Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance
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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
Four strategies for the management of atypical squamous cells (ASC) of undetermined significance (US) were examined. The strategies were:

- immediate colposcopy;
- human papillomavirus (HPV) triage, which included colposcopy if high-risk HPV types were detected;
- repeat cytology, which included a follow-up cytology at 6 and 12 months, and referral for colposcopy if a repeat abnormal result occurred; and
- reclassification of ASC-US as normal, in which a cytological result of ASC-US was ignored.

Two options for cytology (liquid-based versus conventional) were considered. A scenario where ASC could not distinguish between US and high-grade lesions, and different screening frequencies, was also considered.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of adolescent girls aged 13 years, who had never had sex and who were free of disease.

Setting
The setting was primary and secondary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness and resource use data were derived from studies published between 1992 and 2001. The price year was 2000.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies.
A computer-based mathematical model was used to assess the natural history of disease, and to estimate all the costs and survival of a hypothetical cohort of eligible women. The health states were grouped using four categories of cervical health. More specifically, normal, infection with HPV, grade (1, 2 or 3) of cervical intraepithelial neoplasia (CIN), and stage of invasive cancer (local, regional or distant). Both low-grade squamous intraepithelial lesions (LSILs) and high-grade squamous intraepithelial lesions (HSILs) were considered. The base-case was based on the following scenario:

- screening began at age 18 and was biennial in the absence of a cytological abnormality;
- colposcopy was performed for all cytological results of SIL, but treatment was reserved for biopsy-confirmed CIN grade 2-3;
- women treated for CIN grade 2-3, or had biopsy-confirmed CIN grade 1, returned for a repeat cytological test every year;
- women with ASC-US in whom no CIN was identified returned to routine screening;
- compliance was 100%;
- the disease status was confirmed by colposcopy and biopsy.

The model was calibrated by comparing the outputs with population-based data that had not been used to populate the model.

**Outcomes assessed in the review**

The outcomes assessed from the literature were:

- the probability of disease progression from normal to HPV DNA, from HPV DNA to CIN grade 1, from CIN grade 1 to CIN grade 2-3, from CIN grade 2-3 to local invasive cancer, from local invasive cancer to regional invasive cancer, and from regional invasive cancer to distant invasive cancer;
- the probability of disease regression from HPV DNA to normal, from CIN grade 1 to normal, and from CIN grade 2-3 to normal;
- the probability of a cytology result among women with abnormal cytology and CIN grade 2-3 for ASC (either US or high grade), LSIL and HSIL;
- the 5-year cancer survival rate with local invasive cancer, regional invasive cancer, and distant invasive cancer;
- the probability of symptom detection with local invasive cancer, regional invasive cancer, and distant invasive cancer.

The estimated test characteristics were the sensitivity (for LSIL and HSIL) and specificity of conventional and liquid-based cervical cytology, and the HPV DNA test. The utility values associated with specific health states were also derived from the literature.

**Study designs and other criteria for inclusion in the review**

It was unclear whether a formal review of the literature was undertaken. The design of the primary studies was unclear, but some were clinical trials and others were reviews.

**Sources searched to identify primary studies**

Not stated.
Criteria used to ensure the validity of primary studies
Not stated.

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

Number of primary studies included
Approximately 40 primary studies provided the clinical evidence and utility values.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
The probability (plausible range) of disease progression was:

0.0007 - 0.0209 (0.0004 - 0.418) from normal to HPV DNA,
0.0046 (0.0023 - 0.0092) from HPV DNA to CIN grade 1,
0.0011 - 0.0039 (0.0006 - 0.0078) from CIN grade 1 to CIN grade 2-3,
0.0040 (0.0020 - 0.0080) from CIN grade 2-3 to local invasive cancer,
0.0200 (0.0100 - 0.0400) from local invasive cancer to regional invasive cancer, and
0.0250 (0.0125 - 0.0500) from regional invasive cancer to distant invasive cancer.

The probability (plausible range) of disease regression was:
0.0028 - 0.0397 (0.0014 - 0.0794) from HPV DNA to normal,
0.0068 - 0.0128 (0.0034 - 0.0256) from CIN grade 1 to normal, and
0.0029 (0.0015 - 0.0058) from CIN 2-3 to normal.

The probability (plausible range) of a cytology result among women with abnormal cytology and CIN grade 2-3 was:
0.380 (0.010 - 0.668) for ASC,
0.265 (0.010 - 0.468) for ASC-US,
0.115 (0.000 - 0.200) for ASC-high grade,
0.450 (0.290 - 0.650) for LSIL, and
0.170 (0.100 to 0.610) for HSIL.

The 5-year cancer survival rate was 0.86 (range: 0.80 - 0.93) with local invasive cancer, 0.43 (range: 0.28 - 0.66) with regional invasive cancer, and 0.11 (range: 0.04 - 0.33) with distant invasive cancer.
The annual probability of symptom detection was 0.19 (range: 0.10 - 0.66) with local invasive cancer, 0.60 (range: 0.36 - 0.84) with regional invasive cancer, and 0.90 (range: 0.68 - 0.99) with distant invasive cancer.

The sensitivity for LSIL was 70% (range: 50 - 100) with liquid-based cervical cytology, 56% (range: 40 - 100) with conventional cytology, and 83% (range: 50 - 100) with the HPV DNA test.

The sensitivity for HSIL was 80% (range: 50 - 100) with liquid-based cervical cytology, 64% (range: 50 - 100) with conventional cytology, and 93% (range: 50 - 100) with the HPV DNA test.

The specificity was 95% (range: 90 - 100) with liquid-based cervical cytology, 95% (range: 90 - 100) with conventional cytology, 60% (range: 40 - 80) with repeat cervical cytology, and 75/85% (range: 50 - 100) with the HPV DNA test.

The utility values were 0.68 (range: 0.60 - 1) for local cancer, 0.56 (range: 0.40 - 1) for regional cancer, and 0.48 (range: 0.35 - 1) for distant cancer.

Age-specific quality weights were also used for non-cancer states.

Measure of benefits used in the economic analysis
The summary benefit measures used were the life-years gained (LYG) and the quality-adjusted life-years (QALYs) gained. Both were derived from the analytic model. An annual discount rate of 3% was used because of the long time horizon of the model. The utility values were derived from a published study, but no details on the sample used to elicit such values were provided. The absolute reduction in cancer incidence was also reported.

Direct costs
An annual discount rate of 3% was applied to costs that were incurred in the future. The unit costs were reported for almost all items but information on resource use was less clear. Some aggregate costs were also reported. These reflected the sum of the procedure, office visit and woman’s time. The health services considered in the study were screening, clinician’s services, work-up following an abnormal cytological result and any necessary treatment, and inpatient and/or outpatient medical visit. The cost/resource boundary of the study was unclear. The resource use data were derived from the literature. The costs came from Medicare reimbursement rated and published studies. All the costs were presented in 2000 values using the medical care component of the Consumer Price Index.

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

Indirect Costs
The indirect costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were conducted to assess the robustness of the estimated cost-effectiveness ratios to variations in several model inputs. Univariate and multivariate analyses were conducted. Plausible ranges were used but their source was not always clear.

Estimated benefits used in the economic analysis
The absolute reductions in cancer incidence were as follows:
for biennial screening using liquid-based cytology, 84.03% with reclassification of ASC-US as normal, 90.41% with HVP DNA testing, 90.15% with repeat cytology, and 90.54% with immediate colposcopy;

for biennial screening using conventional cytology, 78.87% with reclassification of ASC-US as normal, 86.39% with HPV DNA testing and with 2-visit HPV DNA testing, 84.97% with repeat cytology, and 86.56% with immediate colposcopy;

for biennial screening using conventional cytology and traditional unstratified cytological category of ASC, 74.52% with reclassification of ASC-US as normal, 86.30% with HVP DNA testing and with 2-visit HPV DNA testing, 84.28% with repeat cytology, and 86.56% with immediate colposcopy.

The estimated life expectancy with no screening was 28.69869.

The estimated LYG were as follows:

for biennial screening using liquid-based cytology, 28.78741 with reclassification of ASC-US as normal, 28.79394 with HVP DNA testing, 28.79394 with repeat cytology, and 28.79411 with immediate colposcopy;

for biennial screening using conventional cytology, 28.78186 with reclassification of ASC-US as normal, 28.78997 with HVP DNA testing and with 2-visit HPV DNA testing, 28.78859 with repeat cytology, and 28.79019 with immediate colposcopy;

for biennial screening using conventional cytology and traditional unstratified cytological category of ASC, 28.77807 with reclassification of ASC-US as normal, 28.78987 with HVP DNA testing and with 2-visit HPV DNA testing, 28.78807 with repeat cytology, and 28.79019 with immediate colposcopy.

The estimated QALYs were not reported.

Cost results
The average total lifetime costs were as follows:

for biennial screening using liquid-based cytology, $210 with no screening, $1,423 with reclassification of ASC-US as normal, $1,712 with HVP DNA testing, $1,820 with repeat cytology, and $1,867 with immediate colposcopy;

for biennial screening using conventional cytology, $1,199 with reclassification of ASC-US as normal, $1,472 with HVP DNA testing, $1,479 with 2-visit HPV DNA testing, $1,523 with repeat cytology, and $1,595 with immediate colposcopy;

for biennial screening using conventional cytology and traditional unstratified cytological category of ASC, $1,170 with reclassification of ASC-US as normal, $1,461 with HVP DNA testing, $1,471 with 2-visit HPV DNA testing, $1,520 with repeat cytology, and $1,594 with immediate colposcopy.

Synthesis of costs and benefits
The validation of the model was satisfactory. An incremental cost-effectiveness ratio of each strategy relative to the next least effective strategy was calculated to combine the costs and benefits.

The incremental costs per life-year saved were as follows:

for biennial screening using liquid-based cytology, $13,700 with reclassification of ASC-US as normal versus no screening, $44,400 with HVP DNA testing over reclassification, repeat cytology was dominated (less effective and more costly) by HVP DNA testing, and $905,300 with immediate colposcopy over repeat cytology;

for biennial screening using conventional cytology, $11,900 with reclassification over no screening, $33,600 with HVP DNA testing over reclassification, 2-visit HPV DNA testing was dominated by HVP DNA testing, repeat cytology was
dominated by 2-visit HPV DNA testing, and $570,900 with immediate colposcopy over repeat cytology;
for biennial screening using conventional cytology and traditional unstratified cytological category of ASC, $12,100
with reclassification over no screening, $24,700 with HVP DNA testing over reclassification, 2-visit HPV DNA testing
was dominated by HVP DNA testing, repeat cytology was dominated by 2-visit HPV DNA testing, and $411,500 with
immediate colposcopy over repeat cytology.

Similar results but slightly lower figures were observed when the incremental cost per QALY was calculated.

Different combinations of screening strategies and frequency of screening were also presented in an efficiency curve
(37 strategies).

The sensitivity analyses showed that the base-case results were robust to changes in screening performances, alternative
treatment options for CIN 1, the costs of work-up for abnormal screening test results and the costs of treatment for CIN
grade 2-3 and cervical cancer.

Repeat cytology was not dominated only when the cost of HPV DNA testing exceeded $190.

In general, the relative cost-effectiveness of the strategies did not change order for any cost of colposcopy between
$200 and $600.

Authors' conclusions
Biennial or triennial screening for cervical cancer was, in general, more cost-effective than annual screening. All the
strategies were comparable in terms of survival, but differences in the costs were apparent. In particular, reflex human
papillomavirus (HPV) DNA testing provided clinical benefits similar to those associated with immediate colposcopy,
but was less expensive.

CRD COMMENTARY - Selection of comparators
The choice of the comparators appears to have been appropriate because they covered all available screening strategies
for cervical cancer and represented widely used approaches. A variety of strategies with alternative screening
frequencies were considered. The authors noted that the strategy considered as standard care may vary across centres.
The no screening option was selected as the basic comparator for comparative purposes. You should decide whether
they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used data obtained from published studies. However, a formal review of the literature was
not undertaken and it would appear that the primary studies were identified selectively. In addition, the design of the
primary studies, further information on the patient samples and interventions evaluated, and the methods used to extract
and combine the data, were not provided. Therefore, it is difficult to assess the quality of the evidence used, although
some of the studies were clinical trials or reviews of the literature. Some of the model inputs were varied in the
sensitivity analysis.

Validity of estimate of measure of benefit
The summary benefit measures were appropriate for detecting the impact of the screening strategies on woman's health
and quality of life. However, the total number of QALYs was not reported. The benefits were discounted, as
recommended in the USA. However, near negligible differences were observed in the benefits associated with each
strategy. The patient sample from which the utility values were derived was not described.

Validity of estimate of costs
The authors stated that a societal perspective was adopted, but the indirect costs (i.e. productivity losses due to the
disease) were not considered in the analysis. It appears that costs relevant to the health care system and the patient were
included in the economic evaluation. Detailed information on the unit costs, quantities of resources used, the price year and the source of data was provided. This will enable the study to be replicated in other settings and reflation exercises to be conducted. However, the main limitation to the validity of the cost evaluation was the fact that the costs were treated deterministically. Some categories of costs were varied in the sensitivity analysis. The cost-effectiveness ratios were sensitive to variations in some cost inputs.

Other issues
The authors stated that their findings confirmed those reported in other published studies. The issue of the generalisability of the study results to other settings was not explicitly addressed, but the authors stated that their findings were robust in a variety of settings, as shown in the sensitivity analysis. Due to the similar results in terms of benefits, the evaluation of the costs was crucial to the analysis. Therefore, the use of a stochastic approach to determine the probabilities of each approach being cost-effective over the others would have been useful. The study was conducted on the assumption that all the screening strategies were equally available, but this may not be the case in some settings. The calibration of the model reinforced the robustness of the study.

Implications of the study
The study results suggested that the follow-up of ASC-US is a cost-effective strategy, in particular when HPV DNA testing is used. However, caution is required when interpreting the results of the analysis since clinical and economic conditions may differ according to study setting.

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None stated.

Bibliographic details

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Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Cervical Intraepithelial Neoplasia /diagnosis /economics /prevention & control /virology; Colposcopy /economics; Cost-Benefit Analysis; DNA, Viral /analysis; Disease Progression; Female; Health Status Indicators; Humans; Mass Screening /economics /methods; Models, Theoretical; Papillomaviridae /isolation & purification; Papillomavirus Infections /diagnosis; Quality-Adjusted Life Years; Tumor Virus Infections /diagnosis; United States; Uterine Cervical Dysplasia /diagnosis /economics /prevention & control /virology; Uterine Cervical Neoplasms /diagnosis /economics /prevention & control /virology; Vaginal Smears /economics

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