Cost and cost-effectiveness of conventional and liquid-based cytology in South Africa: A laboratory service provider perspective

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Background. South Africa has a high prevalence of cervical cancer. Early detection can significantly reduce the burden of this disease. New screening technologies to detect cervical pathology have become available in recent years.

Objectives. To determine the cost and cost-effectiveness of liquid-based cytology (LBC) versus conventional cervical cytology, from the perspective of the National Health Laboratory Service (NHLS).

Methods. The unit of effectiveness was defined as the number of cervical intraepithelial neoplasm (CIN) II or higher lesions detected. Costs were assessed retrospectively for the financial year (2010/11) from a laboratory service provider perspective. A cost-effectiveness analysis was performed by combining secondary data collected from NHLS expenditure records and cytology laboratory data sources with data from the literature.

Results. Total average cost per conventional slide was found to be R (South African rands) 64 (95% confidence interval (CI) 59 - 69) compared with R85 (95% CI 77 - 92) for an LBC slide. Conventional cytology was found to be more cost-effective (R10 786; 95% CI 9 335 - 12 699) than LBC (R18 911; 95% CI 16 180 - 22 435) in detecting CIN II or greater lesions. An improvement in the specificity of LBC and/or a decrease in the cost of consumables utilised in processing LBC specimens could potentially make it a cost-effective alternative to conventional cytology.

Conclusion. An estimate of the total average public sector laboratory cost per slide for each modality was calculated. Definitive assessment of cost-effectiveness will require a prospective study that incorporates human papillomavirus testing and is conducted from a societal perspective.

Cervical cancer is preventable if screened for and diagnosed and treated early. In South Africa (SA) it is a major cause of morbidity and mortality and the second most prevalent cancer among women.[1] Organised screening programmes have resulted in a dramatic decrease in the incidence of cervical cancer in many developed countries,[2,3] but because these programmes require a relatively well-functioning healthcare system, success has been somewhat limited in less developed economies.[4] An indispensable health systems component in cytology-based cervical screening is a functioning laboratory service.

In SA, the majority (approximately 84%) of the population is serviced through public sector facilities[5] that refer specimens to the National Health Laboratory Service (NHLS) for laboratory-based diagnostic services. The NHLS processes approximately 80% of all cervical cytology specimens in SA (Irene le Roux, NHLS – unpublished data, 2011). The vast majority of cervical screening in SA is done by conventional Papanicolaou cytology (Pap smears), although newer technologies are available for the cytological diagnosis of cervical disease.

Liquid-based cytology (LBC), introduced in the 1990s, is an alternative method to conventional cytology. Advantages of LBC include fewer unsatisfactory and inadequate slides, a shorter time needed for interpreting slides, and the opportunity for human papillomavirus (HPV) DNA testing on the same sample.[6]

Conventional cytology has been credited with decreasing the incidence of and mortality due to cervical cancer, and has been the centre of cervical screening since the 1960s.[7] It is estimated that

systematic screening can decrease mortality due to cervical cancer by 70%, and it is considered a highly cost-effective intervention.[7] Despite the reported success of conventional cytology there is a wide range of reported sensitivity, usually reported as 50 - 75%.[8]

A number of recent randomised controlled trials comparing LBC and conventional cytology have found the two methods to be comparable in terms of accuracy,[6,9-12] but with LBC providing a significant reduction in smear inadequacy rates.[6,10,11] Inadequacy rates of up to 9.1% for conventional cytology compared with 2.1% for LBC have been documented.[11] High inadequacy rates have significant associated opportunity costs, as women need to be rescreened in the event of an inadequate specimen.

In terms of test sensitivity and specificity, an SA trial found LBC to be comparable to conventional cytology in high-risk, previously unscreened populations.[10] Noting LBC to have higher unit costs than conventional cytology, the authors recommended careful consideration before adopting LBC in resource-poor settings.[10]

Aim and objectives

The primary objective of this study was to estimate the average total cost of processing a cervical cytology slide by the NHLS. Secondly, we aimed to estimate the cost-effectiveness of LBC versus conventional cytology from an NHLS perspective in terms of the number of cervical intraepithelial neoplasm (CIN) II or greater lesions (cases) detected.

Methods

A retrospective study was conducted that included all cervical cytology specimens processed by the six largest NHLS laboratories across SA from 1 April 2010 to 31 March 2011 (*N*=359 474). These six laboratories process approximately 90% of all cervical cytology specimens from the public sector. During the study period the NHLS trialled LBC in two academic hospital-linked laboratories, screeners receiving appropriate training before the trial (Irene le Roux, NHLS – unpublished data, 2011).

Laboratory data were extracted from the NHLS central database and included the variables patient age, cytological diagnosis, name of processing laboratory, and whether a specimen was a conventional or an LBC smear.

Effectiveness measure

Because linkage with histology results was not possible, the number of CIN II or greater lesions detected was determined for each modality based on reported sensitivity and specificity data from previously conducted randomised controlled trials.[10,13] From these test accuracy data, positive predictive values (PPVs) for both conventional and LBC were calculated and adjusted for cervical cancer prevalence in SA.[14] Adjusted PPVs were applied, using two-

by-two tables, to the data extracted from the NHLS central database to generate an estimate of the number of ≥CIN II lesions detected. These estimates were generated for each modality and for two cytology diagnosis cut-off points of interest, atypical squamous cells of undetermined significance or greater (≥ASCUS) and low-grade squamous intraepithelial lesions or greater (≥LSIL), as defined by the Bethesda Classification.[15]

Cost data

Cost data included fixed (capital and overhead costs) and recurrent costs (consumables and labour). These costs were adjusted for inflation using Stats SA CPI data,[16] with all costs being expressed in 2010 South African rand (ZAR) prices. Pertinent capital and consumable costs were informed by site visits and expert interviews. A time-motion study was conducted in all six participating laboratories over a 2-week period to estimate how much time was spent by each staff level on different tasks. Average times were calculated and costed using NHLS salary data. Overhead costs were extracted from year-end balance sheets for the financial year ending 31 March 2011. Total costs for each modality were calculated, and from this the average total cost per slide was found by dividing the total cost by the total number of slides processed.

Analysis

Data were captured in and analysed with Microsoft Excel 2007 and Ersatz Version 1.2 (www.epigear.com). Uncertainty distributions were applied to various model inputs based on the underlying probability distributions of input variables (Table 1).

A bootstrapping procedure was performed to calculate point estimates and 95% confidence intervals (CIs) for outcome measures of interest, namely average cost per slide, number of cases detected, and cost per case detected. A multivariate sensitivity analysis was also performed.

Because LBC was trialled in only two of the six laboratories, the sample size for LBC (*N*=2 381) was considerably smaller than that for conventional slides (*N*=357 093), so LBC estimates were multiplied by a constant to allow for meaningful comparison.

Ethics approval

Ethics approval for the study was granted by the Human Research Ethics Committee at the University of the Witwatersrand (M110951).

Results

Of the 359 474 slides processed during the 2010/11 financial year, 66.7% were collected from women between the ages of 30 and 60 years. Fig. 1 summarises the age distribution, and Fig. 2 the cytological diagnoses, by screening modality.

Table 1. Selected parameters and probability distributions used in the cost-effectiveness model

	Minimum	Maximum	Median	Distribution
Capital costs	-20%	+20%	As per procurement	Uniform
Sensitivity of LBC/LSIL	0.477	0.719	0.603	Triangle

LBC = liquid-based cytology; LSIL = low-grade squamous intraepithelial lesion.

Most of the cytology specimens were normal for both LBC and conventional slides (77.2% v. 73.2%). Conventional cytology diagnosed more slides as high-grade squamous intraepithelial lesions (HSIL) (6.6% v. 3.3%; *p*<0.001) and had a higher percentage of inadequate slides (2.9% v. 0.2%; *p*<0.001).

The total average cost per conventional slide (R64; 95% confidence interval (CI) 59 - 69) was approximately R21 less than the average total cost per LBC slide (R85; 95% CI 77 - 92). Recurrent costs, particularly labour costs, were a major cost contributor, particularly for conventional cytology (65% v. 43% in LBC), suggesting that labour productivity gains are possible if LBC were to be fully employed. This finding is in line with an Irish study that demonstrated a 31% labour productivity improvement at a 73% level of conversion from conventional to LBC screening.[17] However, the capital/labour cost ratio must be taken into consideration in order to improve overall production efficiency. Consumable costs were a large cost contributor to LBC (30% v. 3% in conventional cytology), driven in particular by the Gynae Test Kit required to process LBC specimens. Fig. 3 provides a proportional breakdown of factor costs for each modality.

Based on sensitivity and specificity data from an SA randomised controlled trial directly comparing conventional and LBC,[10] conventional cytology was estimated to detect more (10.33/1 000 screened) CIN II or greater lesions (cases) compared with LBC (7.64/1 000 screened). We calculate that the average cost per case detected, using ≥LSIL as a cytological cut-off point, was almost half for conventional cytology (R6 224; 95% CI 5 017 - 7 645) compared with LBC (R11 096; 95% CI 9 076 - 13 683).

A sensitivity analysis showed the Gynae Test Kit (a component of recurrent consumable costs) used in LBC testing as well as the specificity of LBC testing to have important impacts on the model outcome. For this reason three additional models were run to assess the impact on the cost and cost-effectiveness of LBC if these inputs were adjusted.

Repeating the analysis with a hypothetical 50% reduction in the cost of the Gynae Test Kit decreases the average total cost of an LBC smear to R75 (95% CI 69 - 81), but even this large reduction in cost alone would not be sufficient to outperform conventional cytology, as the average cost per case detected (R9 826; 95% CI 8 082 - 12 171) would still be higher compared with conventional cytology.

In terms of improved specificity, a trial conducted by Biscotti *et al.*[13] calculated higher sensitivity and specificity estimates for LBC than the trial conducted in SA.[10] Applying the manual arm sensitivity and specificity data from this trial greatly improves the cost-effectiveness of LBC. Table 2 summarises these results.

Discussion

In determining the cost of providing cytology services, we utilised local actual cost data. This study therefore provides a relatively accurate estimate of the laboratory costs involved in providing cytology services in the SA public health sector. Current pricing of cytology services in the public sector is largely determined through negotiation between the NHLS and government. With the phased implementation of a National Health Insurance system in SA, it will become increasingly important to determine the cost of services
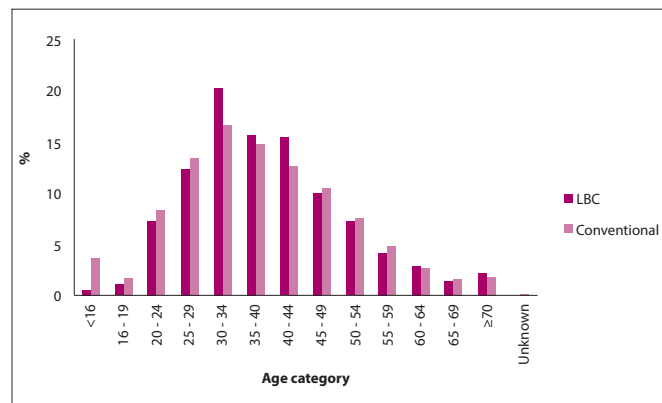

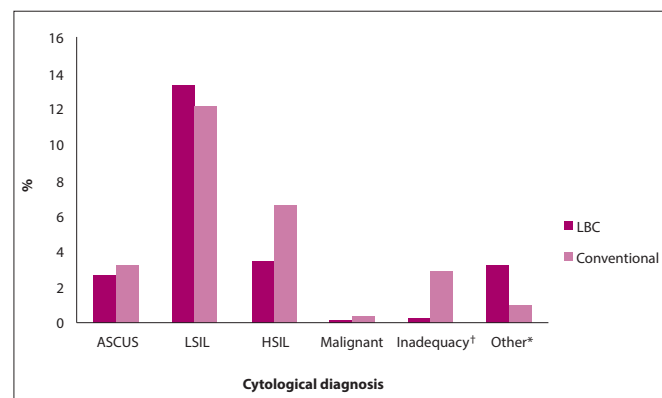*Fig. 1. Age distribution stratified by screening modality.*

Fig. 2. Cytological diagnosis distribution stratified by screening modality ('Other' includes cases of benign changes (924), atypia (1 670), ASC-H (1 330) and AGUS (387); †'Inadequacy' refers to all smears that were unsuitable for cytological diagnosis).*
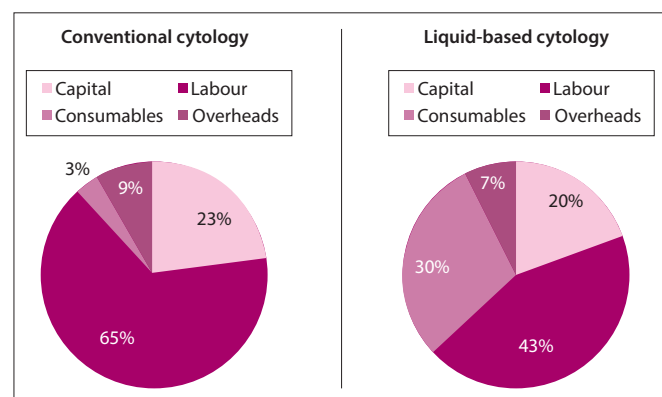

Fig. 3. Proportional input costs for each modality.

accurately. Our findings will assist health managers to price cytology services appropriately and in so doing advance the sustainability of SA's laboratory-based cervical cytology screening programme.

Estimates of the cost-effectiveness of conventional cytology and LBC were also calculated, but their accuracy must be considered in light of the following limitations.

This was a retrospective study, and it was not possible to link patient cytology results with patient histology results. We had to extrapolate the outcome measure of interest based on data from the literature. As there is a relatively wide reported specificity and sensitivity for cervical cytology, this variation in reported test accuracy with

Table 2. Summary of costs and cost-effectiveness

	Source of test accuracy data and reduction in GTK, % (95% CI)			
	Taylor *et al.*[10] with GTK at market price	Taylor *et al.*[10] and a 50% reduction in GTK	Biscotti *et al.*[13] and a 25% reduction in GTK	Biscotti *et al.*[13] and a 50% reduction in GTK
LBC (ZAR), mean (range)				
Average cost per slide	85 (77 - 92)	75 (69 - 81)	80 (74 - 86)	75 (69 - 81)
Cost/case detected: ASCUS	18 911 (16 180 - 22 435)	16 793 (14 179 - 19 904)	2 645 (2 278 - 3 010)	2 478 (2 143 - 2 812)
Cost/case detected: LSIL	11 096 (9 076 - 13 683)	9 826 (8 082 - 12 171)	1 626 (1 395 - 1 876)	1 522 (1 295 - 1 765)
Conventional cytology (ZAR), mean (range)				
Average cost per slide	64 (59 - 69)			
Cost/case detected: ASCUS	10 786 (9 335 - 12 699)			
Cost/case detected: LSIL	6 224 (5 017 - 7 645)			

GTK = Gynae Test Kit; CI = confidence interval; LBC = liquid-based cytology; ASCUS = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion.

relatively dated prevalence data for cervical cancer in SA may affect the findings of the cost-effectiveness analysis. These limitations were ameliorated by utilising sensitivity and specificity data from a large randomised controlled trial that had been conducted in SA;[10] utilising prevalence data from a large multicentre study conducted in SA;[14] and performing uncertainty and multivariate sensitivity analysis and adjusting model inputs accordingly to demonstrate the effects of alternative scenarios.

Further, because LBC was trialled by the NHLS there was a wide discrepancy between the number of LBC and conventional slides processed. This limitation was addressed by taking a micro-costing approach, utilising test accuracy data from a local randomised controlled trial[10] and multiplying LBC estimates with a constant.

We argue that a reduction in the Gynae Test Kit costs would be feasible for the NHLS. As LBC does not currently constitute a major proportion of cervical cytology screening (<0.7% of all cytology specimens), the NHLS has faced prevailing market prices for these kits. Given the economies of scale available to the NHLS, a great reduction in cost may be possible.

Second, not all the benefits of utilising LBC were included in the analysis. The perspective of the study did not include societal costs and HPV testing on LBC samples. Under the assumption that all smears were LBC or conventional, our calculated inadequacy rates would translate into a total of 755 inadequate LBC smears at a cost of R64 175, or a total of 10 389 inadequate conventional smears at a cost of R664 896. This demonstrates some of the potential cost savings of LBC, which would be even greater from a societal perspective, as 9 634 fewer repeat patient visits would have been required if all cytology was liquid based. A number of studies conducted in developed countries have demonstrated HPV testing to be a cost-effective strategy.[18-20] As HPV testing can reduce the number of visits required, it has also been found to be potentially cost-effective in resource-poor settings.[21]

Lastly, we were unable to determine what proportion of slides was analysed using automation technology. Costs were therefore aggregated, and only an average total cost was calculated for each modality.

Conclusion

We have reported an accurate estimation of laboratory cervical screening costs for the SA public sector. The cost-effectiveness of the two modalities is also estimated. A prospective study conducted from a societal perspective that includes HPV testing as part of the cervical screening process is required in order to establish a more definitive view on the cost-effectiveness of LBC in SA.

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