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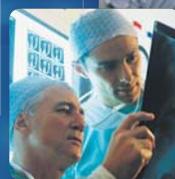


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Liquid-Based Techniques for Cervical
Cancer Screening: Systematic Review
and Cost-Effectiveness Analysis



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Canadian Agency for Drugs and Technologies in Health

**Liquid-Based Techniques for Cervical Cancer Screening:
Systematic Review and Cost-Effectiveness Analysis**

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Authorship

Murray Krahn conceptualized the project. He conceptualized and supervised the decision modelling, revised and edited the text of the report, and wrote the discussion and executive summary.

Barry Rosen was a reviewer for extraction of data from clinical studies and ethical-psychosocial studies, and he directed the quantitative meta-analysis. He provided expert content advice on all sections of the report.

Meg McLachlin contributed to the clinical aspects of this paper regarding cervical neoplasia and screening, and assisted in developing the model regarding cervical neoplasia. She contributed to the revision of all aspects of the paper regarding clinical aspects and screening.

Paul Grootendorst performed the clinical meta-analysis, supported the economic model building and sensitivity analysis, and drafted sections of the clinical methods.

George Tomlinson contributed to the data synthesis plan, data processing, and statistical analysis and interpretation; participated in drafting and revising the report; and approved the final version of the manuscript.

Margaret Sampson was responsible for designing and executing the literature search strategies, writing the methods section and associated appendix on literature searching, and verifying and formatting bibliographic references.

Beate Sander was responsible for development of the protocol, introduction, primary economic analysis, economic literature search, review of economic studies, and health services impact. She reviewed the summary of the clinical section, extracted clinical and pharmacoeconomic data, and designed, built, and ran the economic model.

Andrea Anonychuk assisted in protocol development, search design, and abstract selection; and analyzed the health services impact and other sections.

Andrea Tricco contributed to the data synthesis plan, data processing, and statistical analysis and interpretation; participated in drafting and revising the report; and approved the final version of the manuscript.

Ba' Pham was responsible for the primary writing of the introduction and clinical review sections, assisted in the development of the protocol and the design of the literature search, provided clinical data, contributed to the primary economic and health services impact analyses and other sections, and assisted in responding to reviewers' comments.

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Conflicts of Interest

No conflicts of interest were reported by the authors or reviewers.

Liquid-Based Techniques for Cervical Cancer Screening: Systematic Review and Cost-Effectiveness Analysis

Technology and Condition

Liquid-based cytology (with or without HPV testing) as an alternative to conventional cytology (CC) for cervical cancer screening of sexually active women who are 15 years of age or older.

Issue

Liquid-based cytology (LBC) is more expensive than CC. There is uncertainty about whether the use of this technology is justified.

Methods and Results

A systematic review and Bayesian meta-analysis, economic evaluation, and budget impact analysis were undertaken to compare CC, LBC, and LBC-based human papillomavirus (HPV) triage at one-, two-, and three-year screening intervals. Twenty studies of 68,114 participants suggested that LBC was 6% more sensitive and 4% less specific than CC, on average. An LBC-based HPV triage program could cost an additional \$6.35 per targeted individual. Compared to annual screening with CC, LBC with HPV triage every two years could reduce disease burden — 3,023 women screened would prevent one cancer-related death (a gain of 0.0002 QALYs) — and reduce costs (\$59 per person, discounted) while increasing colposcopy rates by 37.5%. The same screen annually leads to a larger reduction in disease burden (0.0007 QALYs) but increased average costs (\$23 per person, discounted) and colposcopy referrals by 63%.

Implications for Decision Making

- **LBC and CC perform similarly.** The clinical evidence suggests that LBC is similar to CC with respect to sensitivity and specificity. LBC is probably more sensitive and less specific, and may have a lower rate of unsatisfactory specimens.
- **LBC strategies can be cost-effective, but they increase colposcopy referrals.** Model projections suggest that LBC with HPV triage every two years can be cost-saving compared to an annual screening strategy with CC alone.
- **HPV triage is cost-effective.** Direct comparison of all screening and triage strategies show that annual screening with CC or LBC is always more costly and less effective than when paired with HPV triage. Adding HPV triage to annual CC can reduce colposcopy referrals by 5%. Compared to annual CC with HPV triage, LBC with HPV every two years will reduce disease burden further by 0.0004 QALYs, while increasing costs (\$52 per person, discounted) and colposcopy referrals by 72%.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Krahn M, McLachlin M, Pham B, Rosen B, Sander B, Grootendorst P, Tomlinson G, John-Baptiste A, Frikemerid M, Hong Chen M, Woo G, Anonychuk A, Carcone S, Witteman H, Chen W, Liu K, Sampson M, Tricco A. *Liquid-based techniques for cervical cancer screening: Systematic review and cost-effectiveness analysis.*

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EXECUTIVE SUMMARY

The Issue

Cervical cancer is a largely preventable disease among women in Canada. In 2007, it was estimated that 1,350 Canadian women were diagnosed with invasive cervical cancer (ICC), and 390 women died from the disease. Cervical screening programs using the Pap smear, first implemented in the 1950s, have contributed to the decrease in the incidence of cervical cancer. Liquid-based cytology (LBC), which is an alternative to the Pap smear, aims to enhance the detection of precancerous lesions by improving sample and cell preparation. Human papillomavirus (HPV) testing is available to detect HPV DNA in cervical cells. While regular screening using conventional cytology (CC) (i.e., Pap smear) is generally effective, there may be improved sensitivity from using LBC instead of CC. These new techniques are more expensive than the Pap smear.

Objectives

The objective of this report is to assess the effectiveness and cost-effectiveness of LBC versus CC for cervical cancer screening in a population of sexually active women ≥ 15 years of age.

Clinical Effectiveness

Methods: Relevant databases were searched between November 2002 and June 2006. The primary outcomes were sensitivity and specificity, agreement between LBC and CC in split-sample and two-cohort studies, and specimen adequacy. Data were synthesized using Bayesian Markov-chain Monte Carlo methods.

Results: A direct comparison of LBC with CC was done in 20 head-to-head studies with 68,114 participants. LBC offers a gain in sensitivity of 6.4% with a loss of specificity of 4.0%. Given the data, the probability that LBC is more sensitive than CC was 83%. The corresponding probability that LBC is less specific than CC was 72%.

In 47 studies where cervical samples were split and processed with CC and LBC (i.e., split-sample studies), most results were concordant. With LBC, approximately 1% more slides were classified at the threshold of low-grade squamous intraepithelial lesion (LSIL+) when compared to CC. With LBC, between 0.7% and 1.0% more slides were classified as low-grade lesions when compared to CC, according to data from 31 studies where samples from two concurrent cohorts were processed with CC or LBC (i.e., two-cohort studies). According to data from two-cohort studies, with LBC, fewer slides might be classified as high-grade squamous intraepithelial lesion (HSIL+) when compared to CC, although the differences were not statistically significant. On average, with LBC, there were fewer unsatisfactory samples, but the estimates from 66 individual studies varied.

Relative to repeat cytology for the management of atypical squamous cells of undetermined significance (ASCUS), triage strategies using HPV testing resulted in an average gain in sensitivity of 7% and similar specificity. According to data from 24 studies, the HPV triage test resulted in a sensitivity of 86% (95% CI: 81%; 91%) and a specificity of 62% (95% CI: 57%; 66%) for cervical intraepithelial neoplasia grade 2 or above (CIN 2+). The corresponding results for repeat cytology at a threshold of atypical squamous cells of undetermined significance or higher (ASC-US+) show that there was a sensitivity of 79% (95% CI: 73%; 85%) and a specificity of 58% (95% CI: 36%; 80%).

Economic Analysis

Review of economic literature

Methods: The searches were used to obtain economic evaluation studies and HTAs of cervical cancer screening strategies or programs, excluding those in settings where organized programs do not exist. The cost per life-year (LY) gained and the cost per quality-adjusted life-year (QALY) gained were abstracted from included studies and expressed in 2006 Canadian dollars. Nine included studies evaluated comparisons of LBC to CC; and seven evaluated HPV triage strategies for ASC-US.

Results: For screening intervals of ≥ 3 years, all studies suggested that LBC was economically attractive (range \$1,000 to \$52,000 per LY gained, median value \$17,000 per LY gained). Shorter screening intervals were less economically attractive. For screening intervals of ≥ 3 years, HPV triage strategies appeared to be economically attractive. The results were inconsistent for intervals of < 3 years.

Canadian economic evaluation

Methods: We performed an economic evaluation using a simulation model that projects Canadian cervical cancer and related mortality. The three options of CC screening, LBC screening, and LBC screening using an HPV triage strategy were compared.

Results:

- Compared to no screening, current screening programs (i.e., annual screening with CC at approximately 40% coverage) require 46 women to be screened over a lifetime to avoid one cervical cancer case and 109 women to prevent one cancer-related death. This equates with a gain of 0.07664 QALYs and lower average lifetime costs (\$1,723 saving per person, discounted).
- Compared to current screening programs, if annual screening with CC is offered every two years, the relative incidence of cervical cancer and related mortality will increase by approximately 7%.
- Compared to current screening programs, if LBC is offered every year, the relative incidence of cervical cancer will decrease by 7% with a 74% increase in colposcopy referrals and increased average lifetime costs (\$41 increase per person, discounted).
- Compared to current screening programs, if LBC is offered every two years, the disease burden remains similar (QALYs decrease by 0.00006) with a 48% increase in colposcopy referrals and lower average lifetime costs (\$39 per person, discounted).
- HPV triage was a more effective option for ASC-US management than repeated cytology. When paired with a cytological screening strategy (CC or LBC) and interval (one, two or three years), it reduced colposcopy referrals, incidence of cervical cancer, and related mortality.
- Compared to current screening programs, if CC with HPV triage is offered every year, the relative incidence of cancer will decrease by 6% with a 5% reduction in colposcopy referrals and lower average lifetime costs (\$19 per person, discounted).
- Compared to current screening programs, if CC with HPV triage is offered every two years, the relative incidence of cancer will increase by 2% with a 19% reduction in colposcopy referrals and lower average lifetime costs (\$77 per person, discounted).
- Compared to current screening programs, LBC with HPV triage requires 1,134 women to be screened every two years over a lifetime to avoid one cervical cancer case and 3,023 women to prevent one cancer-related death. This equates with a gain of 0.0002 QALYs and reduced average lifetime costs (\$59 per person, discounted).
- Compared to current screening programs, LBC and HPV triage was the only option that reduced disease incidence at two-year screening intervals.

Health Services Impact

Budget impact projections suggest that the additional annual cost to replace CC by LBC in current cervical cancer programs would range from approximately \$262,000 to \$14.6 million across provinces except Ontario, and Newfoundland and Labrador, which were early adopters of LBC. The corresponding additional annual cost to introduce LBC with HPV triage could be \$6.35 per targeted individual and would range from \$255,000 to \$14.2 million, indicating that the introduction of HPV triage could be cost-neutral.

Consistent with data reported in other studies, the use of more sensitive LBC compared with CC in routine screening programs was expected to increase the rate of colposcopy referrals. Compared with current opportunistic screening at an observed screening coverage of approximately 40% every year, screening every two years with LBC could lead to an estimated 48% increase in the rate of colposcopy referrals. The corresponding increase for screening every two years with LBC and HPV triage was approximately 38%. The budget impact analysis suggests an average 12% increase in the first-year projected budgets estimated as estimated in the preceding paragraph to cover for increased colposcopy services.

Conclusions

The clinical evidence suggests no statistical differences in sensitivity and specificity between LBC and CC. LBC is estimated to be on average 6% more sensitive and 4% less specific than CC across a range of cytological thresholds. There is an 83% chance that LBC is more sensitive than CC and a 72% chance that it is less specific. On average, LBC classifies approximately 1% more cell abnormalities than CC at the low-grade threshold of LSIL+. At the high-grade threshold of HSIL+, LBC may classify fewer abnormalities than CC, but the difference is not statistically different. On average, LBC may have a lower rate of unsatisfactory specimens, but the estimated differences from individual studies varied.

HPV triage of ASCUS is more sensitive to detect cervical intraepithelial lesions than repeat cytology. HPV triage has a similar specificity compared to repeated cytology. Model projections suggest that, over a woman's lifetime, LBC is likely to improve health outcomes (e.g., cancer incidence and cancer death) and increases costs when compared with CC at the same screening interval. Model projections also suggest that, over a woman's lifetime, HPV triage reduces costs and improves health outcomes when paired with any cytologic screening strategy.

Direct comparison of all screening and triage strategies show that annual screening with CC or LBC is always more costly and less effective than when paired with HPV triage. HPV triage used with LBC screening at two-year intervals is preferred to CC with HPV triage at a willingness-to-pay threshold of \$50,000 per LY gained, and CC with HPV triage every two years is preferred to LBC with HPV triage at lower willingness-to-pay thresholds. In comparison with current practice, using liquid-based cytology with HPV triage at two-year screening intervals will reduce costs, with a similar or reduced burden of disease. Thus, the health economic evidence suggests that two-year screening strategies using HPV triage, with or without LBC, represents the best use of resources for cervical cancer screening. These results will require revision given the introduction of automated screening, HPV vaccination, and organized screening programs.

ABBREVIATIONS

AGC	atypical glandular cells (Bethesda 2001 terminology)
AGUS	atypical glandular cells of undetermined significance (Bethesda 1998 terminology)
ALTS	Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study
ASC-H	atypical squamous cells of undetermined significance – cannot rule out HSIL (Bethesda 2001 terminology)
ASCUS	atypical squamous cells of undetermined significance (Bethesda 1998 terminology)
ASC-US	atypical squamous cells of undetermined significance – with HSIL ruled out (Bethesda 2001 terminology)
ASCUS+	atypical squamous cells of undetermined significance or higher (Bethesda 1998 terminology)
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	conventional cytology
CIN 1, CIN 2, CIN 3	cervical intraepithelial neoplasia, stage 1, 2, or 3
FIGO	International Federation of Gynecology and Obstetrics
HC II	Hybrid Capture II
HPV	human papillomavirus
HR	high-risk types (of HPV)
HSIL	high-grade squamous intraepithelial lesion
HSIL+	high-grade squamous intraepithelial lesion and higher grade lesions
HTA	health technology assessment
ICC	invasive cervical cancer
ICER	incremental cost-effectiveness ratio
LBC	liquid-based cytology
LR	low-risk types (of HPV)
LSIL	low-grade squamous intraepithelial lesion
LSIL+	low-grade squamous intraepithelial lesion and higher grade lesions
LY	life-year
MeSH	medical subject heading
Pap	Papanicolaou
PCR	polymerase chain reaction
QALY	quality-adjusted life-year
ROC	receiver-operating characteristic
Rx	treatment
SIL	squamous intraepithelial lesion
SR	systematic review
SROC	summary receiver-operating characteristics curve
WTP	willingness to pay
YLS	year of life saved

1 INTRODUCTION

1.1 Background

In Canada, an estimated 1,350 women were diagnosed with cervical cancer, and approximately 390 died because of it in 2007.¹ A decline in the incidence of cervical cancer since the 1950s has been attributed to Papanicolaou (Pap) smear screening programs for the early detection and treatment of precancerous and cancerous lesions.^{2,3} The first program in Canada started in British Columbia in 1949, and screening now occurs everywhere in Canada.^{4,5} Most current screening in organized programs is opportunistic, because there is no legislation to recruit, recall, and follow women for Pap testing or necessary investigations.⁶

The 2003 Pan-Canadian Forum on Cervical Cancer Prevention and Control recommended that each province and territory should prioritize the components of an organized screening program and incrementally implement the components.⁷ The components include a comprehensive population-based cervical cancer screening database, performance indicators and screening targets, public education about the human papillomavirus (HPV), and implementation of new screening techniques.⁷

Among new screening techniques, liquid-based cytology (LBC) provides a uniformly fixed and prepared sample of cervical cells that is relatively free of artefacts and obscuring elements. By improving the presentation of the cells, it aims to improve the detection of cervical lesions.⁸ LBC also provides a platform for HPV DNA testing, which is molecular testing with an analytical sensitivity approaching 100% for the detection of oncogenic HPV types.⁹ The oncogenic (high risk) types of HPV have been proven to be causative agents in virtually all cases of cervical cancer.¹⁰ The potential roles of HPV DNA testing include triage of borderline abnormalities, primary screening in selected age groups, and follow-up of treatment for precancerous or neoplastic lesions.^{11,12}

Most cervical cancer prevention programs consists of cytological screening of asymptomatic individuals to identify those at risk of disease, diagnosis based on colposcopy or biopsy results, and treatment of those with cancer or a cancer precursor.¹³ Triage is an additional step interposed between screening and diagnosis to stratify individuals with positive screening results according to the risk of disease. Typically, a cytologic abnormality is defined by one of three thresholds: atypical squamous cells of undetermined significance or higher (ASCUS+), low-grade squamous intraepithelial lesion and higher grade lesions (LSIL+), and high-grade squamous intraepithelial lesion and higher grade lesions (HSIL+). Histologic diagnosis is defined as cervical intraepithelial neoplasia (CIN) stages 1 to 3 or carcinoma. The relationship between cytological and histological findings appears in Table 1.

Using HPV testing as a triage method, a woman can be tested for infection with any type of HPV. She will be recalled for colposcopy only if her virological results are positive. According to the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS), approximately 40% to 50% of women who exhibit an ASCUS interpretation are HPV-positive.^{14,15} Virtually all the CIN 2 or CIN 3 associated with ASCUS are found in the HPV-positive fraction. Therefore, HPV triage can save approximately 50% of women from unnecessary colposcopy without compromising sensitivity.^{14,15}

Table 1: Correspondence of cytological and histological diagnostic terms				
Cytology (conventional or liquid-based)			Histology (determined by colposcopy or biopsy)	
Testing cut-offs	Cell characteristics used as marker		Actual disease state of cervical tissue	
	1998 terminology	2001 terminology		
	ASCUS	ASC-US	cellular changes	
		ASC-H		
	AGUS	AGC		
LSIL+	ASCUS+	LSIL		CIN 1
		HSIL		CIN 2
				CIN 3
				ICC

AGC=atypical glandular cells; AGUS=atypical glandular cells of undetermined significance; ASC-H=atypical squamous cells of undetermined significance – cannot rule out HSIL; ASCUS=atypical squamous cells of undetermined significance; ASC-US=atypical squamous cells of undetermined significance – with HSIL ruled out; ASCUS+=atypical squamous cells of undetermined significance or higher; CIN 1=cervical intraepithelial neoplasia, stage 1; CIN 2=cervical intraepithelial neoplasia, stage 2; CIN 3=cervical intraepithelial neoplasia, stage 3; HSIL=high-grade squamous intraepithelial lesion; ICC=invasive cervical cancer; LSIL=low-grade squamous intraepithelial lesion.

The field of cervical cancer prevention is evolving with prophylactic HPV vaccines. In phase II and III trials, HPV vaccines against HPV-16/18/6/11 and HPV-16/18 have been shown to protect women from incident HPV infections, persistent infections, and related pre-invasive CIN 2 or CIN 3 induced by the cancer-causing HPV types 16 and 18. Available evidence indicates that the vaccine-induced immune response will also prevent cervical cancer in the long term.¹⁶ Efforts are underway to distribute HPV vaccines to pre-adolescent girls, adolescent girls, and young women.¹⁷ Efforts have also been focused on the design of new prevention strategies with screening and HPV immunization.^{18,19} Cost-effectiveness evaluations of LBC, cytology automation, and screening follow-up algorithms have been identified among the research priorities. Of particular pertinence is the development of protocols to be used when HPV-vaccinated cohorts reach the screening age.^{16,18,19} Previous knowledge, and clinical and economic projections should be updated to take account of the lower cervical cancer risk among vaccinated populations.

In Canada, two provincial cervical cancer screening programs (one in Ontario, and the other in Newfoundland and Labrador) have adopted LBC, and others have considered it.^{6,20,21} Screening techniques evolve over time. Objective reviews of their clinical utility and resource implications in screening programs are essential before the new approaches are implemented.⁸ LBC has been the focus of systematic reviews (SRs) and health technology assessments (HTAs), and many countries have conflicting recommendations.²²⁻²⁷ Some guidelines in the US favour the adoption of LBC and HPV testing.²⁸ Citing lack of evidence, the public health systems in Australia, Switzerland, France, and Germany no longer reimburse LBC.^{29,30} The US Preventive Services Task Force concluded in 2003 that the evidence was insufficient to recommend for or against the routine use of LBC techniques.^{31,32} In Canada, a report from the Canadian Coordinating Office for Health Technology Assessment (now CADTH) suggested that LBC is more sensitive than conventional cytology (CC) in screening populations and may be cost-effective at three-year intervals in cervical cancer screening programs.²²

Health professionals and decision makers overseeing cervical cancer screening programs in Canada are faced with mounting pressure to provide these techniques. This analysis is an update of the 2003 CADTH SRs of the effectiveness and economic evidence, and presents a comprehensive cost-

effectiveness analysis of the use of LBC screening and the use of HPV testing for triage in a Canadian context.

1.2 Overview of Technology

With CC, the clinician smears cervical cells on a glass slide and spray fixes the sample. CC has long been the backbone of cervical cancer screening. This simple and inexpensive test is largely responsible for the declines in cervical-cancer incidence observed worldwide.³³ There is, however, a significant false-negative rate due to sampling, preparation, screening, and interpretation errors.³⁴ A SR evaluating the accuracy of the Pap test concluded that the 94 included studies were of low quality. Results from the SR indicated that the test is moderately accurate (i.e., approximately 68% sensitivity and 75% specificity at the ASCUS threshold) and does not achieve high concurrent sensitivity and specificity.³⁴ In Ontario, 0.58% of CC Pap tests are unsatisfactory because of inadequate sampling and preparation, and often have to be repeated (approximately 7,200 samples from approximately 1.2 million samples in Ontario in 2003).^{6,35}

With LBC, the cervical sample is rinsed immediately in an aliquot of fixative and sent to the laboratory where the final slide is produced. Two companies provide LBC preparation systems that are approved for use in Canada. The ThinPrep Pap Test (CYTYC, Boxborough MA) uses a microprocessor-controlled filtration technique, and the BD SurePath liquid-based Pap Test (BD Diagnostics-Tripath, Burlington NC) uses a density gradient system. Both techniques provide a uniformly fixed and distributed sample of cells. These improvements could lead to better sensitivity of LBC techniques for the detection of cervical lesions.⁸ Both systems require proprietary sampling tools, fixatives, and preparation devices that are associated with an increase in cost per test compared with CC.

Human papillomavirus (HPV) testing detects HPV DNA in cervical cells. Sensitive HPV tests are available, including DNA hybridization and polymerase chain reaction (PCR) tests. The Hybrid Capture II (HC II; Digene Corporation, Gaithersburg MD) uses a modified enzyme-linked immunoabsorbant (ELISA) assay to detect the DNA:RNA hybrids. The test detects a cocktail of 13 high-risk oncogenic HPV types that have been proven to be associated with high-grade lesions of the cervix and invasive cervical cancer.³⁶ HC II can be performed on cervical samples collected with a specific swab, or the test can be performed on the residual cells of an LBC sample. The latter, often called “reflex testing,” does not require the collection of a second sample. Although HC II is the most widely used HPV test, other techniques are being developed.⁸

Different laboratories have used PCR-based methods. PCR methods are considered to be the “gold standard” for analytical sensitivity to detect infectious organisms, including HPV.³⁷ PCRs for HPV detection lack standardization, show different sensitivity and specificity, are time-consuming, and are a demanding job for the laboratory. Recently, a standardized PCR-based technique (AMPLICOR HPV test; Roche Molecular Systems) for the detection of the 13 HR HPV genotypes has been commercialized. This test uses amplification of target DNA by PCR and nucleic acid hybridization for the detection of HR HPV genotypes in cervical cells collected into a transport medium. Studies show that the Hybrid Capture II assay and the AMPLICOR HPV test give comparable results, with both being suitable for routine use.³⁷⁻³⁹ In addition, the recently approved Linear Array HPV genotyping test (Roche Molecular Systems) is a PCR-based HPV detection kit that allows for multiple HPV typing of 37 genotypes.

The use of LBC and HPV triage in routine screening programs could lead to other changes. It is estimated that without Pap screening, cervical cancer would occur in about 1% of women who acquire an HPV infection. For every cancer that occurs, a larger number of precancerous lesions develop, most of which probably regress.⁴⁰ Young women are at low risk of cancer but at risk of over-treatment for low-grade abnormalities. Screening programs using techniques with higher sensitivity than conventional Pap smears without modifying the routine screening interval offer little incremental benefit but increase costs because of over-referral to colposcopy and potential over-treatment.⁴¹

2 THE ISSUE

Cervical cancer is a largely preventable disease among women in Canada. Undergoing a regular Pap test is the most important way to prevent cervical cancer. The incidence of cervical cancer has declined since the 1950s. In 2007, it was estimated that 1,350 Canadian women were diagnosed with invasive cervical cancer (ICC), and 390 women died from the disease. The Pap smear, first used in the 1950s, is a contributing factor in decreasing cervical-cancer incidence and remains the most commonly used technique for cervical cancer screening. New techniques are now available.

LBC, which is an alternative to the Pap smear, aims to enhance the detection of precancerous lesions by improving sample preparation. Sensitive testing is available to detect HPV DNA in cervical cells, especially the 13 high-risk oncogenic HPV types that have been proven to be associated with high-grade lesions of the cervix and ICC. HPV testing can be performed on the residual cells of an LBC sample and is useful for guiding the follow-up management of cytological abnormalities of undetermined significance (i.e., HPV triage) that are detected using LBC. While regular screening using CC (i.e., Pap smear) is generally effective, programs may improve their sensitivity by using LBC instead of CC. The use of LBC in such programs provides a convenient platform for HPV triage. These techniques are more expensive than the Pap smear.

Several HTAs of LBC and HPV testing are available from other countries. It is unknown how well these assessments apply in a Canadian setting. A previous assessment from the Canadian Agency for Drugs and Technologies in Health (CADTH) of data from other jurisdictions concluded that the economic evaluation of these technologies in a Canadian context was needed before cost-effectiveness conclusions could be reached.

The target audience for this report is decision makers at macro-, meso-, and micro-levels, who are considering these techniques for use in cervical cancer screening programs in Canada. These include provincial ministries of health, private and public laboratories, public health officials, community health agencies, preventive oncology programs, and individual practitioners (cytologists, pathologists, obstetrician-gynecologists, and primary health care physicians).

3 OBJECTIVES

The objective of this report is to assess the effectiveness and cost-effectiveness of LBC versus CC for cervical cancer screening in a population of sexually active women ≥ 15 years of age. To achieve this, the report addresses four research questions.

- What is the effectiveness and cost-effectiveness of LBC versus CC?
- What subpopulations and population-based parameters may influence the estimates of effectiveness or cost-effectiveness?
- How does HPV testing affect the cost-effectiveness of LBC-based screening?
- What is the budget impact of adopting LBC and HPV triage from a provincial health care payer's perspective?

4 CLINICAL REVIEW OF LBC

4.1 Methods

The clinical review of LBC followed standard methods for the conduct and reporting of SRs. A protocol was developed a priori and adhered to throughout the review.

4.1.1 Literature search strategy

A SR of studies that assessed the use of LBC as a replacement for CC in cervical cancer screening was conducted. The literature search from the previous CADTH technology assessment report was updated from November 2002 to June 2006. Literature that was published before November 2002 was assumed to be acceptably covered by the previous report.²² The updated literature had no language restrictions and no provision to exclude unpublished studies. It was conducted on BIOSIS Previews, CANCELIT, EMBASE, MEDLINE, and the Cochrane Library (Appendix 1).

4.1.2 Selection criteria and methods

To be included in the SR, the report of a study (i.e., a SR, HTA, or primary study) had to describe comparisons of LBC with CC, with both techniques read manually (i.e., not using an automated screening system).⁴² Two reviewers (BP, GW) independently conducted the screening of potentially relevant citations and resolved disagreement via discussion.

4.1.3 Data abstraction strategy

a) SRs

Data abstracted from each SR or health technology assessment (HTA) included study type (i.e., SR or HTA), searching of multiple databases, search timing, inclusion criteria used in the SR, number of included studies, conclusion regarding LBC effectiveness, and the conclusion regarding whether LBC should be adopted in the scenario being considered. The form for abstracting data was created in MS Excel a priori. One reviewer (WC) independently abstracted data, which another (BP) verified. Outcome data from primary studies included in all SRs were extracted and duplications removed. The data were then updated and synthesized.

b) Primary studies

Study characteristics

The characteristics of the included studies directly comparing LBC and CC were abstracted. These included study location (e.g., setting and country), study population (e.g., characteristics, inclusion and exclusion criteria, and age distribution), and test characteristics. Data pertaining to test characteristics included test type (e.g., ThinPrep, BD SurePath, or CC), collection device (e.g.,

cervical brush or broom), cytological cut-offs (e.g., ASCUS+ or LSIL+), and reference standard (e.g., histology or consensus cytology reading). The MS Excel form for data abstraction was adopted from a previous SR.⁴³

Relative accuracy of LBC and CC

For studies directly comparing LBC and CC, data from 2×2 diagnostic tables (i.e., false or true positive or negative values) according to cytological cut-off and disease status were extracted for each technique (i.e., ThinPrep, BD SurePath, or CC). For instance, diagnostic data from a cross-tabulation of cytological readings (e.g., normal, ASCUS+) and histology (e.g., <CIN 1, CIN 1+) were extracted. When the data were not reported in a 2×2 diagnostic table, the tabular values were recalculated using other data, if feasible. For example, a 2×2 table was reconstructed if the total number of samples, sensitivity, specificity, and positive predictive values were reported.

Accuracy estimates of LBC-specific techniques

Similar procedures were used to extract diagnostic data from studies evaluating LBC-specific techniques (e.g., ThinPrep or BD SurePath) with no corresponding CC data.

Discordance in cytological classifications between LBC and CC

For split-sample studies (i.e., the cervical specimen was first used to make a CC smear, and the remaining cervical cell specimen was used for LBC), discordant data between LBC and CC readings were extracted using a convention adopted from a previous technology assessment of LBC.²⁷ From the cross-tabulation of LBC and CC readings (e.g., negative, ASCUS, LSIL, HSIL, or cancer), the following discordant percentages were calculated: the percentage of cases classified as LSIL+ by LBC but as <LSIL by CC, and the percentage of cases classified as LSIL+ by CC but as <LSIL by LBC. The percentage of cases classified as LSIL+ by LBC and CC was also calculated. The discordance between LBC and CC was assessed at the LSIL+ threshold, because it seemed to be the most consistently reported across many studies, and the LSIL+ threshold is often used as an indication for colposcopy referral.²⁷

For two-cohort studies (i.e., each cervical specimen was examined using CC or LBC but not both), the number of participants and percentage of LSIL+ cases were extracted for each cohort. Similar data were extracted for HSIL+ cases if reported. Also, the percentages of inadequate or unsatisfactory specimens were extracted from studies in which the data were available for comparisons between LBC and CC.²⁷ All outcome data were extracted independently by two reviewers (MF, HW) and verified by another (BP). The MS Excel form for data abstraction was adopted from a previous HTA.²⁷

4.1.4 Strategy for quality assessment

The quality assessment of primary studies directly comparing LBC and CC was conducted using a validated checklist specific to LBC evaluation, which was adopted from a SR.⁴² The checklist includes items for LBC type, study design, study setting, and study validity. The options for assessing study design were split-sample or two-cohort, and the latter included whether groups were randomized. The study setting included family practice, referral clinic, both, or others. For study validity, the use of a reference standard was assessed through a series of queries. Was a reference standard such as histology, cytology, or consensus reading used? Was the reference standard assessed without knowledge of test results (i.e., blind assessment)? Were different reference standards used in a study? In a split-sample study, were all tests, all positive tests, or all discordant tests verified, or

was the verification partial or unclear? Did each cytologist read tests without the knowledge of any other readers' results? In a two-cohort study, were all positive tests or all positive tests plus a random sample of negative tests verified, or was the verification partial or unclear? Were participants randomly allocated to the test? If not randomly allocated, were controls concurrent or historical?

A split-sample study was defined as high quality if cytologists read the tests without knowledge of other readers' results, if a blind reference standard was used (i.e., if outcome-related information and clinical characteristics were masked from the readers), and if (at a minimum) all discordant slides were verified. A two-cohort study was defined as high quality if it used a blind reference standard and verified all positive and at least a random sample of negative slides. Medium-quality studies used a reference standard with methods of blinding or verification that did not meet the requirements for classification as high quality. Studies without a reference standard were classified as low quality.

The MS Excel form for quality assessment was adopted from a previous SR.⁴² One reviewer (AJB) conducted the quality assessment after piloting the procedure with another reviewer (BP) on five studies. Disagreement regarding the piloting material was resolved with discussion. The second reviewer (BP) verified the results from the first reviewer's assessment.

4.1.5 Data analysis

a) *Relative accuracy of LBC and CC*

A meta-analysis assessing the relative accuracy of diagnostic tests calls for concurrent estimates of sensitivity and specificity in a framework that accounts for the fact that a gain in sensitivity necessarily entails a loss in specificity.⁴⁴ The diagnostic performance of LBC and CC was summarized by plotting the true-positive and false-positive values according to the summary receiver-operating characteristics (SROC) curve. The SROC model corresponds to the assumption that the observed differences across studies result from different thresholds for test positivity. The current meta-analysis used a hierarchical SROC model for combining estimated pairs of true-positive and false-positive values from multiple studies.⁴⁴ The hierarchical SROC model allows appropriate incorporation of within- and between-study variability and flexibility in the estimation of summary statistics. The model describes within-study variability using a binomial distribution for the number of positive tests in patients with or without disease. It also allows variability in the positivity criteria and accuracy parameters across studies by modelling related parameters using a normal distribution. A scale parameter is included to account for differences in the variance of outcomes in disease-negative or disease-positive populations.

A fully Bayesian approach to model fitting leads to simulated values from the posterior distribution of the parameters and estimated posterior distributions of a range of parameters. Two reviewers (BP, MHC) conducted the analyses using Markov chain Monte Carlo simulations in WinBugs⁴⁵ and with additional guidance from another reviewer (GT).

b) *Pooled estimates of other outcomes*

The results from individual studies are likely to vary because of differences in study populations, test characteristics, and outcome ascertainment. A random-effects model was used to derive the pooled estimates of accuracy and classification outcomes, including sensitivity and specificity of LBC-specific techniques, discordant percentages from split-sample studies, and cytological classifications from two-cohort studies. Pooled estimates associated with statistically significant heterogeneity (i.e., chi-squared test for heterogeneity at a significance level of 0.1) were asterisked in the summary tables.⁴⁶

It has been suggested that LBC reduces the frequency of unsatisfactory samples. This suggestion was investigated in a SR via a forest plot of differences in rates of unsatisfactory samples between LBC and CC across studies.⁴² The forest plot was revised with new data from the SR.

4.2 Results

4.2.1 Quantity of research available

The literature search on LBC effectiveness (Figure 1) identified 119 studies. The relevant studies included those identified from a UK technology assessment report (n=62),²⁷ a previous CADTH report (n=13),²² and the updated literature search from January 2002 through June 2006 (n=44). After duplicates were removed, 108 primary studies remained. The 44 updated studies were identified via a combination of screening (n=931 potentially relevant citations) and full-text reviewing (n=173 articles).

The relevant studies included those directly comparing LBC and CC (n=20), studies reporting LBC sensitivity or specificity (n=49), and studies reporting unsatisfactory samples (n=66) (Figure 1). Forty-seven split-sample studies provided enough data to assess the discordance between LBC and CC, with 31 two-cohort studies reporting the cytological classification from both techniques. Data on the included studies appear in Appendix 2.

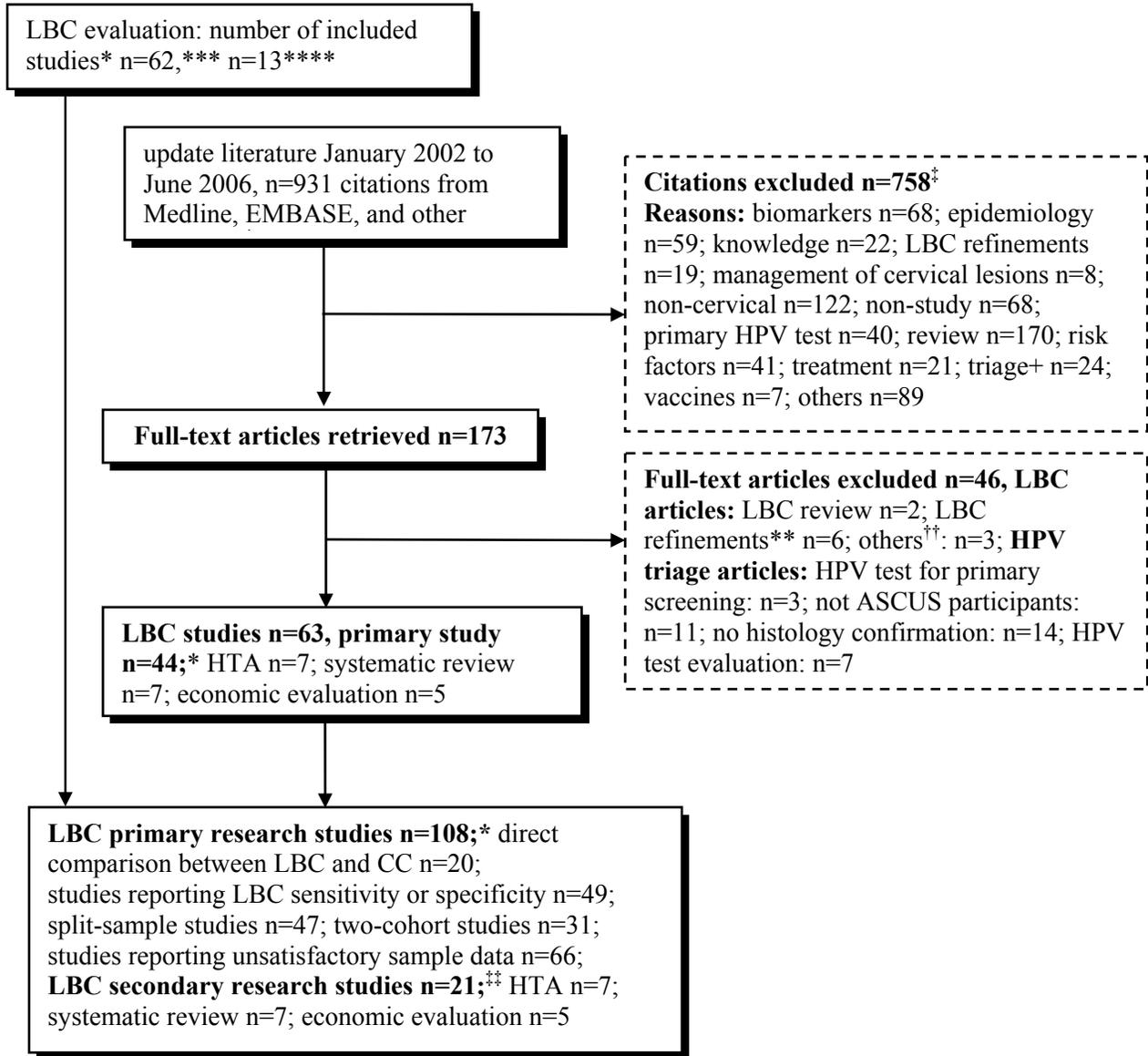
4.2.2 Previous SRs

The updated literature search (Figure 1) identified 14 reports on LBC effectiveness (seven SRs and seven HTA reports) published between 2000 and 2006. Two HTA reports underwent revisions. The CADTH evaluation of LBC that was published in 1997⁴⁷ was updated in 2003.²² The similar British HTA evaluation that was published in 2000 was updated in 2004.^{24,27}

Six SRs concluded that LBC is more effective than CC (Table 1 Appendix 2). These SRs were published in 2000 (n=1), 2001 (n=1), 2003 (n=3), and 2004 (n=1). Five SRs concluded that there was insufficient evidence to draw conclusions about LBC effectiveness. These SRs were published within the same time frame as the previous six: 2002 (n=3), 2003 (n=1), and 2006 (n=1). Three were equivocal in their conclusion. Among the last three, Nanda *et al.* suggested that there were insufficient high-quality data to estimate the sensitivity and specificity of LBC.³⁴ Sulik *et al.* suggested that the use of LBC increased true-positive and false-positive rates, although these inferences were considered to be tentative.⁴⁸ Klinkhamer *et al.* reviewed data for BD SurePath and ThinPrep. They suggested that no definitive statement could be made about the detection rate of LSIL+ and HSIL+ in the comparison between BD SurePath and CC, and that it was likely the detection of LSIL+ and HSIL+ with ThinPrep was more sensitive compared with that of CC. They concluded that more research was needed.⁴⁹

The Davey *et al.* SR examined the effects of study design and quality on the performance of LBC versus that of CC regarding accuracy, rates of unsatisfactory sampling, and cytology classification.⁴² It reviewed 56 published primary studies and critically appraised them with strict methodological criteria. Data were examined for studies overall and stratified by study quality. The overall rates of unsatisfactory slides were 0.75% and 0.81% for LBC and CC respectively.

Figure 1: Literature on LBC



*Numbers do not add up because of overlapping material between literature searches.

†Other databases included BIOSIS, CANCERLIT, PASCAL, and Cochrane Library.

‡Knowledge: studies of knowledge and attitude toward HPV-related diseases; triage+: studies of HPV test for women with ASCUS and higher [e.g., low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL)].

**For example, studies of automated extraction of HPV samples from LBC samples and automated assisted LBC screening.

††Studies of self-sampling, automated screening, and textual imaging.

‡‡Numbers of studies, including back-referencing articles (i.e., found by manually searching reference lists of relevant studies).

ASCUS=atypical squamous cells of undetermined significance; CC=conventional cytology; HPV=human papillomavirus;

HTA=health technology assessment; LBC=liquid-based cytology.

***Karnon²⁷

****Noorani²²

The Karnon *et al.* technology assessment, an update of a previous report,²⁴ examined LBC effectiveness using data from 62 studies.²⁷ The results from a meta-analysis showed a combined rate ratio for false negatives of LBC versus CC of 0.76 (n=14 studies with 5,798 participants) (95% CI: 0.60; 0.98). The respective estimates of LBC and CC sensitivity were 80.1% and 71.5%, indicating that LBC was associated with a 12% relative improvement in sensitivity (an absolute improvement of 8.6%). A meta-analysis of the six studies that compared specificity between CC and LBC showed no difference, and the specificity of LBC was assumed to be unchanged from that of CC. Discordant data from split-sample studies suggested that LBC seemed to result in more slides being classified as LSIL+, instead of the lower diagnosis (e.g., negative or ASCUS) classified using CC. The results for HSIL+ showed a similar pattern to those seen with LSIL+. Data from two-cohort studies seemed to be consistent with data from split-sample studies. LBC was associated with an increase in the classification of LSIL+ and HSIL+. Results from 35 studies reporting the percentage of specimens classified as inadequate or unsatisfactory showed a higher rate of unsatisfactory samples with CC than LBC. The reviewers stated that uncertainties remained, because there are no randomized controlled trials comparing the two techniques with respect to long-term outcomes such as invasive cervical cancer and related mortality.

As part of a technology assessment, Noorani *et al.* systematically reviewed data on LBC effectiveness.²² They identified 13 relevant studies, of which 11 trials (n=4,406 test samples) were included in a meta-analysis of sensitivity. At a threshold of LSIL, the sensitivity was higher for LBC (range 53% to 96%) than for CC (range 35% to 94%). For a cervical-cancer screening population, LBC was more sensitive than CC [sensitivity ratio 1.17 (95% CI: 1.02; 1.35)]. For populations with a high risk of HPV infection, precancerous lesions, or cancer, the sensitivity was not different from that of CC [ratio 1.07 (95% CI: 0.97; 1.18)]. There was no significant difference in specificity between LBC (range 45% to 99.5%) and CC (range 17% to 99.7%). The specificity ratio between the two cytology techniques was 1.35 (95% CI: 0.82; 2.23), indicating no significant difference. Eight trials (n=131,407 samples) reported on the rate of unsatisfactory specimens. LBC had a lower rate of unsatisfactory specimens (range 0.1% to 1.0%) than CC (range 0.1% to 12.0%). The ratio of unsatisfactory samples of LBC versus CC was 0.34 (95% CI: 0.20 to 0.59), suggesting that LBC had fewer unsatisfactory samples than CC. In their conclusions, the authors noted that the failure of some trials to meet validity criteria, including the “limitation of not having all women receive the reference test,” hampered interpretation of the results.

4.2.3 Methodological issues in LBC evaluation

Most of the SRs addressed methodological issues in the primary studies of LBC evaluation (Table 1 Appendix 2). There were concerns about the potential differences between study populations from countries with organized cervical-cancer screening programs (e.g., UK, Nordic countries) and those from countries with opportunistic screening programs (e.g., US, Canada). False-negative smears may be less evident in the context of annual smears than in programs with a three- to five-year recall period.⁵⁰ For example, relatively self-selected cohorts of women in the US may not be comparable to the cohort of UK women. Daily practice by cytotechnologists may also differ across countries.⁵⁰

The study design was generally poor, with few studies using adequate methods to compare tests. No study was classified as ideal quality, because none randomly assigned women to LBC or CC and verified at least all positive slides with a masked reference standard. From 56 studies included in one SR, five met the criteria for high quality, 32 met the criteria for medium quality, and 19 met the criteria for low quality.⁴² The split-sample design was the most common (39/56). This design has the advantage of increased statistical power, because each person acts as her own control, thus reducing

variance.⁴² Several split-sample studies reported an increased detection of abnormalities with LBC.⁵⁰ In most of these studies, there were sparse or non-existent biopsy or histology follow-up data. As a result, the clinical yield of epithelial abnormalities was unknown. In these circumstances, false-positive test results could be misinterpreted as increased sensitivity.⁵⁰ Where a histological reference standard had been used, the test evaluation was often based on discordant test results (one test was negative and the other positive). This discordant analysis has statistical deficiencies and potential bias implications.⁵¹

In two-cohort design studies, the allocation to LBC or CC may not be random.⁴² In cytology, these studies are generally direct-to-vial design, such that the LBC specimen is not preceded by the preparation of a CC slide. Tests are compared in two groups, and each participant undergoes one test only. Ideally, as in all comparative studies, the groups should be the same in all respects apart from the test received. This may not be the case because allocation to the test was likely influenced by other factors.⁴²

Another concern was that the higher sensitivity with LBC may have been predominant for the detection of low-grade lesions.³⁰ The detection of LSILs might be undesirable when considering aspects of specificity. The most appropriate parameter for specificity should relate colposcopic referral due to an abnormal smear with the presence or absence of HSILs.⁵⁰ This impact on specificity is poorly documented.³⁰

The estimates of the rates of inadequate or unsatisfactory samples across studies were subject to variation in reporting terminology (e.g., Bethesda System Terminology for the US and the British Society for Clinical Cytology terminology in the UK) and screening practices. For example, the rates of unsatisfactory samples in screening programs in the UK could range from 1% to 9%, whereas the corresponding rates are typically <1% for programs in North America.^{6,27,50}

4.2.4 Meta-analysis of LBC effectiveness

a) *Relative accuracy of LBC and CC*

The diagnostic performance of cytology techniques involves a trade-off between sensitivity and specificity. An improvement in sensitivity most likely coincides with a decrease in specificity. The estimates of sensitivity and specificity of LBC and CC from 20 head-to-head studies reporting sensitivity and specificity data for both tests are summarized simultaneously (Table 2 Appendix 2). The meta-analysis of data from 20 head-to-head studies including 68,114 participants showed no statistical differences in sensitivity and specificity between LBC and CC (Table 3 Appendix 2). The average sensitivity difference for LBC relative to CC was 6.4% (95% CI: -6.5%; 18.8%, Table 3 Appendix 2). The average specificity difference for LBC relative to CC was -4.0% (-19.8%; 10.6%). Neither trade-off estimate was statistically significant as indicated by the confidence interval boundaries that included the value of zero (i.e., no difference). The hierarchical random-effects model accounted for the across-study heterogeneity in cytology cut-offs, reference standards, and the corresponding reference standard levels (Table 3 Appendix 2).

The trade-off estimates from the main analysis (n=20 studies) were similar to those from the sensitivity analysis that was restricted to high-quality studies (n=6) (Table 3 Appendix 2). According to these high-quality studies, the average difference for LBC relative to CC was 7.7% (-17.2%, 23.5%). The average specificity difference for LBC relative to CC was -4.4% (-19.3%, 43.4%). Restricting data to the 13 studies in which a histology classification from a combination of colposcopy and biopsy was used as a reference standard changed the trade-off estimates. In this

sensitivity analysis, the average sensitivity difference for LBC relative to CC was 1.2% (−16.6%, 16.4%), and the average specificity difference was −0.6% (−18.9%, 17.3%). The trade-off estimates for one LBC technique (n=17 studies) were consistent with those of the main analysis, most likely because most of the data came from studies of this technique (Table 3 Appendix 2).

Using the graph presented by Davey *et al.*, the sensitivity and specificity data from the included studies are plotted on the receiver-operating characteristic (ROC) space (Figure 2).⁴² For each study, there are two points (one for LBC and one for CC) joined by a line. The dotted curves represent the contours defined by a constant diagnostic odds ratio (a measure of test accuracy). These curves enable the differentiation between changing thresholds and an improvement in accuracy. If points move along the curves, the threshold is changing without a change in accuracy. The points lying on curves that are closer to the top left-hand corner of the graph represent higher accuracy. The pairs of points in Figure 2 did not provide any strong evidence that the accuracy of LBC is statistically significantly higher than that of CC.

b) Estimates of LBC sensitivity and specificity

At the cytology cut-off of ASCUS+ to detect CIN 1 or greater (CIN 1+), the sensitivity of one LBC technique was 84% (95% CI: 73%; 95%) and specificity 78% (63%, 93%) (Table 4 Appendix 2). At the cytology cut-off of LSIL+ to detect CIN 1+, the sensitivity of this technique was 71% (61%, 82%) and specificity 86% (73%, 98%). The pooled estimates of sensitivity and specificity of this technique at other cytology cut-offs to detect disease status at different histology levels appear in Table 4 Appendix 2. Although pooled estimates of corresponding data for another LBC technique were not generated, data from individual studies are shown in Table 1 Appendix 3.

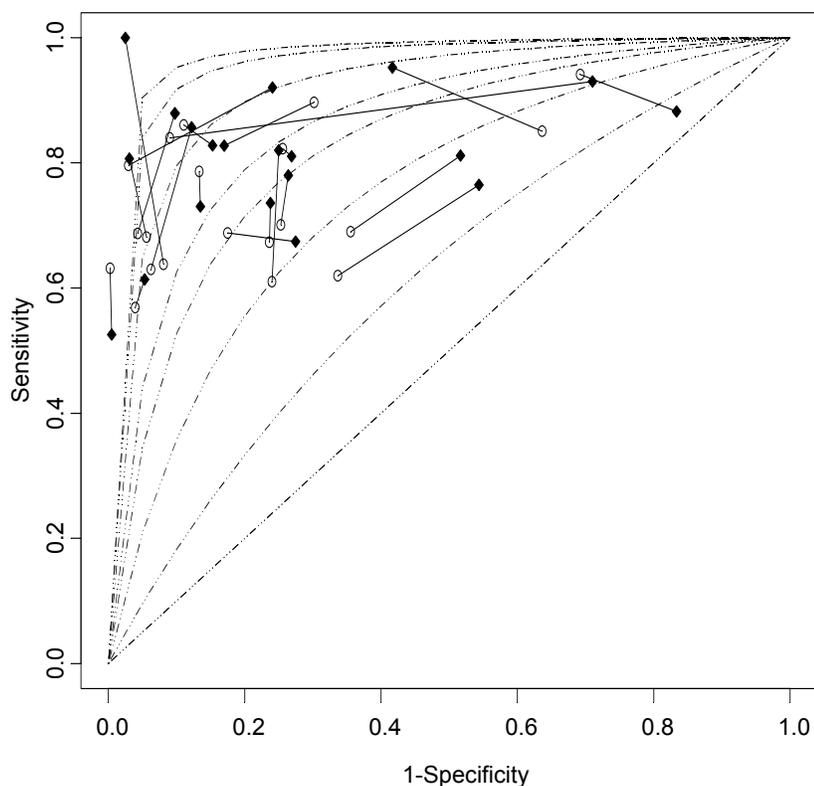
c) Discordant analysis of LBC and CC classifications

In the 33 split-sample studies evaluating one LBC technique (n=113,826 participants), more slides were classified as LSIL+ using LBC instead of the lower diagnosis (i.e., negative or ASCUS) classified using CC, than the reverse situation (i.e., slides classified as LSIL+ using CC but below LSIL using LBC) (Table 5 Appendix 2). In the first scenario, the percentage of slides classified as LSIL+ by LBC but <LSIL by CC was 3.1% (95% CI: 2.0%; 4.1%). The percentage in the reverse situation was 2.2% (1.3%, 3.1%). Both estimates were associated with significant heterogeneity in disease prevalence between study populations.

The percentage of LSIL+ confirmed by using LBC and CC in these studies ranged from 1.4% to 54%, indicating a large variation in study populations (Table 5 Appendix 2). In these split-sample studies, LBC classified approximately 1% more slides as LSIL+ than CC. Similar results were observed in 13 split-sample studies of the other LBC technique (n=24,633 participants). Data from individual split-sample studies are shown in Table 32 Appendix 2.

In 22 two-cohort studies (n=1,903,813 participants), one LBC technique classified significantly more samples as LSIL+ than CC in cross-cohort comparisons [difference=1.3%, (95% CI: 0.02%; 2.6%)] (Table 5 Appendix 2). Twelve studies (n=950,139) reported HSIL+ classifications. From these studies, LBC seemed to classify fewer samples as HSIL+ across cohorts, although the result was not statistically significant [difference of −0.25% (−1.6%, 1.1%)]. In both types of cytology classifications, there was significant heterogeneity across studies. Similar results were observed in 10 two-cohort studies (n=1,208,978) evaluating cytology classifications with the other LBC technique (Table 5 Appendix 2). Data from individual cohort studies are shown in Table 33 Appendix 2.

Figure 2: Sensitivity and specificity of LBC versus CC in head-to-head comparison studies



Solid dots represent LBC; open dots represent CC.

d) Unsatisfactory samples

Data were pooled from 44 studies reporting information on unsatisfactory slides. Overall, 6,674 (0.95%) of 704,813 slides were classified as unsatisfactory using one LBC technique, whereas 13,664 (1.04%) of 1,316,318 CC slides were unsatisfactory. Similarly, data were pooled from 15 studies of another LBC technique, including 597,565 LBC samples and 692,406 CC samples. Overall, 2,539 (0.42%) of 597,565 LBC slides were unsatisfactory, whereas 9,598 (1.39%) of 692,406 CC slides were unsatisfactory. On average, the percentage of unsatisfactory slides from LBC samples was less compared with that from CC samples (Table 5 Appendix 2). The estimates from individual studies were heterogeneous, reflecting differences in screening programs, smear settings, and practices (Figure 1 Appendix 2). In studies with large sample sizes (i.e., small confidence intervals around the difference estimates of LBC versus CC), the difference estimates between the two techniques were close to zero (Figure 1 Appendix 2). Unsatisfactory data from individual studies are shown in Table 34 Appendix 2.

4.3 Discussion

This SR of LBC effectiveness incorporated material from all relevant SRs and added more recent studies. The consolidated data were then subjected to meta-analysis using published methods for the evidence synthesis of diagnostic studies.⁴⁴ Our results quantify the relative accuracy of LBC and CC.

We show that the incorporation of LBC in cervical-cancer screening programs could entail a potential gain of 6% in sensitivity and a loss of 4% in specificity. According to the relative frequency of the observed accuracy data, one interpretation might be that there is no difference between the operating characteristics of these tests, because we cannot exclude the possibility that the observed differences arose by chance alone.

Because the analysis used Bayesian methods, we can supply an alternative interpretation. The chance that LBC is superior to CC can be quantified from the related posterior distributions in our analysis. The posterior probability of LBC being more sensitive than CC is $83\% \pm 37\%$. The chance that LBC is less specific than CC is $72\% \pm 45\%$. The observed sensitivity gain (6.4%) and specificity loss (-4.0%) for LBC relative to CC represent our best estimates of the true difference in operating characteristics of these tests. The likelihood of these differences having arisen by chance is not zero, but neither is it large (17% in the case of sensitivity, 28% in the case of specificity).

These equivocal estimates partly explain the discordant findings from previous SRs. Of the 14 relatively concurrent SRs evaluating LBC effectiveness, six provide data in support of LBC, five do not support LBC, and three remain noncommittal. The trade-off estimates for LBC to replace CC were shown to be associated to study quality.⁴² If the analysis was restricted to data from high-quality studies, the trade-off estimates were a sensitivity gain of 7.7% and a specificity loss of 4.4% for LBC relative to CC. The average trade-off estimates were smaller if the analysis was restricted to data from studies with a histology classification as the reference standard.

There are limitations in our evidence synthesis. The decision to pool data across studies was undertaken in spite of clinical heterogeneity. Study quality, especially the use of a proper reference standard in test evaluation, varied across studies. Most studies were of low quality.⁴² There were differences in study design, blinding of test evaluation, and verification with a reference standard. The included studies were conducted in different screening programs, including organized and opportunistic screening programs (with differences in, for example, screening intervals, screening and cytotechnologists' practices). The handling of clinical heterogeneity in this SR differs from that in other SRs. For example, one SR focused on the effect of study design and quality on different screening outcomes in the evaluation of LBC as an alternative for CC.⁴² We placed less emphasis on identifying and explaining the sources of heterogeneity, and concentrated on quantifying the average effect of LBC on screening outcomes.

Our estimated average gain in LBC sensitivity of $6.4 \pm 6.5\%$ is consistent with the 11% improvement reported in the previous CADTH report.²² In an economic evaluation of LBC, Karnon *et al.* suggested an average gain of 4.0% and 8.4% for LBC sensitivity to detect CIN 3 and CIN 1-2 respectively.²⁷ Our findings that LBC classified more samples as LSIL and fewer as HSIL have been discussed in other SRs.^{30,42,52} The marginal unsatisfactory rates between LBC and CC are similar to those reported previously.⁴² The studies directly comparing LBC and CC included in this SR might differ from those included in a previous SR of CC. The pooled estimates of sensitivity and specificity for CC based on these data are higher than those reported previously by Nanda *et al.*³⁴

The validity of the average trade-off estimates in sensitivity and specificity between LBC and CC seems to depend on the standard reference used in the 20 head-to-head comparison studies reporting sensitivity and specificity data for both tests. When the analysis was restricted to data from the 13 studies in which the recommended standard reference of histology was used, there are no differences in the accuracy trade-off estimates between LBC and CC. The use of standard references, however, is

only one facet of the quality of study conduct. According to a SR, study quality encompasses issues related to study design, appropriate reference standards, blind assessment, and verification of test results.⁴² Using data from six high-quality studies, the average trade-off estimates were a 7.7% sensitivity gain and 4.4% specificity loss between LBC and CC. These estimates were consistent with those from the main analysis using data from 20 head-to-head studies reporting concurrent data for sensitivity and specificity.

Given the heterogeneity of study settings, the average aggregated findings that are reported may not reflect the circumstances of some cervical screening programs. Monolayer cytology was found to be less reliable and more likely to give false-positive and false-negative results than CC in a study conducted with participants from public university and private practices in France.^{53,54} In a South African screening trial, LBC and CC showed no statistically significant differences in accuracy, although the sensitivity of CC was at least 5% higher at all cut-off levels. LBC specimens were significantly less likely to be “satisfactory-but-limited-by” (this Bethesda 2001 terminology has been eliminated) but significantly more likely to be unsatisfactory. The authors of the reported trial concluded that screening programs with low resources should consider the potential benefits and drawbacks of LBC before adopting this technology.⁵⁵ LBC was also reported to have lower sensitivity in other studies conducted in South Korea⁵⁶ and the US.⁵⁷⁻⁵⁹

A large randomized controlled trial has shown no significant difference in sensitivity for CIN 2+ with LBC using one LBC technique compared with CC.⁶⁰ More false-positive results were found with LBC, leading to a lower positive predictive value.⁶⁰ Although the claims made in favour of LBC have not been substantiated, equivalent performance may be enough if LBC has other advantages. For example, LBC provides a convenient platform for concurrent HPV DNA testing, reduces the number of inadequate slides, and increases laboratory throughput in a real-life UK pilot study.⁴⁰ A recent observational study compared the accuracy of one automated LBC imaging system with that of CC.⁶¹ The automated system detected 1.29 more cases of histological high-grade squamous disease per 1,000 women screened than CC, with CIN 1+ as the threshold for colposcopy referral. The automated imaging system on this LBC platform reduced the percentage of unsatisfactory slides (1.8% for imager read cytology versus 3.1% for CC).⁶¹ Uncertainties remained with continuing calls for the acquisition of high-quality data from properly conducted multi-centre randomized controlled trials.^{42,50} Given the diffusion of LBC in cervical screening programs, alternative data sources for evaluation exist. The advantages and deficiencies in new screening techniques may become apparent after years of implementation.

Colgan *et al.* evaluated the adequacy and detection rates of one LBC technique after its implementation in Ontario.⁶ They reported that the unsatisfactory rate for LBC (0.24%) was less than that of CC (0.58%). The detection rate of ASCUS in the LBC group (4.69%) was greater than that in the CC group (3.81%), as was the detection rate of LSIL+ (2.13% versus 1.50% for LBC and CC respectively). There was a trend toward the increased detection of high-grade squamous intraepithelial lesion and higher grade lesions (HSIL+) in LBC (0.34%) relative to CC (0.31%), because the detection rate for carcinoma by LBC declined. These findings suggest that the average effect of LBC estimated from the consolidated data in our SR could be locally applicable.

5 CLINICAL REVIEW OF HPV TRIAGE

The natural history of minor cytologic lesions is difficult to predict on the basis of cytology results. These lesions often regress spontaneously and do not require treatment. Referring all women with minor cytologic lesions for further gynecologic exploration would mean an increase in overdiagnosis and overtreatment. Although most women with an ASCUS smear result do not have clinically significant disease, a proportion of them have histopathologically confirmed high-grade CIN or worse (CIN 2+). Given the evidence on the etiologic role of oncogenic HPV infections in the development of cervical cancer and CIN, HPV testing has been proposed as a triage method to identify women at increased risk of cervical cancer and thus requiring referral for colposcopic exploration.⁴³

5.1 Methods

5.1.1 Literature search strategy

Arbyn *et al.* conducted a SR of virologic versus cytologic triage of women with equivocal Pap smears to detect high-grade intraepithelial neoplasia.⁴³ The literature search was conducted between 1992 and 2002. The current literature search between November 2002 and June 2006 (Appendix 1) was used to update Arbyn *et al.*'s SR.

5.1.2 Selection criteria and method

Similar to Arbyn *et al.*'s SR, the inclusion criteria were study participants who presented with an index CC of ASCUS or AGUS, performance of an HPV DNA test, and participants who were subsequently subjected to colposcopy and colposcopy-directed biopsies for histology verification.⁴³

5.1.3 Data abstraction strategy

Data from Arbyn *et al.*'s SR were extracted.⁴³ Data were abstracted from newly identified studies according to the established methods of the previous SR.⁴³ Abstracted data included characteristics of the study populations, and characteristics of the index Pap test and HPV triage. Accuracy data from 2×2 diagnostic tables were extracted. Data abstraction was conducted by one reviewer (SC) and independently verified by another (BP).

5.1.4 Data analysis

The pooled estimates of sensitivity and specificity were derived using a random-effects model, taking into account the potential clinical heterogeneity among included studies.⁶²

5.2 Results

5.2.1 Quantity of research available

The literature search yielded 45 primary studies, two SRs, five HTA reports, and 12 economic evaluation studies (Figure 3). Accuracy data from all included primary studies appear in Table 35 Appendix 2.

5.2.2 Previous SR

Arbyn *et al.* conducted a meta-analysis of the accuracy of virologic and cytologic triage of women with equivocal Pap smears to detect HSIL (Table 6 Appendix 2).⁶³ Fifteen studies of HPV triage and nine studies of repeated cytology were identified. The sensitivity and specificity estimates of HPV triage to detect CIN 2+ were 95% (95% CI: 93%; 97%) and 67% (95% CI: 58%; 76%) respectively. The sensitivity and specificity of repeat cytology at a threshold of ASCUS+ were 82% (74%, 84%) and 58% (50%, 66%) respectively. Repeat cytology that used higher cytologic thresholds yielded lower sensitivity but higher specificity than HPV triage.

Arbyn *et al.* updated the previous meta-analysis in 2005.¹¹ In 16 studies, the sensitivity and specificity of HPV triage to detect CIN 2+ were 94% (92% to 96%) and 62% (56% to 68%) respectively. The sensitivity of HPV triage was 14% (8% to 20%) higher than repeated cytology using an ASCUS+ cut-off in six studies in which both tests were used. The pooled specificity of HPV triage and repeated cytology were nearly equal [pooled intra-study specificity ratio estimate of 0.99 (0.89, 1.11)]. The reviewers concluded that HPV triage performed better than repeated cytology for ASCUS triage.

Arbyn *et al.* updated the SRs in 2006 to include 20 studies.¹² The sensitivity and specificity of HPV triage to detect CIN 2+ were 93% (90% to 95%) and 63% (58% to 67%) respectively. In seven studies where a repeated Pap smear was taken, the sensitivity of HPV triage was on average 14% higher than repeated cytology at the ASCUS+ cut-off.

5.2.3 Update on HPV triage

From 24 included studies, the sensitivity and specificity of HPV triage to detect CIN 2+ were 86% (81% to 91%) and 62% (57% to 66%) respectively (Table 7 Appendix 2). Inter-study heterogeneity was not statistically significant for sensitivity but significant for specificity. The included studies were clinically heterogeneous as indicated by the reported prevalence of CIN 2+, ranging from 3% to 36%. In nine studies where a repeated Pap smear was taken, the sensitivity and specificity of repeat cytology at a threshold of ASCUS+ were 79% (73%, 85%) and 58% (36%, 80%) respectively.

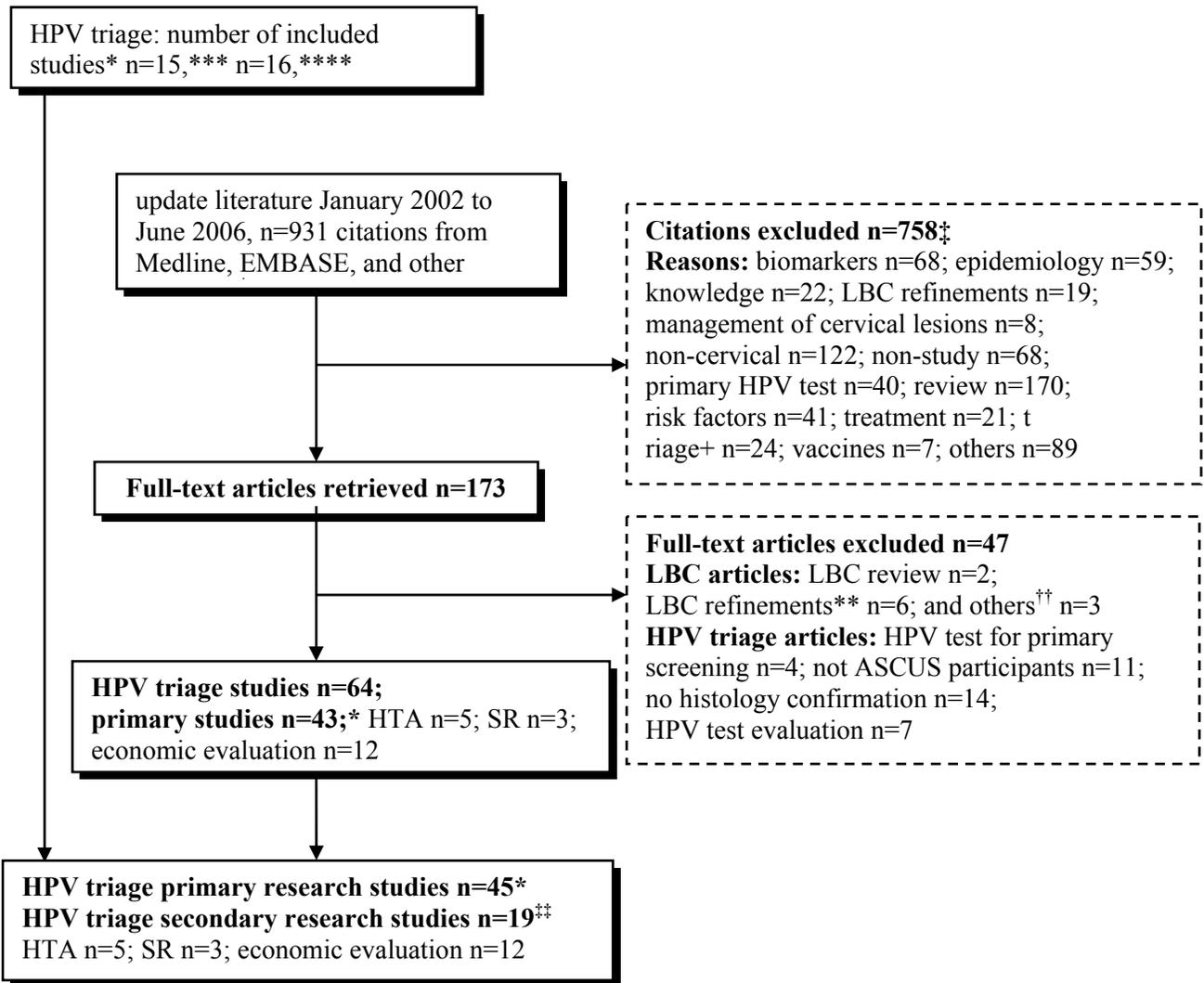
5.3 Discussion

To consolidate data on the utility of HPV triage for individuals with ASCUS cytology, Arbyn *et al.* conducted a SR to address three questions. What is the accuracy of HPV triage to detect histologically confirmed CIN 2+ disease in women with an index smear showing ASCUS? In studies where CC was repeated, what is the accuracy of repeated CC to detect CIN 2+? What are the differences in accuracy in both triage tests?^{11,12}

They concluded that HPV triage could improve accuracy (i.e., higher sensitivity, similar specificity) than repeat CC using the threshold of ASCUS for an outcome of CIN 2 among women with equivocal cytologic results. The sensitivity of repeated cytology at higher thresholds was poor.⁴³

This update corroborates the results from the meta-analyses by Arbyn *et al.*^{11,12,43} and indicates that HPV triage for ASCUS cases has higher sensitivity than repeated cytology for the detection of CIN 2+. This is consistent with the findings from the ALTS trial.

Figure 3: Literature on HPV triage



*Numbers do not add up because of overlapping material between literature searches.

†Other databases included BIOSIS, CANCERLIT, PASCAL, and Cochrane Library.

‡Knowledge: studies of knowledge and attitude towards HPV-related diseases; triage+: studies of HPV test for women with ASCUS and higher [e.g., low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL)].

**For example, studies of automated extraction of HPV samples from LBC samples and automated assisted LBC screening.

††Studies of self-sampling, automated screening, and textual imaging.

‡‡Numbers of studies, including back-referencing articles (i.e., found by manually searching reference lists of relevant studies).

ASCUS=atypical squamous cells of undetermined significance; HC II=Hybrid Capture II; HPV=human papillomavirus; HTA=health technology assessment; LBC=liquid-based cytology; SR=systematic review.

***Arbyn⁴³

****Arbyn¹¹

*****Arbyn¹²

The trial showed that serial cytology using an ASCUS cut-off every six months during two years is as sensitive as one reflex HPV-DNA testing immediately after a first observation of ASCUS. The sensitivity of repeated cytology is conditional on compliance with multiple follow-up visits and involves high costs for referral colposcopy.¹²

Consensus management guidelines for the follow-up of ASCUS cytology include repeat cytology, immediate colposcopy, or HPV triage.⁸ If LBC is used for the initial cytologic sample, reflex HPV testing is considered to be the preferred approach because it obviates the need for a repeat office visit. With CC, there is no residual sample available for HPV testing. The collection of cytology and an HPV sample at the first visit, or later self-collection of an HPV sample, may allow triage HPV testing without an additional office visit if using CC. In this report's primary economic evaluation, these proposed practices were considered to be options for sample collection for HPV reflex testing in screening programs using CC.

6 ECONOMIC ANALYSES

6.1 Review of Economic Studies: Methods

SRs of economic studies evaluating LBC or HPV triage were conducted to provide background material for the primary economic evaluation. Identified studies were assessed for their local applicability with respect to three key points.

- The revised estimates of accuracy show that LBC is 6% more sensitive than CC but 4% less specific than CC across a range of thresholds, according to results from the current meta-analysis.
- The qualitative assessment was done on study populations that are similar to those in Canadian settings, including compliance rates and burden of disease.
- The quantitative assessment was done on the overall costs of care associated with screening and treatment in the prevention of cervical cancer.

6.1.1 Literature search strategy

Relevant economic evaluation studies were identified from the main literature search.

6.1.2 Selection criteria and methods

To be included, a study must describe the cost-effectiveness analysis of LBC or HPV triage to replace CC in a developed cervical-cancer screening program. Screening and full-text review were conducted by two reviewers (GW and BS) and independently verified by another reviewer (BP).

6.1.3 Data abstraction strategy

Each included study was appraised with respect to the statement of the problem, key factors in the evaluation (e.g., comparators), descriptions of cost and effectiveness measures, the decision analytic model, data sources, key assumptions, test characteristics, results of the evaluation, and the handling of uncertainties. A data abstraction form done in MS Excel and adopted from a previous HTA report of LBC was used.²⁷

Data pertaining to health effects (i.e., discounted life expectancy and quality-adjusted life expectancy, if available) and cost (i.e., average discounted cost) were extracted by one reviewer (BS) and verified by another (BP). All extracted data were stratified according to screening options (e.g., CC, LBC, LBC + HPV triage) and screening intervals (e.g., one, two, three years).

6.1.4 Strategy for quality assessment

We used a validated tool for the quality assessment of cost-utility studies to assess the quality of the reporting of included studies. It included funding source, framing, reporting of costs, reporting of results, and discussion.^{64,65} A mean rating of 1 to 7 was used to assess the overall quality of reporting, with a higher rating indicating higher quality. Quality assessment was conducted by one reviewer (BP).

6.1.5 Data analysis methods

All costs were converted to Canadian dollars at the purchasing power parity rate for medical and health care⁶⁶ during the appropriate year and inflated to 2006 using the health and personal care component of the Consumer Price Index.⁶⁷ All costs in subsequent sections are expressed in 2006 Canadian dollars.

Incremental cost-effectiveness estimates of LBC versus CC and LBC + HPV triage versus LBC or CC were derived for different screening intervals. ICER estimates were shown across studies and summarized using the median and range.

6.2 Results

6.2.1 Quantity of research available

The literature search yielded nine cost-effectiveness studies primarily evaluating LBC and CC, and seven studies evaluating HPV triage. Three of the nine LBC studies included additional evaluations of HPV triage strategies.

6.2.2 Cost-effectiveness of LBC – Study characteristics

The characteristics of the included cost-effectiveness studies appear in Table 8 Appendix 2. Most of the included studies used a state-transition model (n=8 of nine studies) to simulate lifetime events of individuals in screening populations. Study settings included the US (n=5, including one in a population of US military beneficiaries),⁶⁸ the UK (n=2), Australia (n=1), and Alberta (n=1) (Table 8 Appendix 2). Most adopted a payer perspective (n=8) and assumed that an ASCUS result would be managed by repeating evaluation of cervical cytology (repeat cytology=7, HPV triage=3). All nine reported average lifetime cost per life-year gained in addition to cervical cancer incidence and related death (n=8), resource utilization (n=3), and other disease outcomes (e.g., CIN 3+ detected n=5; false-positive colposcopy referral n=5). All conducted cost-effectiveness analyses, and two included cost-utility analyses as part of the sensitivity analysis. All state-transition models (except one) reported some model validation.

The conduct and reporting of included cost-effectiveness studies appear in Table 9 Appendix 2. Two industry-funded studies using high marginal sensitivity values for LBC (i.e., >20%) reported

favourable cost-effectiveness results for LBC (Table 9 Appendix 2). These studies were of low quality (Table 10 Appendix 2). The Agency for Healthcare Policy Research report in 1999 evaluated LBC and two re-screening techniques. Citing a lack of data, it provided only generic guidance on how to evaluate new screening tests (Table 9 Appendix 2).

The remaining four studies were of high quality [mean rating of 5.5/7 (n=2), 6 (n=2); Table 10 Appendix 2].^{20,27,68,69} They evaluated LBC for screening populations in the US,⁶⁹ in a population of US military beneficiaries,⁶⁸ in the UK,²⁷ and in Alberta.²⁰ All four studies reported that LBC was cost-effective at one-year²⁰ and three-year^{27,68,69} screening intervals. The UK study stated that LBC might also be cost-effective at the two-year screening interval.²⁷

6.2.3 Cost-effectiveness of LBC versus CC

a) **LBC cost-effectiveness studies**

Over an average lifetime, the marginal gain in life expectancy associated with LBC ranged from 0.24 to 0.95 days, 0.20 to 1.00 days, and 0.46 to 1.79 days for the one-year, two-year, and three-year screening intervals respectively (Table 11 Appendix 2). The marginal gain increased with less frequent screening intervals, albeit with variation in the discount rates for effectiveness across studies. The discount rate was 1.5% in the UK study²⁷ and 3% in most other studies. In each study, the marginal sensitivity with LBC partly contributed to the increase in the marginal gain in life expectancy of prevention programs at increasing screening intervals (Table 11 Appendix 2).

The cost per life-year gained (ICER) ranged from \$21,000 to \$517,000, \$5,000 to \$132,000, and \$1,000 to \$52,000 for the one-year, two-year, and three-year screening intervals respectively (Table 11 Appendix 2). At the three-year screening interval, LBC would be cost-effective at a threshold of \$50,000 per life-year gained. This was consistently reported in all five studies, despite heterogeneity in study framing, model structure, input data, and overall study quality (Tables 9 and 10 Appendix 2). At a two-year screening interval, LBC would be cost-effective at a threshold of \$50,000 per life-year gained in three of the five studies. At a one-year screening interval, it would be cost-effective at the same threshold in one of the four studies. According to the British HTA of LBC, the cost per life-year gained using LBC as an alternative for CC would be <\$50,000 at a two-year or three-year screening interval. This study used an estimate of marginal sensitivity of LBC consistent with the current estimate of LBC effectiveness, assumed no difference in specificity between the techniques, and attained an overall rating of 6 out of a maximum rating of 7 for quality of reporting.²⁷

The cost-effectiveness analysis conducted for the Alberta Cervical Cancer Screening Program showed that a one-year screening interval with LBC would cost \$21,000 per life-year gained (at a 3% dual discount rate for health outcomes and costs).²⁰ The marginal sensitivity with LBC used in the analysis was 8.4%. The authors stated that LBC with two- and three-year screening intervals had ICERs per life-year gained <\$5,000, but the economic gains of introducing LBC for the two- and three-year screening intervals would likely result in an increase in the incidence of invasive cervical cancer and related deaths. The results of this analysis differed from those reported by other studies (Table 11 Appendix 2).

The relative efficiency of LBC could be discerned from a study evaluating the cost-effectiveness of HPV DNA testing as a primary screening test with cervical cytology in women aged ≥ 30 years old in the US.⁷⁰ Goldie *et al.* considered screening defined according to cytology techniques (LBC or CC), use of HPV testing with cytology after the age of 30 years, and frequency of the screening program. The cervical cancer model used in this evaluation has been validated.⁷⁰⁻⁷⁶ This study attained a

quality of reporting score of 5 out of 7. The results pertaining to the comparisons of LBC and CC appear in Table 12 Appendix 2. The ICER for a life-year gained was \$719,000, \$253,000, and \$127,000 for one-, two-, and three-year screening intervals respectively.

Most studies reported results from sensitivity analyses assessing parameter uncertainty. LBC was more cost-effective when LBC and CC sensitivity were low (Table 9 Appendix 2).²⁷ As sensitivity increases, specificity decreases and life expectancy increases. The marginal gains in life expectancy from more sensitive screening decrease with consecutive attempts in incremental increases in sensitivity, whereas the costs associated with decreased specificity rise.⁶⁸ In the Alberta evaluation, results regarding the cost-effectiveness of LBC did not change with a 50% decrease of LBC sensitivity, from a marginal sensitivity estimate of 8.4% for LBC. All results were sensitive to changes in compliance rates to Pap screening and the marginal cost of LBC.²⁰ With a two-year interval, CC became cost-effective if the laboratory cost for LBC was doubled.²⁰ Maxwell *et al.* reported that the results were sensitive to the marginal cost of LBC.⁶⁸ Karnon *et al.* in the UK evaluation reported that the results were robust against the marginal cost of LBC and rates of specimen inadequacy.²⁷

b) Cost-effectiveness of LBC + HPV triage versus LBC in LBC evaluation studies

Three studies reported data on the cost-effectiveness of LBC (with repeated cytology) versus LBC + HPV triage as alternative options for ASCUS management (Table 13 Appendix 2). The marginal gain in discounted life expectancy ranged from approximately 0.38 days (9.1 hours) to over a day across studies. This was comparable to the reported marginal gain estimates for LBC relative to CC.

Relative to repeated cytology, HPV triage on an LBC platform was cost-saving, with better health outcomes, in a study evaluating cervical-cancer screening options for US military beneficiaries.⁶⁸ This option was evaluated to cost <\$10,000 per life-year gained in three-year screening programs in the UK.⁷⁷ The cost-effectiveness analysis conducted in Alberta reported ICERs for HPV triage of \$205,000, \$144,000, and \$62,000 for the one-, two-, and three-year screening intervals respectively.²⁰ These results were not corroborated with those from the two previous studies.

6.2.4 Cost-effectiveness of HPV triage evaluation studies

a) Study characteristics

The characteristics of included studies appear in Table 14 Appendix 2. The conduct and reporting of these studies appear in Table 15 Appendix 2. Seven studies evaluated the cost-effectiveness of HPV triage in women requiring follow-up with an ASCUS smear (n=4) or in women undergoing cytological screening (n=3) in cervical-cancer screening programs across health care systems: US (n=4), UK (n=2), the Netherlands (n=2), France (n=1), and Italy (n=1) (Table 14 Appendix 2).

All studies were based on published, validated cervical-cancer models, including two modelling studies with links to a seminal US clinical trial (i.e., ALTS)^{14,15} and a UK pilot study of LBC,^{77,78} and thus, use efficacy data from these sources (Table 15 Appendix 2). Options for ASCUS management under evaluation included immediate colposcopy (n=2), repeated cytology (n=7), and HPV triage (n=7). The latter was unrestricted by age (n=4) or restricted to testing women ≥ 30 years old (n=3) (Tables 14 and 15 Appendix 2).

The quality of reporting of included studies appears in Table 16 Appendix 2. The ratings for reporting quality (maximum=7) were 4 (n=3), 5 (n=1), and 6 (n=3) (Table 16 Appendix 2).

b) Cost-effectiveness of HPV triage versus repeated cytology for ASC follow-up

Among three studies simulating cohorts of individuals requiring ASC follow-up from LBC screening platforms, HPV triage was cost-saving with better health outcomes compared with repeated CC in one US study.⁷³ In a modelling study that was substantiated with data from a pilot study evaluating new cervical screening techniques in the UK, the reported incremental cost-effectiveness estimate for HPV triage compared with repeated cytology was \$11,000 per life-year gained.⁷⁸ In a study conducted for settings in the Netherlands, HPV triage was associated with lower cost, albeit with lower discounted life expectancy (Table 17 Appendix 2).⁹

Two studies simulated cohorts of screening populations on CC platforms (Table 18 Appendix 2). A US study evaluated the options for ASCUS management in screening programs in four European countries. It reported that compared with repeated CC, HPV triage was cost-effective in the UK (ICER of \$8,000 per life-year gained, screening every three to five years in organized screening programs) and cost-saving with reduced health outcomes in France (screening every three years), Italy (screening every three years), and the Netherlands (screening every five years). Uncertainty remains. In the context of CC screening programs in the US, a high-quality study reported that HPV triage was associated with a cost of \$67,000 per life-year gained compared to repeated CC for a three-year screening interval, \$136,000 for a two-year screening interval, and \$385,000 for a one-year screening interval. Similar findings were reported using the cost per QALY by the study (Table 18 Appendix 2).⁷⁰ These results seemed to be discordant with estimates from the previous four studies.

6.3 Primary Economic Evaluation: Methods

A cost-effectiveness analysis of population-based cervical screening options using LBC or HPV triage was conducted according to HTA guidelines for economic evaluations.⁷⁹

6.3.1 Type of evaluation

The economic evaluation included a series of cost-consequence, cost-effectiveness, and cost-utility analyses.

6.3.2 Target populations

A population of sexually active women ≥ 15 years old was the target population for the cost-effectiveness analysis. The evaluation was also conducted on risk subgroups defined according to Pap screening coverage and prevalence of high-risk (HR) oncogenic HPV infection.

Data from Ontario showed a variation in Pap annual screening coverage across 37 public health units, with rates ranging from 11.6% to 73.9%. The provincial average was approximately 40%.⁸⁰ The coverage rates from these public health units were categorized into four quartiles: 1st quartile, with median coverage of 18.6% (range 11.6% to 25.6%); 2nd quartile, 35.5% (27.2% to 40.1%); 3rd quartile, 46.0% (43.8% to 57.4%); and 4th quartile, 63.2% (59.6% to 73.9%). The cost-effectiveness analyses of LBC and HPV triage were conducted for each quartile to provide data on the effectiveness and cost-effectiveness of these screening options for jurisdictions with different Pap coverage.

In the second analysis, the cost-effectiveness of screening options was stratified by the prevalence of HR HPV infection. The overall estimate of HR HPV prevalence for women attending Pap screening in general practitioners' offices in southern Ontario was 12.1%, ranging from approximately 16% in those aged 15 to 19 years, 24% in those aged 20 to 24 years, 16% in those aged 25 to 29 years, 12% in those aged 30 to 34 years, and lower prevalence in older age groups.^{81,82} The prevalence of HR HPV infection was reported to be approximately 22% in a sample of female university students in Montréal.⁸³ Subgroup cost-effectiveness analyses were conducted to reflect the variation in HR HPV prevalence: 12.1% (i.e., the base case), 6%, 18%, and 24%.

6.3.3 Comparators

Two cytology techniques, LBC and CC; HPV reflex testing for ASCUS management (i.e., HPV triage); and the screening intervals at which they are optimally used were considered in the cost-effectiveness analysis. If LBC is used for the initial cytologic sample, reflex HPV testing obviates the need for a repeat office visit (HPV triage).⁸ With CC, there is no residual sample available for HPV testing. In a screening program with CC, the collection of cytology and an HPV sample at the first visit, or later self-collection of an HPV sample, may allow triage HPV testing without an additional office visit. HPV sample collection could be performed during a recall visit, if the index cytology sample revealed atypical squamous cells of undetermined significance (ASCUS) (Table 2). In the cost-effectiveness analysis, all HPV triage options were considered for women aged ≥ 30 years old with an index smear of ASCUS. Younger women with similar cytology results were managed via repeated cytology.⁸ The screening options to be evaluated appear in Table 2. A hypothetical scenario with no screening was evaluated at the beginning of the cost-effectiveness analysis to provide background information on the cost and cost-effectiveness of current screening programs (i.e., the status quo).

Screening Interval	Cytology Technique	Management of Atypical Squamous Cells of Undetermined Significance (ASCUS)
1, 2, 3 years	CC	repeated CC: HPV triage for women aged ≥ 30 years, 0 additional visit; HPV triage for women aged ≥ 30 years, 1 additional visit
	LBC	repeated LBC: HPV triage for women aged ≥ 30 years

CC=conventional cytology; HPV=human papillomavirus; LBC=liquid-based cytology.

Circumstances	Modelling Option	Cervical Cancer Screening Guidelines Recommendations ⁸
initiation	18 years old	should be initiated within 3 years of 1st vaginal sexual activities
interval	base case: annual screening with empirical coverage; others: every 2 and 3 years	should be done annually until there are 3 consecutive negative Pap tests; should continue every 2 to 3 years after 3 annual negatives <ul style="list-style-type: none"> 3-year interval recommended, supported by adequate recall mechanism those who have not been screened in >5 years should be screened annually until 3 consecutive negatives
cessation	70 years old	may be discontinued after age of 70 years if there are 3 to 4 negatives

a) Characteristics of current screening programs

These screening options were evaluated in the context of typical opportunistic cervical screening programs in Canada. Cytological screening for cervical cancer prevention starts within three years of beginning sexual activity (e.g., age 18 years) and ends at age 69 years, according to current guidelines.⁸ The characteristics of current screening programs to be abstracted in the Canadian cervical cancer model used for this analysis appear in Table 3.

b) Pap screening coverage

Data pertaining to Pap screening coverage are available for screening populations from jurisdictions of the health care systems (Table 4). Without a reliable tracking system to record the current screening status of individuals in the populations, it is difficult to interpret coverage data (Table 4). The reported coverage could be influenced by several factors, including the degree of adherence to current recommendations by physicians (e.g., family practitioners and obstetricians-gynecologists), frequency of routine health examinations in the screening population, individuals' compliance with physician's recommendations regarding routine health examinations, and quality of data (e.g., self reporting, billing data, and screening registry).

For the disease modelling, a typical opportunistic screening program was characterized with an empirical one-year screening coverage of 40% (although in the implementation of the evaluation, age-specific coverage data were used). Accordingly, the two-year screening coverage was set at 64% (i.e., 40% the first year, the remaining 60% was to be screened the following year at a compliance rate of 40%). The implication was that in a cervical screening program with an empirical annual coverage of 40%, approximately 64% of the screening population was seen at least once every two years. Similarly, the three-year screening coverage was set at 78.4%. The program could be scaled up to expand coverage in a similar fashion.

Table 4: Modelled abstraction of Pap coverage with current screening programs			
Source	Data Type	Age Range: % Screened	Details (category, % screened)
Health Canada*	1-year, 1998	18 to 69: 40	British Columbia 37; Manitoba 38; Ontario 37; Nova Scotia 44; Prince Edward Island 40; Newfoundland 40
Ontario CytoBase†	1-year, 2001	20 to 69: 41	age range 20 to 49, 41; 50 to 69, 40
CCHS‡ 2000-1	never screened	18 to 69: 12	age range 18 to 19, 12; 20 to 24, 27; 25 to 34, 11; 35 to 44, 8; 45 to 54, 7; 55 to 64, 8; 65 to 69, 12
	past 3 years	18 to 69: 73	age range 18 to 19, 44; 20 to 24, 66; 25 to 34, 80; 35 to 44, 79; 45 to 54, 75; 55 to 64, 68; 65 to 69, 54
	past year	18 to 69: 53	age range 18 to 19, 36; 20 to 24, 54; 25 to 34, 62; 35 to 44, 54; 45 to 54, 53; 55 to 64, 47; 65 to 69, 36

*Pap test rate according to Health Canada – Cervical cancer screening in Canada: 1998 Surveillance report, 2002.⁸⁴ Data from combination of sources, including physician billing data, data captured from 45% of Pap smears in Ontario; screening data provided by provincial programs and departments of health.

†Pap coverage from CytoBase, a screening registry that covers 80% of all Pap tests in Ontario.³⁵

‡Self-reported data from Canadian Community Health Survey, Statistics Canada CANSIM Table 105 series (Statistics Canada).

For example, if the one-year coverage was to expand by 5% (10%), the two-year coverage and three-year coverage were derived to be 70% (75%) and 83% (88%) respectively. More pertinent to the cost-effectiveness analysis were the references to two-year screening or three-year screening programs. These references inferred the relationship between annual screening coverage and the derived coverage estimates for the two-year or three-year screening intervals.

c) Management of cytology outcomes

In the cost-effectiveness analysis, the management of cytology outcomes was according to current guidelines (Figure 4).⁸ ASCUS results are triaged with repeated cytology at six months or with HPV reflex testing. Women with repeated Pap abnormalities at the six-month follow-up are referred to colposcopy examination. Those with corresponding normal results are subjected to another follow-up at 12 months, and routine screening is resumed after two negative results. Women who test positive for HR HPV-DNA after HPV triage are referred for colposcopy examination. Those who test negative have repeated cytology at 12 months. Those with ASC-H, LSIL, and HSIL are typically referred for colposcopy examination, although those with LSIL results could be managed by repeat cytology at six months and 12 months.⁸ In this analysis, colposcopy outcomes and treatment for HSIL are managed according to current guidelines (Figure 5).⁸⁵

In instances where there are options in the guidelines, one option was selected for the analysis (i.e., pathways that are highlighted in Figure 4). For example, LSIL can be managed by colposcopy or repeated cytology. The evaluation simplified this by assuming that all LSIL cases were referred to colposcopy. This option was selected because LSIL is best managed by colposcopy initially, according to the ALTS trial, which could not identify any other useful triage strategies.^{14,15,86}

6.3.4 Perspective

The cost-effectiveness analysis was conducted according to the perspective of a provincial ministry of health.⁷⁹ Thus, direct medical costs paid by the ministry, such as costs related to screening, diagnosis, and treatment of precancer and cancer lesions, were included.

6.3.5 Time horizon

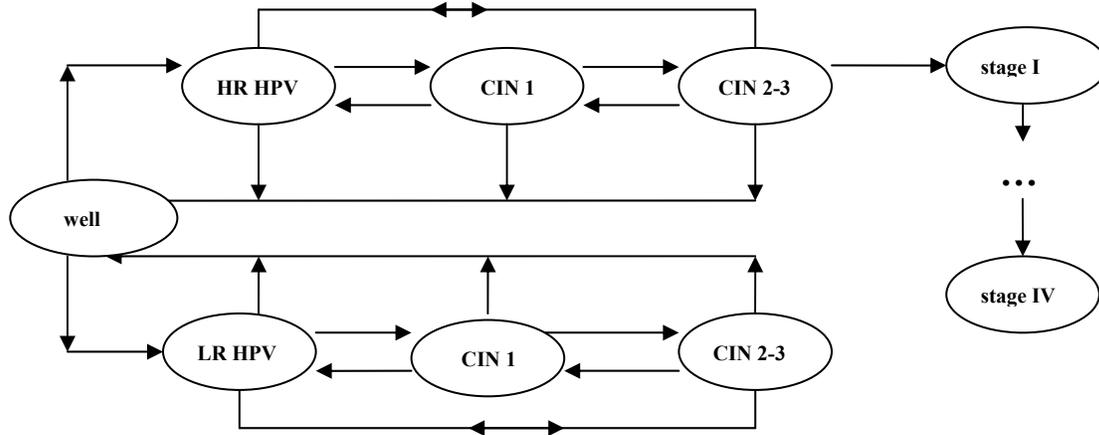
A lifetime horizon was used to adequately capture the long-term effects of a cervical cancer screening program and the long latency between oncogenic HPV infection and cervical cancer.⁸⁷

6.3.6 Canadian Cervical Cancer Model

A Canadian cervical cancer model was developed using TreeAge Pro 2007 software (Suite Release 1.0 TreeAge Software Inc.). First, a cervical cancer disease pathway was modelled including HPV infection (balanced by viral clearance), progression to precancer lesions (partly offset by regression), and invasive cervical cancer (Figure 6).⁸⁸ Next, elements of a cervical screening program were modelled, as they were considered to be interventions that modified the disease pathway.

Along the causal pathway from HPV infection to cervical cancer (Figure 6), lifetime events were simulated for each member of a female birth cohort. At age 13 years, individuals had not had vaginal intercourse and were free of disease. At each six-month transition interval, they faced an age-specific risk of acquiring high-risk (HR) or low-risk (LR) HPV infection because HPV type was considered to be the most significant risk factor for disease progression.⁸⁹ Infection could be transient or persistent; with persistence of HR-HPV infection being considered the necessary condition for invasive cervical cancer. Women who were infected with LR HPV continued to be at risk for HR infection and if infected with HR HPV infection, were presumably on the HR HPV infection pathway to disease progression.

Figure 6: Disease history model



Health states defined using 4 categories: well, HPV infection, cervical intraepithelial neoplasia (CIN 1 or CIN 2-3), and cervical cancer (stages I to IV). CIN 1=cervical intraepithelial neoplasia, stage 1; CIN 2-3=cervical intraepithelial neoplasia, stage 2 or 3; HPV=human papillomavirus; HR=high risk; LR=low risk.

After the spontaneous clearance of a LR or HR infection, type-specific immunity was assumed. The immunity was assumed to be partial in the sense that it would likely offer protection against repeated infections with the same type, although there is still a non-negative probability of re-infection with the same type or other types.^{90,91}

Progression from HPV infection to CIN 1 or CIN 2-3 could be sequential. Progression could be directly from HPV infection to CIN 2-3, especially with HR HPV infection (Figure 6). Resolution of CIN lesions was assumed with simultaneous clearance of the underlying HPV infection.⁹² The pathological states of CIN lesions and related transitions were stratified by the underlying HPV infection (e.g., CIN 1 with an underlying LR infection or CIN 2-3 with HR infection).^{90,93} Only CIN 2-3 from an underlying HR HPV infection could progress to cervical cancer, whereas similar lesions with an underlying LR HPV infection were assumed to be cleared by the immune system or diagnosed and successfully treated with current treatments.

The natural progression from cervical cancer stages I to IV was assumed to be sequential with plausible diagnosis via symptom detection or routine screening. Treated cases of cervical cancer were tracked for five years after treatment because related mortality could occur within this period.⁹⁴ Afterward, cancer survivors resumed a normal life and were subject to age-specific (i.e., non-cervical cancer-related) mortality risk. Women at any age may have a hysterectomy for indications that are unrelated to cervical cancer and be no longer at risk for cervical cancer. Also, they may die at any age because of other causes unrelated to cervical cancer.

All health states in the model were pathology-based with underlying virological status (e.g., HR HPV, LR HPV, CIN 1/HR, CIN 1/LR, CIN 2-3/HR, and CIN 2-3/LR, Figure 6). For example, the health states CIN 2-3 was stratified by HPV genotypes: CIN 2-3/HR and CIN 2-3/LR. CIN-2-3 with an underlying HR HPV infection (i.e., CIN 2-3/HR) could progress to cervical cancer stage I whereas its counterpart with an underlying LR HPV infection (i.e., CIN 2-3 / LR) could not (Figure 6).

HPV infection was defined as detectable or undetectable for high-risk types (HR-HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; e.g., HC II HPV testing) and low-risk types (LR-HPV).^{89,95} Histology via biopsy-confirmed disease was defined as cervical intraepithelial neoplasia grade 1 (CIN 1) or grades 2 to 3 (CIN 2-3), and ICC.⁹⁶⁻⁹⁸ Cytology results are classified as normal, ASC-US, LSIL, or HSIL according to the 2001 Bethesda System.⁹⁹ Invasive cervical cancer was classified into four stages according to the International Federation of Gynecology and Obstetrics (FIGO).¹⁰⁰

The model was calibrated to current Canadian data along the three segments of the causal pathway from HPV infection, cervical precancer, and cancer to ensure its validity before being used in the cost-effectiveness analysis. The model incorporated screening techniques and modalities, and management of cytology abnormalities as interventions that modified the disease pathway. The model “remembered” prior health states once women had certain histological and virological conditions. For example, ASC-US management was modelled with HPV triage or a potential for repeated visits at six or 12 months. Women with a cytology result of ASC-US were followed up according to standard practice but retained the histologic and virological “memory” of their prior health state on the disease pathway. Overall, there were 48 mutually exclusive health states in the model (Figures 5-11 Appendix 2).

6.3.7 Data sources

Guidelines for good practice in decision-analytic modelling in health technology assessment were followed, especially for the proposed literature search practice demonstrated in the case studies of Philips *et al.*¹⁰¹ A series of pertinent clinical questions were generated along segments of the disease pathway (Figure 6). For example, what is the average burden of HPV infection in a Pap screening population? (What is the genotype-specific incidence of HPV infection among women in a typical Pap screening population? What is the age-specific prevalence of HPV infection in such a population?). A series of targeted literature searches were conducted to obtain data. Targeted searches were conducted in the PubMed MeSH database. The number of potentially relevant citations was preset at a maximum of 50. If necessary, the search was refined with additional relevant but specific keywords to reduce the volume of citations eligible for screening. In principle, input data was not selected from one source. Instead, input data to the model and observed data used in the model calibration were selected from the results of targeted searches.

a) **LBC and HPV triage effectiveness**

LBC effectiveness estimates were derived from a SR in which relevant data were consolidated using a Bayesian hierarchical random-effects model that takes into account the trade-off between sensitivity and specificity in diagnostic test evaluation. Estimates from 20 head-to-head studies comparing LBC and CC accuracy indicated a trade-off of 6.4% in sensitivity gain and 4.0% loss in specificity for LBC (Table 19 Appendix 2). Similar trade-off estimates from the six high-quality studies (i.e., 7.7% sensitivity gain and 4.4% specificity loss) and from 13 studies that used histological classifications of lesions as a reference standard (i.e., 1.1% sensitivity gain and 0.6% specificity loss) were also used.

The estimates of unsatisfactory samples were also available from the SR for the cytology techniques. Observed unsatisfactory rates from the report of an LBC implementation in Ontario were used to better reflect Canadian conditions (Table 19 Appendix 2). These observed rates were consistent with the estimates derived from the SR.

Data pertaining to accuracy were extracted from a meta-analysis of diagnostic studies evaluating CC.³⁴ This meta-analysis reported that CC (positive threshold of ASCUS/ASC-US) had a median sensitivity of 68% (range: 31% to 92%) for histologically confirmed CIN 1 (Table 19 Appendix 2).^{34,34} Other estimates of CC from this meta-analysis were also used. Estimates of CC accuracy from this meta-analysis were reasonably consistent with those of a similar overview of European and North American studies.^{102,103}

Sensitivity and specificity data pertaining to virologic versus cytologic triage of women with ASC-US was consolidated via the updated SRs.^{11,12,43} These data were not used in the model because all health states in the model were pathology-based with underlying virology (e.g., HR, LR, CIN 1/HR, CIN 2-3/HR, and CIN 2-3/LR). HPV reflex testing was assumed to detect the presence of type-specific underlying HPV infection. As a result, the analytical sensitivity of HPV testing to detect type-specific HPV was used (Table 19 Appendix 2).⁹²

b) *Epidemiology of HPV infection*

A SR was conducted to identify studies reporting the prevalence and incidence of HPV infection in samples of Canadian participants.¹⁰⁴ Two studies reporting incidence data from longitudinal cohorts were identified.^{83,105} The incident infection with HR HPV (i.e., new infection among those testing negative for HPV) was reported at 12% over 14 months among women aged 15 to 49 years recruited from physicians' practices.¹⁰⁵ In this study, the incident infection was highest among adolescents and young adults, and decreased in older age groups. Similar data were reported based on female university students in the McGill-Concordia study.⁸³

Age-specific six-month probability estimates of HR HPV infection were derived using data from these two studies. Corresponding age-specific estimates for LR HPV infection were derived using an estimate ratio of HR and LR HPV infection. This ratio was estimated using data from studies reporting prevalence data for HR and LR HPV infection identified from the SR of LBC evaluation studies (Table 19 Appendix 2). Age-specific clearance rates of HR and LR HPV infection were derived using data from follow-up studies with Canadian participants.^{83,105}

c) *Clinical parameters*

A targeted search was conducted to identify published cervical-cancer models. Plausible ranges for transition probability estimates governing the disease pathway between persistent HPV infection to CIN 1, CIN 2-3, and ICC Stage 1 appear in Figure 6 and Table 20 Appendix 2.^{71,72} According to these published models, the ranges were defined using relevant data identified from a comprehensive review of the published literature and consultation with an expert panel.^{71,72} The ranges were used to reflect the uncertainty in the transitions. Specific transition probability estimates required by the current model were derived via a calibration step. Transition probability estimates for progression from cervical cancer stages I to IV were extracted from a published model of Pap screening.¹⁰⁶

d) *Epidemiology of precancer and cancer lesions*

The typical distribution of cervical abnormalities among Canadian women undergoing Pap screening was inferred using data from 8.7 million samples between 1996 and 2003 in an Ontario cytology screening registry (Cytobase 2003). Approximately 2.4% of women undergoing annual screening had an ASC-US or ASC diagnosis. The corresponding percentage for LSIL, HSIL, and cervical cancer was 1.6%, 0.3%, and 0.01% respectively. The projected distribution of Pap outcomes from the model was made to be consistent with this observed distribution in the calibration step.

Cervical cancer and related mortality data from 1990 to 2001 were taken from Canadian Cancer Statistics (Table 23 Appendix 2). Demographic data were obtained from Statistics Canada (Table 23 Appendix 2). They were used to derive input data to the model.

e) Costing data

All costs were based on Canadian data and converted to 2006 dollars using the medical care component of the Consumer Price Index for the year of data collection. A targeted search was conducted to identify published Canadian studies reporting costing and resource utilization related to cervical cancer prevention. The targeted search identified five studies. Direct screening costs included those for consumable supplies, cytology tests, office visits, outside-hospital diagnostic procedures, and professional services (Table 21 Appendix 2). The unit costs of CC and LBC tests, HPV reflex testing, and related fees were extracted from one provincial source (Ontario MoH Schedule of Benefit). A weighted average screening cost was derived assuming that 83% of Pap screening was conducted by family physicians and 14% by obstetricians-gynecologists.¹⁰⁷

The average costs of colposcopy and biopsy were derived from a Canadian study reporting resource utilization data from four provinces (Table 21 Appendix 2).¹⁰⁸ The average costs of treatment for CIN 2-3 and cervical cancer stage 1A were derived from a background paper about a HPV immunization program in British Columbia³ and two economic evaluations related to the management of low-grade Pap abnormalities.^{109,110} The average costs for cervical cancer stages 1B to IV were estimated from an Alberta study evaluating LBC and HPV triage.²⁰ This study reports the average cost for stage 1B derived from microcosting data. It estimates average costs for stages II to IV based on a 1.8 ratio of stages II to IV versus stage 1B costs. It also reports the average cost of terminal care during the last 365 days before death.

f) Utility data

The utility values were derived from a published study using time trade-off methods in a study of 150 female volunteers. They were read descriptions, including biopsies, of CIN 1, CIN 2-3, and cervical cancer stage I (Table 19 Appendix 2).¹¹¹ The utility values for non-site-specific cancer that were used in published cervical cancer models for HPV vaccines were used for cervical cancer stages II to IV.^{71,72} Disutility for short-term events such as undergoing evaluation for a false-positive test result was not considered in the model.¹¹²

6.3.8 Model calibration

a) Methods

The model was calibrated along three segments of the disease pathway: HPV infection, precancerous lesions, and cervical cancer. For the HPV infection segment, the age-specific and six-month transition probabilities of incident HPV infection and clearance were derived from Canadian studies. The age-specific prevalence was projected from the model based on these incidence and clearance estimates. The projected prevalence was calibrated to observed data from Canadian studies by adjusting the incidence and clearance estimates preserving their age-specific structures. The calibration step ensured that the prevalence estimates were consistent with corresponding prevalence estimates observed from studies of Pap screening populations in Canada.

For the middle segment of the disease pathway, the modelled distribution of Pap outcomes was calibrated to the observed distribution from a Pap cytology registry.³⁵ For the cervical cancer segment, projected cancer staging distribution was calibrated to the distribution reported in Canadian public health reports.⁸⁴ The modelled incidence of cervical cancer was calibrated to observed data

from the Canadian Cancer Registry from 1990 to 2001.¹ The ratio of death per cervical cancer case was calibrated to corresponding reported data (Canadian Cancer Registry, 2006). This was conducted by scaling the stage-specific and post-treatment time-specific survival curves for the five years after treatment of cervical cancer so that the projected ratio was consistent with the reported one.

Monte-Carlo simulations were conducted by iteratively sampling values from the plausible ranges of clinical parameters governing the disease pathway (Table 20 Appendix 2).^{71,72} For each iteration, observable data were projected from the model. Discrepancy measures were derived by calculating the sum of the squares of the differences between modelled outcomes and corresponding observed data. Sampling parameter values were deemed to be optimal if the simulated configurations minimized all discrepancy measures and maximized the goodness of fit between modelled and observed data.¹¹³

b) Results

The calibration that was undertaken ensures consistency between the model and corresponding real-life scenarios. Age-specific prevalence estimates from the model followed the same prevalence pattern for oncogenic HPV infection reported for women who underwent screening in general practitioners' offices in southern Ontario (deviance chi-squared test, $p=0.65$) (Figure 2 Appendix 2).^{81,82} The projected prevalence was also within the plausible ranges of age-specific prevalence of cervical infection with HR HPV from all Canadian studies identified through a SR (as of December 2006) (Figure 3 Appendix 2).¹⁰⁴

The age-specific cervical cancer rates per 100,000 persons projected from the model were within the plausible ranges of observed data (deviance chi-squared test, $p=0.12$) (Figure 4 Appendix 2). Overall, the model projected 9.77 cervical cancer cases and 3.27 related deaths per 100,000 persons per year. The corresponding annual rates reported by the Canadian Cancer Registry for 1990 to 2001 ranged from 8.15 to 12.27 cases and 2.19 to 3.96 related deaths per 100,000 persons across 10 provinces (Canadian Cancer Registry, 2002).

Table 20 Appendix 2 shows estimates of the probabilities that transitions along the disease pathway would occur during any six-month interval. The projected viral clearance estimates from the model were moderately consistent with the rates of viral clearance observed in Canadian studies (Table 22 Appendix 2). For example, the model estimated that approximately 70% of HR HPV infections cleared after two years. This was consistent with corresponding observations from the McGill-Concordia cohort study (Table 22 Appendix 2).⁸³ The modelled distribution of Pap abnormality was consistent with observed distribution from >8.7 million Pap samples reported in a population-based Pap registry in Ontario from 1996 to 2003 (Table 23 Appendix 2).³⁵ The modelled colposcopy rate, cancer staging distribution, and the ratio of death per cervical cancer cases were reasonably consistent with observed data (Table 23 Appendix 2).

6.3.9 Valuing outcomes

The main outcome measures were average lifetime cost, years of life saved (YLS), incremental quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios. Other outcome measures included incidence of cervical cancer and related mortality per 100,000 persons; rate of colposcopy per 100,000 person-years, discounted life expectancy, and quality-adjusted life expectancy. The lifetime probabilities of cervical cancer and related death were derived. The number needed to screen to prevent a cervical cancer case or cancer-related death was calculated by taking the reciprocal of the difference between related lifetime probabilities for competing screening

options.¹¹⁴⁻¹¹⁶ It was used in the clinical interpretation regarding the effectiveness of screening programs.

6.3.10 Discounting

Following Canadian guidelines, we discounted future costs and health effects at a common rate of 5%.⁷⁹ Thus, the reported discounted life expectancy in the model for a 13-year-old girl will be approximately 19 years, as opposed to an undiscounted life expectancy of 69 years. Discount rates of 0% and 3% were used in sensitivity analyses.

6.3.11 Assessment of uncertainty

The base-case analysis was based on the mean values of model parameters. To assess uncertainty, one-way sensitivity analyses were conducted on key parameters: screening coverage, compliance to follow-up visits for cytology abnormalities, marginal cost of cytology techniques (i.e., LBC cost minus CC cost), marginal sensitivity and specificity of LBC, colposcopy-related costs, treatment costs for cervical cancer, and average cost of terminal cases due to cervical cancer. The model parameters identified to be influential at the one-way sensitivity analysis level were evaluated in a probabilistic sensitivity analysis.

To analyze the combined effect of uncertainty in input parameters on the base-case results, a probabilistic sensitivity analysis of the model was undertaken in which input parameters were allowed to vary across their plausible ranges.²⁷ For example, the uncertainty around the marginal sensitivity and specificity was described using normal distributions according to their estimates from the meta-analysis quantifying the trade-off between LBC and CC. For other model parameters, the uncertainty 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. The advantage of using the triangular distribution to represent uncertainty around parameters in the model is that a definitive range for the parameter of interest is specified, and the sampled values do not fall outside that range. Limitations of the triangular distribution include the fact that the shape of the distribution is rigidly defined and may not represent the true form of the distribution accurately.²⁷

Model outputs were obtained for 2,000 iterations of the probabilistic sensitivity analysis, each informed by a random sample of input parameters from the specified distributions. The results of the probabilistic sensitivity analysis were presented in a cost-effectiveness acceptability curve describing the probability that each available screening option was optimal at different levels of willingness to pay (WTP) per YLS. This curve was estimated by defining the optimal option in each of the 2,000 iterations on the basis of the option with the highest incremental net benefits at each WTP level.²⁷

6.4 Results

6.4.1 Status quo of current screening programs

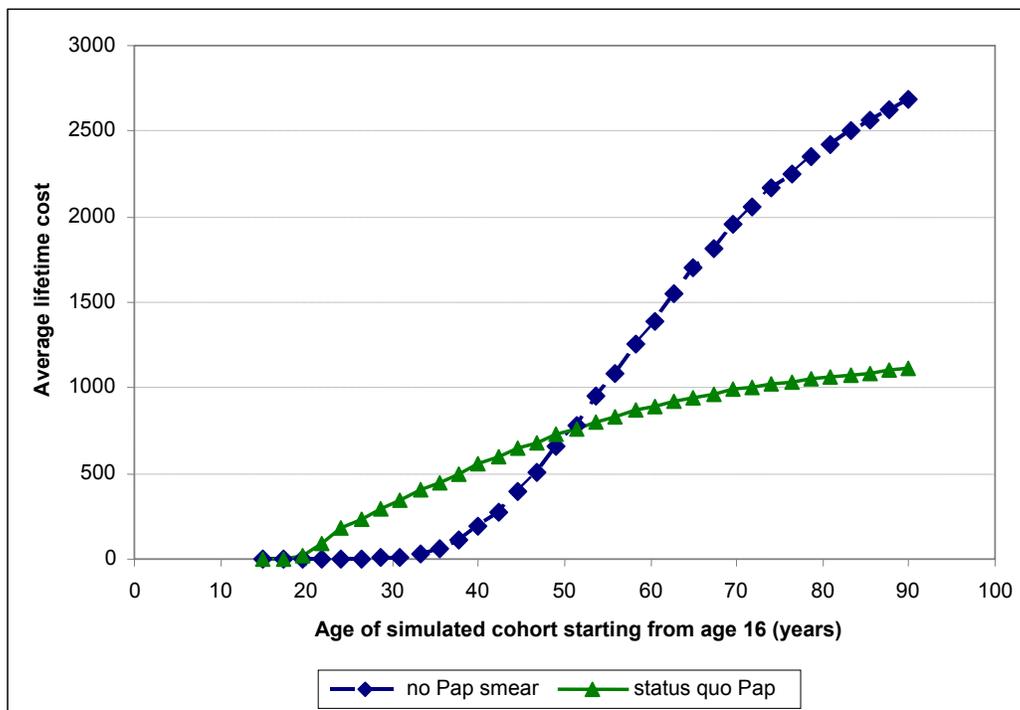
The model was first used to generate data regarding the disease history of HPV infection and cervical cancer in Canada, and profile the effectiveness of the current CC screening programs. Assuming current risk factors for HPV infection and no screening programs by setting screening coverage in the model to zero, several projections were derived. Without screening, the cumulative lifetime risk of cervical cancer would have been 2.87%, cervical cancer incidence 42.22, and related mortality

incidence 16.61 per 100,000 persons. These projections characterized the risk of cervical cancer in women who have never had Pap screening, a subpopulation that continues to exist with current routine screening programs. According to the National Population Health Survey, this subpopulation consists of approximately 10% of the screening population (Table 4).

The burden of disease among this group of women was high, even compared with the pre-screening era before the mid-1960s, when the Pap test was first available. For example, the reported cervical cancer incidence and related mortality for Ontario in 1964 was 27 and eight per 100,000 persons respectively (Cancer Care Ontario’s web site). Changes in risk factors for HPV infection over time and the potential discrepancies between statistics derived from cohort models versus cross-sectional surveys could partly explain the differences between observed and projected estimates.^{71,72}

Without routine screening, cervical cancer lesions could be detected only if the invasive disease became symptomatic. As a result, the average lifetime cost would have consisted only of the costs associated with cervical cancer treatment and terminal care. The average cervical cancer lifetime cost would be \$2,870 (discounted). This value rises after age 40 years (Figure 7). Lifetime treatment costs increased for each successive decade in life (Figure 7).

Figure 7: Average lifetime cost of cervical cancer



Current screening programs reduced the disease burden. With current screening programs, the lifetime risk of cervical cancer was reduced to 0.67%, a 77% reduction compared with no screening. The corresponding cervical cancer incidence was 9.77 per 100,000 persons (approximately 77% reduction) and mortality incidence 3.27 per 100,000 persons (approximately 80% reduction). It was estimated that current screening programs extended life by 7.7 days and quality-adjusted life by 10.1 days (discounted). The undiscounted life expectancy gain was 94 days; the undiscounted quality-adjusted life expectancy gain was 105 days.

Compared with no screening, the average lifetime cervical-cancer-related cost with current screening programs was \$1,147 (approximately 60% reduction). The average lifetime cost consists of two components. First, an average lifetime cost of approximately \$574 was spent on screening and diagnosis, including the costs for colposcopy and biopsy services. The remaining average cost of \$573 was spent on the treatment of precancer lesions and cervical cancer, and terminal care. Compared with no screening, most of the current screening expenditure was upfront for those between 20 and 50 years old, with health benefits and cost savings not realized until after 50 years of age. The cost savings increased with each successive decade after the break-even point at age 50 years (Figure 7).

From a clinical perspective, 46 women would have to be screened over a lifetime with current screening programs to avoid one cervical cancer case. For the prevention of one cervical-cancer-related death, the number needed to screen would be 109.

6.4.2 Economic evaluation of LBC and CC

a) *Long-term outcomes*

The use of LBC techniques to replace CC in current screening programs with a one-year screening interval reduced the cervical cancer incidence estimate from 9.77 to 9.08 (7.1% reduction) and related mortality from 3.27 to 3.03 (7.3% reduction) per 100,000 persons (Table 5). Compared with CC, LBC would extend the discounted life expectancy by approximately 4.1 hours and quality-adjusted life by 4.2 hours. On average, 2,117 women would need to be undergoing annual LBC screening instead of CC screening over a lifetime to avoid one case of cervical cancer. The corresponding number needed to screen with LBC to prevent one related death was 6,163.

LBC was on average 6% more sensitive than CC. Repeated screening every year with the more sensitive LBC to detect slow changes in the disease process leads to an increase in colposcopy referrals. With LBC screening, the number of colposcopy referrals was 1,801 compared with 1,033 with CC screening (74.3% increase) per 100,000 person-years (Table 5). The reported number of colposcopy services was 2,016 for Manitoba, 1,673 for Ontario, and 711 for British Columbia per 100,000 person-years.¹⁰⁸ Given the minimal reduction in disease burden, the excess of colposcopy referrals was most likely indicated for HPV infection, benign cellular changes, or low-grade lesions that would regress on their own. This observation shows the trade-off between early detection of disease that would otherwise resolve spontaneously and the detection of disease that would progress so that treatment would be too late. One way to reduce colposcopy rates would be to use less frequent screening.

Compared with the status quo, screening every two years with CC would increase the cervical incidence estimate from 9.77 to 10.46 (7.1% increase) per 100,000 persons, increase related mortality from 3.27 to 3.50 (7.0% increase), and reduce colposcopy referrals from 1,033 to 881 (14.7% reduction) per 100,000 person-years (Table 5). Screening every two years with LBC would decrease the current cervical incidence estimate from 9.77 to 9.65 (1.2% reduction), decrease related mortality from 3.27 to 3.22 (1.5% reduction), and increase colposcopy referrals from 1,033 to 1,525 (47.6% increase). Compared with the status quo, 1,686 women would have to be screened every two years for life with LBC to prevent one case of cervical cancer. Similarly, 4,248 women would need to be screened to avoid one related death.

Screening every three years with CC would increase the cervical incidence estimate from 9.77 to 11.79 (20.7% increase) per 100,000 persons, increase related mortality from 3.27 to 3.98 (21.7% increase), and reduce colposcopy referrals from 1,033 to 746 (27.8% reduction) per 100,000 person-years (Table 5).

Table 5: Long-term effectiveness and cost-effectiveness of LBC versus CC

Screening Option	Interval	Cost	Cancer Cases/10 ⁵	Deaths/10 ⁵	Colposcopy Rate/10 ⁵	Life-Years	QALY	ICER
no screening	0	\$2,870	42.22	16.61	0	19.536034	17.787440	
Efficiency[*]								
CC	2	\$1,091	10.46	3.50	881	19.556526	17.863407	least expensive
LBC	3	\$1,103	10.85	3.65	1,279	19.556226	17.863055	dominated
CC	3	\$1,108	11.79	3.98	746	19.555560	17.862301	dominated
LBC	2	\$1,108	9.65	3.22	1,525	19.557091	17.864019	\$30,939 per YLS, \$28,572 per QALY
CC	1	\$1,147	9.77	3.27	1,033	19.557168	17.864076	extended dominated
LBC	1	\$1,188	9.08	3.03	1,801	19.557637	17.864557	\$146,617 per YLS, \$148,797 per QALY
Pairwise[†]								
LBC	1	\$1,188	9.08	3.03	1,801	19.557637	17.864557	\$88,148 per YLS, \$85,949 per QALY
CC	1	\$1,147	9.77	3.27	1,033	19.557168	17.864076	reference
LBC	2	\$1,108	9.65	3.22	1,525	19.557091	17.864019	\$30,942 per YLS, \$28,565 per QALY
CC	2	\$1,091	10.46	3.50	881	19.556526	17.863407	reference
LBC	3	\$1,103	10.85	3.65	1,279	19.556226	17.863055	dominant
CC	3	\$1,108	11.79	3.98	746	19.555560	17.862301	reference

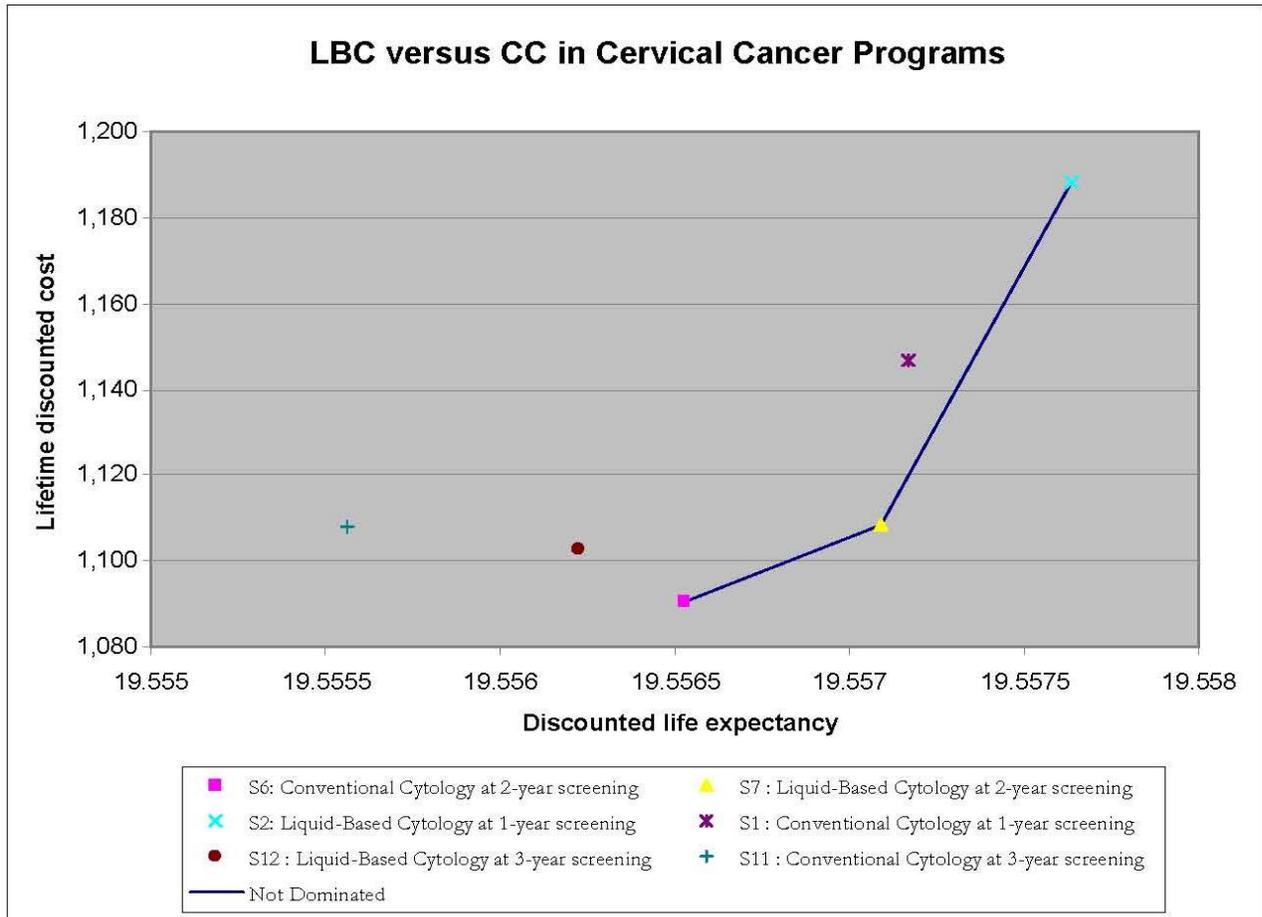
Projected cervical cancer cases and related mortality per 100,000 persons. ICER=incremental cost-effectiveness ratio calculated in each screening interval. *Screening options ordered by lowest to highest cost according to efficiency frontier graph. †Ordered by screening interval in which incremental cost-effectiveness ratios generated by comparing LBC and CC in each interval. CC=conventional cytology; LBC=liquid-based cytology; QALY=quality-adjusted life-year; YLS=year of life saved.

Screening every three years with LBC would increase the current cervical incidence estimate from 9.77 to 10.85 (11.1% increase), increase related mortality from 3.27 to 3.65 (11.6% increase), and increase colposcopy referrals from 1,033 to 1,279 (23.8% increase). Extending the screening interval to every three years resulted in an increased disease burden even with using a more sensitive LBC technique.

b) Cost-effectiveness

With the costs of screening programs taken into consideration, the cost-effectiveness results are shown in an efficiency frontier (Figure 8) with the lifetime costs (discounted costs on the left vertical axis) and clinical benefits (discounted life expectancy on the right horizontal axis) of LBC and CC performed at different screening intervals. Screening options on the efficiency frontier dominate those lying on the left of the curve because they are more effective (i.e., extend life expectancy) and cost less or have a more attractive cost per YLS than the next best option. The slope between two options is steeper when the net change in lifetime cost per YLS is greater. Some options lie near the efficiency frontier, where small changes in input data to model parameters would make them as equally cost-effective as the options lying on the efficiency frontier.

Figure 8: Cost-effectiveness of LBC versus CC for cervical cancer screening programs



CC screening every two years was the least expensive option (Figure 8) but life expectancy was reduced compared with current CC screening programs every year. LBC screening every two years was on the efficiency frontier. It extended life expectancy but at a higher cost than CC every two years. Screening with LBC every two years would cost approximately \$31,000 per YLS compared with screening with CC every two years. Taking quality of life into account, LBC screening every two years would cost \$29,000 per QALY gained compared with CC screening every two years. The small reduction in the cost per QALY as compared with the cost per YLS reflects the fact that early detection and treatment of precancer and cancer lesions alleviate some morbidity unaccounted for in the YLS measure.

Current screening programs of CC screening every year were closed to the efficiency frontier and would be the next best option to be considered an improvement from LBC screening every two years. Compared with LBC screening every two years, current programs were more expensive than LBC screening every two years but extended life expectancy by a small margin. Had these two options been connected on the graph (Figure 8), it would have resulted in a steep slope (i.e., a high cost-effectiveness ratio). The option of CC screening every year dominated through extended dominance by other screening strategies.

The next best option on the efficiency frontier to be considered was annual LBC screening. It extended life expectancy at an incremental cost of \$147,000 per YLS compared with LBC every two years or \$149,000 per QALY. The incremental cost per QALY in this case was higher than the corresponding incremental cost per YLS. One possible explanation is that it was partly due to the decremental effect of frequent screening with a relatively sensitive LBC to detect CIN 1 or CIN 2-3 lesions that would otherwise regress spontaneously. Compared with current screening every year with CC, annual screening with LBC resulted in an incremental cost of \$88,000 per YLS (\$86,000 per QALY).

LBC screening every three years was associated with a lower cost than other options on the efficiency frontier (Figure 8) (except CC screening every two years) and a shorter average life expectancy. It did dominate (i.e., less expensive and more effective) CC screening every three years (Table 5). LBC screening every three years was associated with a higher cost than CC screening every two years, because the reduction in the cost of screening and diagnosis with the three-year screening interval did not seem to be enough to compensate for the treatment costs for precancer and cancer lesions that should have been detected a year earlier.

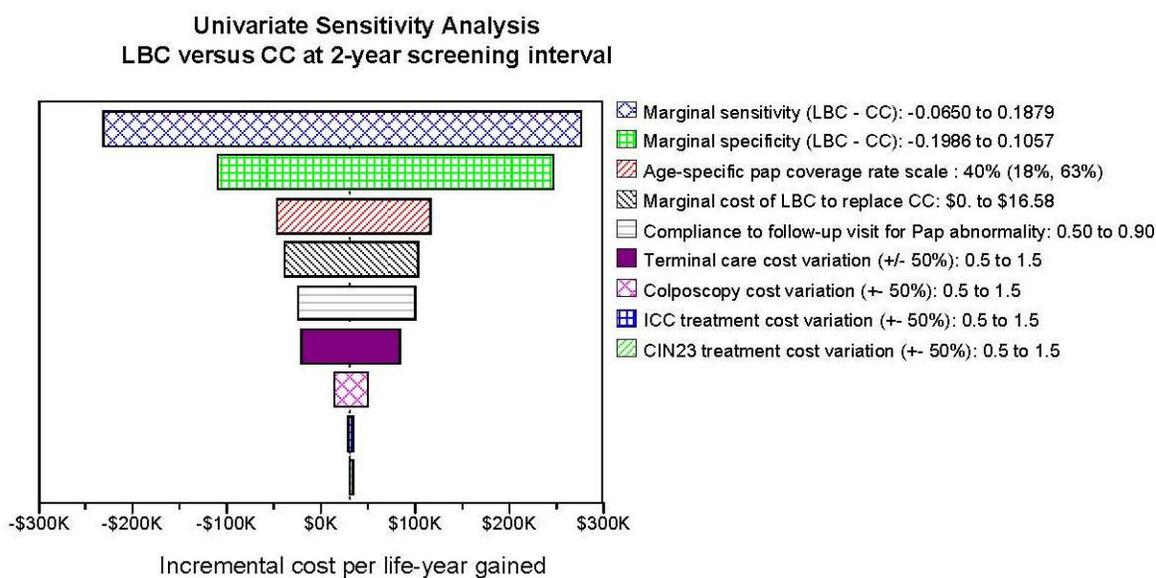
c) Sensitivity Analysis

The results of the cost-effectiveness analysis were sensitive to uncertainty in input data from seven model parameters (Figure 9). Ranking by the order of influence, these parameters included the marginal sensitivity and marginal specificity of LBC, screening coverage, marginal cost of LBC, compliance rate to follow-up visits for cytology abnormality, cost of terminal care for a cervical cancer death, and cost of colposcopy. For a two-year interval screening program, Figure 9 reports the changing incremental cost per YLS between LBC and CC according to plausible ranges of input data from these seven parameters. In the graph, a negative value for the incremental cost per YLS indicates that LBC is dominated by CC (i.e., LBC is more costly with shorter life expectancy) and the vertical line indicates the \$30,942 incremental cost per YLS from the base-case analysis. According to the figure, results from the base case analysis were robust against treatment costs for cervical cancer or pre-cancer lesions CIN 2-3.

Variation in the trade-off estimates between marginal sensitivity and specificity between LBC and CC led to qualitative changes in the conclusion regarding the relative cost-effectiveness of LBC. LBC could be less sensitive than CC by up to 6.5%, according to the results of the meta-analysis. In this range of negative marginal sensitivity for LBC, it was dominated (i.e., less effective and more expensive) by CC. In the positive marginal sensitivity, LBC would be cost-effective at \$275,000 per YLS if the marginal sensitivity (i.e., LBC minus CC) was 1.93%. If the marginal sensitivity increased to 7.5%, LBC became dominant, as this cushion of increasing sensitivity would be sufficient for less frequent screening. Similarly, the cost-effectiveness results were sensitive to the marginal specificity estimates of LBC, ranging from a loss of 19.9% to a gain of 10.6% (Figure 9). The trade-off estimates between sensitivity and specificity needed to be evaluated simultaneously (Table 6).

The trade-off estimates of LBC were derived from the meta-analysis (Table 6). If the marginal accuracy of LBC was estimated according to the six high-quality studies in the meta-analysis (i.e., 7.70% sensitivity gain and 4.40% specificity loss with LBC), LBC would have been cost-effective at \$17,000 per YLS. If the marginal accuracy of LBC was estimated according to the 13 studies in which a histology reference was used (i.e., 1.14% sensitivity gain and 0.57% specificity loss with LBC), LBC would have been associated with a cost of \$298,000 per YLS.

Figure 9: Univariate sensitivity analysis of LBC versus CC at 2-year screening intervals



CC=conventional cytology; ICC=invasive cervical cancer; LBC=liquid-based cytology.

Table 6: Cost-effectiveness of LBC and quality of studies evaluating LBC accuracy	
LBC Versus CC Accuracy Estimates	Incremental Cost-Effectiveness Ratio of LBC Versus CC in 2-Year Screening Programs
main analysis (20 study groups), sensitivity gain 6.43%, specificity loss 4.02%	\$30,939 per YLS
high-quality studies (6 study groups), sensitivity gain 7.70%, specificity loss 4.40%	\$16,568 per YLS
histology standard (13 study groups), sensitivity gain 1.14%, specificity loss 0.57%	\$298,336 per YLS

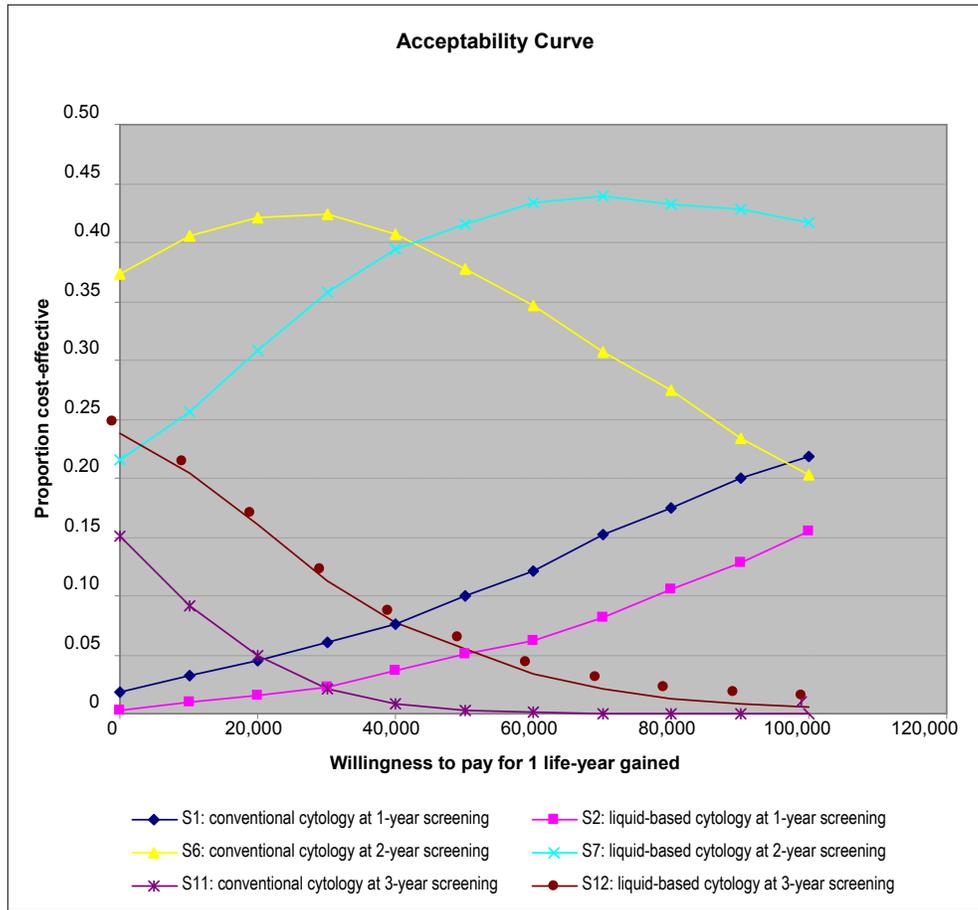
CC=conventional cytology; LBC=liquid-based cytology; YLS=year of life saved.

The CEA results were also sensitive to Pap coverage (Figure 9). LBC would become cost-saving and extend life expectancy in a setting with low screening coverage (e.g., an annual coverage of 18% versus 40% in the base-case scenario). If the annual coverage increased to 63%, LBC screening would have been associated with a cost of \$115,000 per YLS compared with CC screening. The high coverage level would lead to a degree of effectiveness in the screening programs even with a less sensitive CC.

The CEA results were sensitive to the marginal cost of LBC (Figure 9). Compared with screening with CC at two-year intervals, the incremental cost per YLS of LBC increased with increasing marginal cost. If there was no marginal cost difference, LBC screening would dominate CC screening. If the marginal cost was doubled from \$8.29, LBC would have been associated with a cost of \$101,000 per YLS.

Compliance to follow-up visits for cytology abnormalities exerted some influence on the CEA results, similar to the effect reported for screening coverage (Figure 9). If follow-up compliance was <65%, LBC screening would have become dominant. Compliance to follow-up visits in the range of 66% to 74% corresponded to an incremental cost per YLS below \$20,000. At the base value of 76% compliance to follow-up visits, the incremental cost per YLS for LBC versus CC was \$30,939 (Figure 9).

Figure 10: Net benefit of LBC versus CC options



Given uncertainties in data sources, LBC offers best net health benefit in range of willingness to pay >\$40,000 per discounted life-year gained. Analysis used 7 most influential parameters from univariate sensitivity analyses.

Among the items included in the univariate sensitivity analyses, an increase in the cost for terminal care was associated with a decrease in the cost per YLS for LBC versus CC screening in a two-year program (Figure 9). Because of the marginal sensitivity gain, LBC screening would prevent more deaths compared with CC screening. As a result, a 17% increase in the \$44,000 cost of terminal care led to a \$14,000 cost per YLS with LBC. A 50% decrease in the terminal care cost led to an increase in the cost per YLS with LBC to approximately \$83,000. Similar trends were observed with the cost for colposcopy services. Compared with the cost of terminal care, changes in colposcopy cost did not exert as much influence on the CEA results.

Taking health-related quality of life into account, the average lifetime cost of LBC screening every two years compared with CC was \$29,000 per QALY (Table 24 Appendix 2). If the discount rate were 3%, the LBC screening option would have had a lower average lifetime cost and higher life expectancy (Table 24 Appendix 2).

d) Probabilistic sensitivity analysis

To analyze the combined effect of uncertainty in the input data for the seven model parameters identified in the univariate sensitivity analyses, a probabilistic sensitivity analysis was conducted. The results of the probabilistic sensitivity analysis were presented in a cost-effectiveness

acceptability curve (Figure 10). At different levels of willingness to pay (WTP), the incremental cost per YLS for each screening option was converted to an incremental net benefit. For example, the incremental cost per YLS for LBC compared with CC at a two-year screening interval was \$31,000. At a WTP of \$20,000 per YLS, the corresponding incremental net benefit was approximately 1.55 YLS. At this WTP level, all options were ranked according to their incremental net benefits.²⁷

At a one-year screening interval, CC always offered better incremental net benefits than LBC (Figure 10). With screening every year, the marginal sensitivity gain with LBC was not essential for program effectiveness. In contrast, LBC offered better incremental net benefits than CC at a three-year screening interval. The ranking between LBC and CC in a two-year screening program changed according to the WTP levels (Figure 10). For WTP levels <\$40,000 per YLS, CC offered the highest incremental net benefits. The use of LBC in a two-year screening program offered the highest incremental net benefits for WTP levels >\$40,000 per YLS.

e) LBC versus CC comparisons

- Compared to no screening, current screening programs (i.e., annual screening with CC at approximately 40% coverage) require 46 women to be screened over a lifetime to avoid one cervical cancer case, and 109 women to prevent one cancer-related death (Table 5). This equates with a gain of 0.07664 QALYs and lower average lifetime costs (\$1,723 saving per person, discounted).
- Compared to current screening programs, if annual screening with CC is offered every two years (e.g., 64% coverage for screening every two years), the relative incidence of cervical cancer and related mortality will increase by approximately 7%.
- Compared to current screening programs, if LBC is offered every year, the relative incidence of cervical cancer will decrease by 7% with a 74% increase in colposcopy referrals and increased average lifetime costs (\$41 increase per person, discounted).
- Compared to current screening programs, if LBC is offered every two years, the disease burden remains similar (QALYs decrease by 0.00006) with a 48% increase in colposcopy referrals and lower average lifetime costs (\$39 per person, discounted).
- Compared with screening with CC every two years, screening with LBC every two years is cost-effective at approximately \$31,000 per YLS. Using the relative accuracy estimates of LBC and CC from high-quality studies, screening with LBC every two years is cost-effective at approximately \$17,000 per YLS. Taking key parameter uncertainty into account, LBC screening every two years is likeliest to produce the highest net health benefits if the willingness to pay for one discounted life-year gained is >\$40,000.
- At a three-year screening interval, LBC screening has higher average life-years and cost saving, compared with CC screening at the same interval. Compared with current screening programs, LBC screening every three years, however, increases the incidence of cervical cancer and related mortality by approximately 11%.

6.4.3 HPV triage

HPV triage was evaluated as an option for the management of cytology abnormalities with undetermined significance for an index Pap sample with CC or LBC. For CC screening, the sample collection for HPV triage was managed with or without an additional visit.

a) Long-term outcomes

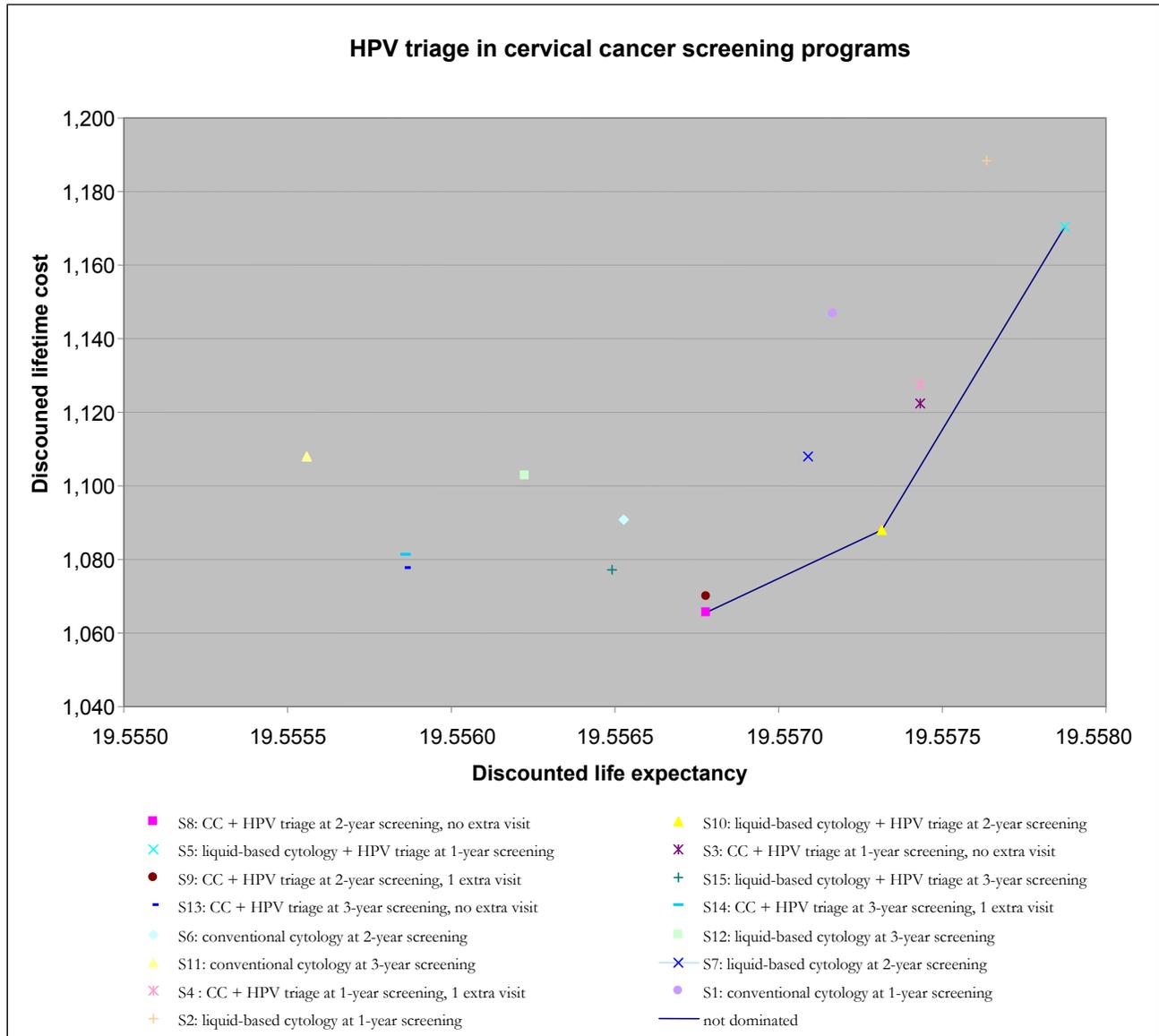
HPV triage was a more effective option for ASC-US management than repeated CC. It reduced cervical cancer incidence, and related mortality and colposcopy referrals. It also extended life expectancy and quality-of-life expectancy. This effectiveness was achieved at each screening interval independent of the index cytology techniques (Table 7).

Table 7: Long-term effectiveness and costs of all screening options							
Screening Options	Interval	Cost (\$)	Cancer Cases/ 10⁵	Deaths/ 10⁵	Colposcopy Rate/10⁵	Life-Years	QALY
no screening	0	2,870	42.22	16.61	0	19.536034	17.787440
S1: CC	1	1,147	9.77	3.27	1,033	19.557168	17.864076
S3: CC+HPV triage 0	1	1,122	9.23	3.10	977	19.557432	17.864370
S4: CC+HPV triage 1	1	1,128	9.23	3.10	977	19.557432	17.864370
S2: LBC	1	1,188	9.08	3.03	1,801	19.557637	17.864557
S5: LBC+HPV triage	1	1,170	8.64	2.89	1,681	19.557872	17.864813
S6: CC	2	1,091	10.46	3.50	881	19.556526	17.863407
S8: CC+HPV triage 0	2	1,066	9.98	3.34	834	19.556778	17.863694
S9: CC+HPV triage 1	2	1,070	9.98	3.34	834	19.556778	17.863694
S7: LBC	2	1,108	9.65	3.22	1,525	19.557091	17.864019
S10: LBC+HPV triage	2	1,088	9.23	3.08	1,420	19.557314	17.864267
S11: CC	3	1,108	11.79	3.98	746	19.555560	17.862301
S13: CC+HPV triage 0	3	1,078	11.25	3.79	707	19.555858	17.862651
S14: CC+HPV triage 1	3	1,081	11.25	3.79	707	19.555858	17.862651
S12: LBC	3	1,103	10.85	3.65	1,279	19.556226	17.863055
S15: LBC+HPV triage	3	1,077	10.38	3.49	1,190	19.556491	17.863361

CC = conventional cytology; CC + HPV triage 0 = screening option with sample for HPV triage collected concurrent with original Pap smear or self-sampling, without additional visit; CC + HPV triage 1 = screening option with 1 additional visit to collect cervical cells sample for HPV triage sample; HPV = human papillomavirus; ICER = incremental cost-effectiveness ratio; LBC = liquid-based cytology; LBC + HPV triage = liquid-based cytology with HPV triage; QALY = quality-adjusted life-year.

With current CC screening programs every year, HPV triage compared with repeated CC reduced cervical cancer incidence from 9.77 to 9.23 (5.6% reduction) and related mortality from 3.27 to 3.10 (5.2% reduction) per 100,000 persons. It reduced colposcopy referrals from 1,033 to 977 (5.4% reduction) per 100,000 person-years. It extended the discounted life expectancy by approximately 2.3 hours and quality-adjusted life-years by 2.6 hours (Table 7). The percentage reduction in these outcome measures was similar for HPV triage with CC or LBC screening programs every two or three years (Table 7).

Figure 11: Cost-effectiveness of LBC, CC, and HPV triage



In the analysis of LBC and CC, LBC screening every two years reduced disease burden by a small margin but increased colposcopy referrals compared with current CC programs every year. Compared with current CC programs every year, LBC and HPV triage every two years reduced cervical cancer incidence from 9.77 to 9.23 (5.5% reduction) (Table 7) and related mortality from 3.27 to 3.08 (5.8% reduction). This screening option increased colposcopy referrals from 1,033 to 1,420 (37.5% increase) per 100,000 person-years. Compared with current CC screening programs every year, 1,134 women would need to be screened every two years with LBC and HPV triage to avoid one cervical cancer case. The corresponding number needed to screen to prevent one related death was 3,023. Among the screening options considered with LBC or CC at different screening intervals, LBC and HPV triage was the only option that reduced disease incidence at a two-year screening interval (Table 7).

b) Cost-effectiveness of HPV triage

The cost-effectiveness results of adding HPV triage into screening options that are being considered appear in Figure 11.

Screening with CC cytology at a two-year interval with HPV triage was the least expensive option, without the additional visit to collect samples for HPV testing. The option of CC screening with HPV triage requiring an additional visit was also closed to the efficiency frontier (Figure 11). The next best option was LBC and HPV triage in a two-year screening program, yielding a \$42,000 per YLS or \$39,000 per QALY, compared with the least expensive option (Table 25 Appendix 2).

In Figure 11, the LBC and HPV triage option in a one-year screening program extended life expectancy the most but at an increased incremental cost, as indicated by the steep slope of the line between this option and the next best option on the efficiency frontier (i.e., LBC and HPV triage in a two-year screening program). Compared with the next best option, LBC and HPV triage in a one-year screening program yielded an incremental cost of \$148,000 per YLS or \$151,000 per QALY (Table 25 Appendix 2). The options of CC and HPV triage in a one-year screening program with or without an additional visit for sample collection were closed to the efficiency frontier. They both extended life expectancy as compared with the LBC and HPV triage with two-year screening interval but at higher incremental lifetime costs.

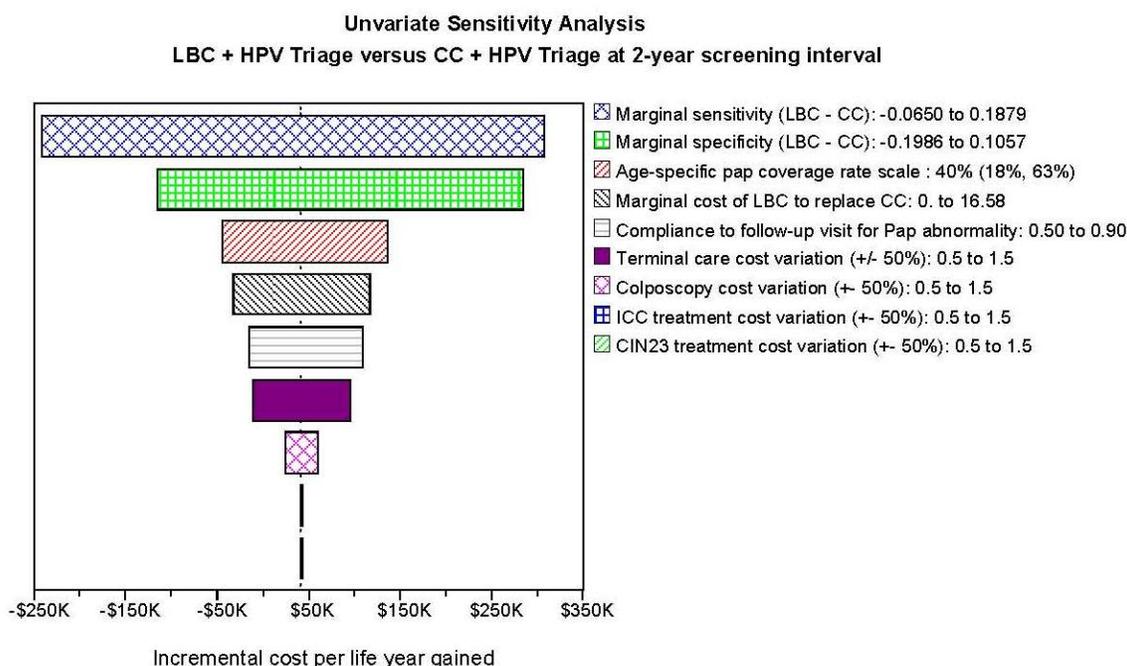
The LBC and HPV triage screening every three years dominated CC and HPV triage every three years (i.e., lower cost and longer life expectancy) (Figure 11). This option, however, was a distance from the efficiency frontier.

c) Sensitivity analysis

The results of the cost-effectiveness analysis were sensitive to uncertainty in input data from model parameters (Figure 12). For a two-year interval screening program, Figure 12 reports the changing incremental cost per YLS for LBC and HPV triage versus CC and HPV triage (without an additional visit) according to plausible ranges of input data from several parameters. In the graph, a negative value for the incremental cost per YLS indicates that LBC and HPV triage is dominated by CC and HPV triage (i.e., higher lifetime cost and shorter life expectancy), and the vertical line indicates the \$42,000 incremental cost per YLS from the base-case analysis. The results from the base-case analysis were robust against treatment costs for cervical cancer or CIN 2-3 lesions (Figure 12). They were sensitive to input data from marginal sensitivity, marginal specificity, screening coverage, marginal cost of LBC, compliance rate to follow-up visits for cytology abnormality, cost of terminal care for a cervical cancer case one year before expiration, and cost of colposcopy (Figure 12).

In the base-case analysis, the trade-off in accuracy between LBC and CC was estimated to be a 6.4% gain in sensitivity and a 4.0% loss in specificity. The meta-analysis showed that LBC and HPV triage screening every two years was associated with an incremental cost of \$42,000 per YLS, compared with CC and HPV triage screening every two years (Table 25 Appendix 2).

Figure 12: Univariate sensitivity analysis of LBC + HPV triage versus CC + HPV triage at 2-year screening interval



CC=conventional cytology; CIN 2-3 = cervical intraepithelial neoplasia stages 2 to 3; HPV=human papillomavirus; ICC=invasive cervical cancer; LBC=liquid-based cytology.

If the marginal accuracy of LBC was estimated according to the six high-quality studies in the meta-analysis (i.e., 7.70% sensitivity gain and 4.40% specificity loss with LBC), LBC and HPV triage would have been cost-effective at \$27,000 per YLS. If the marginal accuracy of LBC was estimated according to the 13 studies in which a histology reference was used (i.e., 1.14% sensitivity gain and 0.57% specificity loss with LBC), LBC and HPV triage would have been associated with an incremental lifetime cost of \$321,000 per YLS.

The effect of other model parameters on the incremental cost-effectiveness estimates of LBC and HPV triage versus CC and HPV triage in a two-year screening program was similar in direction to those discussed in the cost-effectiveness analysis of LBC versus CC. The seven influential parameters identified in 16 were included in a probabilistic sensitivity analysis. Taking health-related quality of life into account, the average lifetime cost of LBC and HPV triage screening every two years compared with corresponding screening with CC was \$39,000 per QALY (Table 26 Appendix 2). If the discount rate were 3%, the LBC screening option would have been associated with lower average lifetime cost and higher life expectancy (Table 26 Appendix 2).

The main estimate for the average lifetime cost of LBC and HPV triage screening every two years compared with corresponding screening with CC was robust against changes in the cost of HPV reflex testing. If the current cost of HPV testing of \$90 was reduced to \$50, the cost-effectiveness estimate was reduced to approximately \$38,000 per YLS. The cost-effectiveness estimate increased to \$46,000 per YLS if the cost of HPV reflex testing increased to \$130 (Table 26 Appendix 2).

Table 8: Cost-effectiveness of LBC and HPV triage and quality of studies evaluating LBC accuracy

Estimates of relative sensitivity and specificity of LBC and CC	Incremental Cost-Effectiveness Ratio (LBC and HPV triage versus CC and HPV triage for 2-year screening programs)
main analysis (20 study groups): sensitivity gain 6.43%; specificity loss 4.02%	\$41,832 per YLS
high-quality studies (6 study groups): sensitivity gain 7.70%; specificity loss 4.40%	\$26,480 per YLS
histology standard (13 study groups): sensitivity gain 1.14%; specificity loss 0.57%	\$321,339 per YLS

d) Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis evaluating LBC and HPV triage appear in Figure 13. HPV triage options always dominate repeated cytology using the same cytology technique for the index smear (Figure 13). This was evident as none of the repeated LBC or CC options for ASC-US management at different screening intervals appeared on the cost-effectiveness acceptability plane (Figure 13). In addition, the screening options involving CC with HPV triage requiring an additional visit to collect samples for HPV testing did not appear on the plot (Figure 13).

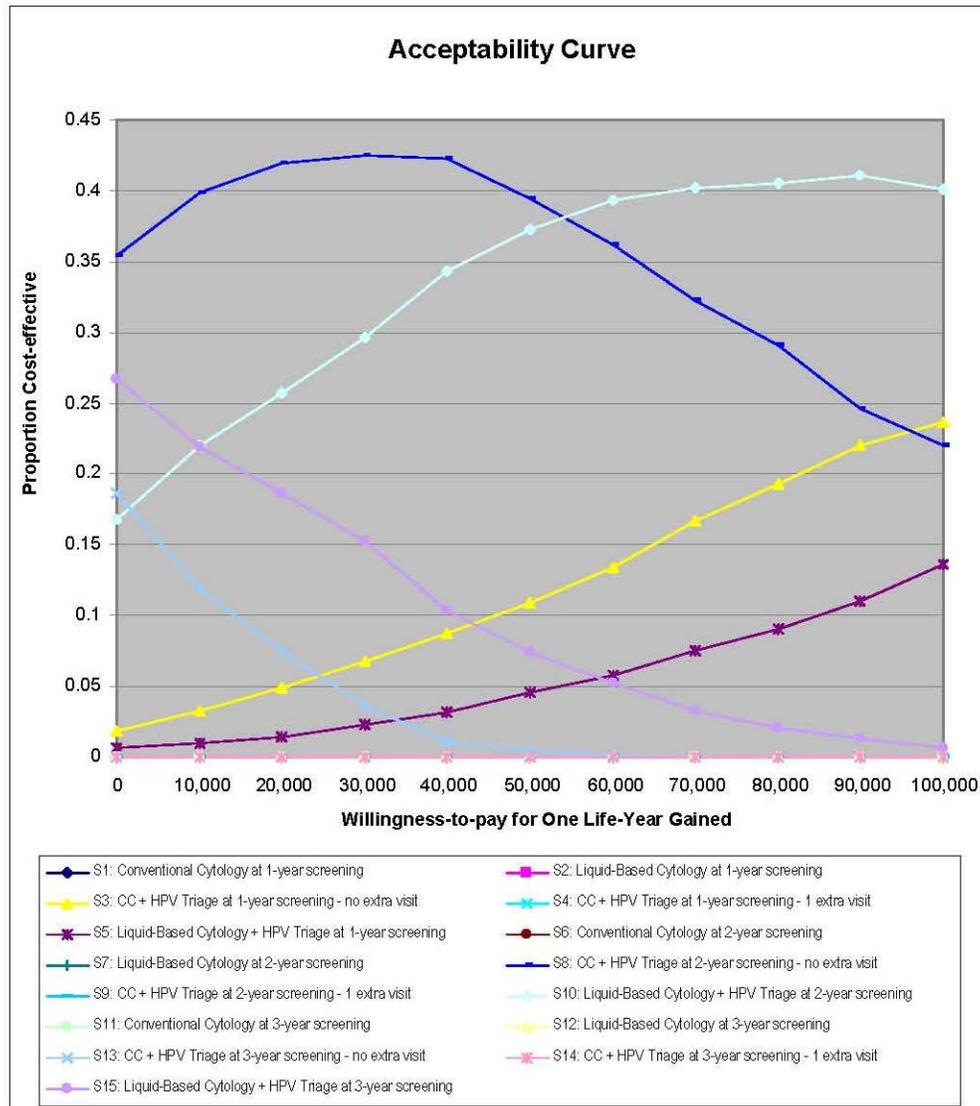
At a one-year screening interval, CC and HPV triage screening offered better incremental net benefits than LBC and HPV triage screening, regardless of WTP levels (Figure 13). At a three-year screening interval, LBC and HPV triage screening always offered better incremental net benefits than CC and HPV triage screening, regardless of WTP levels. Optimal incremental net benefits for two-year screening programs changed according to WTP levels. For a WTP <\$50,000 per YLS, CC and HPV triage screening every two years offered better incremental net benefits than LBC and HPV triage screening of the same frequency. LBC and HPV triage offered the highest incremental net benefits for a WTP >\$50,000 per YLS.

e) HPV triage analysis

- HPV triage was a more effective option for ASCUS management than repeated cytology. When paired with a cytological screening strategy (CC or LBC) and interval (one, two, or three years), it reduced the incidence of colposcopy referrals, cervical cancer, and related mortality.
- Compared to current screening programs (i.e., annual screening with CC at approximately 40% coverage), if CC with HPV triage is offered every year, the relative incidence of cancer will decrease by 6% with a 5% reduction in colposcopy referrals and lower average lifetime costs (\$19 per person, discounted).
- Compared to current screening programs, if CC with HPV triage is offered every two years, the relative incidence of cancer will increase by 2% with a 19% reduction in colposcopy referrals and lower average lifetime costs (\$77 per person, discounted).
- Compared to current screening programs, LBC with HPV triage requires 1,134 women to be screened every two years over a lifetime to avoid one cervical cancer case and 3,023 women to prevent one cancer-related death. This equates with a gain of 0.0002 QALYs and increased average lifetime costs (\$59 per person, discounted).
- Compared to current screening programs, LBC and HPV triage was the only option that reduced disease incidence at two-year screening intervals.

- LBC and HPV triage every two years was cost-effective at approximately \$42,000 per YLS, compared with CC and HPV triage every two years without an additional visit for sample collection for HPV testing. Using the relative accuracy estimates of LBC and CC from high-quality studies, its cost-effectiveness ratio was \$27,000 per YLS. Taking key parameter uncertainty into account, LBC and HPV triage screening every two years was likeliest to produce the highest net health benefits if the WTP for one discounted life-year gained was >\$50,000. With a WTP of <\$50,000, CC and HPV triage without an additional visit produced the highest net benefits.

Figure 13: Net benefit of LBC, CC, and HPV triage options



Analysis conducted using 7 most influential parameters identified in univariate sensitivity analyses.

6.4.4 Subgroup analyses

a) **Screening coverage**

In areas with low Pap screening coverage (e.g., median coverage 19% and range 12% to 26%), LBC screening every two years was cost saving with better health outcomes compared with CC screening every two years (Table 27 Appendix 2). With low Pap coverage, a sensitive cytology could be more likely to attain the efficiency of lower incremental lifetime cost and higher average life-years. In areas with Pap screening coverage less than the national average of 40% (e.g., median 36%, range 27% to 40%), screening with LBC every two years was cost-effective at the incremental cost of \$14,000 per YLS, compared with screening with CC every two years. The cost-effectiveness level was attained with LBC because, on average, it was more sensitive than CC.

For areas with Pap screening coverage above the national average of 40% (e.g., median 46%, range 44% to 57%), screening with LBC every two years became less efficient, at an incremental cost of \$54,000 per YLS, as compared with screening with CC every two years. With a median coverage of 46%, approximately 71% of the target population were screened once every two years (i.e., 46% in the first year, the remaining 54% were screened at a coverage rate of 46% the next year). Because of the high screening coverage, a less sensitive cytology technique could reduce disease burden. As a result, the additional sensitivity gain by LBC became less essential for program efficiency at this level of coverage.

For areas with high Pap screening coverage (e.g., median 63%, range 60% to 74%), approximately 95% of the target population were screened once every three years. The high coverage rendered less frequent screening options efficient. LBC screening every three years had an incremental lifetime cost of \$25,000 per YLS, compared with screening with CC every three years. Screening every three years lessened the public-health costs of screening programs.

b) **Risk of HPV infection**

In the main analysis, screening with LBC every two years yielded an incremental lifetime cost of approximately \$31,000 per YLS, compared with CC screening every two years. This efficiency level was attained at a prevalence of oncogenic HPV infection of approximately 12%. In subpopulations with a lower risk for HPV infection at a prevalence of approximately 6%, LBC screening every two years was associated with an incremental lifetime cost of \$127,568 per YLS, compared with CC screening every two years. At a less frequent screening such as every three years, the corresponding cost-effectiveness ratio of LBC versus CC was \$62,000 per YLS (Table 27 Appendix 2).

In subpopulations with a higher risk for HPV infection, LBC screening extended life-years at a lower lifetime cost compared with CC screening (Table 27 Appendix 2). The higher the risk of HPV infection, the larger were the marginal health benefits associated with LBC screening. The average lifetime costs, however, increased with higher burden of HPV infection (Table 27 Appendix 2).

7 DISCUSSION

For the last 50 years, cervical cancer screening in Canada has relied on the Pap smear or conventional cytology (CC). This simple inexpensive test has led to decreases in the morbidity and mortality associated with cervical cancer. The interpretation of the Pap smear can be limited by inconsistent fixation or obscuring factors. Canadian studies of women with cervical cancer show that

almost 10% had undergone Pap smear screening, but the tests were technically limited.¹¹⁷ To address the issues of Pap test quality, liquid-based fixation methods (LBC) have been developed to provide consistent fixation and preparation of the cells. Rather than the clinician smearing the cells on a glass slide, the cervical sample is placed immediately in fixative, and the Pap test is then produced using a standard method in the laboratory. The resulting samples have a consistent appearance, and obscuring factors such as inflammation are minimized. The residual cells left after the Pap test is produced can be used for additional testing such as HPV DNA. The enhanced quality of the LBC sample comes with additional costs because these tests require proprietary equipment for sample collection and preparation.

This report evaluates the effectiveness and cost-effectiveness of LBC as an alternative to CC in cervical screening programs in Canada, taking into account options for ASC management. A series of SRs was conducted to examine previous SRs and primary studies of LBC and HPV triage. Data were consolidated in a Bayesian meta-analysis to quantify the trade-off in diagnostic accuracy between the two cytology techniques. Our analysis suggests that our best estimate shows LBC is approximately 6% more sensitive and 4% less specific than CC. These differences were not statistically significant in a frequentist analysis. A Bayesian analysis suggested that there was an 83% chance that LBC is more sensitive than CC and a 72% chance that LBC is less specific than CC. LBC was also estimated to reduce the rate of unsatisfactory specimens. The impact of these differences on lifetime costs and long-term outcomes was projected using a Markov cohort simulation model.

The economic evaluation of LBC versus CC showed that LBC was marginally more effective (fewer cancers, fewer cancer deaths, and longer life expectancy) for every screening interval compared (one, two, or three years). For each screening interval, LBC was marginally more costly, except with the three-year interval. For each interval compared, LBC increased the colposcopy rate. In the direct comparison of six CC and LBC programs, two-year CC was least costly. Two-year LBC was associated with an ICER of \$31,000 per life-year gained. Annual LBC was associated with an ICER of \$146,000. All other programs, including the current practice of annual CC screening, were dominated. Probabilistic sensitivity analysis suggested that a WTP threshold of <\$40,000 per life-year gained favoured two-year CC screening, whereas a WTP threshold of >\$40,000 per life-year gained favoured two-year LBC screening. Extending current programs to screening every two years with LBC reduced the disease burden and lowered average lifetime costs. Thus, in a pairwise comparison, two-year screening with LBC dominated (was less costly and improved health) the current practice of annual CC screening.

LBC serves as a platform for HPV testing and facilitates management of equivocal lesions.¹² For every screening interval, LBC improved health outcomes relative to CC alone. Adding HPV triage to CC- or LBC-based screening improved health outcomes for every interval. LBC generally increased net costs in comparison with CC, but HPV triage reduced net costs compared with LBC or CC. The least costly strategy was CC + HPV triage at a two-year interval, with no additional screening visit. The next most costly non-dominated strategy was LBC + HPV triage at a two-year interval, with an ICER of \$22,000 per life-year gained. The next most costly non-dominated strategy was LBC and HPV triage at a one-year interval with an ICER of \$147,000 per life-year gained. In a pairwise comparison with current screening practice, the policy of LBC and HPV triage at a two-year interval decreased costs (by >\$80 per person) and improved health.

The outputs of our model were compatible with those of previous studies. The reported median lifetime cost per YLS for studies evaluating two-year screening with LBC was \$41,000, expressed in

2006 Canadian dollars. Our corresponding estimate for the Canadian settings was \$31,000 per YLS. Our finding that LBC screening dominated CC screening every three years by prolonging life-years while reducing lifetime costs is also consistent with those reported in previous studies.^{20,27}

The current research was conducted during a period of heightened awareness of the potential effectiveness of HPV vaccines. Studies have reported the economic impact of cervical cancer vaccination programs. A Canadian study reported that HPV vaccination of 12-year-old females could be cost-effective at an average lifetime cost between \$21,000 and \$31,000 per QALY in 2006 Canadian dollars.¹¹⁸ Five other studies have shown that vaccinating pre-adolescent females could be cost-effective at an incremental cost-effectiveness estimate ranging from \$5,000 to \$42,000 per QALY (all estimates converted to 2006 Canadian currency for comparison).^{70,119-122} The best policy of LBC and HPV triage identified in this analysis offered a similar incremental cost per QALY.

The current cervical cancer model adopted practices from simulation studies of HPV vaccines. In the model, health states along the disease pathway and those related to ASC-management were stratified by HR or LR HPV infection with differential risks for progression and regression.^{71,72,76} The calibration practice followed those used in early economic evaluation studies of HPV vaccines.^{71,72} The model was made to be consistent with observable Canadian data along the causal pathway between HPV infection and cervical cancer. The marginal gain estimates from the current model were consistent with those from previous cost-effectiveness studies that we systematically reviewed. In a hypothetical scenario of no screening, our estimate of the reduction in cervical cancer mortality attributable to current screening programs was consistent with that reported for systematic screening in the UK.⁴⁰ These observations provide evidence of external consistency for the current Canadian cervical cancer model, with respect to the validity of its structure, input, and output data.

The current cost-effectiveness analysis used Canadian costs from recent studies. The average costs for colposcopy and related services were taken from a resource utilization study with data from four provinces.¹⁰⁸ The estimates of unsatisfactory specimens for both cytology techniques were derived from a study reporting experience with LBC implementation in Ontario.⁶ The average treatment costs for precancer lesions and the earliest cervical cancer stage were derived from a background paper on HPV immunization program in British Columbia³ and economic evaluation studies of ASC and LSIL management.^{109,110} Other average costs for stage-specific cervical cancer were derived from a micro-costing exercise conducted for an evaluation of LBC and HPV testing in Alberta.²⁰

Our results were sensitive to uncertainty in several model parameters. The most noticeable parameter was the gain in sensitivity with LBC relative to CC that accounted for approximately 56% of the variation due to the overall parameter uncertainty. This cost-effectiveness analysis took into account the trade-off estimates in sensitivity and specificity between the alternative screening techniques, including the suggestion that the estimates of LBC accuracy were correlated with study quality.⁴² We found that basing our estimates of test performance characteristics only on high-quality studies improved the economic attractiveness of LBC and LBC with HPV triage. For example, in our baseline analysis, using 20 studies concurrently reporting sensitivity and specificity, the average lifetime cost per YLS for LBC and CC screening every two years was estimated to be \$31,000. Using data from six high-quality studies, the corresponding ratio was \$17,000. Similar changes were observed with the cost-effectiveness estimates of LBC and HPV triage.

Our study focused on LBC performed manually with reasonably low differential sensitivity compared with conventional cytology. A 2006 clinical review of cervical cytology screening suggests that LBC assists adjunctive testing and can achieve greater laboratory efficiency by

reducing inadequate slides and increasing throughput.⁴⁰ According to this review, automated testing on liquid-based samples may be demonstrable as a means of maintaining or even increasing diagnostic accuracy while achieving efficiencies in the laboratory, thereby requiring less labour-intensive effort to maintain efficacy. Our study showed that a small improvement in LBC sensitivity could lead to a large impact on program efficiency when the test was used in routine population-based screening programs over time.

Subpopulations with barriers to current Pap screening were considered in this cost-effectiveness analysis. The small cushion of sensitivity gain with LBC seemed to reduce the average lifetime cost per YLS of LBC-based screening programs for under-screening subpopulations. In high coverage subpopulations, the choice of LBC or CC generally did not improve the economic attractiveness of LBC-based screening programs. Of interest was the scenario of low lesion prevalence post HPV vaccination.^{18,19} Current subgroup analyses showed a high average lifetime cost per YLS for cytology screening programs under low lesion prevalence situations. It will be important to maintain efficient screening programs because the vaccination history of women in their teens and older will be sporadic.

The National Advisory Committee on Immunization statement on HPV vaccines listed three considerations with respect to cervical cancer screening in women vaccinated against HPV infection.¹²³ While the first HPV vaccine has been shown to be effective against cancer precursors caused by HPV-16 and HPV-18, these two HR HPV types are responsible for about 70% of cervical cancer. Women who have been vaccinated will still be susceptible to other HR HPV types. Even if those types are less prevalent than HPV-16 or HPV-18, these women should expect to take part in the currently recommended cervical cancer screening programs. Women who were sexually active before receiving the vaccine may have been infected with HPV-16 or HPV-18. Therefore, any sexually active woman should continue to take part in the routine cervical cancer screening program. As more females receive the vaccine, the screening programs may be modified in type or frequency of screening. This is an area requiring research and surveillance before guidelines can change.

In Canada, many recommendations have been made in the past 30 years to develop comprehensive and organized cervical cancer screening programs.¹²⁴ These national recommendations, which include population-based recruitment, recall, follow-up, and quality management components, require the support of computerized information systems. Eight of the 13 provinces and territories have recommended or implemented elements of an organized screening program. Programs (full or partial) have been implemented in British Columbia (1960), Nova Scotia (1991), Manitoba (1999), Alberta (2000), Ontario (2000), Saskatchewan (2001), Prince Edward Island (2001), and Newfoundland and Labrador (2003). In 2003, the Pan-Canadian Forum on Cervical Screening recognized that national reporting on some indicators was limited because there was – and still is – no centralized database, and they recommended the implementation of a comprehensive population-based cervical screening database.⁷ Such computerized information systems could facilitate the implementation of the two-year screening strategies with LBC and HPV triage as suggested by this cost-effectiveness analysis.

Current cervical screening guidelines recommend that the Pap smear should be started within three years of sexual debut, done annually until three consecutive negative results appear, and continued every two to three years thereafter.⁸ This leads to an observed annual coverage of approximately 40% for each provincial average, although annual coverage could fluctuate regionally in a province.⁸⁴ Our evaluation tried to handle these variations in subgroup analyses mimicking fluctuation in screening

coverage across health jurisdictions. This cost-effectiveness analysis showed that LBC and HPV triage were particularly effective and cost-effective in jurisdictions with low screening coverage.

This analysis showed an increase in colposcopy referrals with LBC alone and LBC and HPV triage, though less so for the latter option because of the decrease in follow-up visits with HPV reflex testing. The main clinical interest in cervical cancer prevention is the detection of high-grade lesions that have a potential for progression to cervical cancer. The early detection of HPV infection and low-grade precancerous lesions, most of which would spontaneously resolve, may be less desirable because it could lead to patients with anxiety, unnecessary referrals, and potential overtreatment.^{40,93} These negative aspects of screening programs, especially their unintended effect on quality of life, have not yet been evaluated and are not easily measured. The negative impact could increase proportionally to the number of screening rounds and thus be greater in scenarios of frequent screening. This would offer another reason besides cost-effectiveness considerations to weigh the relative harm and benefits associated with all screening frequencies in secondary prevention programs with more sensitive tests.^{41,125}

7.1 Study Limitations

There are several limitations in this cost-effectiveness analysis. First, there is uncertainty whether the notion of screening every two or three years abstracted in the model could be applicable in current Canadian opportunistic screening programs. Consensus meetings in 1998 and 2003 regarding the state of cervical cancer screening programs in Canada recommended a conversion to organized programs. This cost-effectiveness analysis provided data and insight for the selection of optimal fixed screening intervals in future organized programs.

Second, the number of LYS by alternative screening options was used as the primary measure of health benefits, rather than the preferred measure of QALYs. This is consistent with other economic evaluations and HTAs of cervical screening options. Work has been undertaken, however, to estimate the potential reduction in quality of life associated with test abnormalities (including false-positives) or precancerous lesions.¹¹⁹ In this cost-effectiveness analysis, the most recent utility estimates were used but the average lifetime cost per QALY was reported as a secondary measure of health benefits. The results of these analyses were similar in terms of cost per life-year gained, regardless of whether life-years were quality-adjusted. Thus, we would not expect that conclusions based on the evaluation of utility ratios would be qualitatively different.

Third, despite efforts in this report to ensure external consistency (i.e., consistency between the decision model and the corresponding real-life scenarios they are purported to represent), parameter uncertainties and model uncertainties always remain. One area of concern is the matching between the values simulated for a single cohort and cross-sectional data from multiple cohorts. There may be cohort effects that affect cancer incidence and mortality (e.g., variation in exposure to HPV, risk factors of cervical cancer, and factors that affect cervical cancer diagnosis). This validation did not account for these potential cohort effects.¹²⁶

Fourth, all the data on HPV triage included in this report pertain to the Digene Hybrid-Capture test (versions I and II). Similar tests are becoming available. The Roche Amplicor test is now available and can be used to detect the presence of an infection with ≥ 1 of the 13 HR HPV types. It distinguishes HR HPV infections from no HPV infection but does not allow the identification of specific genotypes. Also available is the Roche Linear Array HPV genotyping test for 37 HPV types.

While inferences from this report are based on data from reports published until June 2006, with all describing HC II, the knowledge is generalizable to the new tests. The sensitivity and specificity data pertaining to virologic versus cytologic triage of women with ASC-US consolidated via the updated SRs are specific to HC II. The data, however, were not used in the cost-effectiveness analysis. In the underlying decision analytic model, HPV reflex testing was assumed to detect the presence of type-specific underlying HPV infection, which was assumed to be known in the simulation. As a result, the analytical sensitivity and specificity of HC II were used (Table 19 Appendix 1). The analytical accuracy of the new tests is similar to that of HC II. The cost-effectiveness inference from this report is most likely to be applicable to the new tests, as long as the price is not higher than that of HC II.

8 HEALTH SERVICES IMPACT

The budget impact analysis adopted a provincial ministry of health perspective.¹²⁷

8.1 Population Impact

The population impact of cervical screening was summarized with respect to screening population and coverage, cervical cancer and mortality incidence, prevalence of potentially persistent HR HPV infection in those ≥ 30 years old, colposcopy services, and related costs (Table 28 Appendix 2).

The provincial population of women aged 18 to 69 years in 2006 who were targeted for cervical screening was estimated to range from approximately 44,000 in Prince Edward Island to 3.8 million in Ontario. The reported average screening coverage each year was relatively consistent at 40% across the provinces. The estimated annual number of screening tests performed in each province ranged from approximately 18,000 tests in Prince Edward Island to 1.4 million tests in Ontario.

The cervical cancer incidence was estimated to range from approximately 8.15 to 12.27 per 100,000 persons across provinces. The corresponding incidence for cervical cancer related death ranged from 2.19 to 3.96 per 100,000 persons across provinces.

High-risk HPV prevalence among women above age 30 years was estimated with available data from selected cities in four provinces.¹⁰⁴ HPV infection in women above age 30 years could be considered persistent infection that, given a long latency, could trigger cervical cellular changes.⁹⁵ High-risk HPV prevalence ranged from 4.4% in women >30 years old residing in St John's, Newfoundland; 7.2% in Montréal, Québec; 8.7% among women who underwent routine Pap smear in southern Ontario, to 13.2% among women in British Columbia (Table 28 Appendix 2).

Data related to colposcopy services were derived from a 2005 utilization study with available data from five western provinces.¹⁰⁸ The reported number of colposcopy examinations in 2004 ranged from approximately 5,000 in Saskatchewan to 100,000 in Ontario in 2000. The corresponding colposcopy services per 100,000 persons ranged from 711 in British Columbia to 2,016 in Manitoba (Table 28 Appendix 2). The total cost of colposcopy expressed in 2006 dollars for the five provinces ranged from approximately \$361,000 in British Columbia to \$2.5 million in Ontario.

The burden of HPV-related infection has been quantified. In British Columbia, the cost of HPV-related disease was estimated to be \$50 million in 2005.³ Cervical cancer prevention including screening and follow-up and treatment of precancerous and cancer lesions accounted for

approximately 72% of the total cost. The burden of genital warts, HPV, cervical dysplasia, and cervical cancer in Canada has also been quantified.¹²⁸ The study estimated that each year in Canada, 36,000 new cases of genital warts, 177,000 new cases of CIN 1, 52,000 new cases of CIN 2-3, 1,100 new cases of cervical cancer, and 450 cervical cancer deaths occur. The total annual cost to diagnose and treat these conditions is approximately \$300 million. Most of the cost is attributable to cytology testing and related services, accounting for approximately 82% of the total cost.

The social impact of HPV-related burden is considerable albeit related data are qualitative. The anxiety experienced by many women when they have a cervical screening test is documented in the literature and acknowledged by those who care for these women.⁴⁰ For some women, fear that they have or may be found to have cancer engenders anxiety. For others, depression, anger, and the stigma associated with sexually transmitted infection are psychosocial factors.¹²⁹ This issue has been emphasized in a study that addressed the impact of testing positive for HPV on women undergoing screening.¹³⁰

Compared with women who receive a normal result, women who receive results of a mild abnormality have elevated anxiety levels and those referred for colposcopy have higher levels.¹³¹ After colposcopy, anxiety levels tend to fall, and those kept under cytological surveillance experience less anxiety over time.¹³² Many women have a poor understanding of cervical screening, and it has been shown that improving communication with women can reduce anxiety.¹³³

Efforts have been made to improve information access, with the aim of not only reducing anxiety, but also being more transparent about the benefits and limitations of cytology.⁴⁰ HPV testing, which is going to play an increasing role in cervical screening, presents new challenges for women and their partners in terms of education and understanding. In a study of women with ASCUS-LSIL who experienced HPV testing, those who were HPV-positive were more anxious than those who were HPV-negative. Women who were HPV-positive were more anxious than those who had not experienced HPV testing.¹³⁴ Another study examining the psychosocial impact of testing positive for HPV in routine cervical screening in the UK reported that women who tested positive for HPV demonstrated significantly greater concerns about their sexual relationships than women who tested negative. Findings from this study suggested that there was a negative impact on feelings about sexual relationships among women who were HPV-positive, which was consistent with a lack of public awareness about the sexually transmitted etiology of cervical abnormalities.¹³⁰

The introduction of vaccines to prevent HPV infection may affect how screening is done in the future. Women who are vaccinated will still require screening, because current HPV vaccines are only protective against HPV-16 and HPV-18, which have been attributable to approximately 70% of cervical cancer. Also, the prophylactic vaccines are not designed to protect women who may have already been infected with HPV-16 or HPV-18. As more women become vaccinated, research will be needed to determine if screening programs should be modified in light of a lower prevalence of precancer lesions.

8.2 Budget Impact

The cost-effectiveness analysis suggests that two-year cervical cancer screening strategies with LBC and HPV triage represent an optimal use of resources. In current opportunistic programs, cervical screening is conducted as part of a routine physical examination without mechanisms for recall and follow-up. It remains unclear how two-year screening strategies with LBC and HPV triage would be

implemented without the use of population-based cervical screening databases containing information about the target population of eligible women, all screening tests completed, results of all screening tests, all follow-up tests, diagnoses, and outcomes.⁷

Given this uncertainty, the budget impact analysis was conducted for the first year of LBC implementation. It is expected that the impact during the years after implementation would be similar to that of the first year unless adherence to a two-year screening interval by physicians and screened individuals leads to a reduction in the number of screening tests conducted every year. As this scenario is probably unlikely with the adoption of only LBC and HPV triage, the focus of the budget impact analysis was for the first year of LBC and HPV triage implementation. The impact for a few subsequent years was assumed to be similar to that of the first year.

8.2.1 Methods

a) *Main budget impact analysis*

First, the average cost estimates of follow-up and management of cytology abnormalities were derived (Table 29 Appendix 2). For example, the average cost of follow-up and management of HSIL was estimated to include costs for two colposcopies at six and 12 months and two subsequent cytology follow-up visits (Figure 4).⁸ Given indexed cytology with a HSIL result, a colposcopy examination including a biopsy was assumed if the underlying neoplasia was CIN 1+; otherwise, only a colposcopy examination was assumed. A similar conditional probability of CIN 2+ given HSIL was derived to indicate whether treatment for cervical neoplasia was indicated (Table 29 Appendix 2).

The conditional probabilities used in the cost estimates (Table 29 Appendix 2) were derived using data from studies reporting cross-classification of cytology and histology results. These studies were identified as part of the SR of LBC effectiveness.

The impact of the LBC and HPV triage implementation was first estimated for British Columbia. The estimation was based on sample statistics including approximately 539,000 screening tests (Table 30 Appendix 2).¹³⁵ The impact of LBC implementation on a CC screening program was assumed to be similar to that of the Ontario pilot project with data from approximately 406,000 CC and 379,000 LBC tests.⁶ Using these data, the relative changes to cytology classification were derived before and after LBC implementation. These estimated changes were applied to the observed cytology outcome data from British Columbia. The marginal LBC cost for approximately 539,000 screening tests was estimated to be approximately \$4.5 million in 2006. The impact of LBC adoption in the follow-up and management of cytology abnormalities was estimated to be approximately \$2.9 million. The total impact due to LBC implementation in the first year in British Columbia was estimated to be \$7.4 million. This averaged to approximately \$5.95 per individual in the screening population. Similarly, the total impact due to LBC and HPV triage implementation was estimated to be \$7.2 million, and the cost per individual in the screening population was estimated to be \$5.80 (Table 30 Appendix 2).

The average impact cost per individual estimates for LBC and HPV triage in British Columbia were applied to the other screening populations, to derive the budget impact of the remaining provinces (Table 28 Appendix 2). The estimates of the LBC and HPV triage impact for Ontario, and Newfoundland and Labrador were included for validation purposes because cytology services in these two provinces have been converted to LBC.

Several assumptions were used in the estimation.

- LBC adoption has no impact on the usage patterns of cytological screening across all provinces.
- The conversion of a laboratory using CC to one using LBC would take three to six months. Most laboratories could convert within a year, as it would be difficult to keep the two techniques in operation concurrently.
- The distribution of cytology outcomes using CC and LBC after a conversion would be similar to that observed in the implementation of LBC BD SurePath as reported in the pilot study for the Ontario Cervical Screening Program (Table 30 Appendix 2).⁶
- Follow-up visits of CC abnormalities and related health services were accounted for up to one year from the indexed Pap smear.⁸
- Given the short duration of conversion from CC to LBC, the health services impact from the conversion was mainly due to the marginal accuracy of LBC, leading to small modifications on cytology outcomes consistent with observed changes in the LBC BD SurePath implementation in the Ontario Cervical Screening Program.⁶
- The use of HPV triage could affect the rates and outcomes of referral to colposcopy.¹³⁶ The main budget analysis assumes that the impact of HPV triage was the reduction of one cytology follow-up visit. The increase in colposcopy rates due to LBC and HPV triage was incorporated into the budget impact analysis separately.

b) Sensitivity analysis

The cost-effectiveness analysis of LBC and HPV triage suggests a potential for an increase in colposcopy services with the use of LBC in population-based screening programs. This increase could happen within the first year of implementation. To keep it simple, the main budget impact analysis did not take into account this potential. In a sensitivity analysis, the projected increases in colposcopy services under the adoption of LBC only or LBC with HPV triage derived from the decision analytic model were applied to the observed colposcopy services reported for five western provinces (Table 28 Appendix 2). In this scenario, the estimated impacts of LBC and HPV triage implementation were derived. Similar estimates for the remaining provinces were derived using data from the five western provinces¹⁰⁸ and made proportional to population sizes.

8.2.2 Results

Across provinces, the first-year budget impact estimates were lower with LBC and HPV triage compared with those with LBC alone (Table 28 Appendix 2), although the differences were generally small relative to the impact estimate for each option. For example, the first-year budget impact estimate for Nova Scotia was \$1.82 million for LBC and \$1.78 for LBC and HPV triage in 2006 dollars (Table 9). The average cost per targeted individual was \$5.95 for LBC implementation and \$5.80 for the implementation of LBC and HPV triage.

Province	Estimated Budget Impact (\$ millions)	Province	Estimated Budget Impact (\$ millions)
British Columbia	7.600 to 7.797	Québec	14.223 to 14.591
Alberta	5.672 to 5.819	New Brunswick	1.421 to 1.458
Saskatchewan	1.723 to 1.819	Nova Scotia	1.776 to 1.822
Manitoba	2.043 to 2.096	Prince Edward Island	0.255 to 0.262
Ontario	22.034 to 22.604	Newfoundland and Labrador	1.028 to 1.055

Estimates for Ontario, and Newfoundland and Labrador provided for bench-marking with observed data, as these 2 provinces have implemented LBC. HPV=human papillomavirus; LBC=liquid-based cytology.

Across provinces, the first-year budget impact estimates would need to increase by an average of 12% to account for the potential increase in colposcopy services associated with LBC implementation (Table 28 Appendix 2). Taking this potential increase into account, the average cost per targeted individual was \$6.35 for LBC and HPV triage implementation, ranging from a low of \$5.91 in British Columbia to a high of \$6.74 in Manitoba.

8.3 Planning, Implementation, Utilization, and Legal or Regulatory Considerations

A pilot study evaluating the use of LBC and HPV triage was conducted in the UK.¹³⁷ In the first few months after initiation, the study reported high rates of HPV positivity and referral to colposcopy. Subsequently, the authors reported that the addition of HPV triage in women with low-grade cytological abnormalities doubled the rate of referral to colposcopy but decreased the rate of repeated smears by approximately 70%.¹³⁶ This cost-effectiveness analysis suggests that screening every two years with LBC increases the rate of colposcopy referral by approximately 48% compared with CC in opportunistic programs with observed coverage of approximately 40% every year. The use of LBC and HPV triage in screening programs at two-year intervals also increased the rate of colposcopy referral by approximately 38%. These consistent findings suggest that an increase in colposcopy referrals needs to be planned for in the implementation of LBC and HPV triage.

The budget impact analysis suggests an increase of approximately 12% in the first-year budget for the implementation of LBC and HPV triage to cover for the possible increase in colposcopy referrals. This budgetary item, however, was estimated without considering other programmatic implications on human resources, training, workload management, and the potential negative impact of a corresponding increase in waiting lists for delayed colposcopy services.

A higher knowledge of HPV infection and related diseases could increase the acceptability of new techniques for cervical cancer screening. The level of knowledge, however, varied in studies that gauged the level of HPV awareness among health care providers.^{138,139} In a Canadian study of Québec gynecologists, 61% answered correctly regarding the proportion of cervical cancer related to oncogenic HPV types.¹³⁸ In one study, the mean HPV knowledge score was 2 out of 5 (standard deviation 1.3), with a higher score indicating better knowledge.¹³⁹ In another study involving pediatricians, the percentage of correct answers varied from 20% to 98%.¹⁴⁰

The level of HPV awareness was gauged in three studies including participants from the general public. In a survey of women attending physician's clinics, 52% of participants had heard of HPV.¹⁴¹ In another survey of the general public, 23% of participants had heard of HPV.¹⁴² Women recruited from television, radio, or the Internet answered 71% of general questions on HPV correctly.¹⁴³

Education programs for providers and target screening populations could increase screening coverage, especially education regarding the causal relationship between HPV infection and cervical cancer. Information regarding the roles of HPV testing in the early detection of precancerous lesions should be included to increase knowledge among these groups. Informing women and providers of the preventive roles of cervical screening and HPV testing could increase community understanding, support, and compliance.

Problems in relation to cervical screening have resulted in litigation.²⁷ Legal considerations regarding the potential false-negatives and false-positives associated with LBC and HPV triage were not

represented in the cost-effectiveness analysis. There was no attempt to quantify consequences with respect to reduced or increased litigation costs if CC is replaced by LBC in the reported analyses.

8.4 Ethical Considerations

The uptake of cervical screening is not uniform across Canada, and some disadvantaged population groups are reported to have lower coverage.¹⁴⁴ A British technology assessment of LBC suggested that improvements in cervical cytology techniques should be considered alongside ways to improve coverage and to make provisions so that the provision of cancer prevention services is more equitable.²⁷

9 CONCLUSIONS

The clinical evidence suggests no statistical differences in sensitivity and specificity between LBC and CC. LBC is estimated to be on average 6% more sensitive and 4% less specific than CC across a range of cytological thresholds. There is an 83% chance that LBC is more sensitive than CC and a 72% chance that it is less specific. On average, LBC classifies approximately 1% more cell abnormalities than CC at the low-grade threshold of LSIL+. At the high-grade threshold of HSIL+, LBC may classify fewer abnormalities than CC, but the difference is not statistically different. On average, LBC may have a lower rate of unsatisfactory specimens, but the estimated differences from individual studies varied.

HPV triage of ASCUS is more sensitive to detect cervical intraepithelial lesions than repeat cytology. HPV triage has a similar specificity compared to repeated cytology. Model projections suggest that, over a woman's lifetime, LBC is likely to improve health outcomes (e.g., cancer incidence and cancer death) and increases costs when compared with CC at the same screening interval. Model projections also suggest that, over a woman's lifetime, HPV triage reduces costs and improves health outcomes when paired with any cytologic screening strategy.

Direct comparison of all screening and triage strategies show that annual screening with CC or LBC is always more costly and less effective than when paired with HPV triage. HPV triage used with LBC screening at two-year intervals is preferred to CC with HPV triage at a willingness-to-pay threshold of \$50,000 per LY gained, and CC with HPV triage every two years is preferred to LBC with HPV triage at lower willingness-to-pay thresholds. In comparison with current practice, using liquid-based cytology with HPV triage at two-year screening intervals will reduce costs, with a similar or reduced burden of disease. Thus, the health economic evidence suggests that two-year screening strategies using HPV triage, with or without LBC, represents the best use of resources for cervical cancer screening. These results will require revision given the introduction of automated screening, HPV vaccination, and organized screening programs.

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APPENDICES

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