Technology assessment report commissioned by the HTA Programme on behalf of The National Institute for Clinical Excellence

Liquid-based cytology in cervical screening: an updated rapid and systematic review.

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Jon Karnon carried out the review of the economic literature, undertook the statistical analyses and the economic modelling analysis.
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Euphemia McGoogan provided clinical advice throughout the project.

CONFLICT OF INTEREST

None of the authors has any financial interest in any of the companies producing products for liquid-based cytology. Dr McGoogan has received research funding from AutoCyte Inc. and Cytyc Corporation for studying the properties of their products.

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Summary

This report presents the results of a review of effectiveness and cost-effectiveness that updates an earlier published report with the same objectives, published in January 2000.

Description of Proposed Service

Liquid-based cytology is a new method of preparing cervical samples for cytological examination. Unlike the conventional 'smear' preparation it involves making a suspension of cells from the sample and this is used to produce a thin layer of cells on a slide. The new intervention would thus form part of the process of population screening to reduce the incidence of invasive cervical cancer.

Epidemiology and Background

Around 4 million women per annum in England have a cervical screening test. Currently the age standardised incidence of cervical cancer is around 9 per 100,000 per annum. The mortality rate in 1997 was 3.7 per 100,000 per annum.

Number and Quality of Studies and Direction of Evidence

There were no randomised trials using an outcome such as invasive cancer or mortality as outcome measures. A few studies attempted to compare the sensitivity and specificity of the existing technique with liquid-based cytology by using a histological examination 'gold-standard'. Most comparisons were split-sample studies comparing cytological results.

Summary of Benefits

From the evidence available, it is likely that the liquid-based cytology technique will reduce the number of false negative test results. Modelling analyses undertaken as part of this study indicate that this will reduce the incidence of invasive cancer.

There is now more evidence to support improvements emanating from the use of liquid-based cytology screening in terms of a reduced number of unsatisfactory specimens and a decrease in the time needed to obtain the smear samples.

Costs

The estimated annual gross cost of consumables and operating equipment associated with introducing the new technique is about £10 million in England.

Cost-Effectiveness

No UK-based studies providing direct evidence regarding the cost-effectiveness of liquid-based cytology screening were identified. Analyses based upon models of disease natural history, conducted in this study, show that conventional pap smear screening is extendedly dominated by liquid-based cytology (liquid-based cytology is always more cost-effective compared to conventional pap smear testing over the same screening interval). Comparing liquid-based cytology across alternative screening intervals gives a cost-effectiveness of under £10,000 per life year gained when screening is undertaken every 3 years. The cost-effectiveness results are relatively stable under most conditions, though if screening outcomes such as borderline results and colposcopy are assumed to induce even small amounts of disutility then liquid based cytology screening at 5-yearly intervals may be the most cost-effective option.

Limitations of the calculations (assumptions made)

There are gaps in the evidence describing the underlying natural history of the disease. Similarly, the true sensitivity of the screening tests, both conventional smears and liquid-based cytology, is unobservable without subjecting women to otherwise unnecessary and relatively invasive investigations. These characteristics have thus been estimated by fitting of mathematical models of the disease and intervention to observable events such as actual incidence.

Other important issues regarding implications

It is clear that increasing the coverage of the cervical screening programme is also an important way of reducing the burden of invasive cervical cancer. In addition, a range of economic evaluations were identified in the updated systematic search (1999-2002) that assessed the economic impact of cervical screening approaches other than conventional pap smear testing and liquid-based cytology techniques, including semi-automated slide analysis, HPV testing as an adjunct or alternative to pap smear testing, and protocols for the management of atypical screening results.

The aggregate analysis of the cost-effectiveness of potential combinations of these approaches to screening for cervical cancer are outside the scope of the current review, though it is noted that the relative cost-effectiveness of all relevant screening programme configurations should be analysed simultaneously.

LIST OF ABBREVIATIONS

AGUS	Atypical Glandular Cells of Uncertain Significance
AHCPR	Agency for Health Care Policy and Research, USA
ASCUS	Atypical Squamous Cells of Uncertain Significance
CA	Cancer
FDA	Food and Drug Administration
HGIL	High Grade Glandular Intraepithelial Lesion
HPV	Human Papilloma Virus
HSIL	High Grade Squamous Intraepithelial Lesion
HSIL+	High Grade Squamous Intraepithelial Lesion and Carcinoma
HTA	Health Technology Assessment
LSIL	Low Grade Squamous Intraepithelial Lesion
LSIL+	Low Grade Squamous Intraepithelial Lesion as well as higher grade lesions
LYG	Life Year Gained
QALY	Quality Adjusted Life Year
QoL	Quality of Life

1. Aim of the review

Liquid-based cytology is one of a number of current developments in screening technology, and has been described as the one most likely to have an early impact on the NHS. Potentially the technique should improve the quality and readability of the slides, thus reducing the number of false negatives and inadequate slides. It would, however, involve significant capital investment, reorganisation of the service, and significant running costs.

The current report is intended to update an earlier HTA report, published in January 2000, which addressed the following question: "What is the effectiveness and cost-effectiveness of liquid-based cytology for cervical screening compared with conventional smear testing?"

NICE guidance published on the basis of the earlier report concluded that, whilst liquid based cytology 'could provide significant and important benefits…. [The] quality of the evidence is variable and… there is insufficient evidence to justify the nationwide introduction of LBC technology at this time'. Instead, the committee recommended the undertaking of a series of pilot implementation projects to investigate the feasibility of liquid-based cytology in terms of workload, productivity and detection rates. The evaluation of the introduction of liquid based cytology at these pilot sites updates important sections of the modelling analysis used to inform the cost-effectiveness of liquid based cytology.[1] In addition, an evaluation of a similar series of pilot studies, completed in Scotland[2], and an updated systematic review of the literature, are used to update the analysis of effectiveness and cost-effectiveness.

2. Background

2.1 Description of the underlying health problem

Incidence and mortality have fallen by more than 40% since the NHS Cervical Screening Programme was implemented in 1988, although there was a substantial increase in cervical adenocarcinoma in the early 60s. It has been suggested that the observed changes in incidence and mortality may, in part be attributable to a cohort effect, with cohorts born before 1935 and those born in the 1980's onwards having a lower underlying risk than those born in the 1960s.[3] The age-standardised incidence of invasive cervical cancer in England in 1997 was estimated to be 9.3 per 100,000 per annum[4] and recent trends are shown in Table 1. There has been a reduction in incidence during the 1990s since the peak incidence of the mid to late 1980s.

Table 1 Age Standardised Incidence and Mortality from Cervical Cancer, England

Year	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97
Mortality	7.0	6.9	6.7	6.4	6.4	6.1	6.2	6.5	6.1	6.1	5.6	5.5	5.0	4.9	4.7	4.1	4.1	4.0	3.7
Incidence	14.5	15.0	15.1	14.7	14.6	15.0	16.2	15.9	15.6	15.9	14.6	15.2	12.7	12.2	11.1	10.9	10.3	n/a	9.3

Rates per 100,000 per annum - directly age standardised using the European standard population. Incidence was not given for 1996 and the 1997 value is an estimate.[4]

Mortality from cervical cancer has been falling in England by 1-2% each year from the mid 1950s. Following the introduction of the organised screening programme in 1987/88 the fall has accelerated and is now about 7% per annum (Table 1). In 1997, therefore, the age standardised mortality rate was 3.7 per 100,000 per annum. [4]

2.1.1 Significance in terms of ill-health

For an average PCT of 100,000 population there are around 6 incident cases of invasive cervical cancer each year and about 3 deaths each year. There will, however, be large numbers of women needing to be screened, and substantial numbers of these would need further examination and treatment for pre-malignant disease. Some indication of these numbers will be given in the following section.

2.2 Current service provision

Currently a nation-wide cervical screening programme is in place. Women aged 20-64 are invited to be screened (although coverage figures are usually estimated from the 25-64 year age group),[5] and the national policy is that eligible women should be screened every three to five years. In 2000-01 in England 3.6 million women were screened, the majority (2.4 million) after a formal invitation from the screening programme. Coverage was relatively high - 83% of women - (i.e. the proportion less than 5 years since their last test). In that time, laboratories examined an estimated 4.1 million smears.[5] Coverage has increased substantially in the last 10 years from a figure of only 22% in 1987/88.[5]

Screening at present involves taking a sample of cells from the cervix uteri obtained under direct vision using a vaginal speculum. Usually a spatula broom type device or cyto-brush are used to sweep around the cervix and take a sample of cells. After taking the sample, the method in current use is to "smear" the material onto a glass slide, which is then rapidly sprayed with or immersed in a fixative solution to preserve the cells. This slide is sent to the laboratory where it is stained and then examined by a cytologist. The microscopic examination of these smears takes around 4-10 minutes (to screen one slide) and is often repeated by a second cytologist. The staining using the Papanicolaou method, has resulted in the technique being known as the 'Pap' test. It is important to emphasise the need for a high degree of training for all staff involved.[4] A quality assurance programme has been introduced with guidelines for clinical practice and programme management.[6]

Women who have negative smears and no signs of abnormality will be invited for re-screening in 3-5 years. Those in whom abnormalities are detected are managed according to the degree of cellular abnormality detected. This can range from a repeat smear in a reduced time period to referral for colposcopy and biopsy. Treatment is then in accordance with the result of the colposcopy examination and biopsy.

Currently (data for England, 2000-01) about 8-9% of smears are considered "abnormal" (any grade). Some 2.4% show mild dyskaryosis, but 0.91% show moderate dyskaryosis, and 0.73% show severe dyskaryosis or worse.[5] Women with changes in these latter two categories are referred for immediate colposcopy.[7] Women with changes in the first category are referred if the abnormality persists on a repeat smear. Although the proportion of smears showing any abnormality has been increasing during the 1990s, the proportion of those with severe dyskaryosis has remained fairly steady during this period.[4]

An increasing proportion of smears are reported as "inadequate", that is unable to be interpreted. They may be too thick or too thin; obscured by inflammatory cells or blood; incorrectly labelled; or fail to contain sufficient numbers of the right type of cells. In these cases the woman is recalled so that the smear can be repeated. Currently around 9% of smears are reported as inadequate.[7]

Some indication of the scale of the cervical screening programme is given in Table 2.

Table 2 The Scale of the Cervical Screening Programme and Associated Further Treatment in an Average Health Authority

	Approximate numbers per annum in an average primary care trust (100,000 population)*
Number of cervical smears taken	7286
Number of repeat cervical smears	670
Total number of referrals for colposcopy	104
Number of referrals for colposcopy for higher grade lesions	47

* Based on NHS Cervical Screening 2002 Review

Patients having repeat smears fall into two groups – those whose first smear was technically inadequate; and those whose smears are repeated after a shorter interval because of concerns about possible abnormalities (borderline and mild dyskaryosis). These women are asked to attend for repeat smears at reduced time intervals and only when two are consecutively negative do they return to the normal screening interval.[8]

2.2.1 Limitations of Cervical Screening Testing Methods

Like all screening tests, the cervical smear or any new cytological method are not perfect tests. Thus, in considering a new screening methodology it is important to consider its limitations alongside those of existing methods.

Sensitivity is the proportion of truly diseased persons in the screened population who are identified by the screening test.[9] In other words, sensitivity assesses the propensity of a test to avoid false negatives – that is giving a negative result when disease is actually present in the woman. These false negatives can arise in a variety of ways:

when there are no abnormal cells on the specimen because of failure in collecting cells from lesions or transferring such cells to the slide;
when there are abnormal cells present in the sample that have not been detected or have been misinterpreted in the laboratory;
when the disease is rapidly progressing and the lesion itself was not present at the time of sampling. This situation is considered to be quite uncommon.[10]

Specificity is the proportion of truly non-diseased persons who are so identified by the screening test.[9] In other words, specificity assesses the propensity of a test to avoid false positives - that is giving a positive result when the true result is negative. In assessing the performance of a new test compared with the current screening methods it is important to consider whether sensitivity is only increased at the expense of a loss of specificity and hence an increase in the women referred for unnecessary further investigation and intervention.

With most screening tests there is to some extent a 'trade off' between sensitivity and specificity. If the threshold of the test is set to give higher sensitivity then this will be at the expense of reduced specificity; similarly increasing the specificity will tend to reduce the sensitivity. As with other screening methods, the relationship between sensitivity and specificity in cervical screening can be formally assessed by plotting a receiver operating characteristic curve (see for example Fahey et al.).[11]

A wide range of performance has been reported by Fahey for sensitivity and specificity with current cervical smear tests.[11] In part this is due to differences between studies in respect of what is considered a positive result. If low thresholds are set, a newer test may be able to improve on the detection of abnormalities of lesser severity, but may be no different in respect of its sensitivity for detecting high-grade lesions or in influencing the incidence of invasive cancer. As a broad approximation, Fahey's review concluded that the sensitivity for conventional smears was on average about 55-65% and the specificity 65-70%. As the reference test itself may not be perfect, Boyko has suggested that the sensitivity and specificity are prevalence dependent and that the sensitivity may be underestimated.[12] Moreover, estimates of sensitivity and specificity require a reference diagnosis to be defined for positive and negative results. However, in cervical cytology screening no consistently used reference exists. Ideally one would compare against biopsy diagnosis, but this raises the ethical implications of carrying out an invasive procedure on women with negative cytology. This may be justified in high-risk women, but this would be a biased assessment of the sensitivity of the test in the general population.

Finally, and most importantly, the sensitivity of any one test still does not fully represent the sensitivity of programme as a whole. One false negative test may be of no significance if the abnormality is picked up before the development of invasive or symptomatic disease when the woman is next screened. Thus, the programme sensitivity will be a function of the screening interval and it may, for example, be a better policy to reduce the screening interval and/or ensure women do not miss a screening round than improve on the sensitivity of individual tests. This introduces the concept which will be discussed later of the sensitivity of the whole screening programme rather than of individual screening tests within it.

2.2.2 Current Service Cost

Cervical screening – including the cost of treating pre-cancerous lesions - has been estimated to cost around £135 million each year in England,[13] (but it is unclear whether this includes all the relevant costs).

2.2.3 Variation in services - Coverage and Screening Interval

Coverage of the cervical screening programme in England varies quite widely. For five year (or less) testing, some 12 (out of 100) health authorities in 1998/9 had coverage below the national target of 80%, while 10

health authorities had coverage of over 90%. Three year testing coverage was more variable, with only three health authorities having a coverage of 80% or more, while 12 had coverage of under 60%.[4] This reflected the fact that around 60% of health authorities invited women every three years, and 15% had a mixed policy, inviting women every three or five years depending on their age.[14] Whether the demise of the health authorities and the uptake of this responsibility by PCT's in England, will have any impact on the coverage remains to be seen.

2.3 Description of the new intervention in cervical screening

2.3.1 Intervention

Liquid-based cytology for cervical screening aims to improve the quality of the conventional cervical smear through an improved slide preparation technique following collection of the sample in the standard way. This is designed to produce a more representative sample of the specimen, with reduced obscuring background material. This should allow faster and more reliable screening by laboratory staff.

It is perhaps worth noting that suggestions for methods to improve the cervical specimen cytology have also been made in the past. For example, Steven et al. suggested chemical depolymerisation of cervical mucin to help produce monolayers.[15] Neugebauer et al. in 1981 described a sedimentation velocity separation method;[16] and a pulse wash method was suggested by Näslund.[17,18]

The liquid-based cytology technique that is the subject of the present report involves not making a smear of the material obtained on the spatula/collection device but rinsing it in a preservative fluid so generating a suspension of cells which is subsequently used to deposit a monolayer of cells on the slide. Almost all of the cells collected from the cervix should thus be present in the fluid. The subsequent stages of the procedure result in a smaller, but more representative cell sample from the cervical specimen than is obtained in a conventional smear. Cellular preservation is said to be enhanced, the preparation is more of a monolayer and contamination (blood cells, pus and mucus) is reduced.[19] Moreover, improved fixation allows more consistent staining.

These preparation techniques are claimed to reduce the proportion of specimens classified as technically unsatisfactory for evaluation. A further advantage is that the cell suspension in preservative can be retained and used for later testing such as for Human Papilloma Virus (HPV), chlamydia, and other molecular biological tests.[20,21,22,23]

The products currently available that use this liquid-based methodology are summarised below (full details are not intended to be given here – merely the main points of the process). Products are listed alphabetically.

Surepath® - Previously known as Autocyte®, CytoRich™ - (Pathlore Ltd, Nottingham, UK)

A sample from the cervix is collected using a plastic collection device. The head of the collection device is detached into a vial containing a proprietary transport fluid (CytoRich™). In the laboratory the vials are vortex mixed and the cell suspension is treated through a density gradient centrifugation process to remove red blood cells and other clinically non-significant material and to enrich the cell suspension. The centrifuge tubes are loaded onto an AutoCytePrep 'robot' which handles 48 samples at a time. The cell pellet is re-suspended and an aliquot is transferred to a settling chamber mounted on a microscope slide. The cells are allowed to sediment under gravity to form a thin layer on the slide. Excess fluid and cells are removed and the slide is then stained automatically as part of the process. If the preparation is considered inadequate or unsatisfactory it is possible to revert to the original cell pellet and prepare another slide using a larger aliquot of suspension. In the USA, Food and Drug Administration (FDA) approval has been given to the AutoCytePrep system.

CYTOSCREEN® (Altrix Healthcare Plc)

A proprietary plastic collection device (CYTOPREP®) is used to collect a cervical sample and the head is detached into a vial of proprietary transport fluid (CYTeasy™). In the laboratory the vials are placed on a shaker before a photometric reading is taken to assess cellularity. An appropriate aliquot of the sample is centrifuged onto a glass slide. Staining follows using normal laboratory staining procedures. Samples are said to be "processed with the CYTOSCREEN® method using standard laboratory equipment, readily available in the market and in most labs." "The only innovations centre in the composition of the preservative and the method of establishing the volume of sample necessary to produce a fully CYTOPREP® representative sample and an adequate quantity of cells". (Altrix Healthcare's submission to NICE, October 1999).

LABONORD Easy Prep® (Surgipath Europe Ltd.)
Samples are taken using a plastic collection device and transferred to proprietary fixative fluid. An aliquot of the fluid is placed in a separation chamber with a strip of absorbent paper punched to produce a 250mm hole; eight chambers are placed together in a clamping unit. The plastic chamber retains the cell suspension in place during sedimentation whilst the absorbent paper gently removes the fluid resulting in a dry, thin layer of cells. *"*This is a method for producing a liquid-based preparation that is said to have the advantages of the methodology, but does not rely on the use of additional expensive instrumentation and uses standard laboratory equipment". *(*Surgipath Europe's submission to NICE, January 2000).

ThinPrep (Cytyc Corporation)
This was developed in 1996 and is currently available as the ThinPrep®3000 System. A plastic collection device is rinsed thoroughly into a vial containing a proprietary transport fluid (PreservCyt®). In the laboratory, each vial is placed individually in the ThinPrep®3000 Processor. There are three key phases to the process.

dispersion: to produce a randomised cell suspension breaking up cell clumps and mucus.

- cell collection: a negative pressure pulse is produced which draws the fluid through a filter trapping a layer of cellular material. The flow of fluid through the filter is monitored and controlled to optimise cell collection.

cell transfer: the cellular material on the filter is transferred to a glass slide which is then deposited into a vial of fixative. Subsequent staining and microscopic evaluation of the slides proceeds in a similar manner to a conventional smear. The ThinPrep®3000 process system is designed to improve productivity further by providing automated batch-processing of up to 80 specimens per cycle, 140,000 smears per year.

2.3.2 Identification of patients and important sub-groups

It is assumed for the purpose of this review that, if introduced, the methodology would be to replace the existing fixed cervical smear specimens that are currently used in the cervical screening programme. In other words, that there are no sub-groups for whom it would be introduced preferentially.

2.3.3 Criteria for the introduction of the technology

Similarly, the criteria for the introduction of the technology, if the liquid-based cytology methodology were introduced, would be the same as for those for the existing cervical screening programme. That is that women between the ages of 20 to 64 years are invited to have a free cervical screening test every three to five years.

2.3.4 Personnel involved

Those carrying out the speculum examination and collection of the cervical material need training in respect of the new method of handling the specimen thus obtained. Instead of making a smear onto a glass slide the material is transferred into a vial of preservative fluid, a simpler and easier procedure than the traditional 'smear' preparation.

In the laboratory, an additional resource is required to produce the new slide preparations. Training will be required for those staff involved in these new processes. In addition, cytologists need to be trained to interpret these new slide preparations. It is said that the slides are quicker to assess but also that more concentration is required making them more tiring to read (this will be discussed later).

2.3.5 Setting

The setting for this intervention is in two main sites. The cervical specimen is usually taken in a primary care setting by the general practitioner or practice nurse, at a community clinic such as a family planning or well-woman clinic, or at a colposcopy clinic. Using the liquid-based cytology method would not change these arrangements although some of the equipment required would be a little different.

Transport of specimens to the laboratory may need different arrangements. Many trusts and health authorities have pathology collection vans and thus do not use the postal service. However, the vials are bulkier, and this may need greater capacity in the collection vehicles. In addition, there is the possibility that it will not be possible to use the Royal Mail, (as occurs in some areas) if fluids containing alcohols are used in the transport

medium. However, in the ongoing pilot in England LBC vials are being collected using the same Trust van system as used for the conventional smears in all three pilot sites.

The cervical samples are currently sent to a pathology laboratory, usually based in a hospital and under the overall responsibility of a consultant pathologist. Again, using the liquid-based cytology method, there would be no substantial change to these arrangements, but rather more substantial changes would be needed in the staff and equipment required.

2.3.6 Equipment required

The equipment required at the taking of the cervical sample is different with liquid-based cytology. Instead of making smears on glass slides, applying a fixative and leaving the slide for dying and labelling, the smear taker obtains a sample using a broom-like device. The broom is then placed in a plastic vial containing a cell preservative and labelled. Thus instead of producing and fixing a smear at the time of obtaining the specimen, a cell suspension is sent to the laboratory.

At the laboratory, processing devices are used to prepare the cell suspension and transfer a sample of cells to microscope slides. These are perhaps the main items of capital expenditure that the new methodology involves. Although the staining and slide preparation procedures are broadly similar to conventional smears there may be different equipment involved at this stage also.

Although the use of automated analysis equipment is outside the scope of this report, it is important to consider that these new preparation techniques may greatly facilitate the introduction of such automated analytical methods and are already in use in a number of centres.

In the laboratory extra storage space is needed for the vials; and disposal of the cell suspension will also require additional arrangements and resources.

2.3.7 Degree of diffusion

At present, apart from use in research studies and the ongoing pilot in England, liquid-based cervical cytology has not been introduced for cervical screening in England, although a decision to implement LBC techniques in Scotland has been made. Conversely in the light of report by the NZHTA[X], the NZ NCSP has decided not to purchase or endorse LBC for its population-based screening programme at the present time. It is, however, being used routinely in at least some laboratories in most developed countries.

2.3.8 Anticipated costs

The marginal gross cost of consumables and relevant equipment associated with introducing the new technique in a typical PCT population of 100,000, and generating around 8,800 smears, is approximately £32,000 per annum. In England (4.4 million smears annually) the cost is estimated at around £160 million per annum. This cost may decrease if liquid-based specimens reduce numbers of inadequate smears and thus reduce the need to recall women for a repeat smear and/or with increased productivity and staffing, by education in screening time of individual specimens.

3. Effectiveness of liquid based cytology in cervical screening

Methods for reviewing effectiveness

Three types of literature search were performed:
A clinical effectiveness search
A cost-effectiveness search
A modelling search

The first two concentrated on liquid–based cytology, while the modelling search addressed the wider topic of modelling studies in respect of cervical screening.
Industry submissions to NICE were included in the review.

Databases searched were:

Medline
Embase
Science Citation Index
Cochrane Library
NHS CRD: DARE, NEED and HTA
HealthSTAR
National Research Register

Web pages were contacted for INAHTA members and other Health Technology Assessment (HTA) organisations to determine if HTA reports had been produced on this topic.
A citation search was carried out for studies included in the Australian Health Technology Advisory Committee report.[24]

Search strategies for the MEDLINE searches are shown in appendix 1. Search strategies for all other databases are available from the authors.

3.1.1 Inclusion and exclusion criteria

All health technology assessment and related secondary research studies were included. Primary research studies were included if they attempted to measure an outcome of importance, such as comparison of liquid-based cytology with conventional cervical smears in respect of an assessment of sensitivity and/or specificity, categorisation of specimens, percentage of inadequate or unsatisfactory specimens and specimen interpretation times. There are also in the market place devices developed to automate the analysis and classification of images from conventional pap smears. This methodology was excluded from the update. All papers in languages other than English were excluded because of insufficient time to arrange for translation. All databases were searched from January 1999 up to October 2002.

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With respect to algorithms to select a proportion of slides for manual microscopic rescreening by a cytologist, this computerised image-processing device is not included in this update review of the clinical and cost effectiveness of LBC. Although systems are in development for primary screening of AutoCyte Prep and Thin Prep slides. It is likely that, when fully available, there may be cost implications associated with use of such systems.

3.1.2 Data extraction strategy

All abstracts and papers were double read. For relevant articles data were extracted by one of the authors and checked by the second. Key tabulations and calculations for summary tables were checked by entering the published study data (where available) into a spreadsheet and re-calculating the relevant percentages.

3.1.3 Quality assessment strategy

Studies varied in study design quality and presentation of results. Only those with a clear tabulation of the numerical data were used in the conventional smear versus liquid-cytology assessments. Other comments on the quality of studies and study design are made later in the text in relation to specific study types. For the review update, the methodological quality of primary studies was assessed using the Cochrane model (Irving and Glasziou 1996, modified as described by Broadstock 2000 for the New Zealand Health technology Assessment review[ref]).

3.2 Results

3.2.1 Quantity and Quality of Research Available

In considering what literature should be looked for, the following principles were kept in mind in terms both of study design and outcome measures examined.

The gold-standard outcome measure for evaluation of a new screening methodology is whether it can reduce the incidence, morbidity and/or mortality from cervical cancer. Other patient-based objectives may be important

such as reducing the need for repeat smears because these are likely to cause inconvenience and anxiety and hence impact on a patient's quality of life

If these outcome measures are not available then other measures may provide helpful proxies. Thus, if the sensitivity of the test is improved then more precancerous lesions should be detected. This, however, will only lead to a reduction in incidence, morbidity and/or mortality if the abnormalities detected do progress rather than spontaneously regress, and that the additional detection results in earlier treatment by an interval which reduces incidence, morbidity and/or mortality. It should not be automatically assumed that the detection of additional abnormalities will automatically lead to a reduction in these outcome measures.[10]

Improvements in specificity may be a proxy for reductions in unnecessary repeat screening examinations and indeed further more invasive investigations and treatment.

Other outcome measures such as the proportion of inadequate or unsatisfactory smears may be important both in reducing unnecessary anxiety and costs of repeat smears. Time taken to carry out the examination of smears, and other factors associated with the costs and organisation of the screening programme are also important outcomes.

The literature search results are divided into two types:

- Secondary research - Health Technology Assessment (HTA) reviews
- Primary research

Secondary Research Literature: Health Technology Assessment Reviews
A small number of reviews from other health technology assessment centres were found in the literature search for the original systematic review[ref]. These are listed below:
Australian Health Technology Advisory Committee Report
Canadian Co-ordinating Office for HTA
Agency for Health Care Policy and Research (AHCPR)

For the update report, one additional review was identified:
New Zealand Health Technology Assessment Report

Australian Health Technology Advisory (HTA) Committee Report - April 1998[6]
This report examined both the ThinPrep and AutoCytePrep technologies. Literature available from 1990 to July 1997 was examined. Problems with the available evaluative studies were summarised as shown below:

Low numbers of studies
Difficulty in assessing degree of independence as many are supported by the manufacturers
Lack of randomised controlled trials of technologies
Lack of community based studies
Lack of consistent cytologic threshold for positive and negative results
Variety of definitions as to what constitutes a 'positive smear'
Few studies with biopsy confirmation of positive results
No definition of gold standard for negative results (e.g. subsequent negative smear)
Reviewers not always blinded to outcome when assessing smears
Lack of consistent comparator
Non-random selection of samples
Samples do not reflect usual practice(e.g. high proportion of positive smears)
Review process does not reflect usual practice (e.g. repeated examination of particular slides
Information concerning the comparability of cases and controls not always reported
Sensitivity and specificity generally not reported
Tests of statistical significance often not undertaken or not reported
Lack of recognition that most technologies require a period of familiarisation before specimens can be evaluated appropriately

The main points concluded by the Australian Health Technology Advisory Committee review in respect of the AutoCytePrep and ThinPrep were as follows.

There were few peer-reviewed studies of AutoCytePrep found for evaluation. To date, all comparative studies of AutoCytePrep and conventional smears have been prospective and have used the split-sample technique.
There is one study comparing ThinPrep and AutoCytePrep.
AutoCytePrep has been less well studied than has ThinPrep. It probably has similar benefits, but there are insufficient data to demonstrate comparable improvements in sensitivity.
There is a reduction in the proportion of smears rated unsatisfactory for evaluation when AutoCytePrep is used.
A high level of concurrence between AutoCytePrep and conventional smears has been found.
There is evidence that this technique leads to lower rates of missed diagnoses (i.e. greater sensitivity) compared with conventional smears, but there are insufficient data reliably to estimate the magnitude of relative improvement.
There is evidence that screening time is shorter with AutoCytePrep.
To date, comparative studies of ThinPrep and conventional smears have been prospective and have used the split-sample technique. No data are available on the performance of ThinPrep as a sole preparatory method for cervical cytology.
Some reports of sensitivity and specificity in this literature are limited, as comparison was not made with the gold standard of biopsy confirmation.
There is a reduction in the proportion of smears rated unsatisfactory (by Bethesda criteria) for evaluation when ThinPrep is used.
There is evidence that ThinPrep has a higher sensitivity than conventional smears, and results in a greater number of low-grade lesions being diagnosed. Adjunct use of ThinPrep leads to the recognition of both screening and subsampling errors.
Use of ThinPrep results in a significant increase in the detection of minor non-specific changes.
In recent studies, a high level of concurrence between ThinPrep and conventional smears was found.
There is evidence that the adjunctive use of ThinPrep with conventional smears may increase the detection of biopsy-proven high-grade abnormalities by between 5 per cent and 6 per cent, and increase the detection by between 6 per cent and 11 per cent for all cervical abnormalities
The sampling device used seems to have an impact on the performance of ThinPrep.
There is evidence that screening time is shorter with ThinPrep, but that additional preparatory staffing is required.
There is a significant learning period to become competent in assessing monolayer samples.

In summary, the Australian Health Technology Advisory Committee report concluded that liquid-based slide preparation techniques may increase the detection of biopsy-proven high-grade cervical abnormalities by between 5% and 6%. In addition, it concluded that current studies are finding that these slide preparation techniques reduce the number of slides rated as unsatisfactory, and improve the reading of slides. This, in the Australian setting, would mean that the sensitivity increase would result in an increase in slides reported as high-grade abnormalities from about 1% of smears to 1.05%.

It was estimated that the use of liquid-based cytology would add at least Au$70million (~£29million) per two year screening cycle (in a population just over a quarter the size of England and Wales with a lower coverage rate). If this replaced conventional practice there would be offset savings of Au$25million (~£10million). It was estimated that the costs per additional cancer prevented would be Au$1million (~£400,000) if the technology were used in addition to the current technology. (The year on which these costs are based is not clear, but it is probably no later than 1997).

It was recommended that population-based trials should be carried out comparing this technology with conventional smears. At present, the relative improvement in sensitivity was not considered sufficient to mandate their universal introduction. Until there are data demonstrating the cost-effectiveness of the new technologies from a population basis, their increased uptake cannot be justified from a public health perspective.

Australian practice is for a two year screening cycle so the improvement in sensitivity would have a smaller potential increase in prevention of invasive disease than in a setting where the screening interval was longer. The coverage is, however, lower in Australia than in England and Wales (the assumption for the economic model in the Australian HTA report was that only 63% are screened).

Canadian Co-ordinating Office for HTA - May 1997[20]
Like the Australian report, this report also considered new slide preparation (and automated analytical) methods. The report found that agreement between liquid-based thin layer preparations and conventional

cervical smear is high (in the range 88%-99%). The newer method gives enhanced preservation and distribution of the cells making slides easier and quicker to view although fatigue sets in more quickly. The proportion of unacceptable slides is increased. Many studies were found reporting that monolayer preparation slightly improves detection of low and high grade disease, perhaps due to superior cell preservation and distribution. However, substantial training for cytotechnologists and pathologists was thought to be required and the high cost of these preparation systems was noted. It was stressed that newer techniques should not divert resources and effort from increasing recruitment, information systems, and training and quality-control for laboratories and programs. Again the coverage may be lower in Canada than in England and Wales.

Agency for Health Care Policy and Research (AHCPR) – January 1999[25]
This report carried out a very full and systematic search of the literature and applied quality filters to select papers to review. Only one study was found on liquid-based cytology which met the full criteria of colposcopy/histology reference standards and sufficient data to calculate sensitivity and specificity. Criteria had thus to be modified to include studies that used a cytology reference standard and allowed estimation of sensitivity and specificity. This resulted in including 8 studies of ThinPrep. The main conclusions from the report are set out below.

Despite the demonstrated ability of cervical cytological screening in reducing cervical cancer mortality, the conventional smear test is less sensitive than it is generally believed to be. Studies unaffected by workup bias provided estimates of the specificity of conventional smear screening of 0.98 (95 percent confidence interval; 0.97-0.99) and sensitivity of 0.51 (95 percent confidence interval; 0.37-0.66). The smear test is more accurate when a higher cytological threshold is used with the goal of detecting a high-grade lesion. Lower test thresholds or use of the smear test for detecting low-grade dysplasia results in poorer discrimination.

Existing information fails to provide accurate estimates for specificity of thin-layer cytology technology. The initial requirement for verification of test negatives with colposcopy or histology led to the exclusion of all but one study of ThinPrep. The values reported for sensitivity and specificity using histological or colposcopic reference standards are well within the range of sensitivity and specificity reported for the conventional smear test. However, including studies that directly compare ThinPrep with conventional smear testing (screening or rescreening) using a cytological reference standard results in significant improvements in sensitivity.

The cost-effectiveness of a technology that improves primary screening sensitivity (e.g., thin-layer cytology) is directly related to the frequency of screening - longer intervals result in lower estimates of cost per life year saved.

These findings were relatively insensitive to assumptions about cervical cancer incidence, the cost of technologies, diagnostic strategies for abnormal screening results, age at onset of screening, or most other variables tested.

There is substantial uncertainty about the estimates of sensitivity and specificity of thin-layer cytology. The uncertainty is not reflected in the point estimates for effectiveness or cost-effectiveness. Although it is clear that both thin-layer cytology technologies provide an improvement in effectiveness at higher cost, the imprecision in estimates of effectiveness makes drawing conclusions about the relative cost-effectiveness of thin-layer cytology and computerised rescreening technologies problematic.

Using a modelling approach, however, the AHCPR report concludes that the increased sensitivity would result in moderate improvements in life expectancy at much higher costs than conventional screening methods. When screening intervals are three years (or more), the new method was estimated to have an incremental cost-effectiveness ratio that is "within the range of accepted health care practices" - i.e. below $50,000 (about £30,000) per life-year.

New Zealand Health Technology Report – October 2000[ref]
This report examined the evidence for clinical effectiveness (primarily sensitivity and specificity) and cost effectiveness of introducing automated and semi-automated devices for cervical screening into New Zealand's population-based screening programme. It aimed to update the Australian Health Technology Advisory Committee Report (1998). The two LBC techniques considered were ThinPrep and AutoCyte Prep plus the semi-automated imaging device Autopap. The literature considered included English language material available from January 1997 to May 31, 2000. Only 15 studies were identified on clinical effectiveness of LBC compared with conventional screening, of which nine were at least partially funded by industry involved with

the production of the devices under consideration, and most were severely limited by poor design, inadequate reference standards, and incomplete verification of cytological diagnoses. Studies comparing different LBC preparation techniques were also of limited quality and the author concluded that the clinical effectiveness of ThinPrep and AutoCyte Prep for detection of high-grade abnormalities could not be reliably determined from the existing evidence base. It was also not clear whether one device had any advantages over the other with respect to given outcomes. In terms of semi-automated devices for primary screening and rescreening, there was some limited evidence of potentially increased detection of low-grade abnormalities for AutoPap compared with conventional screening but no increased detection of high grade abnormalities, and a lack of evidence on specificity. All cost effective models were severely limited by the uncertainty surrounding estimates for improved sensitivity and the lack of information on changes to specification, which may occur with the introduction of new devices into a screening programme.

The main conclusions of the report were:

- estimates of test sensitivity and test specification for the new devices could not be reliably determined.
- estimates of test sensitivity and specification were the main source of uncertainty in the economic models investigating clinical effectiveness of new devices.
- any increases in sensitivity resulting from the introduction of new devices may come at the cost of decreased specification.
- high quality is required to generate valid estimates of test sensitivity and specification.

A number of other systematic reviews were published between 1999 and 2002, but irrespective of review quality, the evidence cited duplicated that already reported in the original Health Technology Assessment report.[ref] Therefore these were all excluded from this update report.

Primary Research Literature

Quorum Statement for LBC update

The primary literature search identified several types of study. The were no trials identified which randomised patients to have their cervical samples analysed by either conventional smears or liquid-based slide preparations and then used an outcome measure such as mortality or invasive cancer incidence. In one study, a prospective, randomised controlled design was used to compare Thin Prep with conventional smear taking with all those screening HSIL+ being followed up for 12-15 months with histology or cytology (Obwegeser and Brack 2001). Unfortunately the study focused on the method of sampling and the collection device. In a second study, two separate smears were taken from the same person, each to be analysed by one of the two methods (conventional and liquid based), and the order of smear taking was randomised. [26]

Thus, any attempt to determine the effect of the liquid-based cervical cytology on outcome measures of mortality or invasive cancer incidence, can only be arrived at by attempts at modelling with, therefore, all the assumptions and subsequent uncertainties about the conclusions.

From the national research register, four research studies were identified. Contact with research leads was made. However, results were not available for any of the studies, although two had been completed.

Sensitivity and Specificity Studies

The original report identified ten studies, plus one confidential document, with information on sensitivity and specificity on liquid based cytology techniques compared with conventional smear taking. From the fifteen papers that have been identified as published since the original HTA report, five provided additional information on sensitivity and specificity and their details have been added to the original table (Table 3). For three of these five[26,27,28] details on ages of the subjects studied were not given. In another study, insufficient biopsy data was available for the conventional 'pap' smear slides.[29] Sensitivity and specificity could only be calculated therefore for the liquid based cytology slides.

Sensitivity is the proportion of true positives identified as such, and specificity is the proportion of true negatives correctly thus identified. In order to determine sensitivity and specificity, a gold standard diagnostic measure is needed. This implies that all those having the screening test should, in addition, have the gold standard test administered too. No studies were identified, in either the original or the update literature, which

carried this out for a population of average risk. Indeed, there are doubts about whether this would be a practicable study to undertake as it would mean subjecting large numbers of women to a more invasive test in addition to the screening procedure. Two alternative sorts of sensitivity and specificity study were found, however; those which used a proxy gold standard by carefully reviewing all the available cervical cytology results by additional specialists; and those which did carry out additional examinations (such as colposcopy and biopsy) in high risk women.

In all the studies in the original report, in these two categories, the sensitivity was higher (or the same) in the liquid-based cytology group. In several cases the numbers were very small and the differences were often small and/or not statistically significant. Of the additional five studies identified in the update of this report, in some cases sensitivity is higher in the conventional than in the liquid based cytology group, but again, where tested and reported, no statistically significant difference was found between the two groups. Of the 15 papers cited in the initial review and the update, only five of them cover 'ordinary' populations[30,22,31,32,29] and four of the five report on ThinPrep whilst Bishop *et al*.[31] are the only researchers who compared AutoCyte Prep with conventional methodology. Ten studies contain populations that are 'high risk',[33,34,35,36,37,38,39,40,26,28] again with proportionally more (70%) reporting on ThinPrep compared with AutoCytePrep (30%).

Figure 1 differentiates between studies that compare the alternative screening techniques in ordinary populations, and in high risk populations. The proportions represent false negatives on the basis of LSIL test results or worse being defined as positive. The four studies based on screening ordinary populations finds a statistically significant relative risk (RR) for false negatives of 0.55, whilst the analysis of the high risk populations finds an insignificant RR of 0.88. The aggregate RR is 0.75, where the sensitivity rates for conventional pap smear testing and liquid based cytology are 0.715 and 0.801, respectively. Thus, liquid based cytology is associated with a 12% improvement in sensitivity. Insufficient biopsy data in one study [29] meant that it could not be included in this analysis.

The estimation of sensitivity on the basis of LSIL or worse is not directly comparable to the UK cervical screening programme as LSIL corresponds to a mild dyskaryosis screen result, and covers histologically defined results less than CIN2. However, the aggregate estimate of an improvement in sensitivity of 12% is taken as the best estimate for the aggregate sensitivity rate.

The majority of the identified studies examined ThinPrep, with a few looking at Autocyte. Indirect comparisons of the alternative liquid based cytology techniques found no differences between the results, so the modeling analysis does not differentiate between alternative techniques.

Meta-analysis of the six studies that compared specificity between conventional pap smear testing and liquid based cytology showed no difference, and the specificity of the liquid-based cytology techniques is assumed to remain unchanged from the conventional specificity. Overall, the findings from the additional five studies on sensitivity and specificity of liquid based cytology techniques compared with conventional smear methodology do not change the overall conclusions of the original report.

Figure 1 False negative rates in studies comparing liquid-based cytology with conventional pap smear screening

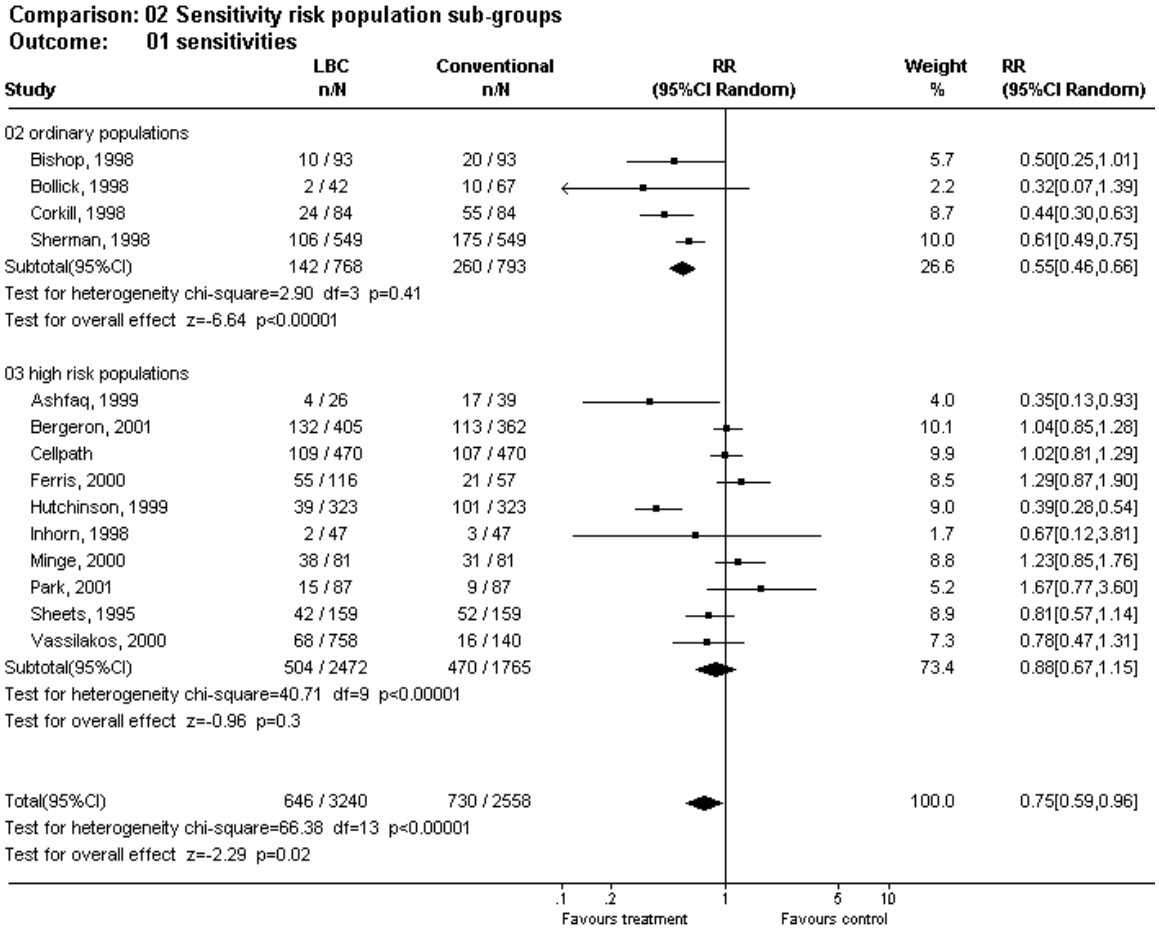


Table 3 Summary of Results of Studies Attempting to Assess Sensitivity and Specificity

Author	Date	Methodology	Smear Sensitivity	Smear Specificity	Liquid-based Sensitivity	Liquid-based Specificity	Definition of Positives and of Reference standard
Sheets[33]	1995	ThinPrep	67.3% (107/159)	76.9% (220/286)	73.6% (117/159)	76.2% (218/286)	Colposcopic biopsy
Ferenczy[23]	1996	ThinPrep	70.1% (n not stated)	74.7% (n not stated)	78.0% (n not stated)	73.6% (n not stated)	LSIL+ based on histology in women referred for colposcopy – no significant difference detected between methods
Corkill[41]	1998	ThinPrep	34.5% (29/84)		71.4% (60/84)		LSIL+ based on an independent pathologist's review of cytology slides
Sherman[42]	1998	ThinPrep	68.1% (374/549)		80.7% (443/549)		LSIL+ based on independent pathologist's masked review of slides – hospital and screening centres
Bishop[43]	1998	AutoCytePrep	78.5% (73/93)		89.2% (83/93)		LSIL+ based on positive biopsy patients (part of a larger study)
Bolick[32]	1998	ThinPrep	85% (57/67)	36% (8/22)	95% (40/42)	58% (7/12)	LSIL+ based on biopsy results (part of a larger study). Numbers are very small
Inhorn[35]	1998	ThinPrep	93.6% (44/47)		95.7% (45/47)		Invasive cervical cancer based on biopsy confirmation. Involves only 47 cases.
Ashfaq[36]	1999	ThinPrep	56% (22/39)		85% (22/26)		Glandular lesions based on biopsy confirmation. Numbers are small.
Hutchinson[44]	1999	ThinPrep	68.7% (222/323)		87.9% (284/323)		LSIL+ based on a final diagnosis which was made by a combination of cytology, histology and cervicography
CellPath	1999	AutoCytePrep	77% (363/470)		77% (361/470)		LSIL+ graded as such by three Reference Pathologists
Vassilakos et al[38]		AutoCytePrep	89% (124/140)		91% (690/758)		HSIL+ confirmed by histology after colposcopy, but includes only ASCUS+ smears so may overestimate sensitivity
Yeoh et al[29] 171 general practices, screening for cervical cancer, ages unknown, Hong Kong	1999	ThinPrep	Insufficient biopsy data		87% (175/201)	53% (10/19)	LSIL+ based on biopsy FU data. Only 220 biopsy records available in part of a larger group studied.

Table 3 Summary of Results of Studies Attempting to Assess Sensitivity and Specificity (continued)

Author	Date	Methodology	Smear Sensitivity	Smear Specificity	Liquid-based Sensitivity	Liquid-based Specificity	Definition of Positives and of Reference standard
Ferris et al[27] Routine screening 79%, colposcopy following abnormal pap smear 21%, USA, age 18+	2000	ThinPrep	63% (95% CI: 49-76%) (36/57)	99.7% (99.4-99.9%) (1846/1851)	53% (43-62%) (61/116)	99.5% (98.8-99.9%) (825/829)	LSIL+ confirmed by pathologist evaluation of histology and cytology.
Minge et al[40] Obstetric and gynaecology high risk population, aged 15-57, USA	2000	AutoCyte Prep	62% (numbers not given)	89% (numbers not given)	53% (numbers not given)	79% (numbers not given)	ASCUS and LSIL+ based on biopsy FU data. Only 134 biopsy records available as part of a larger group studied.
Bergeron et al[26] Patients with previous abnormal cytology, no ages given, USA	2001	AutoCyte Prep	69% (249/362)	83% (66/80)	67% (273/405)	73% (66/91)	LSIL+ confirmed with biopsy by blinded cytopathologist. Note: sensitivity and specificity calculated with 'unsatisfactory' slides omitted.
Park et al[28] Patients with known or suspected cervical abnormality, no ages given, South Korea	2001	ThinPrep	90% (78/87)	70% (37/53)	83% (72/87)	83% (44/53)	ACUS+, confirmed by histology, but 18 cases excluded for calculation of specificity, even though they showed a lesion more severe than LSIL in both methods

LSIL+ signifies a diagnosis of low grade squamous intraepithelial lesions or higher, HSIL+ a signifies diagnosis of high grade intraepithelial lesions or higher (as defined in the Bethesda system – for further explanation see also Table 4).

Split Sample Studies

The most frequent study design was the split sample method. Many of these studies are funded in part or wholly by the manufacturers of the liquid-based preparation technique, With this study design, the cervical specimen, obtained using a variety of collection devices, is used first to make a smear in the conventional manner. Next the remaining cervical cell specimen is used for liquid-based cytology. Two specimens are produced for each patient screened – a conventional smear and a liquid-based preparation. In one study, two specimens were taken and allocated in random order to conventional and liquid-based analysis.[26] Thus the agreement or difference between the two methods can be compared. As slides can be classified into a number of different diagnostic categories (see Table 4) there are many different comparisons possible. However, the main outcome comparison in these studies seems to be those with a diagnosis of low grade squamous intraepithelial lesions or higher (as defined in the Bethesda system and abbreviated in this report to LSIL+ and also known as mild dyskaryosis or worse in the UK classification system). The use of this outcome threshold for comparing these slide preparation methods is justified firstly because it seems to be the most consistently available across a large number of studies. In addition, there have been increases in the proportion of specimens reported as borderline (or atypical squamous cells of uncertain significance – ASCUS) during recent years. This reflects changing practice rather than a change in the underlying prevalence of the relevant cervical changes. Moreover, the proportion of liquid-based specimens classified as borderline or ASCUS tends to be higher at first, but then reduce as cytologists get used to and gain experience with the new slide preparation method. Finally, the AHCPR report[25] implies that the LSIL+ threshold is frequently used in the USA as an indication for colposcopy (and indeed sometimes a lower threshold is advocated).[45]
In the review of new evidence for the update of the original HTA report, the reporting of evidence as a diagnosis of LSIL+ has been maintained, but in addition, where possible, the HSIL+ detection rate has also been calculated from the available new evidence.

Table 4 Comparison of UK and Bethesda Classification Systems

UK	Result code	Bethesda
Inadequate	1	Unsatisfactory
Negative	2	Negative
Borderline changes (HPV is borderline or mild dyskaryosis in UK but LSIL in Bethesda system)	8	Atypical squamous cells of uncertain significance (ASCUS) Atypical glandular cells of uncertain significance (AGUS)
Mild dyskaryosis	3	Low grade squamous intraepithelial lesion (LSIL)
Moderate dyskaryosis	7	High grade squamous intraepithelial lesion (HSIL)
Severe dyskaryosis	4	High grade squamous intraepithelial lesion (HSIL)
Severe dyskaryosis ?invasive	5	Carcinoma
Glandular neoplasia	6	?High grade glandular intraepithelial lesion (HGIL)

Even within the United Kingdom there are some classification differences – thus in Scotland any grade of dyskaryotic glandular cells may be classified as ‘glandular abnormality’ whereas ‘adenocarcinoma’ is reserved for changes suggesting invasive cancer. It is also important to add that many would regard these sorts of conversion tables as being too simplistic.

Table 5 An Example of Tabulation of Split-Sample Results – taken from Hutchinson et al., 1999.[44]

		Conventional smear					
		Negative	ASCUS	LSIL	HSIL	CA	Total
Liquid-Based Method	Negative	7,264	122	137	18	0	7,541
	ASCUS	569	20	43	15	3	650
	LSIL	177	12	64	41	1	295
	HSIL	46	5	17	56	15	139
	CA	1	0	1	3	6	11
	Total	8,057	159	262	133	25	8,636

Studies were included if they gave a clear tabulation of the results that showed the numbers in each possible classification status combination with respect to conventional smear and liquid-based cytology. An example of the sort of tabulation that was used to provide these results is shown in Table 5.[44]

In the above example, in 2.8% [(177+12+46+5+1+0)/8,636] of cases the liquid-based method resulted in a classification of LSIL+ while the conventional smear result was only negative or ASCUS. Conversely there were 2.5% [(137+43+18+15+0+3)/8636] where the conventional smear result was LSIL+ but the liquid-based method result was negative or ASCUS. Both methods agreed that the sample was LSIL+ in 2.4% [(64+17+1+41+56+3+1+15+6)/8,636] of cases.

Table 6, 7 and 8 summarise these results from the studies examined in the original review. Those identified through the update have been added to each table where appropriate. Overall, the liquid-based method seems to result in more slides being classified as LSIL+, which were classified as a lower diagnosis (e.g. negative or ASCUS) by conventional smears than the reverse situation (i.e. slides considered below LSIL+ by liquid-based cytology being considered LSIL+ by conventional smear). This pattern of results is also seen for seven of the eight studies identified for the update of the review.

Studies are of variable size and of variable quality (for example in the blinding of cytologists to the results from the other specimen obtained). The statistical significance of the difference in proportions is also variably reported. Some, albeit a minority, of these split specimen studies find that liquid-based cytology classifies more slides as below LSIL+ than conventional smears more often than the converse.

It is important also to note that there is a considerable variation between studies in respect of the prevalence of significant abnormality and hence the type of population that was studied. The final column of Tables 6, 7 and 8 gives an indication of this – the proportion of LSIL+ (by both methods) varied from only just over 1% to over 50% in the original report and this remains unchanged following the addition of more recently published evidence. In the UK-screened population one would only expect about 4% to be in this LSIL+ category (i.e. mild dyskaryosis or more).[5]

An earlier review of split sample studies was carried out by Austin and Ramzy in 1998.[46] These authors also used the LSIL+ detection as a summary measure and concluded that the liquid-based methods showed overall increased detection of epithelial cell abnormalities. Results varied considerably from study to study and appeared to be influenced by collection devices' different delivery of cellular material in the split sample studied, first to the conventional smear and second to the liquid-based medium. Newer liquid-based preparatory methodologies seemed to be associated with enhanced detection.

Since low grade squamous epithelial lesions may regress, for the studies identified for the update, detection rates for HSIL or higher have been calculated and compared between conventional and liquid-based methods. The results for the HSIL+ show a similar pattern of results to those seen for LSIL+. In four of the six recent studies comparing Thin Prep with conventional smear taking, (Wang, Monosonego, Luthra, Ring) and one of the two that used AutoCyte Prep (Bergeron), the liquid-based method resulted in more slides being classified as HSIL+, which were classified as LSIL or lower by conventional smears.

Table 6 ThinPrep Split Sample Studies

Author	Date	Country	No.	Conv>Liq LSIL+ (HSIL+)	Liq>Conv LSIL+ (HSIL+)	Both LSIL+ (HSIL+)
Hutchinson[47]	1991	USA	443	0.45%	1.13%	18.7%
Hutchinson[37]	1992	USA	2,655	0.68%	2.64%	12.32%
Awen[48]	1994	USA	1,000	0.0%	0.5%	1.3%
Laverty[24]	1994	Australia	1,872	2.4%	3.3%	7.5%
Wilbur[49]	1994	USA	3,218	0.8%	3.1%	17.0%
Aponte-Cipriani[50]	1995	USA	665	0.5%	0.8%	3.0%
Sheets[33]	1995	USA	782	1.5%	3.3%	29.4%
Tezuka[51]	1995	Japan	215	2.3%	0.0%	54.4%
Bur[52]	1995	USA	128	1.6%	1.6%	19.5%
Ferenczy[34]	1996	Canada/ USA	364	7.7%	8.8%	33.5%
Wilbur[53]	1996	USA	259	3.1%	1.9%	13.5%
Lee[54]	1997	USA	6,747	1.9%	3.3%	6.1%
Roberts[55]	1997	Australia	35,560	0.3%	0.5%	1.7%
Corkill[41]	1998	USA	1,583	0.8%	3.7%	1.9%
Hutchinson[44]	1999	Costa Rica	8,636	2.5%	2.8%	2.4%
Wang et al[56]	1999	Taiwan	990	0.1% (0%)	1.7% (1.1%)	3.6% (3.2%)
Monsonego et al[57]	2001	France	5428	0.4% (0.1%)	1.1% (0.2%)	1.4% (0.4%)
Park et al[28]	2001	South Korea	478	2.9% (1.4%)	1.0% (0.6%)	18.2% (13.7%)
Biscotti et al[58]	2002	USA	400	1.0% (0.8%)	3.0% (0.3%)	8.8% (4.0%)
Luthra et al[59]	2002	Kuwait	1024	0.1% (0%)	0.6% (0.1%)	2.4% (0.8%)
Ring et al[60]	2002	Ireland	1300	2.5% (1.7%)	6.2% (2.0%)	27.8% (10.1%)

Conv>Liq LSIL+ This signifies the proportion where the conventional smear result was LSIL+ but the liquid-based method result was negative or ASCUS.

Liq>Conv LSIL+ This signifies the proportion where the liquid-based method result was LSIL+ but the conventional smear result was negative or ASCUS.

Conv>Liq HSIL+ This signifies the proportion where the conventional smear result was HSIL+ but the liquid-based method result was LSIL, ASCUS or negative.

Liq>Conv HSIL+ This signifies the proportion where the liquid-based method result was HSIL+ but the conventional smear result was LSIL, ASCUS or negative.

For more explanation see Table 5 and explanatory text.

Table 7 AutoCytePrep Split Sample Studies

Author	Date	Country	No.	Conv>Liq LSIL+ (HSIL+)	Liq>Conv LSIL+ (HSIL+)	Both LSIL+ (HSIL+)
Vassilakos[61]	1996	Switzerland	560	0.5%	1.3%	3.2%
Takahashi[62]	1997	Japan	2,000	0.4%	0.3%	3.2%
Howell[63]	1998	USA	852	0.8%	1.1%	2.5%
Geyer[64]	1992	USA	551	0.0%	0.7%	12.5%
Sprenger[65]	1996	Germany	2,863	2.0%	5.1%	36.2%
Bishop[31]	1997	USA	2,032	1.1%	3.1%	3.1%
Laverty[66]	1997	Australia	2,064	3.9%	1.6%	5.0%
Wilbur[67]	1997	USA	277	1.1%	6.1%	2.9%
Data on file, CellPath, 1997	1997	?USA	8,983	1.6%	2.15	5.7%
Stevens[68]	1998	Australia	1,325	1.3%	0.2%	3.9%
Minge et al[40]	2000	USA	2,156	1.5% (0.8%)	3.0% (0.6%)	2.8% (0.5%)
Bergeron et al[26]	2001	USA	500	9.8% (12.2%)	12.6% (15.6%)	46.6% (20.2%)

Conv>Liq LSIL+ This signifies the proportion where the conventional smear result was LSIL+ but the liquid-based method result was negative or ASCUS.
Liq>Conv LSIL+ This signifies the proportion where the liquid-based method result was LSIL+ but the conventional smear result was negative or ASCUS.
Conv>Liq HSIL+ This signifies the proportion where the conventional smear result was HSIL+ but the liquid-based method result was LSIL, ASCUS or negative.
Liq>Conv HSIL+ This signifies the proportion where the liquid-based method result was HSIL+ but the conventional smear result was LSIL, ASCUS or negative.
For more explanation see Table 5 and explanatory text.

Table 8 ThinPrep and AutoCytePrep combined – Split Sample Study

Author	Date	Country	No.	Conv>Liq LSIL+	Liq>Conv LSIL+	Both are LSIL+
McGoogan[69]	1996	Scotland	3091	1.0%	0.3%	3.6%

Conv>Liq LSIL+ This signifies the proportion where the conventional smear result was LSIL+ but the liquid-based method result was negative or ASCUS.
Liq>Conv LSIL+ This signifies the proportion where the liquid-based method result was LSIL+ but the conventional smear result was negative or ASCUS.
For more explanation see Table 5 and explanatory text.

Both the preparation techniques in common use, ThinPrep and AutoCytePrep have been studied in this way and both seem to give similar results from these sorts of split sample studies. A detailed review of the potential differences between these two techniques in this respect is beyond the scope of this assessment report.

Further discussion of the interpretation of split-sample studies is provided in section 3.3 of this report.

Two Cohort Studies

The next type of study identified is what we have called here a two cohort analysis. This examines two groups of women, usually from two different time periods whose cervical cytology specimens have been examined by one or other (but not both) slide preparation technique. The outcome used is most often the proportion of specimens classified as at or above a certain diagnostic level of severity (usually LSIL+). The assumption is that, if the women come from the same underlying population, with similar levels of cervical cancer and pre-cancerous changes, then any change in the detection of significant diagnostic changes will be a proxy measure of increased sensitivity. Once again, of the studies identified for the original report, and those in the update

review, an increase in the classification of specimens as LSIL+ was found. The authors often suggest that this is an indication of increased sensitivity. Studies in this category are shown in Table 9.

Not all the studies in this table provide full details of the proportions of specimens graded as HSIL+ but information was available for two of the studies included in the original report and a further six from the update (Table 9). Vassilakos and co-workers found that this increased from 0.38% to 0.68% with the use of the AutoCyte liquid-based cytology method, and Diaz-Rosario and Kabawat[70] found a similar increase of 0.27% to 0.53% using ThinPrep. Both of these two large studies also found a decrease in specimens graded as ASCUS. Similar relationships are reported in all of the more recent literature.

However, as has been discussed earlier in respect of split-sample studies, these cohort studies can only provide a proxy guide to improvements in key test characteristics such as sensitivity.

Table 9 Two Cohort Studies

Author	Date	Method	Country	Numbers – Conventional smear	Numbers – Liquid-based	Conventional smears LSIL+ (HSIL+) detection	Liquid-based LSIL+ (HSIL+) detection
Weintraub[71]	1997	ThinPrep	Switzerland	35,000	18,000	0.70%	2.27%
Bolick[32]	1998	ThinPrep	USA	39,408	10,694	1.12%	2.92%
Dupree[72]	1998	ThinPrep	USA	22,323	19,351	1.19%	1.67%
Papillo[73]	1998	ThinPrep	USA	18,569	8,541	1.63%	2.48%
Vassilakos[74]	1998	CytoRich	Switzerland	15,402	32,655	1.1%	3.6%
Vassilakos[38]	1999	AutoCyte	Switzerland	88,569	111,358	1.58% (0.38%)	2.52% (0.68%)
Carpenter[75]	1999	ThinPrep	USA	5,000	2,727	7.7%	10.5%
DiazRosario[70]	1999	ThinPrep	USA	74,573	56,095	1.85% (0.27%)	3.24% (0.53%)
Guidos[76]	1999	ThinPrep	USA	5,423	9,583	1.11%	3.70%
Tench et l[77]	2000	AutoCyte	USA	10,367	2,231	1.02% (0.46%)	1.7% (0.67%)
Weintraub et al[78]	2000	ThinPrep	Switzerland	130,381	39,864	0.6% (0.1%)	2.3% (0.5%)
Ferris et al[27]	2000	ThinPrep	USA	2,110	1,004	3.6% (1.7%)	11.4% (3.7%)
Marino et al[79]	2001	AutoCyte	USA	41,871	15,534	[#]1.4%,1.3% (0.38%) (0.53%)	2.0% (0.8%)
Day et al[80]	2002	AutoCyte	USA	53,835	18,819	0.9% (0.25%)	1.6% (0.29%)
Baker et al[81]	2002	ThinPrep	USA	4,872	3,286	3.5% (0.7%)	5.1% (1.0%)

[#] Two conventional datasets, current –2000 and historic-1999

Other Outcome Measures

Inadequate specimens

Other outcome measures were found in a number of studies. The rate of inadequate specimens was mentioned in many studies. There was a considerable variation between studies in both the definition of an inadequate (sometimes referred to as an unsatisfactory) specimen and the proportion of slides classified as such. However, the majority of studies reported that liquid-based methods had a larger proportion of specimens classed as totally satisfactory. As, however, what will really influence the need to recall women is the proportion of inadequate or unsatisfactory specimens this outcome is described in more detail here from the studies in which the data were available for comparison between liquid-based and conventional smear methods. i.e. the 20 studies covered in the original systematic review and the 15 papers included in the update. These results are summarised in Table 10. More studies for the original systematic review show a higher inadequate specimen rate with conventional smears than with the liquid-based method, and a similar pattern of results was found in the later evidence from the further 15 studies. It should, however, be noted that these proportions, even for conventional smears, mostly tend to be substantially lower than those seen in the NHS programme – where around 9% of smears are regarded as inadequate. (There are, however, some differences between Bethesda/USA and UK definitions of inadequate in respect of the proportion of the slide that has to have squamous cells).

Table 10 Specimens Classed as Inadequate or Unsatisfactory

	Inadequate or Unsatisfactory specimens		
Author	Conventional Smear	Liquid-based	System
Bolick[32]	1.1% (427/39,408)	0.29% (31/10,694)	ThinPrep
Carpenter[75]	0.6% (of 5,000)	0.3% (of 2,727)	ThinPrep
Diaz-Rosario[70]	0.22% (163/74,573)	0.67% (374/56,095)	ThinPrep
Dupree[72]	2.0% (447/22,323)	3.8% (731/19,351)	ThinPrep
Guidos[76]	1.2% (65/5,423)	0.45% (43/9,583)	ThinPrep
Lee[54]	1.6% (114/5,101)	1.9% (136/5,656)	ThinPrep
Roberts[55]	3.5% (1,258/35,560)	0.66% (235/35,560)	ThinPrep
Shield[82]	17.3% (of 300)	6.3% (of 300)	ThinPrep
Weintraub[71]	0.70% (of 13,163)	0.26% (of 18,294)	ThinPrep
Hutchinson[47]	0.67% (3/446)	0.67% (3/446)	ThinPrep
Laverty[24]	1.5% (of 2,026)	5.2% (of 2,026)	ThinPrep
Aponte-Cipriani[50]	2.7% (of 854)	8.5% (of 854)	ThinPrep
Bishop[43]	1.0% (89/9212)	0.6% (54/9,212)	AutoCyte
Cheuvront[83]	0.67% (141/21,000)	0.73% (15/2,047)	AutoCyte
Vassilakos[61]	5.2% (29/560)	3.8% (21/560)	CytoRich
Laverty[66]	2.6% (56/2125)	0.28% (6/2125)	CytoRich
Howell[63]	0.35% (3/853)	0.0% (0/853)	AutoCyte
Wilbur[67]	3.6% (10/280)	1.1% (3/280)	CytoRich
McGoogan[84]	8% (40/500)	2.4% (12/500)	ThinPrep
Data on file, CellPath, 1997	1.0% (89/9,212)	0.6% (54/9,212)	CytoRich
Data on file, CellPath, 1999	0.33% (8/2,438)	0.78% (19/2,438)	CytoRich
Baker et al[81]	0.7% (44/6,576)	0.8% (37/4,719)	ThinPrep
Bergeron et al[26]	11.6% (58/500)	0.8% (4/500)	AutoCyte
Biscotti et al[58]	0	0.25 (1/400)	ThinPrep
Day et al[80]	4.04% (22,177/18,819)	0.13% (25/53,835)	AutoCyte
Ferris et al[27]	3.8% (76/3114)	1.2% (12/3114)	ThinPrep
Luthra et al[59]	3.5% (36/1024)	4.9% (50/1024)	ThinPrep
Marino et al[79]	0.26% (91/35,496) 0.33% (21/6,375)	0.1% (15/15,534)	AutoCyte
Minge et al[40]	0.89% (19/2156)	0.09% (2/2156)	AutoCyte
Monsonego et al[57]	0.48% (26/5428)	0.53% (29/5428)	ThinPrep
Park et al[28]	1.0% (5/478)	1.0% (5/478)	ThinPrep
Ring et al[60]	2.7% (35/1300)	0.8% (11/1300)	ThinPrep
Tench[77]	2.94% (305/10,367)	0.4% (9/2231)	AutoCyte
Wang et al[56]	1.1% (11/990)	1.1% (11/990)	ThinPrep
Weintraub & Morabia[78]	<1%	<1%	ThinPrep
Yeoh et al[29]	1.36% (99/7258)	0.56% (93/16541)	ThinPrep

Specimen interpretation time

Specimen interpretation times were mentioned in a very few studies.[23],[69] Liquid-based methods seem to be associated with shorter times (around 3 minutes compared with 4-6 minutes for conventional smears). Cytologists in Edinburgh found that screening monolayers required more intense concentration and was more tiring. Individual members of staff reported that they suffered from fatigue more quickly and needed to take more frequent breaks than for conventional microscopy.[69] Papillo et al. found that there are potential savings of 60% in slide evaluation time for liquid-based methods over conventional preparations, although since slide preparation time is longer, the actual savings are reduced slightly.[85] Papillo concluded that the use of thin layer liquid-based technologies may decrease the need for cytotechnologists, but only if this technique were "the sole change we were to expect in cytopathology in the next decade".[86] In two of the more recent studies, the quality of the sample was better in the liquid-based cytology slides.[79,28]

The need for continuous major adjustments in focus is eliminated as the cells are mainly in one focal plane when using a 10x screening objective.

Staff training

The need for adequate staff training in the use of the new method has been commented on by several authors reviewing this new technique. Cytotechnologists initially over-interpreted enhanced cytological features observed in thin layer preparations.[37] Iverson reported that a short educational intervention (over four and a half hours) did not improve the test scores between a control and experimental group of cytotechnologists.[87] These authors concluded that it is important that more training opportunities be made available to provide cytologists with information regarding the cytologic features unique to thin layer preparations necessary to assure accurate interpretation. Spitzer, reviewing recent advances in cervical screening, also draws attention to the training required especially in relation to differences in cellular appearance in these preparations.[88] However Marino et al [79] found that once they had organised the laboratory work flow, using the liquid-based cytology process improved efficiency and accurate sample handling and identification and did not necessitate the addition of any new employees in the laboratory. The learning curve for the staff for screening and interpreting Thin Prep slides was minimal. [79] A Laboratory Guidance Document and Training Log has been agreed for use in Scotland for the demonstration projects set up there (Scottish Cervical Screening Programme 2000).

Homogeneity of specimens

Hutchinson et al.[89] showed that the liquid-based method had greater specimen homogeneity than conventional smears and suggested that this accounted for increased diagnostic accuracy.

Conclusions around effectiveness

In general, there appears to be evidence suggesting that liquid-based cytological methods offer the following advantages over traditional smear techniques:

- A decrease in the proportion of inadequate specimens - although the literature reveals a wide and overlapping range in this proportion with both conventional smears and liquid-based methods.

- An improvement in sensitivity (seen in the earlier studies but not necessarily maintained subsequently) – although this is hard to quantify with the data available in the published literature. This has the potential to help avoid missing a diagnosis of a lesion requiring further treatment.

- A probable decrease in specimen interpretation times – though this is reported in relatively few studies; if confirmed, this may imply that a reduction of primary screener hours is possible.

- The potential to employ other tests such as HPV on the liquid-based specimen collected. In this context the National Screening Committee is currently conducting a pilot of using HPV status to triage women with mild and borderline abnormalities.

The potential to use the liquid-based technique in automated cytological scanning systems - the original impetus for developing liquid-based cytology, but outside the remit of this systematic review update.

There are, however, disadvantages, uncertainties and reservations associated with the liquid-based methodology. These have been already listed by the other HTA reviews described earlier, but perhaps the most important are listed here.

There are still no randomised controlled trial studies comparing important outcomes such as invasive cancer incidence or mortality.

There are increased costs (mainly laboratory costs) associated with the technique. The magnitude of any savings – such as in reduced repeat tests or in the treatment costs of invasive disease – are hard to quantify from the literature available.

Considerable re-training is required for cytological laboratory staff and, to a lesser extent, those taking the cervical specimens.

There are few sensitivity studies using a gold standard comparator. The specificity of the liquid-based method is largely unknown and may be worsened.

The American College of Obstetricians and Gynecologists gave a Committee Opinion Statement on new screening techniques in 1998.[90] This too concluded that there was no large, population-based prospective study to determine whether any of these techniques (including liquid-based cytology) lowers the incidence of invasive cervical cancer or improves the survival rate. Efforts to reduce the false negative rate should not detract from encouraging greater participation in the screening programme. Their statement ended: "The appropriate use of these new techniques requires further investigation. They are currently not the standard of care".

In an editorial, Wain argues that, it is not clear how liquid-based cytology techniques compare with other methods of quality improvement, such as random rescreening of a mandated proportion of smears, directed rescreening of "high-risk" groups and "rapid rescreening".[91]

The New Zealand HTA report (2002) concluded that estimates of sensitivity and specificity for liquid-based devices could not be reliably determined. Existing research does not provide evidence for improved detection of high-grade abnormalities using liquid-based technologies. The vast majority of missed abnormalities should be detected at subsequent screens and therefore a robust cervical screening programme, using conventional screening would do this.

Before reaching a conclusion about liquid-based cytology, however, a number of other important issues should also be considered - these will be described and discussed below.

Assessing Sensitivity

Although the available evidence suggests that test sensitivity is likely to be improved, to date this has not really happened, and one also needs to ask whether is this a sufficient measure. The aim, of course, is to reduce the mortality and morbidity from invasive cervical cancer. To this end there is a cervical screening programme and it is arguable the sensitivity of the programme as a whole which needs to be considered. This can be influenced by a number of factors beyond that of the individual test itself such as:-

The screening coverage of the population – many cancers occur in those who have never been screened or who have been only infrequently screened. Increasing the uptake of screening may be much more effective in reducing invasive disease in a population than increasing the sensitivity of individual tests. In the UK as a whole uptake is fairly high so it may be hard and expensive to increase it still further. However, uptake is also quite variable (for example geographically) and further efforts to target an improvement in uptake may be more effective and cost-effective than an improvement in test sensitivity.

The frequency of screening – if the pre-malignant phase has a long duration compared with the frequency of screening then a single false negative result is likely to be diagnosed correctly at the next screen before the disease has progressed. The sensitivity of the programme is thus a function not only of individual tests but also of screening interval. To make best use of resources to increase the programme sensitivity a balance may have to be struck between investment in more sensitive but more costly tests and investment in more frequent testing. In this context, it is important to note that coverage is already relatively high in England and Wales.

Assessment of Liquid-Based Cytology Using Split Sample Studies

Much of the evidence cited in support of liquid-based cytology is based on results from split-specimen studies. Here the cervical specimen is split between making a conventional smear and use for a liquid-based method. This may be an unfair assessment of both techniques because clearly less of the specimen is available for either. Indeed, because the liquid-based sample is usually the residual specimen after the smear is made there may be a substantial loss in the smear preparation of cellular material which would otherwise be included in the liquid-based sample. To this extent this study methodology may underestimate the improved performance of the liquid-based method. This drawback has been studied and attempts have been made to quantify it.[30] Although the two cohort study methodology does not have the in-built comparison mechanism, it might be a fairer assessment of the improvements in sensitivity provided that the two cohorts are both large enough and genuinely comparable. It is also argued that, in split sample studies, the liquid-based method is clearly the "research" technique, in contrast to the conventional smear as the "standard", and that this itself may introduce bias.

Sawaya and Grimes, in considering new technologies in cervical cytology screening, also discuss the reasons that split sample study designs are suboptimal.[92] An increase in the absolute percentage of women with abnormal results may not mean that these women have abnormal histology. Second, sensitivity cannot be calculated if investigators do not apply the same reference standards to all the women in the study. In the split-sample studies, the reference standard was not applied to all the women in the study so the number of women in the study with disease was unknown. Third, replacement techniques are bi-directional. Compared with conventional smears, they might reclassify some relatively low-grade smears as higher grade or reclassify some relatively high-grade smears as low grade. Although additional higher-grade smears might be uncovered, some might be hidden. Therefore the net benefit is unclear. Although liquid-based methods usually detected more abnormalities than conventional smears, Sawaya and Grimes argue that replacement techniques should be expected to identify at least the abnormalities identified by conventional tests.[92]

Specimen Collection Devices and the Effectiveness of Specimen Collection

In comparing conventional cervical smears with liquid-based cytology and examining the associated literature it became clear that it is important also to consider the specimen collection device. Whilst a full systematic review of this issue was not within the terms of the previous report or this update, the previous report considered the published systematic review and meta-analysis by Martin-Hirsch et al.[93] This concluded that the widely used Ayre's spatula is the least effective device for cervical sampling and should be superseded by extended-tip spatulas. Thus, in respect of collecting endocervical cells the odds ratio for the comparison of extended tip versus Ayre's spatula was 2.25 (95%CI 2.06-2.44) and for the detection of dyskaryosis the odds ratio was 1.21 (1.20-1.33). The collection devices that were better at collecting endocervical cells were also more likely to produce adequate smears (no blood or inflammatory-cell contamination, and sufficient material collected).

The original report stated 'these sort of improvement rates in detection which result from replacing the traditional wooden Ayre's spatula with extended-tip plastic spatulas are of a roughly similar magnitude to the improvements seen with replacing conventional smears with liquid-based methods. This is not to suggest that these two possible changes should be seen as alternatives but it may be important to prioritise their introduction and to ensure that differences in collection device do not confound the comparison of the two cytological techniques.'

Use of the Ayres spatula has now been superceded by that of the extended tip Aylesby spatula in most parts of the UK. In nine of the 15 studies most recent studies (published between 1999 and 2002), the most common device in use was a broom style collection device (Cervex Brush). Only in three studies was the Ayre spatula used.

4. Systematic review of economic evidence for liquid-based cytology services

Overview of economic assessment

There are very few areas of economic evaluation in which the full range of evidence required to determine cost-effectiveness is forthcoming from a single empirical study. Evaluations of screening programmes, in particular, are unlikely to be informed by such studies due to the interval between the intervention (the screen) and the range of relevant outcomes (incidence of invasive cancer, mortality avoided, life years gained, quality adjusted life years (QALYs) gained).

The use of decision modelling techniques to synthesise data from disparate sources in order to estimate these long-term outcomes, and to attach cost and utility weights to the screen population's health profiles, provide a suitable methodology for the evaluation of screening programmes. Indeed, the vast majority of economic evaluations of cervical screening programmes have been undertaken using modelling methods.

This chapter presents the combined results of the review of the economic and modelling evidence relating to liquid-based cytology techniques from the original systematic review[94] and an updated review covering literature published since the completion of the earlier report.

Methods

The initial section of the earlier report aimed to review general issues in the health economic modelling of cervical cancer screening, which generated classification criteria (relevant factors and outcomes), for the evaluation of the published evidence on liquid-based services and provide input for the modelling of cervical screening for the UK.

The updated systematic search focussed on economic assessments of liquid-based cytology screening techniques. Details of this systematic search are presented in Chapter 2. A generic proforma for the critical appraisal of modelling studies in health economics, expanded to include the relevant factors specific to cervical cytology screening, is used in systematically reviewing the studies identified. The key outcomes derived are:

Proportion developing invasive cancer;
Proportion dying from invasive cancer;
Additional days of life/life years gained;
Average lifetime costs;
Cost per life year gained, incremental;

Results

The following sections describe the findings of the review, firstly with respect to issues relevant to the modelling of cervical screening programmes, and secondly relating to estimates of the cost-effectiveness of liquid-based cytology techniques compared to conventional pap smear testing.

Topic review of issues in health economic modelling of cervical cancer screening

The following factors have been identified from the literature on models of cervical cancer as relevant parameters for the development and validation of models to represent the cost-effectiveness of alternative cervical screening programmes. The parameters are categorised as either observable or unobservable clinical input parameters, key clinical events for the validation of cervical screening models, or cost parameters.

Unobservable factors
Onset of cervical intraepithelial neoplasia (CIN)
Regression of pre-invasive stages
Progression of pre-invasive stages
Duration of pre-invasive and invasive stage
Test sensitivity
pre-invasive stage
invasive stage

Relationship between prognosis and stage at identification

Observable factors
Participation rate
False positive rate
Pre-invasive stages
Invasive cancer
Clinical survival
Death from other causes
Morbidity associated with
Stage at identification
Unnecessary treatments arising from false positive screen results

Observable events for use in calibrating and validating a model.
Clinical incidence
Mortality from cancer
Detection rate pre-invasive
Detection rate invasive
Death from other causes

Costs
Cost of screen test
Capital purchase costs
Costs of screen initiated therapies/treatments (e.g. colposcopy)
The key parameter driving the differential long-term effectiveness of alternative screening technologies is the sensitivity of the different technologies (based on the proportion of false negative results). Test specificity (based on the proportion of false positives), together with the screening test costs, have the largest impact on the costs associated with alternative screening programmes. Specificity may also have a significant impact on programme effectiveness if short-term utility effects are accounted for within an analysis.

Systematic review of economic studies for liquid-based cytology services

In the original HTA report, the systematic search for health economic studies of liquid-based cytology services in cervical cancer identified three studies. Two studies were national health technology assessment agency reports, one from the AHCPR of USA, published in 1999,[25] the other from the Australian Health Technology Advisory Committee, published in 1997.[10] The other study was an article published in a peer-reviewed journal in 1999, which focussed on the US health care system.[95]

The updated systematic search identified four economic evaluations that have been published since the completion of the original literature search[96-99], though one of the four identified studies[96] is a journal version of the above AHCPR report. In addition, the draft report of the evaluation of HPV/LBC cervical screening pilot studies in England and Wales includes an assessment of the cost-effectiveness of liquid-based cytology, which updates the model described in the original HTA report with data obtained from the pilot studies.[1]

The following sections briefly review the comparators included, the methodologies and the results reported by the full set of identified studies. A detailed summary table of the studies is presented in Appendix 2.

Comparators

The only named liquid-based cytology technique that is assessed in any of the evaluations is the ThinPrep (2000?) system. Brown & Garber,[95] and Hutchinson et al,[37] compare ThinPrep with 10% random rescreening to conventional pap smear testing with 10% random rescreening.

The other identified studies do not evaluate named liquid-based cytology techniques. The AHCPR report and Myers et al.,[96] evaluate hypothetical new screening techniques (based on liquid-based cytology and assisted rescreening) with varying levels of sensitivity, specificity and additional cost, with the aim of establishing values for these parameters at which a new technique would be considered cost-effective.

Montz et al,[98] and Moss et al,[1] test cost-effectiveness of a generic liquid-based cytology technique compared to conventional pap smear testing (Montz et al include 10% random rescreening for both interventions[98]) as part of their baseline analysis, whilst Raab et al[99] assess the necessary increase in the number of HSIL test results by a liquid-based cytology technique, compared to observed detection rates, for it to be cost-effective.

The review by the Australian Health Technology Advisory Committee estimates the potential for health gain from a generic technology aimed at improving the test characteristics.

The studies assess the stated comparators over a varying series of screening intervals, ranging from 1 to 10 years, other than the Australian report (2-year interval), Raab et al[99] (1-year), Montz et al[98] (based on self-reported compliance rates), and Moss et al[1] (5-year interval).

Methodologies

The majority of the identified economic evaluations use a state transition methodology to model the natural history of the disease together with a model of the screening intervention and subsequent diagnosis and treatment.[95,100,96,101,98,1] Of these five studies, only Moss et al[1] present their analysis from a UK perspective, the remaining studies cover the US perspective.

All of the modelling studies simulate the life experience of a cohort of women, though applying screening over varying age ranges and assessing the cost-effectiveness of alternative screening intervals. The basic structure of the models is similar, with the natural history of cervical cancer being modelled as a progression through a series of pre-cancerous states (defined as either SILs or CINs – the AHCPR also include an initial HPV state on the assumption that all cervical cancer arises from HPV infection), from which women progress to cancer (defined as single state or a series states, e.g. local, regional, and distant). The natural history sections of all models, except Moss et al,[1] are populated with age-specific disease incidence, progression and regression rates.

Raab et al[99] state that a decision analytic model is used, but it is unclear what type of model is used. It could be a decision tree that represents one round of screening with life expectancy and treatment cost estimates attached to the different terminal nodes of the tree. The model describes progression rates from HSIL to different stages of cancer, LSIL screen results are ignored on the basis that they will be picked up at the next screen (a single screen interval of 1-year is tested).

The review by the Australian Health Technology Advisory Committee does not estimate the lifetime impact of the technologies, rather it describes the number of cancer cases detected through the estimation of the number of LSILs and HSILs that progress to cancer. The approach is similar to that adopted by Raab et al, in that the effectiveness of new technologies is described in terms of an increase in the number of positive screen tests. This study also only considers the cost-effectiveness of a single round of screening, and thus does not account for the cumulative effect of screening over specified intervals (i.e. missed abnormalities in one round may be picked up in later rounds).

Assumptions regarding test characteristics vary between the studies, most notably Brown & Garber[95] assume a sensitivity rate of 80% for conventional pap smears, whilst the other studies use more conservative estimates (Raab et al[99] do not apply a sensitivity rate as cancer incidence is based on observed test results). Most studies assume a constant sensitivity rate across the different pre-cancer states, but Hutchinson et al[44] present differential sensitivity rates for LSIL and HSIL results, whilst Moss et al[1] present differential sensitivity rates for CIN I, II, and III. Specificity is either not mentioned or assumed to be equal across screening techniques in all baseline analyses.

[Moss et al[1] use the same model as used in the original LBC HTA report, and use identical data to populate the model other than for parameters describing the costs, and inadequacy rates, of conventional pap smear screening and LBC screening].

Other than Raab et al,[99] who only consider HSIL test results, all of the studies assume that LSIL or worse test results are investigated with colposcopy, whilst all but one study assume that ASCUS results are rescreened and investigated with colposcopy if rescreen is abnormal. Brown & Garber[95] treat ASCUS results as normal.

None of the US-based evaluations accommodate the impact of alternatives rates of inadequate screens on the costs associated with liquid-based cytology, whilst Moss et al assume that inadequate smears are replaced with

adequate tests. In the Australian report it is unclear whether savings from reduced inadequate smears are included.

All studies adopt a health service perspective, though Brown and Garber [95] claim a societal perspective in the methodological description. The US studies discount costs and health benefits at 3% (0-5%), whilst Moss et al[1] follow Treasury guidelines and discount costs and health benefits at 6% and 1.5%, respectively.

Results

The main results from the economic studies that presented incremental cost-effectiveness data are presented in Table 11.[100,95,101,98,1] The cost data is converted to pound sterling in the year of the original analysis and then uprated to 2002 costs using the NHS Pay and Prices Index (note that this is not intended to estimate cost-effectiveness in the UK setting but rather to aid comparison between the results). Only the data relating to conventional pap smear testing and liquid-based cytology techniques have been extracted, and cost-effectiveness ratios have been recalculated to account for new rank ordering and the exclusion of dominated and extendedly dominated screening options.[102]

Table 11 Results reported in identified economic evaluations of liquid-based cytology

	Average cost*	Cancer incidence†	Life days saved‡	Cost per life year saved
AHCPR report, 1999[100a]				
No Pap	£893	3014.6	-	
Pap 3-yearly	£1,108	506	19.2	£2,840
Improved Pap 3-yearly	£1,240	246	21.4	£15,215
Improved Pap 2-yearly	£1,433	132	22.84	£33,988
Improved Pap every year	£2,000	33	23.64	£179,730
Brown & Garber, 1999[95b]				
Pap 4-yearly	£446	330	23.91	
ThinPrep 4-yearly	£505	280	25.07	£14,138
ThinPrep 3-yearly	£695	250	25.73	£80,023
ThinPrep 2-yearly	£1,059	220	26.19	£219,962
ThinPrep every year	£2,194	190	26.8	£517,214
Hutchinson et al, 2000[101c]				
Pap 10-yearly	£556	-	3.5	
ThinPrep 10-yearly	£569	-	5.1	£2,060
ThinPrep 5-yearly	£647	-	6.9	£10,989
ThinPrep 3-yearly	£729	200	7.7	£25,993
ThinPrep 2-yearly	£836	123	8.2	£54,268
ThinPrep every year	£1,191	38	8.8	£150,039
Montz et al, 2001[98 d]				
Pap, self-reported compliance	-	11.8 per year	-	
LBC, same compliance	-	8 per year	-	£10,627
Moss et al, 2002[1e]				
Pap 5-yearly	£58.28	-	48.91	
LBC 5-yearly	£57.07	-	49.64	Dominant

* Lifetime costs converted to UK £s at exchange rate in year of analysis, then uprated to 2002 costs using NHS pay & prices index (other than Moss et al, 2002[1]).

† lifetime cases of cervical cancer cases per 100,000 unless stated

‡ Compared to no screening (dominated and extendedly dominated strategies are excluded, other than Moss et al, 2002[1])

[a] includes 10% random rescreening, base case assumes 60% reduction in false negative rate for improved screening (Pap sensitivity 0.51, improved sensitivity 0.804); costs and life years discounted at 3%, originally presented as 1997 US$.

[b] includes 10% random rescreening, base case assumes Pap sensitivity 0.8, ThinPrep 0.919; costs and life years discounted at 3%, originally presented as 1996 US$. Cancer incidence data only available to nearest 10.

[c] includes 10% random rescreening, base case assumes Pap sensitivity 0.504-0.552 (LSIL-HSIL), ThinPrep 0.75-0.822; costs discounted at 3%, discounting of life years not mentioned, originally presented as 1997 US$.

[d] includes 10% random rescreening, base case assumes Pap sensitivity 0.51, LBC 0.73; costs and life years discounted at 3%, originally presented as 1997 US$.

[e] LBC data averaged over 3 sites, base case assumes CIN stage-specific sensitivity rates 0.37-0.5, LBC improves sensitivity by 2-15%. UK costs originally, year not specified. Discount rates not specified.

The assorted US-based studies present quite different levels of absolute costs and effects (life days saved), though the relative values of the life days saved between the screening options are similar between the different studies. Thus, differences in the incremental cost-effectiveness ratios are mainly due to differences in the costs associated with each screening strategy.

However, it is noted that the exclusion of dominated strategies leads to the exclusion of conventional pap smear testing as a screening option other than as the baseline screening option (i.e. the cheapest screening option) in all studies. Based on a threshold cost-effectiveness ratio of $50,000, the rearrangement of the US-based cost-effectiveness data shows that liquid-based cytology is the most cost-effective strategy either at a 2-year or 3-year screening interval (the self-reported compliance rates used by Montz et al[98] equates to a screening interval of between 2 and 3 years).

The Australian report presents a range of estimated costs per additional potential cancer case [avoided], where cancer cases are determined by assuming that 1% and 12% of LSIL and HSIL screen tests progress to cancer, respectively. A 15% increase in positive screens, of which 90% are LSILs, and an additional cost of $20 per screen leads to an incremental cost-effectiveness ratio of Aus$138,000 (£72,108, 2002 costs).

Raab et al[99] present only a figure describing the number of additional HSILs that would need to be detected at a range of additional costs for a new technology to fall within different thresholds for the cost of gaining an additional life year. This figure shows, for example, that for a cut-off of $50,000 per life year gained, and an incremental cost of $10 per test, an additional 236 HSILs would need to be detected per 10,000 women screened.

The UK-based study updates the results of the economic model presented in the earlier HTA report with new data describing screening costs and inadequacy rates, though only results for a 5-year interval are presented. Ordering the results in an incremental manner, using the average values from the three pilot sites for the costs and effects of liquid-based cytology, this study estimates very little difference in both costs and life days saved between cervical screening based on conventional pap smear testing and liquid-based cytology techniques, though the incremental analysis shows that the liquid-based cytology techniques gain an extra 0.73 life days and save £1.21 per woman screened, i.e. liquid-based cytology dominates conventional pap smear testing.

Conclusions

The identified economic evaluations comparing liquid-based cytology techniques to conventional pap smear testing reviewed in this chapter can be placed in three categories. The first category describes those studies that felt the uncertainty surrounding the relative values of the test characteristics (sensitivity and specificity) of liquid-based cytology in particular, was too great to usefully inform the results of an economic analysis.[99] These analyses are of limited value to policymakers, other than to emphasise the need for further research (though no potential value for the research is described).

The second category of cost-effectiveness analyses includes the remaining set of US-based analyses. [100,95,101,98] These analyses all estimated a most likely value for the test characteristics of the alternative screening techniques, enabling the calculation of mean cost-effectiveness ratios. In addition to being US-based, other key common features of these analyses include the assumption of a generic sensitivity rates (i.e. sensitivity is the same for low- and high-grade lesions) and no consideration of the impact of liquid-based cytology techniques on the rate of inadequate smears. The relevance of these studies to the UK is limited due to the use of US-based incidence rates and costs, as well as the general application of the Bethesda classification index to describe pre-cancerous lesions. Furthermore, the assumed improvement in the sensitivity rate of liquid-based cytology techniques compared to conventional pap smear testing is significantly higher than that assumed in the earlier UK HTA report,[94] and the subsequent pilot sites evaluation.[1] If the stated sensitivity rates are accepted, the inclusion of differential inadequacy rates further improves the cost-effectiveness of liquid-based cytology, which could reduce the recommended screening intervals.

However, the apparent cost-effectiveness of liquid-based cytology derived from the baseline results in this category of analyses is not as clear-cut as it appears. The AHCPR report[100] describes substantial uncertainty around the baseline estimates of sensitivity and specificity, and finds that both sensitivity and specificity are important in determining cost-effectiveness.

Brown & Garber[95] find that liquid based cytology primary screening is dominated, that is costs more and saves fewer life years, by automated rescreening techniques. Conversely, Hutchinson et al[101] assume ThinPrep has a higher sensitivity rate than the automated rescreening techniques and finds that the liquid-based cytology technique is cost-effective.

The third category consists of the only identified UK-based study,[1] which updated the economic analysis reported in the original HTA report.[94] Using data derived from three pilot study sites assessing the using of liquid-based cytology in UK settings, Moss et al[1] found no evidence to alter any of the parameters specified in the earlier report, other than the costs of the respective screening tests and the assumed inadequacy rates. The assumption of similar rates of sensitivity and specificity in this latter report should not be interpreted as a confirmation of the initially assumed rates, rather that the pilot studies were not designed to estimate sensitivity and specificity. Whilst there remains significant uncertainty regarding the relative sensitivity of the alternative screening techniques, there appears to be a consensus that the sensitivity of liquid-based cytology techniques is unlikely to be worse than that of conventional pap smear testing. If the assumption of equal specificity between the alternative techniques is also strong, then the results of the pilot studies indicate that, at worst, liquid-based cytology techniques have very similar aggregate costs and save very similar numbers of life years. If quality of life effects are incorporated it may be that the reduction in the number of inadequate smears would improve the aggregate utility of women screened. Best case scenarios, in which sensitivity rates are improved with liquid-based cytology techniques, may increase aggregate costs (due to additional treatments for women with true positive smears who would not progress to cancer), though it is likely that accompanying increase in cancers prevented (and hence life years saved) would be achieved at a cost-effectiveness ratio well below the commonly quoted £30,000 acceptable threshold. The analysis reported in the following chapter, which further updates the analysis undertaken by Moss et al,[1] confirms this prediction.

However, as alluded to above, a range of economic evaluations were identified in the updated systematic literature search (1999-2002) that assessed the economic impact of cervical screening approaches other than conventional pap smear testing and liquid-based cytology techniques. Smith et al[103] analysed the cost-effectiveness of AutoPap, the semi-automated slide analysis device (as included in the analyses reported by Brown & Garber,[95] and Hutchinson et al,[101]), whilst a range of authors reported economic analyses of HPV testing as an adjunct or alternative to pap smear testing. Another study was identified that evaluated the economic impact of alternative protocols for the management of atypical (ASCUS) screen results.[104]

The aggregate analysis of the cost-effectiveness of potential combinations of these approaches to screening for cervical cancer are outside the scope of the current review, though it is noted that the relative cost-effectiveness of all relevant screening programme configurations should be analysed simultaneously.

Modelling the health economic impact of liquid-based cytology within the UK

Modelling methods

Model Overview

The question to be addressed by the model is: "What would be the likely impact of the new liquid-based cytology screening techniques, in terms of incidence of cervical cancer, associated mortality, and in terms of the costs and cost-effectiveness, when compared with conventional smear testing for a typical UK population?"

The model developed here provides a macro-simulation of the life experience of a cohort of women followed from age 18 to 95 years. The model has three elements: a state transition methodology is used to simulate the natural history of the disease; a model of the screening intervention interacts with this to assess the impact of the screening programme; and a life table is used to reflect age-specific all cause mortality. Health outcomes, resource utilisation and costs are estimated for the cohort. A health service perspective of costs is taken in the analysis and only direct costs are considered. The baseline analyses discounts costs at 6% and life years at 1.5%.

The same model as reported in the earlier HTA report is used, which is based closely on the work reported by Sherlaw-Johnson, Gallivan, Jenkins and Jones.[105] The structure of the model remains the same as that described in the earlier HTA report, though Sherlaw-Johnson and colleagues have updated the parameterisation of their model to incorporate age-specific incidence rates for CIN1 (previously a constant rate had been assumed) and updated estimates of the effectiveness of conventional pap smear testing,[106], which are included in the current analysis. The updated systematic review has concentrated on updating the test characteristics parameters (sensitivity and specificity) for liquid-based cytology and conventional pap smear testing. More reliable estimates of the rate of inadequate smears, and the screening costs, associated with both approaches are also incorporated from the recent evaluation of the HPV/LBC cervical screening pilot studies.[1]

The following sections describe the assumptions around the input parameters for the model, covering the natural history of cervical cancer, the screening interventions, screening and treatment costs and the outcomes collected from the model. The main assumptions are then summarized and a table describing the full set of input parameter values presented.

Natural History of Cervical Cancer

Pre-invasive cancer is classified histologically into three categories of cervical intraepithelial neoplasia; CIN1, CIN2, CIN3. For the purposes of this model, incidence of disease is defined as the onset of CIN1. In the absence of any intervention, the disease is assumed to progress through each pre-invasive stage and from CIN3 to invasive cancer, with the proviso that regression to a disease-free state may occur from CIN1 only. It is recognised that there is some evidence that the higher grades of CIN may also regress,[107] and this possibility is explored in sensitivity analyses.

The model calculates state transitions at intervals of six months. Within any six-month interval progression can only occur to the next immediate state, with the exception of CIN1 lesions where a proportion of fast growing lesions may progress to CIN3. The baseline disease progression state transition matrix is presented in Table 12. Disease progression and the proportion of fast growing cancers are assumed not to be age-specific. No further incident cases of CIN1 are assumed to arise after the age of 68, pre-invasive lesions present at the age of 68 years are assumed to progress at the rates previously identified.

Age-specific all cause mortality is estimated from interim life tables produced by the Government Actuary's Department based on data for the years 1992-1994 for females within England and Wales.[108] A constant risk is assumed for mortality from invasive cancer. This mortality is based upon an average life expectancy with invasive cancer present in an unscreened population of approximately 10 years, corresponding to approximately 55% overall survival at 5 years post diagnosis and treatment,[109] and a mean duration pre-diagnosis of approximately 5 years. This is based crudely upon previous modelling work undertaken by Eddy.[110]

Screening Interventions

For the purposes of this model, a cohort of 100,000 women aged 15 years is defined. Screening is assumed to be taken up by a certain percentage of women in this cohort, this is defined as the coverage of screening. Baseline coverage is estimated at 85% - ranging from 80% to 90% based on the range of Regional coverage rates reported.[5] Women are assumed either to attend screening at the regular intervals or not at all. Screening is undertaken between the ages of 21 and 64 years at regular intervals. The model can be used to evaluate any given screening interval, however intervals from 2 to 5 years are analysed.

The conventional smear screening test results are classified into five states - negative, borderline, mild, moderate and severe. In addition, screening slides may be classed as inadequate. For the purposes of this model, inadequate slides are simply assumed to require an immediate rescreen, these slides are then assumed to be adequate. The impact of inadequate slides is therefore merely to increase the total number of slides processed by the inadequate percentage. Also, for the purposes of the model, the states borderline and mild are grouped together as are the moderate and severe results.

The screen test characteristics are defined in terms of the probability of achieving the different test results given the underlying histological state: the true test specificity and sensitivity. The baseline test characteristics for the conventional smear screen test are given in Table 12, which are based on the latest estimate presented by Jenkins et al.[106] This characterisation of test results allows the modelling of differential sensitivity by lesion grade (CIN1, CIN2, CIN3, and invasive cancer).

The England and Wales, and Scottish, pilot studies were not set-up to investigate rates of sensitivity. Moss et al[1] did not find any clear evidence of differences between the pre-pilot (conventional pap smear) and pilot period in terms of rates of borderline to severe dyskaryosis test results, though the analyses of data describing outcome of referral to colposcopy estimate that the sensitivity rate for CIN3 could have improved from 50% (for conventional pap smear testing) to 54% for liquid based cytology.

The Scottish report[2] presented data describing the percentage of tests that were unsatisfactory, or displayed abnormal results for both conventional pap smear and liquid based cytology (50% of the smears tested during the pilot study at each of the sites continued to use conventional pap smear testing), though it is unclear how many tests were undertaken for each technique (either 15,000 or 30,000). These data show that liquid based cytology testing identified around double the number of mild, moderate and severe test results compared to conventional pap smear, and the increase is consistent across the three results. However, no analysis of the outcome of these tests after colposcopy is presented and so it difficult to assess the impact of these data.

Of the other studies identified in the literature review, only three presented data that could be used to compare liquid based cytology and conventional pap smear testing with respect to separate sensitivity rates for different lesion grades. A meta-analysis of these studies for the three specified histological findings (CIN1, CIN2/3, and invasive cancer) shows that there is no significant difference between the techniques in any of the three categories, though the number of cases included is small.

The small numbers informing differential sensitivity rates precluded their use, so an aggregate estimate of an improvement in sensitivity based on the meta-analysis of false negative rates for conventional pap smear testing and liquid-based cytology screening, as presented in Figure 1 (Chapter 3), is taken as the best source for the estimation of the relative difference in sensitivity rates between the two screening approaches. Positive screen results are defined as LSIL+, and so are not strictly comparable to the UK classification system. The meta-analysis estimates false negative rates of 28.5% (sensitivity 71.5%) and 19.9% (81.1%) for conventional pap smear and liquid-based cytology screening, respectively. The relative improvement in sensitivity of liquid-based cytology compared to conventional pap smear testing is calculated as:

$(0.8106-0.7146)/0.7146 = 0.12$

The estimate of improved sensitivity for CIN3 lesions of 4%, presented by Moss et al[1] is used as the best estimate for such lesions. On the basis of a 12% aggregate improvement and a 4% improvement in CIN3 sensitivity, an improvement of 13.4% was imputed for CIN1/2 sensitivity (as shown in Table 12).

Table 12 Estimation of differential sensitivity rates

	CIN3	CIN1/2	Aggregate
Proportion of identified cases*	0.141	0.859	
Sensitivity†:			
Conventional pap smear	0.6400	0.5888	0.5960
Liquid-based cytology	0.6656	0.6679	0.6676
Improvement	4.0%	13.4%	12.0%

* Cervical screening programme. England: 2001-02

† Conventional rates from Jenkins et al 1996[106], CIN3 improvement[1], aggregate improvement (Meta-analysis), CIN1/2 improvement (imputed).

The majority of the identified studies examined ThinPrep, with a few looking at Autocyte. Indirect comparisons of the alternative liquid based cytology techniques found no differences between the results, so the modelling analysis does not differentiate between alternative techniques.

Meta-analysis of the six studies that compared specificity of conventional pap smear testing and liquid based cytology showed no difference, and the specificity of the liquid-based cytology techniques is assumed to equal to specificity for conventional pap smear testing.

Two intervention policies based on screening test results are modelled:

Policy A: Immediate colposcopy for all women with an abnormal smear test from borderline/mild or worse.

Policy B: Immediate colposcopy for all women with a smear test result of moderate or severe, rescreen at 6 months for all women with a borderline or mild screen test result and colposcopy for all women who have a second borderline or worse smear test result.

The baseline health and health economic outcomes are presented for Policy B.

Colposcopies are assumed to be 100% sensitive and specific. It is assumed that all abnormalities found at colposcopy are treated. An overall effectiveness of treatment is used within the model and those patients successfully treated are assumed to return to the clear state. The baseline effectiveness is taken from the NHSCSP guidelines on quality standards expected from colposcopy.[111]

Costs

Total direct costs of screening, diagnosis and treatment are included within the model and estimated from the following unit costs:

- conventional smear test;
- liquid-based cytology techniques;
- colposcopies;
- treatment of pre-invasive lesions;
- treatment of invasive cancer.

The evaluation of the HPV/LBC pilot sites included a detailed costing exercise for both conventional pap smear testing and liquid based cytology testing, which covered primary care costs (e.g. taking smears, administrative letters), as well as the respective costs associated with slide preparation and smear reading.[1] These costs are transferred directly into the current evaluation.

Primary care screening costs were based on questionnaires sent to samples of general practices across the three pilot sites to estimate consultation costs for liquid based cytology, and to a sample of practices in Oxfordshire to obtain equivalent data for conventional pap smear sample taking. The collected data show a significant difference between the two techniques in total consultation time with a mean time of 13 minutes 20 seconds for conventional pap smear testing and 8 minutes 35 seconds for liquid based cytology. Staff unit costs are applied assuming practice nurses undertake 80% of samples and GPs take 20%. Administration costs are assumed to be similar between the techniques.

Slide preparation costs include capital and labour costs, which were estimated for three alternative pieces of liquid based cytology equipment (ThinPrep T3000 and T2000, and the Autocyte package), as well as for the slide staining equipment required for conventional pap smear testing. The baseline estimates assume a laboratory processing 60,000 smears per annum. The three liquid based cytology approaches involve more preparation costs than conventional pap smear testing, though the ThinPrep systems require more inputs than the Autocyte system. Similar results are also found for the relative costs of the consumables required for the alternative techniques.

To assess costs associated with screening the smears, screening staff completed record sheets over three weeks. The costs attached to these data accounted for different staff mixes used to undertake the different phases of screening (primary screening, checking, and rapid review). No significant difference between liquid based cytology and conventional pap smear testing were found, though the conventional approach was slightly more expensive.

The cost analysis also includes various other laboratory costs, such as overheads, non-screening staff time, and the cost of non-screening staff (secretaries, etc). These costs were assumed to be equal across the techniques.

Moss et al[1] also estimated the one-off transition cost of converting laboratories to liquid based cytology (subsequent training costs are assumed to be similar between the alternative techniques). The transition costs included the time required to provide initial training for smear takers and readers, which includes staff time, travel costs and training coordinator and materials costs. Other costs include handling the backlog of tests during the transition phase, structural changes to laboratories, and changes to the bar coding system.

The total national cost was estimated to be £10.1 million. Apportioning these costs as a cost per smear assuming an average of 3.9 million smears per year over a useful lifetime for liquid based cytology of 20 years, leads to an additional cost per liquid based cytology smear of £0.13. The transition cost would not vary significantly if alternative assumptions regarding the annual number of smears or the lifetime of the technology varied, e.g. assuming 3 million tests per year and a 10-year lifetime gives a cost per screen of £0.34.

[Note that the cost of purchasing the slide preparation equipment is not included in the implementation cost of £10.1 million, rather these costs are included in a separate category (preparation equipment cost) to inform a comparison with conventional preparation equipment costs].

Colposcopy is routinely undertaken in a gynaecology outpatient setting. Practice may vary between individual hospitals, though increasingly colposcopy and treatment by cervical 'conization' of any abnormalities is undertaken within a single outpatient appointment. In situations where colposcopy and treatment are undertaken at different visits, these would still constitute a single outpatient consultation in terms of charging. Thus a typical charge for gynaecology outpatient appointments is used as a proxy for the cost of colposcopy and subsequent treatment where necessary, with the recognised proviso that these charges may not represent the true costs of colposcopy and treatment.

Treatment of invasive cancer is dependent on the stage of cancer at diagnosis. Recommended procedures in detection, diagnosis and evaluation of cervical carcinoma are detailed by Obralic et al [109] under the FIGO staging system. These provide recommendations for the use of surgery, radiation therapy and chemotherapy, and identify the stages at which these are appropriate. Surgical interventions include cervical conization, extrafascial hysterectomy and radical hysterectomy with bilateral pelvic lymphadenectomy. Radiation therapy may be appropriate as an adjunct to surgical intervention or may be used with patients who have more advanced disease who are not candidates for radical surgery. Cervical conization is increasingly being adopted for stage Ia1 carcinomas. 30% of screen-detected cancers are assumed treatable by conization in the model.

In terms of resource utilisation, hysterectomies are classified as HRG (Health Resource Group) M07 'Upper genital tract major procedures'. For the purposes of this economic model, the cost associated with HRG M07 has been used as a proxy for the cost of treating the remaining patients diagnosed with invasive cancer. This HRG cost, however, does not take into account costs of subsequent radiation therapy, costs of palliative care and long-term support cost. This cost is also assumed to apply to those patients who die from cervical cancer. Thus, this cost is almost certainly an underestimate of the costs associated with treating invasive cancer, which will introduce a bias against screening policies and specifically screening developments that improve screen test characteristics.

Rates of inadequate smears

The evaluation of the England and Wales pilot studies is used to inform inadequacy rates for liquid based cytology, as well as for conventional pap smear testing.[1] Moss et al analysed data describing rates of inadequacy from the three pilot sites over a five-year period prior to the introduction of liquid based cytology to estimate rates for conventional pap smear testing, as well as over the 12-month pilot period to obtain rates for liquid based cytology.

Lower rates of inadequacy were observed in the liquid based cytology techniques than previously assumed,[94] especially at the site using the AutoCyte system (9.7% conventional, 2% Thinprep, and 0.9% Autocyte). Though the lower inadequacy rates reported at the Autocyte site are tempered by the introduction of new reporting guidelines at this site, which may have increased the number of negative results that would previously have been categorised as inadequate.

Model assumptions and input parameter values

The following bullets describe the main assumptions in the model used to compare the alternative cervical screening approaches:

- In the absence of any intervention, disease progresses through each pre-invasive stage and from CIN3 to invasive cancer, though a proportion of patients may move directly from CIN1 to CIN3.
- Disease can regress to a disease free state from CIN1 only.
- The model incorporates age-specific incidence of CIN1 between the ages of 15 and 68 years. No further incident cases of CIN1 are assumed to arise after the age of 68.
- Disease progression and the proportion of fast growing cancers are assumed not to be age-specific.
- Pre-invasive lesions present at the age of 64 years are assumed to progress at the rates previously identified.
- A constant risk is assumed for mortality from invasive cancer.
- Screening is taken up by a certain percentage of women in this cohort.
- Women are assumed either to attend screening at regular intervals or not at all.
- Inadequate slides are assumed to require an immediate rescreen, these subsequent slides are assumed to be adequate.
- Colposcopies are assumed to be 100% sensitive and specific. It is assumed that all abnormalities found at colposcopy are treated.
- HRG M07 is used as a proxy for the cost of treating the remaining patients diagnosed with invasive cancer more advanced than stage Ia1. This HRG cost, however, does not take into account costs of subsequent radiation therapy, costs of palliative care and long-term support cost. This cost is also applied to patients who die from cervical cancer.

Table 13 presents all the parameter values used in the model, together with ranges and sources, except for the age-specific incidence rates of CIN1 (personal communication: C Sherlaw-Johnson, as used in reference[106]), which are presented in Table 14.

Table 15 presents details of the costings for the alternative screening techniques as adopted from the England and Wales pilot sites evaluation.[1] Three baseline costs for liquid-based cytology screening are presented, representing the estimated costs for three alternative technologies (ThinPrep3000, ThinPrep2000, and Autocyte), including estimated costs of conversion (spread over the anticipated lifetime of liquid-based cytology screening – 20 years). The estimated costs for the Autocyte system are less than conventional pap smear testing. As there are no grounds to differentiate between the effectiveness Autocyte and ThinPrep

systems the baseline cost-effectiveness analysis uses the estimated costs for the newest ThinPrep system (ThinPrep3000, £19.71 per screen), on the basis that the Autocyte system may be assumed to be at least as cost-effective.

Table 13 Description of Parameters used in the Model

Description	Baseline	Minimum	Maximum	Reference
Management variables				
Female population	100,000			-
Start age (years)	18			-
First screen age	21			-
Last screen age	64			-
Policy[a]	B	A		-
Screening interval	3	2	5	-
Discount rate: costs	6%	0%	10%	-
Discount rate: health benefits	1.5%	0%	10%	-
6 month progression rates				
Progression rates from clear to CIN 1	See table 14			
Regression rates from CIN 1 to Clear	2.0%			[105]
Regression rates from CIN 2 to Clear	0%		1.5%	[107]
Regression rates from CIN 3 to Clear	0%		1.1%	[107]
Progression rates from CIN 1 to CIN 2	6.0%			[105]
Progression rates from CIN 1 to CIN 3	2.5%			[105]
Progression rates from CIN 2 to CIN 3	15%			[105]
Progression rates from CIN 3 to IC	1.0%			[105]
Progression factor (for sensitivity analysis)[b]	100%	50%	150%	-
Incidence factor (for sensitivity analysis)[c]	100%	75%	125%	-
Effectiveness and mortality				
Effectiveness of cervical conization	90%	80%	100%	[108,109]
Effectiveness of hysterectomy	85%	75%	95%	[108]
Screen detected cancers suitable for cervical conization (stage la1 carcinomas)	30%	10%	50%	[d]
6-month mortality rates associated with invasive cancer	2%	0%	4%	[112,108]

Table 13 Description of Parameters used in the Model (continued)

Description	Baseline	Minimum	Maximum	Reference
Test characteristics				
Specificity of test	96.6%	95%	98.2%	[106]
False borderline/mild test result	2.9%	1.8%	4%	[106]
False moderate/severe test result	0.5%	0%	1%	[106]
Proportion of CIN1 lesions that give:				
negative test result	34%	20%	48%	[106]
borderline/mild test result	52%	41%	63%	[106]
moderate/severe test result	14%	11%	17%	[106]
Proportion of CIN 2 lesions that give:				
negative test result	59%	40%	78%	[106]
borderline/mild test result	23%	12%	34%	[106]
moderate/severe test result	18%	10%	26%	[106]
Proportion of CIN 3 lesions that give:				
negative test result	36%	20%	52%	[106]
borderline/mild test result	23%	17%	29%	[106]
moderate/severe test result	41%	31%	51%	[106]
Proportion of invasive cancers that give:				
borderline/mild test result	40%	20%	60%	[106]
moderate/severe test result	60%	40%	80%	[106]
Other test characteristics				
Inadequate conventional smear slides	9%	7.8%	11.3%	[1]
Inadequate liquid-based cytology samples	1.4%	1.0%	2.4%	[1]
CIN1/CIN2: sensitivity improvement with liquid-based cytology	13.4%	6.7%	20.1%	[e]
CIN3/IC: sensitivity improvement with liquid-based cytology	4%	2%	6%	[e]
Percentage of women who take up screening	85%	80%	90%	2
Treatment costs				
Cost of colposcopy and conization	£185	£135	£235	[f]
Cost of surgical treatment of invasive cancer	£1,700	£1,000	£2,400	[113]

[a] Policy B: borderline/mild smears retested at 6 months, followed by colposcopy if retest is non-normal; Policy A: immediate colposcopy for borderline/mild test results.
[b] this factor is applied to all progression rates simultaneously
[c] this factor is applied to incidence of CIN1
[d] personal communication: E McGoogan
[e] see text
[f] personal communication: typical NHS Trust

Table 14 Age-specific progression rates from clear to CIN1

Age	Probability of contracting CIN	Age	Probability of contracting CIN
15	0.02%	31	0.10%
16	0.05%	32	0.10%
17	0.09%	33	0.09%
18	0.14%	34	0.09%
19	0.17%	35	0.08%
20	0.19%	36	0.08%
21	0.22%	37	0.07%
22	0.22%	38	0.07%
23	0.22%	39	0.07%
24	0.20%	40 – 46	0.06%
25	0.19%	47 – 50	0.05%
26	0.16%	51 – 52	0.04%
27	0.15%	53 – 57	0.03%
28	0.13%	58 – 64	0.02%
29	0.11%	65 – 67	0.01%
30	0.10%	68 +	0.00%

As used in reference[114]

Table 15 Details of cost estimates for alternative screening techniques

Cost item	Convent-ional	Liquid based cytology		
		T3000®	T2000®	Autocyte
Smear taker staff cost	£7.66	£4.93	£4.93	£4.93
Administration cost	£3.00	£3.00	£3.00	£3.00
Preparation equipment cost	£0.04	£0.52	£0.36	£0.22
Preparation staff cost	£0.02	£0.06	£0.41	£0.20
Consumable cost	£0.27	£4.07	£4.07	£2.00
Smear reading cost	£2.26	£1.99	£1.99	£1.99
Other laboratory cost	£8.42	£8.42	£8.42	£8.42
Conversion costs†	-	£0.13	£0.13	£0.13
Total (baseline)	**£21.67**	**£23.12**	**£23.31**	**£20.89**
Smear taker time increased*	£21.67	£25.27	£25.46	£23.04
LBC worst case	£21.67	£28.17	£27.74	£24.50
LBC best case	£21.67	£20.52	£20.71	£19.38

* Assuming liquid based cytology smear taking is 1 minute (rather than 5 minutes) quicker than conventional pap smear.
† Cost per smear based on 3.9 million smears per year over 20-year useful lifetime for liquid based cytology.

Outcomes Generated by the Model

The model generates a range of health and economic outcomes under a set of screening policy comparisons. The key health outcomes generated are:

- annual incidence of invasive cancer;
- percentage of women having invasive cancer at some point in their life;
- life years (days/hours) gained.

The key resource outcomes generated are:

- number of smear tests undertaken;
- number of colposcopies undertaken.

The key health economic outcomes generated are:

- cost per invasive cancer avoided;
- cost per life year gained.

Note that insufficient quality of life information is currently available to estimate a cost per quality adjusted life year.

Model validation

Overall Incidence of Invasive Cancers

Reported incidence of invasive cervical cancers across all ages is 12 per 100,000 per annum,[115] which is comparable with the predicted incidence by the current model of 11.64 for Policy B (rescreen at 6 months for all women with a borderline or mild screen test result), 85% coverage and screening at 3-yearly intervals. Implementing Policy A under similar assumptions predicts an incidence rate of just over 10.

Age Specific Incidence with a Policy of No Screening

The age-specific incidence figures predicted by the model described here for cervical cancer under a no screening policy are compared with the equivalent figures predicted by the model described in the AHCPR report. The incidences predicted by the two models are shown in Figure 3, which shows that the two models predict virtually the same pattern of incidence over a lifetime.

Figure 3 Age Specific Incidence of Invasive Cancer Predicted by the UK Model and the AHCPR Model in the Absence of Screening

Age Specific Incidence with a Policy of Screening Every 5 Years

The age specific incidence figures for cervical cancer under a policy of screening every 5 years predicted by the model are compared with the equivalent figures from the Trent Cancer Registry for 1993.[115] These incidence figures are shown in Figure 4. Rather than settle to a constant level, the age-specific incidence rises gradually over time. There is a similar rise and subsequent decline of incidence in the older age groups. In the model this arises from the discontinuation of regular screening at 64 years of age - this may also be true in practice.

Figure 4 Age Specific Incidence of Invasive Cancer Predicted by the UK Model Under a 3 Year Screening Policy and Current Reported Incidence

Test Programme Characteristics

The distribution of test results as a proportion of all tests predicted by the model is compared with the distribution as reported by the NHSCSP,[5] and the results are shown in Table 16. As can be seen, despite the good overall prediction of invasive cancer incidence under screening, the predicted distribution of test results underestimates the number of borderline/mild and moderate/severe test results. The most likely implication of this underestimation, together with the good prediction of overall incidence, is that the baseline test specificity used within the model is too high. Indeed, if the specificity is revised as shown in Table 16, the predicted number of tests matches almost exactly the actual recorded distribution. If this is the source of the discrepancy, then the benefits from screening will remain unchanged (morbidity from unnecessary testing excluded) though the costs associated with smear tests and colposcopies will rise. However, since there is little strong evidence to suggest that the specificity of liquid based testing is improved compared to conventional screening (whatever level is set), the impact on the relative costs and cost effectiveness of liquid cytology versus conventional screening is small.

Table 16 Predicted versus Actual Distribution of Test Results

	Specificity	Negative	Bordeline / mild	Severe
NHSCSP Statistics	?	93.0%	5.5%	1.5%
UK model	Baseline 96.6%	95.3%	3.6%	1.0%
Revised UK model	94%	92.8%	5.2%	2.0%

Modelling results

The results are presented in three sections. The first section describes the baseline results obtained by analyzing the model using the most likely values for each input parameter. The second section presents the results of the deterministic sensitivity analyses, which involve the analysis of the model with only single, or limited combinations, of parameters being changed to assess the impact on the baseline results. Finally, the results of a fully stochastic analysis of the model is presented in which a distribution of the models outputs are obtained by analyzing the model allowing all parameters to vary between the ranges specified in Tables 13 and 15.

Baseline results

Health Outcomes

The key cervical cancer screening programme health outcomes are summarised in Table 17. The interventions are set out in increasing order of effectiveness and where incremental outcomes are given these are incremental over the immediately preceding intervention.

Table 17 Key Health Outcomes arising from the Introduction of Liquid-based Cytology

		Annual incidence of invasive cancer	Percentage of women who have invasive cancer	Percentage of all deaths from cancer	Incremental life days gained	Incremental life days gained (discounted)
No screening		0.0534%	3.4213%	1.73%		
Screening At 5 years	Conventional	0.0152%	0.9765%	0.08%	126.45	56.77
	Liquid-based	0.0119%	0.7662%	0.04%	3.09	1.48
Screening At 3 years	Conventional	0.0116%	0.7491%	0.03%	1.26	0.63
	Liquid-based	0.0098%	0.6333%	0.01%	1.18	0.58
Screening 2 years	Conventional	0.0101%	0.6508%	0.02%	0.14	0.08
	Liquid-based	0.0091%	0.5845%	0.01%	0.51	0.25

Conventional screening at three to five years is predicted to reduce the annual incidence of cervical cancer from approximately 53 per 100,000 women per annum to between 12 and 15 per 100,000 per annum, this prediction compares well with the actual incidence currently recorded. The introduction of liquid-based cytology techniques has the potential to reduce this incidence to between 10 and 12 per 100,000 women per annum.

Conventional screening at a 5-year interval is estimated to increase the life expectancy of the average 18-year-old women by around 126 days (undiscounted). Compared to conventional pap smear testing, liquid-based screening at five year intervals is estimated to reduce the incidence of cervical cancer and increase life expectancy, however this improvement does not match the improvement expected from moving from a five-year to a three-year screening interval with conventional screening.

Liquid based cytology screening over a two-year interval would save the greatest number of life-days (over 132 undiscounted, 60 discounted).

Resource Usage

Liquid-based cytology techniques reduce the average lifetime number of smear tests for a woman primarily from the reduction in inadequate slide production and consequential reduction in rescreening. The average number of colposcopies is expected to increase as the number of borderline+ screening test results increases. Table 18 presents the expected lifetime number of screens and colposcopies for an 18-year-old woman. Note that this presents a health commissioning perspective and therefore includes the whole population, not just individuals who attend screening.

Table 18 Average Lifetime Resource Usage Per Woman

		Number of smear tests	Number of colposcopies
No screening		--	--
Screening at 5 years	Conventional	8.42	0.10
	Liquid-based	7.84	0.11
Screening at 3 years	Conventional	13.99	0.14
	Liquid-based	13.02	0.14
Screening at 2 years	Conventional	20.51	0.18
	Liquid-based	19.08	0.18

Health Economic Outcomes

The incremental costs per invasive cancer avoided for the primary screening options under consideration are presented in Table 19. These results show that, for screening intervals of both 3- and 5-years, conventional pap smear testing is extendedly dominated by liquid based cytology, e.g. 5-yearly liquid based cytology screening has a lower incremental cost-effectiveness ratio compared to 5-yearly conventional pap smear screening, than the latter option has compared to no screening.

The presentation of both average and incremental cost-effectiveness ratios illustrates that, compared to conventional screening at 5 years, all of the other screening options appear cost-effective. However, when the appropriate incremental approach to defining cost-effectiveness is estimated, it is apparent that conventional pap smear testing is dominated, and that liquid-based cytology screening at 5-year intervals is not a cost-effective option.

Table 19 Incremental Cost Per Invasive Cancer Avoided

		Invasive cancers (per 100,000 population)	Total cost	Average cost per cancer avoided*	Incremental cost per cancer avoided†	Extendedly dominated options excluded‡
No screening		3421	£315,139			
Screening at 5 years	Conv	977	£6,097,143		£2,365	
	LBC	766	£6,076,121	Dominant	Dominant	£2,170
Screening at 3 years	Conv	749	£9,288,541	£14,034	£187,539	
	LBC	633	£9,251,014	£9,190	Dominant	£23,889
Screening at 2 years	Conv	651	£13,228,210	£21,896	Dominated	
	LBC	584	£13,164,750	£18,028	Dominant	£80,092

Costs discounted at 6%, invasive cancer not discounted.
Conv = conventional pap smear testing.
* Compared to conventional screening at 5 years.
† Each screening option is compared to next less costly option, e.g. LBC screening every 5 years is compared to conventional pap smear testing every five years, conventional pap smear testing every 5 years is compared to no screening.
‡ Options are extendedly dominated if the following option has a lower incremental cost-effectiveness ratio (i.e. the next option would always be chosen if the dominated option were chosen).

Table 20 presents the cost per life year gained for the screening options being analysed. The options are arranged in order of increasing effectiveness, and incremental cost-effectiveness is shown. The results show that all of the conventional pap smear screening options are extendedly dominated, and when the cost-effectiveness ratios are re-estimated to exclude dominated options, screening at a regular interval of three years using liquid based cytology is cost-effective, whilst screening at 2-year intervals approaches a reasonable level of cost-effectiveness.

Table 20 Cost Per Life Year Gained of Cervical Cancer Screening Interventions

		Lifetime cost*	Incremental life years gained*	Average cost per life year gained†	Incremental cost per life year gained‡	Extendedly dominated options excluded¶
No screening		£315,139				
Screening At 5 years	Conv	£6,097,143	15553		£372	
	LBC	£6,076,121	405	Dominant	Dominant	£361
Screening At 3 years	Conv	£9,288,541	172	£7,874	£18,685	
	LBC	£9,251,014	158	£7,781	Dominant	£9,621
Screening At 2 years	Conv	£13,228,210	23	£17,594	£175,596	
	LBC	£13,164,750	69	£17,437	Dominant	£42,882

Costs discounted at 6%, life years discounted at 1.5%
* per 100,000 women (uptake rate 85%).
† Compared to conventional pap smear testing at 5-yearly intervals
‡ Each screening option is compared to next less costly option, e.g. LBC screening every 5 years is compared to conventional pap smear testing every five years, conventional pap smear testing every 5 years is compared to no screening.
¶ Options are extendedly dominated if the following option has a lower incremental cost-effectiveness ratio (i.e. the next option would always be chosen if the dominated option were chosen).

Deterministic sensitivity analysis

Disease Natural History

Table 21 describes the impact on the cost per life year saved of decreasing and increasing the incidence rates for CIN1. The main result of this sensitivity analysis is that if incidence of CIN is 25% higher then 2-yearly screens using liquid based cytology would be cost-effective assuming a £30,000 threshold for the acceptable cost of gaining an additional life year.

Table 21 Sensitivity Analysis for CIN1 Incidence Rates

		Incremental cost per life year gained*		
Disease progression		75%	Baseline	125%
No screening		--	--	--
Screening at 5 years	Conventional	£641	£372	£247
	Liquid-based	Dominant (£622)	Dominant (£361)	Dominant (£241)
Screening at 3 years	Conventional	£33,076	£18,685	£12,024
	Liquid-based	Dominant (£16,961)	Dominant (£9,621)	Dominant (£6,225)
Screening at 2 years	Conventional	£311,665	£175,596	£112,610
	Liquid-based	Dominant (£75,781)	Dominant (£42,882)	Dominant (£27,657)

* cost-effectiveness ratios comparing screening options to next less costly option are presented, in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

As noted above, there is some evidence that CIN2 and CIN3 lesions can regress.[107] Table 22 presents the results of analyses incorporating the possibility of such regressions to a clear state. Such data assumptions reduce the cost-effectiveness of screening, though the impact is minimal.

Table 22 Sensitivity Analysis for Disease Regression Rates (from CIN2 and CIN3)

		Incremental cost per life year gained*	
Disease progression		Regression from CIN2 (1.5%) and CIN3 (1.1%)	Baseline
No screening		--	--
Screening at 5 years	Conventional	£489	£372
	Liquid-based	Dominant (£475)	Dominant (£361)
Screening at 3 years	Conventional	£21,174	£18,685
	Liquid-based	Dominant (£11,065)	Dominant (£9,621)
Screening at 2 years	Conventional	£182,741	£175,596
	Liquid-based	Dominant (£47,578)	Dominant (£42,882)

* cost-effectiveness ratios comparing screening options to next less costly option are presented, in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

There is no direct, and little indirect evidence regarding the natural history of cervical cancer in terms of the progression rates between pre-invasive states. What evidence does exist has been generated from the fitting of mathematical models, such as the one described here, where the structure is based upon a hypothesised course for the disease. The impact of doubling and halving the disease progression rates is examined in Table 23. Reducing the progression rates increases the revised cost-effectiveness ratio for 3-yearly liquid-based cytology screening quite substantially, such that 5-yearly screening could be the most cost-effective option.

Table 23 Sensitivity Analysis for Disease Progression Rates

		Incremental cost per life year gained*		
Disease progression		50%	Baseline	150%
No screening		--	--	--
Screening at 5 years	Conventional	£904	£372	£249
	Liquid-based	£121 (£886)	Dominant (£361)	Dominant (£240)
Screening at 3 years	Conventional	£64,815	£18,685	£9,978
	Liquid-based	Dominant (£30,895)	Dominant (£9,621)	Dominant (£5,360)
Screening at 2 years	Conventional	£951,937	£175,596	£74,917
	Liquid-based	Dominant (£152,767)	Dominant (£42,882)	Dominant (£22,311)

* cost-effectiveness ratios comparing screening options to next less costly option are presented, in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

Sensitivity Analysis for Test Characteristics

The impact of uncertainty concerning the improvements in test sensitivity obtained from liquid-based cytology based screening is presented in Table 24. These results show that liquid based cytology is a more cost-effective option at 3- and 2-yearly screening intervals when sensitivity is lower than when the higher estimates of sensitivity are used. This is because, at the higher sensitivity rates, there are fewer missed cases when screening at 5-yearly intervals. Indeed, a 2-yearly screening programme may be cost-effective if the lower rates of liquid-based cytology sensitivity are proven.

Table 24 Sensitivity Analysis for Improvement in Test Sensitivity of Liquid-based cytology

		Incremental cost per life year gained*		
Sensitivity improvement CIN1/CIN2 CIN3		6.8% 2%	Baseline 13.4% 4%	20% 6%
No screening		--	--	--
Screening at 5 years	Conventional	£372	£372	£372
	Liquid-based	Dominant (£365)	Dominant (£361)	Dominant (£358)
Screening at 3 years	Conventional	£9,106	£18,685	£126,123
	Liquid-based	Dominant (£7,140)	Dominant (£9,621)	Dominant (£13,590)
Screening at 2 years	Conventional	£44,192	£175,596	Dominated
	Liquid-based	Dominant (£29,984)	Dominant (£42,882)	Dominant (£64,015)

* cost-effectiveness ratios comparing screening options to next less costly option are presented, in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

There remains some uncertainty around the sensitivity rates associated with conventional pap smear testing, such that the impact of alternative assumptions regarding these rates are tested in Table 25. These results show that if sensitivity is better than assumed in the baseline (lower false negative rate), liquid-based cytology becomes relatively less cost-effective though similar conclusions may be reached about 3-yearly liquid-based cytology screening being the most cost-effective option. However, if pap smear testing is less sensitive that assumed in the baseline, then 2-yearly liquid-based cytology screening may be cost-effective.

Table 25 Sensitivity Analysis for Improvement in Test Sensitivity of Conventional Pap Smear Testing

		Incremental cost per life year gained*		
Sensitivity† CIN1 FNR CIN2 FNR CIN3 FNR		20% 40% 20%	Baseline 34% 59% 36%	48% 78% 52%
No screening		--	--	--
Screening at 5 years	Conventional	£367	£372	£379
	Liquid-based	Dominant (£358)	Dominant (£361)	Dominant (£365)
Screening at 3 years	Conventional	£29,566	£18,685	£12,748
	Liquid-based	Dominant (£14,475)	Dominant (£9,621)	Dominant (£6,672)
Screening at 2 years	Conventional	£340,503	£175,596	£108,196
	Liquid-based	Dominant (£70,048)	Dominant (£42,882)	Dominant (£27,091)

* cost-effectiveness ratios comparing screening options to next less costly option are presented, in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.
† FNR = false negative rate

The impact of uncertainty concerning improvements in the rate of inadequate cervical smears, as well as the combination of test inadequacy and low and high sensitivity rates for liquid based cytology, is presented in Table 26. These results show that the inadequacy rate has only a small impact on the cost-effectiveness results.

Table 26 Sensitivity Analysis for Improvement in Test Adequacy

		Incremental cost per life year gained*			
% improvement in inadequacy rate		0%	0%	0%	Baseline 9% to 1.4%
Sens improvement CIN1/CIN2 CIN3/cancer		Baseline 13.4% 4%	 6.8% 2%	 20% 6%	Baseline 13.4% 4%
No screening				--	--
Screening at 5 years	Conv	£372	£372	£372	£372
	LBC	£925	£1,634	£699	Dominant (£361)
Screening at 3 years	Conv	£16,382	£7,987	£110,520	£18,685
	LBC	£3,699 (£10,306)	£6,327 (£7,649)	£2,865 (£14,558)	Dominant (£9,621)
Screening at 2 years	Conv	£148,122	£37,300	Dominated	£175,596
	LBC	£12,216 (£45,944)	£20,517 (£32,126)	£9,575 (£68,585)	Dominant (£42,882)

* cost-effectiveness ratios comparing screening options to next less costly option are presented, in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

Sensitivity Analysis for Costs

The impact of uncertainty concerning the increase in marginal costs arising from the introduction of liquid-based cytology is presented in Table 27. Using the upper bound of the estimated costs for liquid-based cytology does not greatly affect relative cost-effectiveness.

Table 27 Sensitivity Analysis for Marginal Sample Cost for Liquid-based Cytology

		Incremental cost per life year gained*		
Marginal cost of liquid-based cytology		-£1.15	Baseline £1.45	£6.50
No screening		--	--	--
Screening at 5 years	Conventional	£372	£372	£372
	Liquid-based	Dominant (£324)	Dominant (£361)	£2,795
Screening at 3 years	Conventional	£22,141	£18,685	£11,973
	Liquid-based	Dominant (£8,592)	Dominant (£9,621)	£11,234 (£11,619)
Screening at 2 years	Conventional	£216,818	£175,596	£95,530
	Liquid-based	Dominant (£38,287)	Dominant (£42,882)	£37,372 (£51,805)

* cost-effectiveness ratios comparing screening options to next less costly option are presented, in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

Sensitivity Analysis for Discounting of Costs and Life Years Gained

The impact of different assumption concerning the discounting of costs and life years gained are presented in Table 28. It can be seen that discounting assumptions, especially regarding the discounting of life years gained, have a marked impact on the potential cost-effectiveness of both conventional and liquid-based cytology techniques. Nevertheless, liquid-based cytology at a screening interval of five years still remains a cost-effective option under all discounting options. The importance of the discounting assumptions arises from the fact that most benefits are distant in the future relative to screening costs. This is especially true when estimating the expected life costs at the age of 18 years. The impact of discounting would be expected to lessen as you

estimated the remaining life benefits at increasing ages. This would tend to increase the relative benefits to be obtained from screening at reduced intervals at ages where incidence of pre-invasive disease is highest. A two-way sensitivity analysis for the marginal costs arising from the introduction of liquid-based cytology and discounting assumptions is also presented in Table 28.

Table 28 Sensitivity Analysis for Discount Rates

		Incremental Cost Per Life Year Gained*			
Discount factors	Cost Life years	0% 0%	6% 1.5%	6% 6%	0% 0%
Additional cost of LBC		Baseline (£1.45)	Baseline (£1.45)	Baseline (£1.45)	£6.50
No screening		--	--	--	--
Screening at 5 years	Conventional	£515	£372	£3,040	£9,381
	Liquid-based	Dominant (£494)	Dominant (£361)	Dominant (£2,929)	£56,463
Screening at 3 years	Conventional	£36,923	£18,685	£104,141	£283,666
	Liquid-based	Dominant (£18,611)	Dominant (£9,621)	Dominant (£54,156)	£225,447 (£256,080)
Screening at 2 years	Conventional	£404,821	£175,596	£680,433	£1,441,093
	Liquid-based	Dominant (£82,548)	Dominant (£42,882)	Dominant (£213,853)	£744,249 (£966,811)

* cost-effectiveness ratios comparing screening options to next less costly option are presented, in cases of dominance the revised ratio excluding the dominated option is presented in parentheses.

The final deterministic sensitivity analysis tested the impact of the effects of the screening programme on women's quality of life. These analyses assumed that quality of life could be affected in three ways. Firstly, women with invasive cancer are assumed to experience reduced quality of life for the remainder of their life. Secondly, women who undergo a colposcopy following an abnormal screening result (regardless of the outcome of the colposcopy) are assumed to experience a temporary decrease in their quality of life. Thirdly, women who receive a borderline result following screening for cervical cancer (which is subsequently followed by a clear result) are also assumed to experience a temporary decrease in their quality of life.

Table ?? presents the results of analyses in which a range of assumptions regarding the possible utility decrement associated with abnormal screen results and subsequent treatment. These results show that if abnormal screening results have a disutility effect on women, then the likelihood of a 5-yearly screening interval being the optimal screening option is substantially increased. Assuming a single annual utility decrement of 2% for women experiencing a borderline result followed by a clear result, and a 3% decrement for women undergoing a colposcopy, the incremental cost per QALY of moving from a 5-yearly screening programme (with liquid-based cytology) to a 3-yearly liquid-based cytology screening programme is over £30,000.

Table 24 Sensitivity Analysis for quality of life impact of screening

		Incremental cost per QALY gained			
Utility values*		IC – 0.6 B'line – 0.95 Colp'y – 0.9	IC – 0.6 B'line – 0.975 Colp'y – 0.95	IC – 0.6 B'line – 0.98 Colp'y – 0.97	Baseline: no utility adjustments
No screening		--	--	--	--
Screening at 5 years	Conv	£266	£253	£250	£372
	LBC	Dominant (£258)	Dominant (£246)	Dominant (£243)	Dominant (£361)
Screening at 3 years	Conv	Dominated	Dominated	Dominated	£18,685
	LBC	Dominated	Dominated	Dominant (£31,005)	Dominant (£9,621)
Screening at 2 years	Conv	Dominated	Dominated	Dominated	£175,596
	LBC	Dominated	Dominated	Dominated	Dominant (£42,882)

* The utility value for invasive cancer (IC) is applied over the remainder of a women's life, whilst the utility values for receiving a borderline (B'line) or colposcopy (Colp'y) are only applied to the year in which the event occurs.

Stochastic sensitivity analysis

To analyse the combined effect of uncertainty in all the input parameters on the baseline results a stochastic analysis of the model was undertaken in which the input parameters were allowed to vary between the ranges specified in Tables 13 and 15. The uncertainty in around each parameter was described in the form of a triangular distribution, whereby the range for each parameter informed the minimum and maximum values for each distribution. Model outputs were obtained for 5000 separate iterations, each informed by a random sample of input parameters from the specified distributions.

Table 31 shows the mean estimates of cost-effectiveness, as well as the 2.5^{th} and 97.5^{th} percentile for all possible incremental comparisons between the available screening options. Of particular interest is the noted range of cost-effectiveness when liquid based cytology screening at 5-yearly intervals is compared to liquid based cytology screening at 3-year intervals (if conventional Pap smear testing at 3-yearly intervals is excluded), which shows that the upper limit is £54,143. the incremental cost-effectiveness ratio for liquid based cytology screening at 2-yearly intervals is even more left-skewed, showing an upper limit of over £260,000.

Table 31 Mean and confidence limit estimates from stochastic analysis

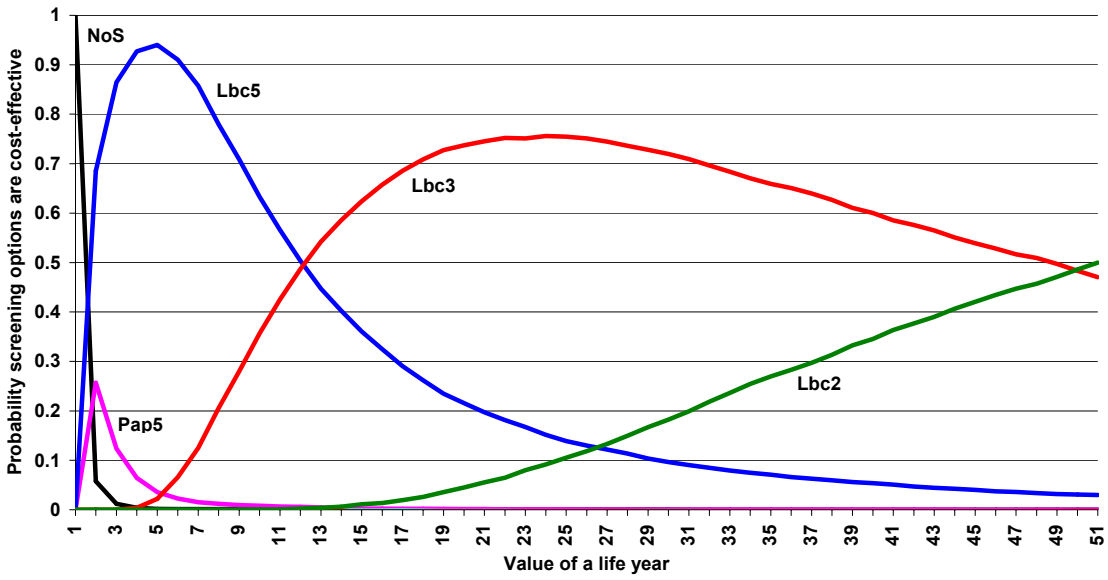
From:	To:	Mean*	2.5th%*	97.5th%*
No screening	Pap 5-yearly	£370	£202	£1,409
Pap 5-yearly	LBC 5-yearly	Dominant	Dominant	£4,809
No screening	LBC 5-yearly	£360	£201	£1,433
LBC 5-yearly	Pap 3-yearly	£18,616	£6,331	£128,958
Pap 3-yearly	LBC 3-yearly	Dominant	Dominant	£20,175
LBC 5-yearly	LBC 3-yearly	£9,585	£4,082	£54,143
LBC 3-yearly	Pap 2-yearly	£174,945	£37,579	Dominated
Pap 2-yearly	LBC 2-yearly	Dominant	Dominant	£68,095
LBC 3-yearly	LBC 2-yearly	£42,723	£16,854	£262,475

* Dominant indicates that the 'To:' option is less costly and more effective than the 'From:' option, e.g. for the mean values, LBC 5-yearly is less costly and more effective than Pap 5-yearly.

The results of the stochastic analysis are also presented in the form of a cost-effectiveness acceptability curve, which describes the probability that each of the available screening options will be the optimal screening programme at different levels of willingness to pay to gain an additional life year. This curve is estimated by defining the optimal programme within each of the 5000 iterations undertaken to inform the stochastic analysis, on the basis of the programme with the highest incremental net benefits at each willingness to pay level. The estimated acceptability curve is presented in Figure 5.

The acceptability curve shows that at low levels of willingness to pay to gain life years, up to around £10,000, the model predicts that liquid based cytology screening every five years is most likely to be the most cost-effective option. At willingness to pay levels between around £10,000 and £50,000 liquid based cytology screening every 3 years has the highest probabilities of being cost-effective, whilst at levels above £50,000 liquid based cytology screening at 2-yearly intervals becomes the most likely cost-effective option.

Figure 5 **Cost effectiveness acceptability curve for alternative screening options for cervical cancer screening**



Conclusions of economic modelling analysis

Simplifying assumptions have been incorporated into the modelling analysis of the cost-effectiveness of alternative cervical screening options, such as the use of constant rates of progression between alternative CIN stages and invasive cancer, and the assumption of 100% sensitivity and specificity of colposcopy. Also, morbidity and mortality associated with invasive cancer have been modelled crudely, specifically the costs are underestimated and survival overestimated for the highest grade cancers, again this would introduce a small bias against improved screening techniques.

However, since the original modeling analysis reported in the earlier HTA report, more certain estimates of the cost per slide associated with both conventional pap smear testing and the new liquid based cytology screening techniques, as well as more concrete estimates of the relative inadequacy rates associated with the two techniques have become available.[1] The baseline results with these new data indicate that liquid based cytology is a cost-effective alternative to conventional pap smear screening at all three screening intervals, and that comparing liquid based cytology across the screening intervals indicates that a 3-year interval is almost certainly cost-effective compared to a 5-year interval. A number of the analyses indicate that, using liquid based cytology, a 2-year interval may well be cost-effective.

The stochastic sensitivity analysis describes the impact of the total uncertainty in the model by varying all parameters simultaneously to define a distribution of the models outputs that can be analysed statistically. The results of the stochastic analysis show that liquid based cytology screening at 3 yearly intervals is the most likely cost-effective option if society is willing to spend between £10,000 and £50,000 to gain additional life years.

The main economic analysis uses the number of life years saved by alternative screening options as the main measure of health benefits, rather than the preferred measure of quality adjusted life years (QALYs), due to the uncertainties surrounding utility values associated with the various health states associated with cervical cancer and screening, for example, no reliable work has been undertaken to estimate the utility effects of alternative screening test results, nor the impact of being in a pre-symptomatic cancer state. However, a range of utility

decrements associated with the screening outcomes borderline result followed by a clear result, and the experience of a colposcopy, as well as estimating a utility value for women diagnosed with cervical cancer. The results of these analyses show that the utility decrements had a significant impact on the choice of screening interval, whereby seemingly small utility decrements resulted in liquid based cytology screening at 3-year intervals producing fewer QALYs at greater cost than liquid based cytology screening at 5 year intervals.

6. Conclusions

Implications of screening tests

Financial impact for patients and others

The potential benefits to women screened, in addition to potential reduction of invasive cancer and of mortality, include reduced anxiety associated with a reduced need for repeat screening due to inadequate specimens, and associated reductions in traveling and related expenses. No attempt has been made to quantify these benefits in the reported economic analyses.

Society and legal implications

Problems in relation to cervical screening have resulted in litigation. While there is a potential to reduce payments for damages and associated litigation costs if false-negative results are reduced, liquid based cytology will have a sensitivity that is not perfect, so false-negative results will still occur. There has been no attempt to quantify benefits with respect to reduced litigation costs in the reported economic analyses.

Health targets

Reduction in cancer mortality is a key target in the Our Healthier Nation initiative.[116]

Fair access and equity issues

The uptake of cervical screening is not uniform across the country and some disadvantaged groups of the population are said to have lower utilization rates. Improvements in cervical cytology methods should be considered alongside ways to improve uptake and to make provision of this service more equitable.

Dissemination and implementation

It is not within the scope of this report to produce a detailed dissemination and implementation plan for the NHS for liquid based cytology. If a decision is made to adopt liquid based cytology then such a plan would be needed, which would need to consider aspects such as training, workforce planning, quality management, and the relevant logistics (e.g. storage space).

Recommendations

This updated analysis provides more certainty with regard to the potential cost-effectiveness of liquid-based cytology compared to conventional pap smear testing. A full cost-effectiveness study of liquid-based cytology based on a trial of its introduction in low-prevalence population would provide more definitive information than is possible by modelling studies, though the results of the modelling analysis provide a robust argument that liquid-based cytology is a cost-effective alternative to conventional cervical cancer screening, such that the large expenditure required to fund a trial is probably not justified.

However, as described in Chapter 4, a range of economic evaluations were identified in the updated systematic search (1999-2002) that assessed the economic impact of cervical screening approaches other than conventional pap smear testing and liquid-based cytology techniques, including semi-automated slide analysis, HPV testing as an adjunct or alternative to pap smear testing, and protocols for the management of atypical screen results.

The aggregate analysis of the cost-effectiveness of potential combinations of these approaches to screening for cervical cancer are outside the scope of the current review, though it is noted that the relative cost-effectiveness of all relevant screening programme configurations should be analysed simultaneously.

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Appendix 1 Search Strategy

1999-2002, Ovid Biomed; Searches undertaken October 2002

Medline – sensitivity/specificity search

Cervix neoplasms/
Cervical intraepithelial neoplasia/
Cervix dysplasia/
Vaginal smears/
Cytological techniques/
Histocytological preparation techniques/
Cytodiagnosis/
Or/1-7
Fluid based.tw
Thinlayer.tw
Thinprep.tw
(Thin adj3 prep$).tw
(Thin adj3 layer$).tw
Monolayer$.tw
(Mono adj3 layer$).tw
Liquid$.tw
Cytyc.tw
Cytorich.tw
Cyto rich.tw
Autocyte prep.tw
Or/9-20
Exp "Sensitivity and specificity"/
Sensitivity.tw
Exp Diagnosis/
Exp Pathology/
Specificity.tw
Or/22-26
8 and 21 and 27

Medline – economics search

Cervix neoplasms/
Cervical intraepithelial neoplasia/
Cervix dysplasia/
Vaginal smears/
Di.fs
Exp diagnosis/
or/1-3
5 or 6
7 and 8
4 or 9
Fluid based.tw
Thinlayer.tw
Thinprep.tw
(Thin adj3 prep$).tw
(Thin) adj3 (layer$).tw
Monolayer$.tw
(Mono adj3 layer$).tw
Liquid$.tw
Cytyc.tw
Cytorich.tw
Cyto rich.tw
Autocyte prep.tw
Or/11-22
10 and 23
Economics/
Exp "Costs and cost analysis"/

Economic value of life/
Exp Economics, hospital/
Exp Economics, medical/
Economics, nursing/
Exp models, economic/
Economics, pharmaceutical/
Exp “Fees and charges”/
Exp Budgets/
Ec.fs
(Cost or costs or costed or costly or costing$).tw
(Economic$ or pharmacoeconomic$ or price$ or pricing).tw
Or/25-37
24 and 38

Medline – Modelling search

Vaginal smears/
Cervix neoplasms/
Cytodiagnosis/
Mass screening/
3 or 4
2 and 5
1 or 6
Models, theoretical/
Models, organizational/
Exp models, statistical/
Markov Chains/
Or/8-11
7 and 12

Appendix 2 Systematic review of economic evaluations of liquid based cytology techniques

Table A2 Review of economic evaluations included in original LBC review

Study	Brown & Garber, 1999	AHCPR, 1999/ Myers et al, 2000a & b*	Australian Health Technology Advisory Committee, 1998
Title	Cost-effectiveness of Three Methods to Enhance the Sensitivity of Papanicolaou Testing.	Evaluation of Cervical Cytology/ Setting the target for a better cervical screening test: characteristics of a cost-effective tests for cervical neoplasia screening	Review of Automated and Semi-Automated Cervical Screening Devices.
A statement of the problem	Evaluation of cost-effectiveness of ThinPrep as a primary screen with 10% random rescreening, and AutoPap and Papnet as rescreening selection devices, compared to conventional pap smear testing with 10% random rescreening and no screening.	What are the ranges of incremental cost, sensitivity and screening frequency that meet conventional levels of cost per life year saved (defined as US$50,000) for technologies that improve conventional test performance by 1) improving the sensitivity of the initial screening step or 2) allowing 100% rescreening at improved sensitivity.	To provide an estimate of the potential additional costs and benefits of the use of automated and semi-automated technologies in a two-year screening cycle. Slide preparation and automated rescreening devices are not considered separately. The analysis aims to investigate the likely performance of a generic technology for improving test characteristics compared with a baseline conventional test screening.
A discussion of the need for modelling.	Implied by the lack of empirical economic evidence though not stated directly.	Systematic search undertaken for economic evidence.	A dearth of health economic evidence for the monolayer technologies identified through a systematic search.
A description of the relevant factors and outcomes	Factors included: disease incidence and progression, age dependent; regression of pre-invasive lesions; test characteristics; success of treatment for diagnosed abnormalities, stage dependent; all cause mortality; costs of screening and treatment. Health benefits are	Factors include: age-specific prevalence of HVP infection, LSIL and HSIL; progression and regression rates associated with HPV infection, LSIL and HSIL; test characteristics; unrelated mortality and hysterectomy rates; diagnosis and treatment management strategies; stage-specific treatment success rates; stage-specific cancer survival; screening and treatment costs. Health benefits are life years saved.	Factors included: increase in low and high grade abnormalities detected; progression of low- and high-grade lesions to invasive cancer. Health benefits are measured in terms of 'additional cancer cases detected'.
A description of model including: type of model; time frame; perspective; and setting	Nine state, time varying state transition model is used to model the life experience of cohort of women aged 20 to 65. The model used is not fully described but is attributed to Eddy[83,85] A societal perspective is used to analyse costs. A rate of 3% (0-5%) is used to discount both health benefits and costs.	A twenty state Markov model of the natural history of cervical cancer with an intervention model of possible screening strategies is used to model the life experience of cohort of women from age 15 to 85. A direct health care perspective is used to analyse costs. A rate of 3% (0-5%) is used to discount both health benefits and costs.	A simple model for estimated the number of cancer cases potentially avoided is described.

A description of data sources, with description of respective strengths and weaknesses	Test characteristics obtained from a systematic search and review (MEDLINE, key journals were hand searched and the equipment suppliers were contacted for unpublished evidence). Disease progression rates are not given but again referenced to Eddy. All direct costs of screening are included (training costs not included). Data from peer reviewed published articles, manufacturers publicly available documentation and survey of pathology laboratories in Northern California. Capital and training costs not included but estimated at under US$0.25 per slide and equal for all technologies. References included.[54,39] Costs of care figures from Eddy[83] updated to 1996 US dollars. Marginal consumable cost of ThinPrep $9.75	Test characteristics obtained from a systematic search and review (MEDLINE, CancerLit, HealthSTAR, CINAHL, EMBASE and EconLit databases. Recently published journals were handsearched and web resources were consulted). Full inclusion/exclusion criteria and results are reported and estimates of test characteristics are made. Precancerous lesions are classified according to the Bethesda system, invasive cancer is staged according to the FIGO classification system. Costs of screening, diagnosing and treating cervical cancer were estimated using private insurance claims, Medicare fee schedules and secondary data sources. Costs were adjusted to 1997 US dollars.	The model assumes that the new techniques increase the total proportion of abnormal readings whilst the distribution of these readings between grades is unchanged. A wide range of values for the relative increase in abnormalities is used. Average unit costs for treatment and diagnosis are estimated from routinely available Australian statistics. A range of generic marginal test costs is evaluated.
Key stated assumptions relating to model structure and data	All cancers develop from preinvasive lesions, which may spontaneously regress. The majority of cancers (85-90%) develop from a long preinvasive phase.	All cervical cancer arises from HPV infection. HPV can progress directly to LSIL or HSIL. HPV infection can regress to a well state, LSIL can regress to a latent HPV state or well, and HSIL can regress to LSIL, HPV or well. Women treated for SIL have a reduced progression rate. Parameter estimates were chosen to bias results in favour of improving test sensitivity. A hysterectomy state is included, though the natural history model was not corrected for hysterectomy rates.	
Definition of test results and abnormal test result threshold	Abnormal test results are categorised as LSIL, HSIL or cancer.	Abnormal test results are categorised as atypical (ASCUS or AGUS), LSIL, HSIL or cancer, though true positives based on histologic diagnosis of LSIL or worse. Invasive cancer is staged according to the FIGO classification system (stages I to IV, plus terminal care).	
Representation of inadequacy rates	No mention of differential inadequacy rates	No mention of differential inadequacy rates	
Management strategy for atypical	ASCUS results are treated as normal screens and not investigated further.	ASCUS results are rescreened within 6 months and receive colposcopy if results are abnormal.	

screening results			
Test characteristics parameters	Conventional pap smear testing, 80% sensitivity Primary ThinPrep screen, 91.9% sensitivity, with 10% random rescreening, 92.6% sensitivity. AutoPap and Papnet assisted rescreening, 95.4% and >97% (97% was assumed to be the maximum) sensitivity, respectively. Sensitivity and specificity does not differentiate between the higher disease states.	Conventional pap smear testing, 51% sensitivity 97% specificity. New technologies, sensitivity 51-99%, specificity 97-72.75%. Sensitivity and specificity does not differentiate between the higher disease states.	
Disease progression rates	Disease progression rates are not given, but referenced to Eddy.	Age-specific regression rates: HPV 70% regress over 18 months ages 15-24, 50% ages 25-29, 15% ages 30+. LSIL 90% of regressions go directly to well, 65% regress over 72 months ages 15-34, 40% ages 35+. HSIL 50% each regress to LSIL and well, 35% regress over 72 months. Progression rates: HPV to LSIL 20% over 36 months, 10% progress directly to HSIL; LSIL to HSIL 10% over 72 months ages 15-34, 35% ages 35+; HSIL to cancer 40% over 120 months.	
Screening intervals tested	1, 2, 3 and 4 years	1, 2, 3, and 5 years	
Marginal cost of new technology	ThinPrep $9.75; AutoPap $5.00; Papnet $10.00	Baseline $10, range US$0-15	
Validation	Not mentioned	Model predicted peak cancer incidence and age-specific incidence curves similar to referenced unscreened populations. Age-specific prevalence of HPV, LSIL and HSIL are consistent with cross-sectional data.	
Results	Pap smear with AutoPap-assisted rescreen is the most cost-effective option for all intervals above 1 year (conventional pap smears are cost-effective for a 1-year interval). Comparison between screening intervals presented diagrammatically – assuming a $50k threshold, AutoPap-assisted rescreen testing every 4 years is most cost-effective option.	Comparing different sensitivity rates separately across increasing screening intervals (with threshold of $50k) a test with baseline sensitivity (51%) the optimal interval is 2 years, if sensitivity is increased to 75% the optimal interval is 3 years.	
Sensitivity analysis results	Parameters: range of population (e.g. risk of cancer, ages screened) and test characteristics, and treatment costs and discount rate. Cancer incidence has largest effect of the population parameters. If sensitivity of conventional screening were 50% (commonly assumed by other studies)	Parameters: sensitivity, specificity, and screening cost. Threshold analyses for combinations of sensitivity and specificity are presented for separate screening intervals, e.g. for a 3-year interval, to get under the $50k threshold a new technology would need to	

	AutoPap rescreening would dominate conventional screening. ThinPrep is cost-effective if additional sensitivity is 50% higher than baseline assumption.	increase sensitivity by 45% and not lose more than around 10% specificity.	
Discussion	Results are not sensitive to al but the largest changes in test characteristics, though such changes are within the reported ranges. The discussion centres on rescreening strategies (as ThinPrep primary screening is shown to be non-cost-effective). Previous work is cited that implies manual rescreening of 100% tests is more cost-effective than Papnet or AutoPap. Findings may change as new ecidence on sensitivity becomes available, especially if tests differ in classification of alternatives stages of abnormality. ThinPrep may be used to detect HPV as part of a triage system (large clinical trial mentioned – ALTS).	New tests with increased sensitivity, even with low marginal test costs, will disproportionately increase total costs relative to health benefits (life years saved), i.e. the cost-effectiveness ratio will increase relative to pap smears compared to no screening. Found that small changes in test specificity can have a great impact on cost-effectiveness. Documentation of specificity is essential. The impact of morbidity on quality of life may be incorporated by linking treatment data to different stages of cervical cancer. It is also necessary to account for false positives on quality of life. Main message: improved sensitivity is not enough for a new test to be cost-effective. New tests based on specific HPV types or that use biomarkers might improve specificity, reduce screening frequency, and can be used in conjunction with less expensive treatments of low-grade abnormalities.	

* Myers et al presents the results of the AHCPR analysis in a peer-reviewed journal.

Table A2 (cont.) Review of economic evaluations identified in addition to those included in original LBC review

Study	Hutchinson et al, 2000	Montz et al, 2001	Raab et al, 1999
Title	Clinical and cost implications of new technologies for cervical cancer screening: the impact of test sensitivity	Impact of increasing Papanicolaou sensitivity and compliance: a modelled cost and outcome analysis	The cost-effectiveness of the cytology laboratory and new cytology technologies in cervical cancer prevention
A statement of the problem	To compare available technologies for cervical screening using actual program utilisation patterns (for validation). New technologies are conventional screening with Autopap selected rescreening, conventional screening with AutoPap pre-screening, ThinPrep primary testing with 10% rescreening.	To model the impact of increasing screening compliance or implementing liquid-based cytology in populations with known compliance patterns and risk profiles on rates of detection of cervical precancers, compared to conventional Pap smear testing with 10% random rescreening.	To study the cost-effectiveness component of the laboratory in cervicovaginal screening, and to assess how cost-effectiveness changed with the introduction of new technologies. Cost-effectiveness is assessed using laboratory-based costs alone, and overall costs.
A discussion of the need for modelling	Implied by the lack of empirical economic evidence though not stated directly.	Implied by the lack of empirical economic evidence though not stated directly.	Due to the need to incorporate treatment and follow-up costs and probabilities in the determination of the overall cost-effectiveness of screening.
A description of the relevant factors and outcomes	Factors include: age-specific hysterectomy rates; test characteristics; age-specific incidence of CIN lesions; progression and regression of CIN lesions; compliance rates; incidence rates by stage; age-specific deaths in screened and unscreened cohorts; screening and treatment costs. Health benefits are the average incidence of cervical cancer over the course of screening and life years saved.	As for Hutchinson et al, 2000	Factors include: distribution of screening results; progression of HSIL to cancer (total and within 1 year); stage of cancer at diagnosis; probability of HSIL given alternative atypical screening results, stage-specific life expectancies; screening and treatment costs; increase in HSIL diagnoses required for new technologies to be cost-effective. Health effects are cancers developing, false positive results, and life expectancy.
A description of model including: type of model; time frame; perspective; and setting	A Markov model describes progression from a screening pool to four test result states (true and false positive and negative), as well as to cancer diagnosis, hysterectomy and non-cancer death. Other states describe progression from cancer treatment (1-cycle tunnel state) and cancer survival to further survival or death. Women aged 20-65 are included. Natural history of cervical cancer includes only two precancer stages: CIN and CIS. A payer perspective included only medical costs and health benefits. Costs and outcomes are both discounted at 3%.	As for Hutchinson et al, 2000	Unclear what type of model is used, but could be decision tree to represent one round of screening with life expectancy estimates added to endpoints. A health care perspective is implied, life expectancies discounted at 5%, but no other details of discounting are presented.
A description of data sources, with description of respective strengths and	'Widely accepted reference values are used in determining the effect [an] event or intervention may have.' No details of literature review given. Sensitivity same as baseline figures from AHCPR, age-specific CIN incidence from literature. Cancer	As for Hutchinson et al, 2000	Baseline test result distribution and laboratory costs direct from hospital records. Life expectancies from SEER and National Center for Statistics. Probability and other cost data from literature (no details of search given).

weaknesses	incidence and mortality rates from US National Cancer institute, hysterectomy rates from the Center for Disease Control. Screening compliance rates from referenced survey. Effectiveness rates for new technologies taken from manufacturers' submissions for FDA approval.		
Key stated assumptions relating to model structure and data	Women treated for CIN or CIS are returned to the screening pool. CIN and CIS lesions can both regress. Differentiate between preparation error (abnormal cells not represented) and screening error (abnormal cells present but missed) (which occur in a ratio of 3:1).	As for Hutchinson et al, 2000	Sampling or screening errors do not occur (sensitivity equals 100%, though alternative techniques pick up different numbers of cases, i.e. analysis disregards missed cases).
Definition of test results and abnormal test result threshold	Positive screening results are categorised as LSIL, HSIL, AGUS, squamous cell carcinoma, or adenocarcinoma. Women with ASCUS results were referred for a second screen within a year True positive test results are categorised as all grades of CIN, carcinoma in situ or cancer.	As for Hutchinson et al, 2000	Abnormal test results are categorised as atypical (ASCUS or AGUS), LSIL, HSIL or cancer. False positives based on those not having evidence of disease on follow-up. LSILs were assumed not to progress top cancer as womassumed to have yearly smears.
Representation of inadequacy rates	Differential inadequacy rates mentioned in discussion – up to 50% reduction in inadequate screens, which if included would reduce cost-effectiveness ratio.	As for Hutchinson et al, 2000	The micro-costing of the screen costs accounted for a rescreen rate, though no differential rate is included.
Management strategy for atypical screening results	All women with a positive screening result are forwarded to colposcopy and treated appropriately. Women with ASCUS results were referred for a second screen within a year and referred for colposcopy if ASCUS or worse.	As for Hutchinson et al, 2000	LSILs and atypical screen results are not studied because it is assumed that, if they progress to HSIL, they will be picked up at the next annual screen.
Test characteristics parameters	Conventional pap smear testing, 50.4% (LSIL) & 55.2% (HSIL) sensitivity AutoPap rescreening, 55.3% (LSIL) & 52.3% (HSIL) sensitivity AutoPap pre-screening 55.2% (LSIL) & 59.2% (HSIL) sensitivity ThinPrep primary screening 75% (LSIL) & 82.2% (HSIL) sensitivity	Conventional pap smear, 51% sensitivity LBC, 73% sensitivity	False negatives are not recorded, only the difference in abnormal screens where the same proportion of abnormal screen results are assumed to represent HSIL, of which a constant proportion will progress to cancer.
Disease progression rates	Age-specific regression rates used: 65% CIN regress over 6 years ages 20-34; 40% CIN regress over 6 years ages 35+. 35% CIS lesions regress over 6 years. CIN to IS 6 years, CIS to cancer 10 years. 10% of CIN cases that progress to cancer progress within 1	As for Hutchinson et al, 2000	10% HSILs progress to cancer, 25% of the 10% progress within 1 year.

	year.		
Screening intervals tested	1, 2, 3, 5, & 10 years	Baseline compliance based on self-reported survey, increased compliance rates based on government targets for 2000 and 2010.	1 year
Marginal cost of new technology	US$9.75	As for Hutchinson et al, 2000	US$0-50
Validation	Compared to cancer incidence rates based on self-reported compliance rates, e.g. 85% every 2 years, 5% every 5 years, 5% every 10 years and 5% never.	As for Hutchinson et al, 2000	Not mentioned.
Results	ThinPrep is the most cost-effective option for all intervals above 1 year (conventional pap smears are cost-effective for a 1-year interval). Comparison between screening intervals presented diagrammatically – assuming a $50k threshold, ThinPrep testing every 2 years is most cost-effective option.	LBC gains additional life years at a cost of $15,296 given self-reported compliance rates.	New technologies included as part of sensitivity analysis. Only presented is the cost per additional HSIL detected, for a range of potential additional costs of new technology. If a new technology costs an additional $10, 236 additional HSILs would need to be detected to get under the $50k threshold. (NB one-year screening interval).
Sensitivity analysis results	Parameters: test sensitivity and intervention costs. Using lower sensitivity rates and treatment costs reduced the cost-effectiveness of new technologies, but the rank order remained the same. Also tests cost-effectiveness using data describing actual compliance rates (as used for validation), which shows ThinPrep is cost-effective in the full population, but not in a population comprising women who are screened at least every 3 years.	Parameters: test sensitivity and compliance rates. Incidence rates, not cost-effectiveness ratios are presented for alternative sensitivity rate assumptions. LBC is shown to be cost-effective over all compliance assumptions.	As above
Discussion	Regarding effectiveness of rescreening devices, states that studies are underway that will provide better estimates (manufacturer's data are used in current study). Lack of hard data on management of ASCUS screens, require analysis of follow-up protocols. If test sensitivity is increased by 50% with a new test, the new test will be cost-effective despite increase per-test cost.	The use of LBC in conjunction with efforts to increase compliance is recommended.	Cervicovaginal screening of low-risk groups may not be cost-effective, though other patient outcomes (patient satisfaction or freedom of choice) may justify screening such groups. If women receive yearly smears, the added cost of a new technology to detect LSILs is not justified. The cost of a new technology would have to be low to justify a modest gain in HSIL detection.

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