SIL to normal;
- in patients with HPV DNA positivity;
- progression rates in patients with detectable persistent high-risk HPV DNA from normal to low-grade SIL, from low-grade SIL to high-grade SIL, from high-grade SIL to invasive cancer;
- regression rate in patients with detectable persistent high-risk HPV DNA from low-grade SIL to normal and from high-grade SIL to normal;
- progression rates in patients with no, low-risk, or transient detectable HPV DNA from normal to low-grade SIL, from low-grade SIL to high-grade SIL, from high-grade SIL to invasive cancer;
- regression rate in patients with no, low-risk, or transient detectable HPV DNA from low-grade SIL to normal and from high-grade SIL to normal;
- sensitivity and specificity of cervical cytology, DVI, HPV probe assay (clinician- or-self-collected), and screening tests in sequence (DVI+ through HPV+); and
- efficacy and rates of minor and major complications with cryotherapy; and
- cancer stage distribution, 5-year survival invasive cervical cancer, and HIV-related monthly mortality rates.

Study designs and other criteria for inclusion in the review
Not stated.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
The authors stated that priority was given to studies with larger sample sizes, well-defined control groups, and longer follow-up.

Methods used to judge relevance and validity, and for extracting data
Not stated.
Number of primary studies included
Approximately 58 studies were used as sources of effectiveness evidence.

Methods of combining primary studies
Primary studies were combined using narrative methods.

Investigation of differences between primary studies
Not stated.

Results of the review
The results of the review were as follows:

Prevalence data were 22% for HPV DNA detected, 3.20% for low-grade SIL, 2.40% for high-grade SIL, 0.17% for local invasive cancer, 0.20% for regional invasive cancer, 0.03% for distant invasive cancer, and 8% for HIV.

The progression rates in the overall population (HPV status unknown) were 3.0/y from normal to low-grade SIL, 4.8/y from low-grade to high-grade SIL, 1.5/y from high-grade SIL to cancer; the regression rates 60 in 4 y from low-grade SIL to normal and 25 in 4 y from high-grade SIL to normal.

In patients with HPV DNA positivity, the progression rates in patients with detectable persistent high-risk HPV DNA were 3.5/y from normal to low-grade SIL, 17.0/y from low-grade SIL to high-grade SIL, 2.0/y from high-grade SIL to invasive cancer; the regression rate in patients with detectable persistent high-risk HPV DNA was 20 in 4 y from low-grade SIL to normal and 10 in 4 y from high-grade SIL to normal.

The progression rates in patients with no, low-risk, or transient detectable HPV DNA were 1.0/y from normal to low-grade SIL, 1.8/y from low-grade SIL to high-grade SIL, and 0 from high-grade SIL to invasive cancer; the regression rate in patients with no, low-risk, or transient detectable HPV DNA was 60 in 4 y from low-grade SIL to normal and 30 in 4 y from high-grade SIL to normal.

The regression rate in patients with no, low-risk, or transient detectable HPV DNA was 60 in 4 y from low-grade SIL to normal and 30 in 4 y from high-grade SIL to normal.

The sensitivity and specificity values were 60% and 95% for cervical cytology, 68% and 85% for DVI, 84% and 88% for clinician-collected HPV probe assay and 67% and 83% for self-collected HPV probe assay, 46% and 98% for screening tests in sequence (DVI+ through HPV+).

Efficacy of cryotherapy was 80-90% and rates of minor and major complications were 5% and 1% respectively.

Cancer stage distribution was 41.7% for local invasive disease, 50% for regional invasive disease, and 8.3% for distant invasive disease.

Five-year survival was 78% for local invasive cancer, 44% for regional invasive cancer, and 8% for distant invasive cancer.

HIV-related monthly mortality rates were 0.0023 with CD4 cells greater than 500 x 10^6/L, 0.2787 with CD4 cells between 200 and 500 x 10^6/L, and 2.2373 with CD4 cells less than 200 x 10^6/L.

Methods used to derive estimates of effectiveness
The authors used some assumptions in the decision model. Some assumptions were based on the published literature, while other assumptions were made due to the lack of published data.
Estimates of effectiveness and key assumptions
All women suitable for outpatient treatment received cryotherapy and 10% of them received no benefit, while another 10% developed recurrent disease within 1 year. It was also assumed that all women with positive screening results underwent DVI prior to cryotherapy and those with a 4-quadrant lesion or suspicious cancer were referred to a physician;

10% of screen-positive women had a 4-quadrant lesion or suspicious cancer and were referred to a physician; those with cancer underwent staging and treatment consistent with current practice in South Africa, and those without cancer underwent a loop electrosurgical excision procedure (50%), conization (25%), or no treatment (25%);

2% of all women with high-grade disease had undetected microinvasive cancer or adenocarcinoma in situ;

one third of women with microinvasive cancer or adenocarcinoma in situ were undetected, one third were referred to a physician, and one third were treated with cryosurgery.

Other assumptions were reported in detail in the study.

Measure of benefits used in the economic analysis
Life-years saved (LYS) were used as the benefit measure in the economic analysis. They were obtained through modelling and a 3% discount rate was applied. The reduction in cervical cancer incidence was also reported.

Direct costs
A 3% discount rate was used as lifetime costs were assessed. Unit costs were reported, but quantities of resources were given only for some items. The economic evaluations included the following health service costs: screening tests, visits, diagnostic work-up, and treatment. It was assumed that chemotherapy treatment was not available, thus its cost was not included in the analysis. The cost/resource boundary adopted in the analysis of direct costs was that of the public sector in South Africa. Resource use was derived from published studies, while estimation of costs was based on actual data derived from the Representative Association of Medical Schemes for most direct costs. The cost of an HPV test was derived from the quoted price of the test kit for developing countries. Costs for hospitalisation were based on a study carried out at the University of Cape Town. Data estimated by the World Bank were then employed to estimate the cost of treating opportunistic infections and providing palliative care. The price year was 1999.

Statistical analysis of costs
Costs were treated deterministically in the base case.

Indirect Costs
Indirect costs were included to assess the time spent on travelling and attending screening and treatment visits. Data were based on two national surveys evaluating household income, taking into account the unemployment rate in South Africa. Discounting was applied using a 3% rate and the price year was 1999. The overall cost/resource boundary was that of society. Time loss was reported in detail in the analysis.

Currency
South African rand (R) converted to US dollars ($) at an exchange rate of R6.2=$1.

Sensitivity analysis
To investigate the problem of variability in data, several sensitivity analyses were conducted varying most of the variables used in the decision model within the ranges reported in the literature. One-, two-, and three-way sensitivity analyses were conducted.
**Estimated benefits used in the economic analysis**
When screening strategies were performed once in a lifetime, the expected life expectancy (in years) and the reduction in cervical cancer incidence were 19.099 and 0 with no screening, 19.169 and 25% with one-visit DVI and 19.185 and 32% with one-visit HVP testing;

19.161 and 23% with two-visit self-collected HPV, 19.139 and 15% with two-visit DVI followed by HPV, 19.172 and 27% with two-visit clinician-collected HPV, and 19.151 and 19% with two-visit cervical cytology; and

19.143 and 17% with three-visit cervical cytology.

**Cost results**
Total lifetime costs were $40 with no screening, $39.19 with one-visit DVI and $41.13 with one-visit HVP testing;

$41.61 with two-visit self-collected HPV, $41.77 with two-visit DVI followed by HPV, $42.90 with two-visit clinician-collected HPV, and $44.19 with two-visit cervical cytology; and

$46.44 with three-visit cervical cytology.

**Synthesis of costs and benefits**
An incremental cost-effectiveness analysis was conducted to combine costs and benefits of the screening strategies. When assessing the relative efficiency of the different screening strategies, five strategies dominated the remaining options these being:

one-visit DVI lifetime (cost-saving);

2-visit DVI lifetime ($70 per LYS);

every 5-year DVI ($140 per LYS);

every 3-year DVI ($460 per LYS); and

every 3-year HPV ($11,500 per LYS).

When screening strategies were performed once in a lifetime, comparing each strategy with the no-screening option, one-visit DVI was cost-saving, while the cost-effectiveness ratio was $14 with one-visit HPV testing; $26 with two-visit self-collected HPV, $44 with two-visit DVI followed by HPV, $39 with two-visit clinician-collected HPV, and $81 with two-visit cervical cytology; and $147 with three-visit cervical cytology.

When the strategies were compared incrementally, again, one-visit DVI was cost-saving over no screening, one-visit HPV testing cost $118 over one-visit DVI, while the remaining strategies were dominated.

Although the results were sensitive to variations in natural history of SIL, sensitivity and cost of the screening tests, the expected ranking of interventions did not change in the one-way sensitivity analyses. Results changed moderately when two- and three-way sensitivity analyses were conducted, but one-visit DVI was generally the most cost-effective screening option.

**Authors' conclusions**
The authors concluded that in the population of South African women, a single-lifetime screening with DVI or HPV DNA testing coupled with immediate cryotherapy cost less than $50 per woman and were generally more cost-effective than other screening strategies.
CRD COMMENTARY - Selection of comparators
As regards the choice of the comparators, the authors stated that all alternative screening strategies considered in the study were potential interventions for the detection of cervical cancer in the general population. However, the authors noted that some screening options were not feasible in some developing countries. The basic comparator of "no-screening" was also considered in order to assess the active value of the screening strategies. You, as a user of this database, should decide whether they represent widely used health interventions in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on data derived from published studies. A formal review of the literature was not undertaken, but the authors included a relevant number of primary studies, which were combined using narrative methods. The search method employed was not described. The authors stated that effectiveness evidence was mainly derived from studies with larger sample sizes, well-defined control groups, and longer follow-up. However, it was recognised that primary studies differed in terms of entry criteria, designs, and time horizon. Some assumptions were also made in the decision model and were then investigated in the sensitivity analyses.

Validity of estimate of measure of benefit
The benefit measure used in the economic analysis was expected survival, measured through life-years saved. This measure ensures the comparability of the benefits of the interventions examined in the present study with those estimated in other screening strategies. Appropriate discounting of future life-years saved was conducted.

Validity of estimate of costs
The analysis of costs was performed from the perspective of society and it appears that all relevant categories of costs were included in the study. Quantities of resources used and unit costs were reported only for some cost items included in the economic evaluation. The price year was stated, thus simplifying reflation exercises in other settings. A detailed breakdown of costs was given. Although costs were treated deterministically in the base case, sensitivity analyses were conducted on specific cost components of the analysis. The sources of cost and resource use data were reported and appropriate discounting was performed. The authors stated that up-front costs of initiating new screening programmes or of providing ongoing training and supervision of clinicians practising DVI were not included due to regional variability.

Other issues
The authors made some comparisons of their findings with those from other studies. As regards the generalisability of the study results to other settings, the authors commented that their findings should not be generalised to countries other than South Africa as many country-dependent assumptions were made in the analysis. The authors commented on some limitations of their study.

Implications of the study
The authors suggest that further research should assess efficacy and complications of cryotherapy performed without colposcopy in low-resource settings.

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None given.

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