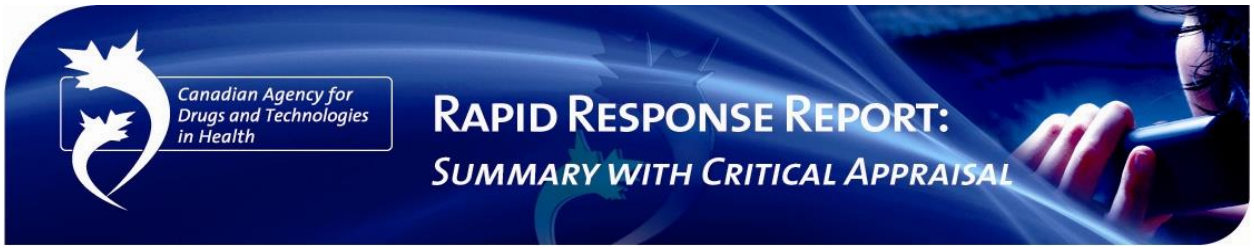

TITLE: Self-Collected versus Clinician Collected Samples for Sexually Transmitted Infection Testing in Women: A Review of Comparative Clinical Effectiveness Cost-Effectiveness, and Guidelines

DATE: 22 June 2016

CONTEXT AND POLICY ISSUES

Sexually transmitted infections (STIs) are a serious and growing public health concern in Canada, particularly among women.[1] Individuals may become infected with an STI following unprotected sexual activity with a person who is infected, or through nonsexual contact, such as sharing needles, during childbirth, or breast-feeding.[2] STIs can be caused by bacteria (e.g., *Chlamydia trichomatis* or *Neisseria gonorrhoeae*), parasites (e.g., *Trichomonas vaginalis*), or viruses (e.g., human papillomavirus).[3] All STIs are treatable; however, infections caused by viruses cannot be cured.[2]

Rates of reported STI cases have been steadily increasing in Canada since the late 1990s.[4] Chlamydia is the most commonly reported bacterial STI in Canada, with women aged 15 to 24 years being most affected.[4] The prevalence of chlamydia increased by 57.6% between 2003 and 2012, from 189.6 to 298.7 reported cases per 100,000 Canadians.[4] In 2012, the rate of Canadian women infected with chlamydia (383.5 per 100,000) was almost twice the rate reported among men (212.0 per 100,000).[4] Gonorrhea and syphilis are other bacterial STIs which are also being increasingly reported; however, these infections are more common among men than women in Canada.[4] In 2012, the rate of reported cases of gonorrhea and infectious syphilis was markedly higher among Canadian men than women (41.3 versus 31.0 per 100,000 and 11.0 versus 0.5 per 100,000, respectively).[4] In contrast with bacterial STIs, human papillomavirus (HPV) is the most common viral STI, with approximately 75% of sexually active women having an HPV infection at some point in their lives.[5] Many types of HPV have been identified, which can cause various health outcomes such as skin lesions (e.g. anogenital warts) or worse, cervical cancer.[5]

Many women infected with an STI may not have any symptoms and may be unaware of their condition.[2] Untreated infections may lead to unintended health consequences; these are particularly worrisome in women as they can cause serious infection of the female reproductive organs, including pelvic inflammatory disease (PID), long-lasting pelvic pain, complications of

pregnancy, infertility, and cervical cancers.[6] Therefore, early detection and treatment of STIs is critical for reducing infection transmission and related complications.

Despite recommendations for regular and targeted screening for STIs,[7,8] participation in traditional clinic-based screening has been met with limited success and infection control remains suboptimal.[6] Accordingly, self-collection of samples for STI testing in women has been suggested as a feasible, less invasive alternative to clinician examination and sampling, and a method that may be able to overcome some of the existing diagnostic challenges.[9,10] While the less invasive nature of the self-sampling method may be well-accepted among women and may potentially encourage screening attendance,[10] the accuracy and cost-effectiveness of self-collected samples in comparison with samples collected by clinicians requires careful assessment and consideration before widespread uptake.

The purpose of this report is to examine the clinical effectiveness, cost-effectiveness, and evidence-based guidelines regarding the use self-collected samples for STI testing, as compared with samples collected by clinicians.

RESEARCH QUESTIONS

1. What is the comparative effectiveness of testing for sexually transmitted infections in women using self-collected versus clinician-collected samples?

2. What is the cost-effectiveness of testing for sexually transmitted infections in women using self-collected versus clinician-collected samples?

3. What are the evidence-based guidelines regarding the use of self-collected samples to test for sexually transmitted infections in women?

KEY FINDINGS

One systematic review and nine screening test accuracy studies were identified relating to the comparative clinical effectiveness of testing for sexually transmitted infection in women using self-collected versus clinician-collected samples. Based on the identified published literature, self-collected samples were commonly associated with high sensitivity and high specificity in comparison with samples collected by clinicians. Study findings also revealed that there was good agreement between the two sampling methods.

Two published economic evaluations were identified regarding the comparative cost-effectiveness of self-collected versus clinician-collected samples for STI testing in women. Findings revealed that a home-based self-sampling strategy may be cost-effective in comparison with standard clinic STI testing and collection of specimens by clinicians. However, results warrant careful interpretation owing to shortcoming in the economic model and limited applicability to the Canadian setting.

No relevant published evidence-based guidelines were identified regarding the use of self-collected samples for STI testing in women.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including MEDLINE via Ovid, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and May 25, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult women who are undergoing STI screening for HPV, chlamydia, gonorrhea, trichomoniasis or syphilis (including pregnant women, women with a history of drug use or history of risky behaviour)
Intervention	Self-collected samples (vaginal, cervical, rectal, or urine)
Comparator	Clinician-collected samples (vaginal, cervical, or rectal)
Outcomes	Q1: Clinical effectiveness (comparative accuracy) Q2: Cost-effectiveness Q3: Evidence-based guidelines regarding the use of self-collection methods for STI screening
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

HPV = Human papillomavirus; STI = sexually transmitted infection

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Health technology assessment reports, systematic reviews (SRs) and meta-analyses were excluded if there was incomplete reporting of methods or if they were superseded by an updated review or more recent rigorous review. Screening test accuracy studies were excluded if they were described within a SR selected for inclusion in this report. Furthermore, health economic studies which reported only direct costs that were not cost-effectiveness, cost-utility, cost-comparison, or cost-benefit analyses were excluded. Guidelines were excluded if they did not clearly indicate a formal literature search and an assessment of the quality of the evidence upon which the recommendations were based.

Given the volume of published studies relating to research question 1, literature published from 2015 to present was reviewed for this question in order to capture the most recent and relevant information. Date limits for research questions 2 and 3 were kept unchanged (2011 to present).

Critical Appraisal of Individual Studies

The quality of included studies was assessed based on their study design. SRs and meta-analyses were critically appraised using the AMSTAR instrument,[11] while the methodological quality of screening test accuracy studies was assessed using the QUADAS-2 tool.[12] Economic evaluations selected for inclusion were appraised using the Drummond checklist.[13] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study was performed and described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 666 citations were identified in the literature search. Following screening of titles and abstracts, 587 citations were excluded and 79 potentially relevant reports from the electronic search were retrieved for full-text review; no relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 67 publications were excluded for various reasons. Twelve publications met the revised selection criteria and were included in this report. Appendix 1: Selection of Included Studies details the study selection process through a PRISMA flowchart and lists the reasons for exclusion.

Additional studies of potential interest that did not meet the selection criteria are provided in Appendix 5: Additional References of Potential Interest.

Summary of Study Characteristics

A brief overview of the studies selected for inclusion is presented in Appendix 2: Characteristics of Included Publications.

Study Design

One SR with meta-analysis,[14] two crossover RCTs,[15,16] and seven cross-sectional studies[17-23] were identified regarding the comparative clinical effectiveness of self-collected samples versus clinician-collected samples for the detection of STIs in women. Two economic evaluations[24,25] were identified which compared the cost-effectiveness of home-based self-sampling and clinic-based screening strategies. No relevant evidence-based guidelines were identified in the published literature regarding the use of self-collection methods for STI screening in women.

Country of Origin

The included SR[14] was conducted in Canada. Primary clinical studies relating to screening test accuracy were conducted across a range of different settings, including Switzerland,[22] Haiti,[21] South Africa,[20] Hong Kong,[15] Papua New Guinea,[19] Malaysia,[16,23] Canada,[17] and the United States.[18] The identified economic evaluations were conducted in the United States.[24,25]

Patient Population

The target population considered within the identified SR[14] comprised adult patients (men and women) undergoing STI screening for chlamydia and/or gonorrhea infection. Similarly, one cross-sectional screening accuracy study included women undergoing STI screening for chlamydia and gonorrhea infection. All other screening test accuracy studies comprised women undergoing HPV screening; in all cases, women in these studies samples were concomitantly screened for cervical cancer.

The target population within one economic evaluation[24] comprised women undergoing screening for chlamydia, gonorrhea, and trichomoniasis infection, while the second economic evaluation[25] focused on women undergoing screening for chlamydia only.

Interventions and Comparators

The main intervention of interest (index test) across included studies was self-collected specimens for STI diagnosis, while the main comparator of interest (reference test) comprised clinician-collected samples for detecting STIs. The majority of included studies examined self-collected vaginal specimens in comparison with clinician-collected cervical samples; however, two studies compared self-collected cervical samples with clinician-collected cervical samples,[16,23] and another study compared clinician-collected vaginal samples with self-collected vaginal samples.[17] The included SR compared different types of self-collected and clinician-collected samples for detecting chlamydia and gonorrhea, including urine, vaginal, cervical, and rectal specimens.

Both of the included economic evaluations compared an internet-based self-sampling strategy for STI diagnosis with a clinic-referral strategy involving standard clinic-based STI screening and treatment.

Outcomes

Clinical outcomes related to the comparative effectiveness of self-collected versus clinician-collected samples for STI screening in women generally consisted of measures of screening test validity (e.g. sensitivity and specificity) and measures of screening test reliability (e.g. raw overall agreement and agreement beyond chance). Namely, the included SR[14] and one cross-sectional study[18] reported test validity outcomes, while five studies[15-17,21,23] exclusively reported test reliability outcomes. Three studies reported measures of both test validity and reliability.[19,20,22]

The included cost-effectiveness analyses assessed the economic benefits of using an internet-based self-sampling strategy in comparison with conventional clinic-based screening for STIs in women, and quantified the economic benefits as incremental costs per STI detected in one study,[24] and incremental costs per case of pelvic inflammatory disease (PID) averted.[25]

Summary of Critical Appraisal

A detailed overview of the strengths and limitations of each study selected for inclusion can be found in Appendix 3: Critical Appraisal of Included Publications.

Systematic Reviews and Meta-Analyses

The included SR and meta-analysis[14] was generally well conducted. The review authors used an *a priori* design by publishing a study protocol before the conduct of the review, performed a comprehensive literature search across several electronic databases, and enforced data extraction by two independent reviewers. In addition, the review authors provided a list of included studies and detailed the individual study characteristics, assessed the scientific quality of the included studies using the QUADAS checklist, and used appropriate methods to statistically combine results of included studies in a meta-analysis. However, it was unclear whether duplicate article screening was performed prior to data extraction and whether a search for unpublished studies or grey literature supplemented the initial searches. Both of these features would have reduced the risk of bias in the selection of studies during the initial stages of the review process. Moreover, while the scientific quality of included studies was assessed, it was not reported in sufficient detail within the publication, and study quality was not considered in the formulation of the review's conclusions. Similarly, the likelihood of publication bias was mentioned by the review authors, but there was no evidence of a formal assessment using statistical methods or visual inspection of forest plots. Finally, while the review authors disclosed no potential conflicts of interest, funding sources of included studies were not reported.

Screening Test Accuracy Studies

Assessment of the scientific quality of included screening test accuracy studies revealed that the primary analyses were generally well conducted, with the majority of studies showing low risk of bias and minimal concerns regarding applicability. Namely, the quality of these studies was strengthened by a number of factors relating to patient selection, interpretation of the index (self-collected sample) and reference tests (clinician-collected sample), and the flow and timing of screening test techniques. These factors include the avoidance of a case-control design in which the diagnosis or screening outcome is known prior to the administration of the screening test, as well as the use of a short time interval between the index test and the reference test (i.e. clinician-collection was performed either immediately after self-sampling or within the shortest delay). Additionally, included studies avoided inappropriate exclusions of patients during the selection process by aiming to include a patient spectrum similar to the population in which the test would be used in practice (i.e. patients undergoing STI testing in whom infection is suspected). Moreover, index test results were likely interpreted without knowledge of the results of the reference test, and vice-versa, given that self-collected and clinician-collected specimens were tested for the presence of STI at the same time using laboratory analysis across all included studies; two studies[16,23] specified that all specimens were assessed by a trained pathologist who was blinded to the source of sampling. The reference test used across all included studies (clinician-collected sample) was likely to classify patients appropriately based on the assumption that clinician-collected samples are 100% sensitive when tested in the laboratory, and all patients within each study sample received the same reference test. With the exception of one study,[23] all patients who were initially recruited were included in the analysis. Despite these strengths, it was unclear whether a consecutive or random sample of patients was enrolled in four included studies,[17,18,20,23] and one study[21] reported recruitment of a convenience sample of patients, which brings into question the internal validity of these studies. Finally, concerns regarding applicability were generally low given that study samples across the included test accuracy studies matched the question posed in this report, the conduct and interpretation of the index test did not differ from the question posed in this report, and the target condition defined by the reference test was in line with relevant STIs defined by the question

posed in this report. It was unclear whether the inclusion of HIV-positive women in one study[20] was directly relevant to the review question and whether this sample may have limited comparability with other study samples, and five studies[15,16,21-23] reported the exclusion of pregnant women from their study samples, which may be relevant to the review question posed.

Economic Evaluations

The two included economic evaluations appeared generally well-designed, and the applicability of the analyses was strengthened by the use of a clearly focused question of economic importance, consideration of relevant treatment comparators, reporting of methods and sources for the valuation of clinical benefits and estimation of resource use and costs. In addition, authors of both studies reported incremental analyses, assessed the robustness of study findings through several sensitivity analyses, and drew conclusions based on the reported data. However, a number of weaknesses related to the economic model preclude a clear interpretation of results and limit its use in aiding decision-making. First, the relevance of the internet-based sampling strategies modeled in both economic evaluations may be limited when considering the use of self-collection in a clinic setting or other setting outside of the home. Seconds, there was a lack of transparency in the economic models of both published evaluations as neither study provided a decision tree schematic which outlines the progression of patients and associated probabilities. In one economic evaluation,[24] efficacy inputs and probability estimates were based on single study sources and one feasibility study, which was a significant driver of the reported results. This study also failed to incorporate costs related to untreated STI infection. Assumptions regarding screening efficacy and other modeling parameters in the second economic evaluation[25] were similarly sourced from single studies or based on unpublished data, which brings into question the reliability and validity of the economic outcomes. Furthermore, the choice of variables for sensitivity analyses was not chosen *a priori* nor justified, and neither economic evaluation performed a probabilistic sensitivity analysis. Finally, given the perspective adopted in these analyses was that of the health care payer in the United States, applicability of study findings to the Canadian decision-making context may be limited.

Summary of Findings

What is the comparative effectiveness of testing for sexually transmitted infections in women using self-collected versus clinician collected samples?

The comparative clinical effectiveness of self-collected versus clinician-collected samples for the detection of STIs in women is summarized below based on the comparative accuracy of the two screening techniques. A detailed overview of the results of each included study is presented in Appendix 4: Main Study Findings and Author's Conclusions.

Screening method validity

One SR[14] assessed the validity of self-collected samples for the detection of chlamydia and gonorrhea in women by statistically combining test accuracy results of multiple studies. The pooled analysis of six chlamydia studies revealed that self-collected vaginal samples had a high sensitivity and specificity (92% and 98%, respectively) when compared with clinician-collected cervical samples. One study on women undergoing screening for gonorrhea was also identified in this review, and the self-sampling method had a sensitivity and specificity of 98% and 97%, respectively, in comparison with the clinician collection technique. In addition to comparing self-

collected vaginal specimens with clinician-collected cervical samples, authors of this review also pooled data comparing self-collected urine samples with clinician-collected cervical samples and self-collected rectal swabs with clinician-collected rectal samples. The pooled sensitivities and specificities relating to self-collected samples from different anatomical sites were also high; however, the authors concluded that the sensitivity and specificity of vaginal self-collected swabs compared to clinician-collected cervical samples supports the use of vaginal self-sampling for chlamydia and gonorrhea testing over other methods.

The validity of self-collected vaginal specimens versus clinician-collected cervical specimens was also assessed in four studies which examined women undergoing HPV testing. Findings from three studies[18,19,22] on women without comorbid infections revealed that the sensitivity and specificity of the self-collection sampling technique, as compared with the clinician sampling reference test, ranged from 84.6% to 96.5% and 66.2% to 93.9%, respectively; the highest sensitivity was found among a sample of 130 women using a flocked vaginal dry swab without transport medium,[18] which also had the lowest specificity of all four studies, and the highest specificity was generated in a sample of 1,005 women using a cytobrush self-sampling device.[19] One study examined the validity of the self-collection method in a sample 325 HIV-infected women using a tampon-based self-collection device for HPV testing;[26] results of this study showed that self-sampling had a sensitivity of 77.4% and specificity of 77.7%. It was unclear whether the presence of comorbid infection during HPV testing resulted in decreased sensitivity and specificity of self-collected samples, when compared with samples collected by clinicians.

Screening method reliability

Eight studies[15-17,19-23] examined the reliability of self-collected samples versus clinician-collected samples in terms of virological findings (i.e. STI positivity).In all cases, reliability was assessed as agreement between sampling methods, measured as raw overall agreement (crude or chance agreement [%]) and agreement beyond chance or chance-corrected agreement (measured by kappa statistic).

In five studies which compared self-collected vaginal samples with clinician-collected cervical samples among women undergoing HPV testing, overall agreement ranged between 70.8% and 93.4%, which represents the proportion of concordant cases or the number of times agreement has occurred (true positives and true negatives) between the self-sampling and clinician-collection methods; the highest agreement occurred in a sample of 1,005 women using a cytobrush device,[19] and lowest crude agreement was found among women undergoing HPV testing using two self-sampling devices, both of which had similar overall agreement values relating to the comparison of self-collected and clinician-collected samples.[22] Conversely, chance-corrected agreement across these studies ranged from 0.54 to 0.74, which represents moderate to substantial agreement between the self-sampling method and clinician-collection technique for the detection of HPV infection in women. Overall, authors of these studies drew the conclusion that self-collected vaginal specimens showed good agreement with clinician-collected cervical specimens for the detection of HPV infection.

Studies comparing self-collected cervical specimens with clinician-collected cervical samples among women undergoing HPV testing revealed similar results.[16,23] Namely, in one study which reported raw overall agreement between sampling methods, agreement occurred in 85.4% of cases.[23] Moreover, one study reported a kappa statistic of 0.50,[23] representing moderate agreement, and another study reported a kappa value of 0.71,[16] which indicated that there was

substantial agreement beyond chance between the two sampling methods in their ability to detect high-risk HPV infection.
One study evaluated the reliability of self-collected vaginal samples in comparison with clinician-collected vaginal samples among women undergoing screening for chlamydia and gonorrhea infection.[17] Findings revealed that crude agreement between the sampling methods in women undergoing chlamydia and gonorrhea testing was 94.7% and 98.4%, respectively. In addition, chance-corrected agreement between chlamydia and gonorrhea sampling techniques, respectively, was 0.64 and 0.56, which represents moderate to substantial agreement.

What is the cost-effectiveness of testing for sexually transmitted infections in women using self-collected versus clinician collected samples?

Two published economic evaluations assessed the comparative cost-effectiveness of home-based self-sampling strategies in comparison with clinic-based screening strategies for diagnosing and treating STIs in women.

More specifically, one economic evaluation[24] examined the comparative cost-effectiveness of an internet-based home self-sampling strategy (eSTI) versus referral to standard clinic-based STI screening and treatment in women undergoing screening for chlamydia, gonorrhea, and trichomoniasis infections. From the perspective of the health care payer, base-case results revealed that the eSTI strategy was associated with higher total costs than the clinic referral strategy ($96,088 versus $71,668, respectively), but that home-based testing also led to a higher number of STIs detected among the modeled population (75 versus 45 STIs detected, respectively). Therefore, the total incremental cost associated with home-based self-sampling ($1,281 per STI detected) was lower than the total incremental cost associated with a clinic-based screening strategy ($1,593 per STI detected). These findings were robust to changes in several model parameters, including the assumed STI prevalence rate, rate of return of self-sampling kits, clinic visit rates, office visit costs, and clinic STI test costs. Based on these findings, the authors concluded that eSTI may be a cost-effective strategy for STI screening in the context of a future clinical trial as well as for clinical practice.

The second economic evaluation[25] similarly assessed the comparative cost-effectiveness of an internet-based STI screening strategy versus clinic-based screening in women undergoing screening for chlamydia infection. Unlike the previous study, this cost-effectiveness analysis incorporated estimates of screening test validity for the self-collected and clinician-collected samples, and modeled the medical costs averted through the prevention of pelvic inflammatory disease (PID) and related complications of untreated chlamydia infection. Based on the health care payer perspective, the total costs associated with the self-sampling strategy amounted to $860,000, as compared with $902,000 for the clinic screening strategy. Furthermore, the number of positive chlamydia cases detected by the self-sampling and clinic-based screening strategies was 303 and 232 cases, respectively. Therefore, the internet-based self-screening strategy dominated the clinic screening strategy in that it was both less costly and more effective, per case of PID averted. Results were insensitive to changes in modeling assumptions (i.e. chlamydia prevalence, internet-based screening kit return rate, clinic-based screening rate, cost for PID sequelae treatment), and the authors drew the conclusion that an internet-based self-sampling strategy is cost-effective in comparison with traditional, clinic-based STI screening among women.

What are the evidence-based guidelines regarding the use of self-collected samples to test for sexually transmitted infections in women?

No relevant published evidence-based guidelines were identified regarding the use of self-collected versus clinician-collected samples for detecting STIs in women.

Limitations

Studies relating to the comparative clinical effectiveness of self-collected samples versus clinician-collected specimens for STI testing included in this report were generally well designed and addressed the research questions posed. While the included SR and test accuracy studies were strengthened by the use of appropriate and sound practices in the conduct of their research and reporting of their findings, a number of limitations remain unaddressed. For instance, while the authors of the included SR assessed the scientific quality of screening test accuracy studies included in their publication, there was a lack of transparency in the reporting of their quality assessment findings and scientific quality was not adequately addressed in formulating the conclusions of the review, which may impact the validity of the conclusions. In addition, while the SR reported pooled analyses relating to screening test validity, measures of agreement or reliability between different sample collection methods were not reported. This shortcoming was also seen in the primary studies on screening test accuracy, where there was inconsistent reporting of both measured test validity and test reliability. Furthermore, there was considerable variability in the types of self-sampling devices and the assays used for virological laboratory analysis across the included studies, which may impact the measurement of comparative accuracy of the two sampling techniques. Variability in comparisons between specimens collected from different anatomical sites precludes a clear assessment of the overall comparative accuracy between self-collected samples and clinician-collected samples. Additionally, non-random or non-consecutive enrollment of participants across a number of primary clinical studies may increase the risk of bias, and it was uncertain if the number of enrolled participants across studies was large enough to establish the evidence of test accuracy. Several estimates of test validity and reliability across a number of studies were accompanied by a wide confidence interval, which indicates a lack of precision in the obtained estimates; this may be partly related to an inadequate number of study participants. Finally, given the differences in patient demographics and the setting from which participants were recruited, generalizability of study findings to the Canadian context may be limited.

The validity of the included cost-effectiveness analyses is also limited by a number of shortcomings in the economic modeling, particularly relating to the reliance on multiple assumptions unsupported by high quality clinical evidence, and the nature of the home-based interventions which may not reflect the costs and benefits incurred by patients who self-sample outside of the home setting. The transferability of study findings and their usefulness in aiding decision-making is further limited by the non-Canadian perspective adopted in the both economic analyses.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Based on the identified published literature, self-collected samples were found to be a valid and reliable method for STI testing in women in comparison with clinician-collected samples. Namely, self-sampling was generally associated with high sensitivity and high specificity when compared with samples collected by clinicians. In addition, there was moderate to substantial

agreement between the two sampling methods. These findings should be cautiously interpreted owing to the variation in self-sampling devices and assays used across the included studies, as well as the variation in specimens collected from different anatomical sites. Generalizability to the Canadian policy-making setting should also be carefully assessed.

The identified economic evaluations revealed that a home-based self-sampling strategy may be cost-effective in comparison with standard clinic STI testing provided that the number of women who are willing to self-sample at home will be unwilling to attend a clinic, such that the clinic attendance rate and associated samples collected by clinicians would never exceed the number of self-collected samples. Results of these cost-effectiveness analyses therefore warrant careful interpretation owing to a number of weaknesses related to the economic model, including the reliance on potentially tenuous assumptions which have not been rigorously assessed in clinical trials or clinical practice. Given the lack of well-designed independent analyses from the Canadian perspective, de novo modeling which incorporates more recent Canadian evidence is required is required to address this evidence gap.

Evidence-based guidelines regarding the use of self-collected samples for STI testing in women were not identified in the published literature.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

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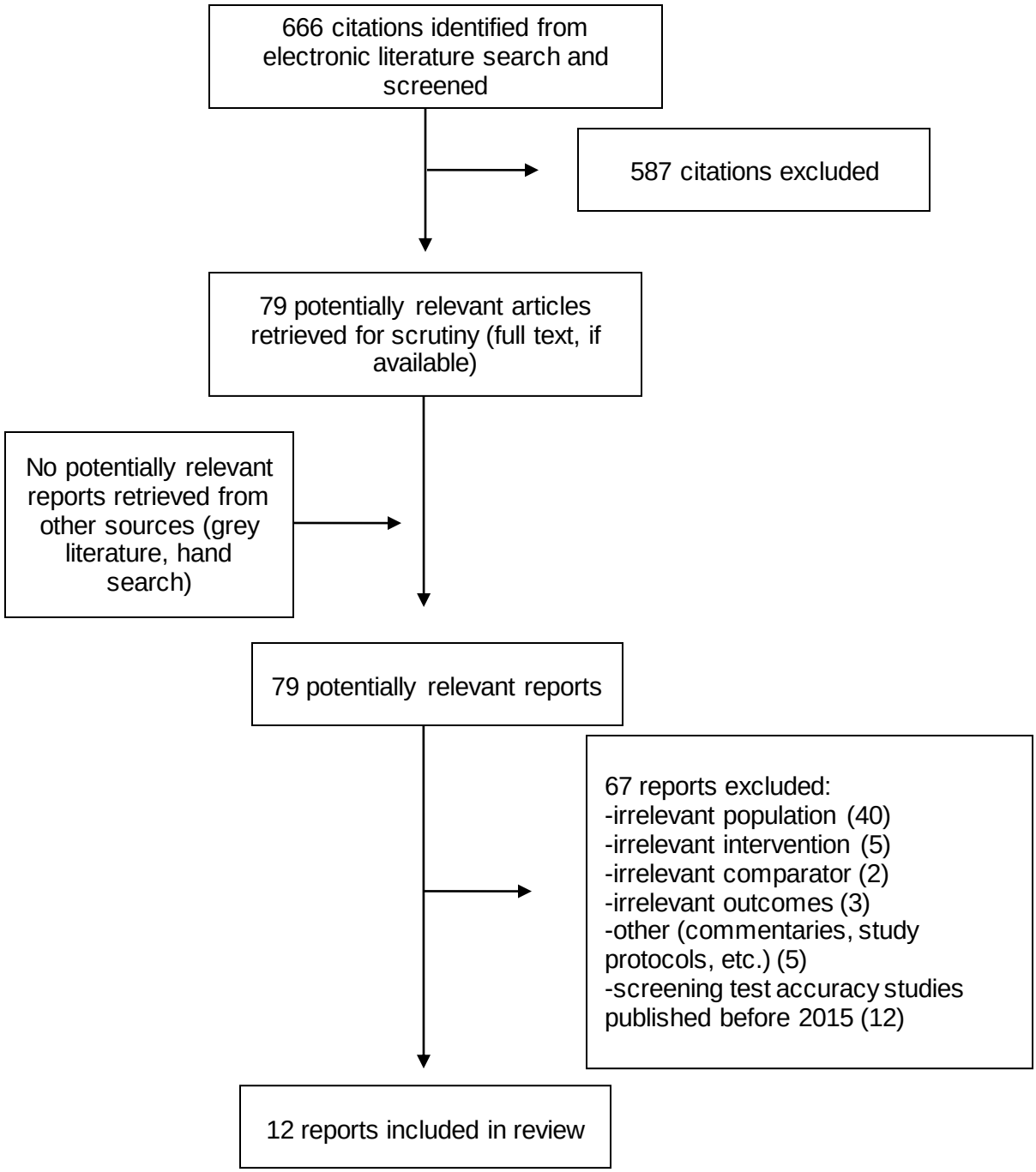
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Lunny, 2015[14] Canada	21 included studies: 20 NRS (cross-sectional) and 1 RCT; Chlamydia only (n): 14 Chlamydia and gonorrhea (n): 6 Gonorrhea only (n): 1	Men and women undergoing STI screening for CT and/or GC infection; Women only (n): 14 Women and men (n): 7 Men only (n): 6	Self-collected sample (urine, vaginal, cervical, and rectal)	Clinician-collected sample (vaginal, cervical, and rectal)	Sensitivity and specificity of specific comparable anatomic sites Follow-up: Clinic visit only

CT = chlamydia trichomatis; GC = neisseria gonorrhea; n = number; NRS = non-randomized study; RCT = randomized controlled trial; STI = sexually transmitted infection

Table A2: Characteristics of Included Screening Test Accuracy Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size	Index Test(s)	Reference Test(s)	Outcomes
Arias, 2016[17] Canada	Cross-sectional	Women undergoing STI screening for CT and GC infection **n = 189;** 110 women from a street youth clinic Mean age (y): 23.5±4.7 (range 16-26) 79 women from a therapeutic abortion clinic Mean age (y): 24.2±5.3 (range 16-41)	Self-collected **vaginal** sample Device: Dry swab (HerSwab) Specific assay: AC2	Physician-collected **vaginal** sample Device: Aptima swab Specific assay: AC2	Raw overall agreement between sample types; Agreement between sampling techniques in terms of virological assessment (measured by kappa statistic)

Table A2: Characteristics of Included Screening Test Accuracy Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size	Index Test(s)	Reference Test(s)	Outcomes
Harvey, 2016[18] United States	Cross-sectional	Women in temporary residential programs (emergency shelter and recovery program at a community health center) undergoing HPV screening and screening for cervical cancer **n = 47;** Median age (y): 31.4 (IQR 26.8-42.2)	Self-collected **vaginal** sample Device: Swab (unspecified) Specific assay: HC2 via PCR platform	Physician-collected **cervical** sample Device: Cervical swab (unspecified) and cervical ThinPrep Papanicolaou test Specific assay: HC2 via PCR platform	Screening test accuracy (measured by SN, SP, PPV, NPV)
Toliman, 2016[19] Papua New Guinea	Cross-sectional	Women undergoing routine cervical screening (including HPV screening) **n = 1005;** Age (y): NR	Self-collected **vaginal** sample Device: Cytobrush Specific assay: Xpert® HPV Point of Care test	Clinician-collected **cervical** sample Device: Cytobrush Specific assay: Xpert® HPV Point of Care test	Positive, negative, and overall percentage agreement between sampling techniques in terms of virological assessment (overall agreement measured by kappa statistic)
Wong, 2016[15] Hong Kong	Crossover RCT	Women undergoing routine cervical screening (including HPV screening) **n = 392;** Mean age (y): 50.9±8.1	Self-collected **vaginal** sample Device: Dacron swab Specific assay: linear array HPV genotyping test via PCR platform	Clinician-collected **cervical** sample Device: Cytobrush Specific assay: linear array HPV genotyping test via PCT platform	Agreement between sampling techniques in terms of virological assessment (measured by kappa statistic)
Adamson, 2015[20] South Africa	Cross-sectional	HIV-infected women undergoing HPV screening and cervical cancer	Self-collected **vaginal** sample	Nurse-collected **cervical** sample	Prevalence of hrHPV mRNA between sample collection

Table A2: Characteristics of Included Screening Test Accuracy Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size	Index Test(s)	Reference Test(s)	Outcomes
		screening **n = 325;** Median age (y) 41.6 (IQR 34.9-47.5)	Device: Mini-sized tampon Specific assay: Aptima HPV assay	Device: Broom-like collection device Specific assay: Aptima HPV assay	methods; Screening test accuracy (measured by SN and SP); Agreement between sampling techniques in terms of virological assessment (measured by kappa statistic)
Boggan, 2015[21] Haiti	Cross-sectional	Women undergoing HPV screening and cervical cancer screening **n = 1845;** Median age (y): 41 (IQR 34-48)	Self-collected **vaginal** sample Device: Dacron brush Specific assay: HC2	Physician-collected **cervical** sample Device: Dacron brush Specific assay: HC2	Agreement between sampling techniques in terms of virological and cytological assessment (measured by kappa statistic)
Catarino, 2015[22] Switzerland	Cross-sectional	Women undergoing HPV screening and cervical cancer screening **n = 130;** Median age (y): 42 (IQR 34-50)	Two self-collected **vaginal** samples Device 1: Mid-turbinate flocked vaginal dry swab (FLOQSwabs™) Device 2: Cytobrush (Rovers® Viba-Brush) applied to an FTA elute cartridge Specific assay: Anyplex II HPV28 (H28) detection test via real-time PCT	Physician-collected **cervical** sample Device: Wet swab (ESwab) Specific assay: Anyplex II HPV28 (H28) detection test via real-time PCR	Screening test accuracy (measured by SN, SP, PPV, NPV); Agreement between sampling techniques in terms of virological and cytological assessment (measured by kappa statistic)

Table A2: Characteristics of Included Screening Test Accuracy Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics, Sample Size	Index Test(s)	Reference Test(s)	Outcomes
Latiff, 2015[23] Malaysia	Cross-sectional	Women referred to primary health clinics in rural setting for HPV screening and cervical cancer screening **n = 486;** IT group median age (y): 45 (range 20-70) RT group median age (y): 46 (range 21-71)	Self-collected **cervical** sample Device: KSSD Specific assay: QIAmp DNA Blood minikit	Physician-collected **cervical** sample Device: Cytobrush Specific assay: QIAmp DNA Blood minikit	Concordance of HPV DNA genotype between sample types; Agreement between sampling techniques in terms of virological and cytological assessment (measured by kappa statistic)
Latiff, 2015[16] Malaysia	Cross-over RCT	Women in reproductive age (15-49 years old) undergoing HPV screening and cervical cancer screening **n = 258;** 202 women (78.3 %) in reproductive age; 56 women (21.7%) in menopausal period Mean age (y): 40.41±11.28	Self-collected **cervical** sample Device: Cervisafe® self-administered cervical smear Specific assay: HPV XpressMatirx TM kit via PCR platform	Physician-collected **cervical** sample Device: Endocervical brush with detachable tip Specific assay: HPV XpressMatirx TM kit via PCR platform	Agreement between sampling techniques in terms of virological and cytological assessment (measured by kappa statistic)

AC2 = Aptima Combo 2; CT = chlamydia trichomatis; GC = neisseria gonorrhea; HC2 = Hybrid Capture 2 high-risk HPV DNA test; HPV = human papillomavirus; IQR = interquartile range; IT = index test; KSSD = Kato self-sampling device; n = number; NPV = negative predictive value; NR = not reported; PCR = polymerase chain reaction; PPV = positive predictive value; RCT = randomized controlled trial; RT = reference test; SN = sensitivity; SP = specificity; STI = sexually transmitted infection; y = years

Table A3: Characteristics of Included Economic Evaluations

First author, Publication Year, Country	Type of Analysis, Model, Perspective	Intervention vs. Comparator	Study Population	Time Horizon	Main Assumptions
Blake, 2015[24] United States	CEA, decision-tree, HCP perspective and clinical trial perspective	Home self-sampling strategy (eSTI with participants receiving a home collection kit for STI screening and an e-prescription for treatment) vs. clinic referral strategy (referral to standard clinic based STI screening and treatment)	Women undergoing screening for CT, GC, and TV infection using NAATs	NR	• Efficacy inputs based on published literature and a demonstration project (feasibility study) conducted previously by the same authors • Participant testing rate assumed to be higher for the eSTI arm (67%), as compared with the clinic-referral arm (40%) • STI prevalence was conservatively estimated (8%) based on regions where authors plan to conduct future comparative efficacy trial, and based on CT prevalence • A proportion of eSTI arm participants who do not retrieve their positive test results online would be require DIS assistance • eSTI arm participants would have the option of treatment in a clinic or through an online electronic prescription sent to a pharmacy of their choice; 64.2 % of women were assumed to choose e-prescription • Model assumed that both home-sampling and clinic-referral strategies would use the same highly-sensitive (≥90%) and highly specific (≥99%) diagnostic test, and that all infections would be detected if the test is completed • Model incorporated costs of screening, result notification, and treatment of positives

Table A3: Characteristics of Included Economic Evaluations

First author, Publication Year, Country	Type of Analysis, Model, Perspective	Intervention vs. Comparator	Study Population	Time Horizon	Main Assumptions
					• Costs reported in 2013 US dollars
Huang, 2011[25] United States	CEA, decision tree, HCP perspective	Internet-based (IWTK) self-sampling screening strategy vs. clinic-based screening strategy	Women undergoing screening for CT infection using NAATs	2, 5, and 10 years	• Sample return rate of participants in internet-based strategy was estimated based on unpublished data collected by IWTK, and clinic-based screening rate was estimated by applying published data from a single study to IWTK data. • Estimates of sensitivity and specificity of the self-sampled vaginal and clinician-collected endocervical specimens via NAATs were derived from a modified meta-analysis • Same prevalence estimate was assumed for both screening strategies, and based on study results from IWTK activities • Proportion of women with positive CT test results who received treatment was based on IWTK tracking records for the internet-based screening strategy, and from STI and family planning clinics for the clinic-based strategy • Treatment success rates and prevalence of PID among untreated CT-positive cases were derived from the published literature. • Model incorporated programmatic screening, treatment costs, and medical costs averted through prevention of PID and related complications of untreated CT

Table A3: Characteristics of Included Economic Evaluations

First author, Publication Year, Country	Type of Analysis, Model, Perspective	Intervention vs. Comparator	Study Population	Time Horizon	Main Assumptions
					infection • Costs were discounted at 3% per annum • Costs reported in 2010 US dollars

CEA = cost-effectiveness analysis; CT = chlamydia trichomatis; DIS = Disease Intervention Specialists; eSTI = electronic STI system; GC = neisseria gonorrhea; HCP = health care payer; IWTK = www.iwantthekit.org; NAAT: nucleic acid amplification test; NR = not reported; PID = pelvic inflammatory disease; STI = sexually transmitted infections; TV: trichomonas vaginalis

APPENDIX 3: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[11]

Strengths	Limitations
Lunny, 2015[14]	
• Research questions posed and inclusion criteria used were established *a priori* through a published study protocol • Data extraction was performed by two independent reviewers, and any disagreements were adjudicated by a third reviewer • A comprehensive search of the literature (electronic databases and manual search of key academic journals) was performed. • A list of included studies and study characteristics was provided. • Methodological quality assessment of included studies was performed and documented using the QUADAS checklist. • Methods used to statistically combine results of included studies were appropriate and justified (meta-analyses conducted according to the Cochrane Collaboration' methodology for systematic reviews of Diagnostic Test Accuracy). • Review authors disclosed no potential conflicts of interest.	• Unclear whether duplicate article screening was performed • Unclear whether the literature search was supplemented by a search for "grey literature". • List of excluded studies was not provided nor referenced (only reasons for exclusion are provided). • The scientific quality of each included study was not reported in detail (by quality domains of the QUADAS checklist), and study quality did not appear to have been considered in formulating conclusions of the review. • Likelihood of publication was mentioned, but no evidence of formal assessment using statistical methods or visual inspection • Sources of funding of included studies were not described.

Table A5: Risk of Bias and Applicability Concerns in Screening Test Accuracy Studies using QUADAS-2[12]

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Arias, 2016[17]	?	⊖	⊖	⊖	⊖	⊖	⊖
Harvey, 2016[18]	?	⊖	⊖	⊖	⊖	⊖	⊖
Toliman, 2016[19]	⊖	⊖	⊖	⊖	⊖	⊖	⊖
Wong, 2016[15]	⊖	⊖	⊖	⊖	⊖	⊖	⊖
Adamson, 2015[20]	?	⊖	⊖	⊖	?	⊖	⊖
Boggan, 2015[21]	⊗	⊖	⊖	⊖	⊖	⊖	⊖
Catarino, 2015[22]	⊖	⊖	⊖	⊖	⊖	⊖	⊖
Latiff, 2015[23]	?	⊖	⊖	⊗	⊖	⊖	⊖
Latiff, 2015[16]	⊖	⊖	⊖	⊖	⊖	⊖	⊖

Legend: ⊖ = Low; ⊗ = High; ? = Unclear; N/A = not applicable

Table A6: Strengths and Limitations of Screening Test Accuracy Studies using QUADAS-2[12]

Strengths	Limitations
Arias, 2016[17]	
Risk of Bias *Patient Selection* • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • Index test results were likely interpreted without knowledge of the results of the reference standard (both self-collected and clinician-collected specimens sent for laboratory testing at the same time) *Reference Standard* • The reference standard was likely to classify patients appropriately • The reference standard results were likely interpreted without knowledge of the results of the index test given that both test specimens were sent for laboratory testing on the day of collection, and all samples were tested for the presence of STI using an assay *Flow and Timing* • There was an appropriate interval between the index test and the reference standard (tests conducted following one another) • All patients received a reference standard • All patients received the same reference standard • All patients were included in the analysis Applicability • Included patients match the review question (i.e. women undergoing STI screening; women from a street youth clinic and therapeutic abortion clinic may be relevant) • Index test, its conduct and interpretation does not differ from the review question • Target condition (chlamydia and gonorrhea) as defined by the reference standard matches the relevant STIs defined by the review question	Risk of Bias *Patient Selection* • Unclear whether a consecutive or random sample of patients was enrolled Applicability • Low concern regarding applicability
Harvey, 2016[18]	
Risk of Bias *Patient Selection* • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • Index test results were likely interpreted without knowledge of the results of the reference standard given that index test was always conducted before the reference standard *Reference Standard*	Risk of Bias *Patient Selection* • Unclear whether a consecutive or random sample of patients was enrolled Applicability • Low concern regarding applicability

Table A6: Strengths and Limitations of Screening Test Accuracy Studies using QUADAS-2[12]	
Strengths	**Limitations**
• The reference standard was likely to classify patients appropriately • The reference standard results were likely interpreted without knowledge of the results of the index test *Flow and Timing* • There was an appropriate interval between the index test and the reference standard (physician collection conducted immediately following self-sampling) • All patients received a reference standard • All patients received the same reference standard • All patients were included in the analysis <u>Applicability</u> • Included patients match the review question (i.e. women undergoing STI screening; women in temporary residential programs may be relevant) • Index test, its conduct and interpretation does not differ from the review question • Target condition (HPV) as defined by the reference standard matches the relevant STIs defined by the review question	
Toliman, 2016[19]	
<u>Risk of Bias</u> *Patient Selection* • A consecutive sample of patients was enrolled • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • Index test results were likely interpreted without knowledge of the results of the reference standard (i.e. HPV testing of vaginal and cervical specimens was conducted side-by-side) *Reference Standard* • The reference standard was likely to classify patients appropriately • The reference standard results were likely interpreted without knowledge of the results of the index test *Flow and Timing* • There was an appropriate interval between the index test and the reference standard (physician collection conducted immediately following self-sampling) • All patients received a reference standard • All patients received the same reference standard	<u>Risk of Bias</u> • No concerns regarding risk of bias <u>Applicability</u> • Low concern regarding applicability

Table A6: Strengths and Limitations of Screening Test Accuracy Studies using QUADAS-2[12]	
Strengths	**Limitations**
• All patients were included in the analysis Applicability • Included patients match the review question (i.e. women undergoing STI screening) • Index test, its conduct and interpretation does not differ from the review question • Target condition (HPV) as defined by the reference standard matches the relevant STIs defined by the review question	
Wong, 2016[15]	
Risk of Bias *Patient Selection* • A random sample of patients was enrolled • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • Index test results were likely interpreted without knowledge of the results of the reference standard (i.e. HPV testing of vaginal and cervical specimens was conducted concomitantly) *Reference Standard* • The reference standard was likely to classify patients appropriately • The reference standard results were likely interpreted without knowledge of the results of the index test *Flow and Timing* • There was an appropriate interval between the index test and the reference standard (30- to 45-minute intervals between sampling methods) • All patients received a reference standard • All patients received the same reference standard • All patients were included in the analysis Applicability • Included patients match the review question (i.e. women undergoing STI screening); however, pregnant women were excluded from the study, which may be relevant to the review question • Index test, its conduct and interpretation does not differ from the review question • Target condition (HPV) as defined by the reference standard matches the relevant STIs defined by the review question	Risk of Bias • No concerns regarding risk of bias Applicability • Low concern regarding applicability

Table A6: Strengths and Limitations of Screening Test Accuracy Studies using QUADAS-2[12]

Strengths	Limitations
Adamson, 2015[20]	
Risk of Bias *Patient Selection* • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • Index test results were likely interpreted without knowledge of the results of the reference standard (HPV detection via laboratory testing of self-collected vaginal and nurse-collected cervical specimens) *Reference Standard* • The reference standard was likely to classify patients appropriately • The reference standard results were likely interpreted without knowledge of the results of the index test *Flow and Timing* • There was an appropriate interval between the index test and the reference standard (one to two hours) • All patients received a reference standard • All patients received the same reference standard Applicability • Index test, its conduct and interpretation does not differ from the review question • Target condition (HPV) as defined by the reference standard matches the relevant STIs defined by the review question	Risk of Bias *Patient Selection* • Unclear whether a consecutive or random sample of patients was enrolled *Flow and Timing* • Not all patients were included in the analysis (nine clinician-collected specimens and eight self-collected specimens had invalid results and we excluded); risk of bias is low given <10% loss to follow-up Applicability • Included patients have an underlying condition (only HIV-positive women recruited), and may not be directly relevant to the review question or comparable to other study samples; HIV-positivity or other pre-existing condition was not specified as an exclusion criterion
Boggan, 2015[21]	
Risk of Bias *Patient Selection* • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • Index test results were likely interpreted without knowledge of the results of the reference standard given that index test was always conducted before the reference standard *Reference Standard* • The reference standard was likely to classify patients appropriately • The reference standard results were likely interpreted without knowledge of the results of the index test *Flow and Timing* • There was an appropriate interval between the index test and the reference standard (physician	Risk of Bias *Patient Selection* • A convenience (non-random) sample of patients was enrolled *Flow and Timing* • Not all patients were included in the analysis (cervical screening data was not available for 9 participants); risk of bias is low given <1% loss to follow-up Applicability • Low concern regarding applicability

Table A6: Strengths and Limitations of Screening Test Accuracy Studies using QUADAS-2[12]

Strengths	Limitations
collection performed immediately following self-sampling) • All patients received a reference standard • All patients received the same reference standard Applicability • Included patients match the review question (i.e. women undergoing STI screening); however, pregnant women were excluded from the study, which may be relevant to the review question • Index test, its conduct and interpretation does not differ from the review question • Target condition (HPV) as defined by the reference standard matches the relevant STIs defined by the review question	
Catarino, 2015[22]	
Risk of Bias *Patient Selection* • A consecutive sample of patients was enrolled • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • Index test results were likely interpreted without knowledge of the results of the reference standard given that index test was always conducted before the reference standard *Reference Standard* • The reference standard was likely to classify patients appropriately • The reference standard results were likely interpreted without knowledge of the results of the index test *Flow and Timing* • There was an appropriate interval between the index test and the reference standard (physician collection performed immediately following self-sampling) • All patients received a reference standard • All patients received the same reference standard • All patients were included in the analysis Applicability • Included patients match the review question (i.e. women undergoing STI screening); however, pregnant women were excluded from the study, which may be relevant to the review question • Index test, its conduct and interpretation does not differ from the review question	Risk of Bias • No concerns regarding risk of bias Applicability • Low concern regarding applicability

Table A6: Strengths and Limitations of Screening Test Accuracy Studies using QUADAS-2[12]	
Strengths	**Limitations**
• Target condition (HPV) as defined by the reference standard matches the relevant STIs defined by the review question	
Latiff, 2015[23]	
Risk of Bias *Patient Selection* • A case-control design was avoided • The study avoided inappropriate exclusions *Index Test* • Index test results were likely interpreted without knowledge of the results of the reference standard given that index test was always conducted before the reference standard; in addition, all specimens were assessed by a cyto-screener technologist and pathologist who were both blinded to the sampling techniques *Reference Standard* • The reference standard was likely to classify patients appropriately • The reference standard results were likely interpreted without knowledge of the results of the index test (all specimens were assessed by a cyto-screener technologist and pathologist who were both blinded to the sampling techniques) *Flow and Timing* • There was an appropriate interval between the index test and the reference standard (one hour) • All patients received a reference standard • All patients received the same reference standard Applicability • Included patients match the review question (i.e. women undergoing STI screening); however, pregnant women were excluded from the study, which may be relevant to the review question • Index test, its conduct and interpretation does not differ from the review question • Target condition (HPV) as defined by the reference standard matches the relevant STIs defined by the review question	Risk of Bias *Patient Selection* • Unclear whether a consecutive or random sample of patients was enrolled *Flow and Timing* • Not all patients were included in the analysis for HPV DNA detection (226 of 486 women (47%) underwent HPV testing) • Applicability • Low concern regarding applicability
Latiff, 2015[16]	
Risk of Bias *Patient Selection* • A random sample of patients was enrolled • A case-control design was avoided • The study avoided inappropriate exclusions	Risk of Bias • No concerns regarding risk of bias Applicability • Low concern regarding applicability

Table A6: Strengths and Limitations of Screening Test Accuracy Studies using QUADAS-2[12]	
Strengths	**Limitations**
Index Test • Index test results were likely interpreted without knowledge of the results of the reference standard (cervical specimen analysis was performed by a pathologist blinded to the source of sampling) *Reference Standard* • The reference standard was likely to classify patients appropriately • The reference standard results were likely interpreted without knowledge of the results of the index test (cervical specimen analysis was performed by a pathologist blinded to the source of sampling) *Flow and Timing* • There was an appropriate interval between the index test and the reference standard (physician collected samples were collected immediately following self-sampling, and vice-versa) • All patients received a reference standard • All patients received the same reference standard • All patients were included in the analysis <u>Applicability</u> • Included patients match the review question (i.e. women undergoing STI screening); however, pregnant women were excluded from the study, which may be relevant to the review question • Index test, its conduct and interpretation does not differ from the review question • Target condition (HPV) as defined by the reference standard matches the relevant STIs defined by the review question	

Table A7: Strengths and Limitations of Economic Studies using Drummond[13]

Strengths	Limitations
Blake, 2015[24]	
• Research question and economic importance of question stated (i.e. decision analysis for a future comparative effectiveness trial comparing home-based and clinic-based STI screening) • Perspective of the analysis was clearly stated and justified • Alternatives being compared were clearly described, and rationale for the choice of comparators was stated • Type of economic model used was stated • Source of efficacy estimates (probability estimates) used and cost data was provided • Quantities of resource use were reported separately from their unit costs • One-way and best/worst case sensitivity analyses were conducted and findings were clearly reported • Incremental analysis was reported • Conclusions follow from the data reported, and are accompanied with the appropriate caveats • Study authors disclosed potential conflicts of interest	• Internet-based self-sampling strategy may not be relevant to self-collection in a clinic setting or other setting where STI screening may occur • Choice of model used and key parameters on which it is base was not adequately justified • Decision tree schematic was not provided and model progression was not described in sufficient detail • Time horizon of costs and benefits was not stated, and explanation was not given for the lack of discounting • Efficacy inputs and probability estimates were based on limited evidence (feasibility study) • Reliance on multiple assumptions unsupported by published evidence • Model did not incorporate costs related to untreated CT, NG, or TV • Choice of variables for sensitivity analysis was not justified • Probabilistic sensitivity analyses were not conducted • Applicability of findings may be limited to Canadian setting
Huang, 2011[25]	
• Research question and economic importance of question stated • Perspective of the analysis was clearly stated and justified • Alternatives being compared were clearly described, and rationale for the choice of comparators was stated • Type of economic model used was stated • Time horizon and discount rate was stated and justified • Source of efficacy estimates (probability estimates) used and cost data was provided • Quantities of resource use were reported separately from their unit costs • Threshold and one-way sensitivity analyses were conducted and findings were clearly reported • Incremental analysis was reported • Conclusions follow from the data reported, and are accompanied with the appropriate caveats • Study authors disclosed potential conflicts of interest	• Internet-based self-sampling strategy may not be relevant to self-collection in a clinic setting or other setting where STI screening may occur • Choice of model used and key parameters on which it is base was not adequately justified • Decision tree schematic was not provided and model progression was not described in sufficient detail • Efficacy inputs and probability estimates were based on evidence from single studies and unpublished data • Choice of variables for sensitivity analysis was not justified • Probabilistic sensitivity analyses were not conducted • Applicability of findings may be limited to Canadian setting

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Systematic Reviews and Meta-analyses	
Lunny, 2015[14]	
SC vs. CC samples for chlamydia screening: <u>SC urine vs. CC cervical samples (8 studies)</u> • SN = 0.87 (95% CI = 0.81-0.91) • SP = 0.99 (95% CI = 0.98-1.00) <u>SC vaginal vs. CC cervical samples (6 studies)</u> • SN = 0.92 (95% CI = 0.87-0.95) • SP = 0.98 (95% CI = 0.97-0.99) <u>SC rectal vs. CC rectal samples (1 study)</u> • SN = 0.88 (95% CI = 0.79-0.94) • SP = 0.99 (95% CI = 0.98-0.99) **SC vs. CC samples for gonorrhea screening:** <u>SC urine vs. CC cervical samples (3 studies)</u> • SN = 0.79 (95% CI = 0.70-0.88) • SP = 0.99 (95% CI = 0.99-1.00) • <u>SC vaginal vs. CC cervical samples (1 study)</u> • SN = 0.98 (95% CI = 0.88-1.00) • SP = 0.97 (95% CI = 0.94-0.99) <u>SC rectal vs. CC rectal samples (1 study)</u> • SN = 0.85 (95% CI = 0.55-0.98) • SP = 1.00 (95% CI = 0.99-1.00)	• "The sensitivity and specificity of vaginal self-collected swabs compared to swabs collected by clinicians supports the use of vaginal swab self-collection for chlamydia and gonorrhoea testing." (p.18) • "Urine samples for gonorrhea collected by […] women had comparably high sensitivity and specificity, so could be recommended as they can be left at room temperature for several days, allowing for the possibility of mail-in home-based testing." (p.19) • In populations that may not go for testing at all, do not have the option of clinical testing, or who refuse a clinical examination, self-collected screening would be a good alternative." (p.18)
Clinical Studies (Screening Accuracy Studies)	
Arias, 2016[17]	
<u>SC vaginal vs. CC vaginal samples for chlamydia:</u> Overall agreement = 94.7% (95% CI = 90.2-97.3) κ = 0.64 (95% CI = 0.43-0.85) <u>SC vaginal vs. CC vaginal samples for gonorrhea:</u> Overall agreement = 98.4% (95% CI = 95.1-99.6) κ = 0.56 (95% CI = 0.13-1.0)	• "The HerSwab [self-collection device] was well accepted in terms of ease and comfort for vaginal self-sampling in this population of young women avoiding pelvic examination, demonstrating good agreement compared with a [physician-collected vaginal] sample." (p.128)
Harvey, 2016[18]	
<u>SC vaginal vs. CC cervical samples for HPV:</u> SN = 84.6% (95% CI = 54.6-98.1) SP = 88.2% (95% CI = 72.6-96.7) PPV = 77.3% (95% CI = 44.9-92.2) NPV = 93.8% (95% CI =79.2-99.2)	• "Vaginal self-swab for HPV detection was a well-accepted and accurate method for cervical cancer screening." (p.547)

Table A8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Toliman, 2016[19]	
SC vaginal vs. CC cervical samples for HPV: ***HPV-16*** SN = 94.3% (95% CI = 92.8-95.8) SP = 99.6% (95% CI = 99.2-100.0) Overall agreement = 99.4% (95% CI = 98.9-99.9) κ = 0.91 (95% CI = 0.86-0.97) ***HPV-18/45*** SN = 81.3% (95% CI = 78.8-83.8) SP = 98.8% (95% CI = 98.1-99.5) Overall agreement = 98.5% (95% CI = 97.7-99.3) κ = 0.63 (95% CI = 0.48-0.77) ***Other hrHPV*** SN = 91.1% (95% CI = 89.3-92.9) SP = 94.8% (95% CI = 94.3-96.2) Overall agreement = 94.4% (95% CI = 92.9-95.9) κ = 0.72 (95% CI =0.65-0.79) ***All hrHPV*** SN = 90.3% (95% CI = 88.4-92.2) SP = 93.9% (95% CI = 92.9-95.4) Overall agreement = 93.4% (95% CI = 91.8-95.0) κ = 0.74 (95% CI = 0.70-0.79)	• "Self-collected vaginal specimens had excellent agreement with clinician-collected cervical specimens for the detection of hrHPV infection using the Xpert® HPV Test. This approach provides for the first time an opportunity to incorporate point-of-care hrHPV testing into clinical cervical screening algorithms in high-burden, low-income settings." (p.7)
Wong, 2016[15]	
SC vaginal vs. CC cervical samples for HPV: Detection rate for HPV positivity was 7.7% (30/392) with physician sampling and 11.7% (46/392) with self-sampling. Overall agreement = NR; there were a total of 24 discordant pairs of the HPV-positive results between SC and CC samples κ = 0.652 (95% CI = NR)	• "HPV DNA self-sampling was well accepted and a feasible alternative tool for cervical cancer screening. […] HPV DNA self-sampling would markedly improve the rate of participation of women in cervical screening." (p.E9) • "There was moderate to good agreement in HPV detection between the self-sampling and Pap smear samples." (p.E10)
Adamson, 2015[20]	
SC vaginal vs. CC cervical samples for HPV: SC hrHPV prevalence = 43.5% (95% CI = 38.0-49.0; n = 138) CC hrHPV prevalence = 36.7 % (95% CI = 31.4-42.0) There was no statistically significant difference in the rate of test positivity for hrHPV mRNA between CC and SC specimen (36.7% vs. 43.5%; P = 0.08) SN = 77.4% (95% CI = 69.8-85.0) SP = 77.7% (95% CI = 71.9-83.6) Overall agreement = 77.6% (95% CI = NR) κ = 0.54 (95% CI = 0.44-0.63)	• "Tampon-based self-collection is acceptable to women and has similar hrHPV mRNA positivity rates as clinician-collection, but has reduced sensitivity and specificity compared to clinician-collection. The hrHPV mRNA prevalence in our study population is high, but similar to other high-risk populations, and highlights the need for improved cervical cancer screening." (p.2)

Table A8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Boggan, 2015[21]	
SC vaginal vs. CC cervical samples for HPV: Overall agreement = 91.4% (95% CI = NR) κ = 0.73 (95% CI = 0.69-0.77) SC vaginal sampling resulted in a higher detection rate for HPV, with 53 women positive on their CC cervical sample (11.9% positive women) and 105 (23.5%) on only their vaginal sample.	• "HPV screening was feasible in a large population of women in a low-resource, Caribbean setting, which should allow for development of screen-and-treat strategies to optimize public health resources using HPV self-sampling." (p.659)
Catarino, 2015[22]	
s-DRY vs. CC cervical samples for HPV: SN = 96.5% (95% CI = 90.1-98.8) SP = 62.2% (95% CI = 47.6-74.9) PPV = 82.2% (95% CI = 74.2-89.0) NPV = 90.3% (95% CI = 75.1-96.7) Overall agreement = 72.3% (95% CI = NR) κ = 0.61 (95% CI = NR) s-FTA vs. CC cervical samples for HPV: SN = 85.4% (95% CI = 76.4-91.5) SP = 82.2% (95% CI = 68.7-90.7) PPV = 89.9% (95% CI = 81.3-94.8) NPV = 75.5% (95% CI = 61.9-85.4) Overall agreement = 70.8% (95% CI = NR) κ = 0.56 (95% CI = NR) s-DRY vs. s-FTA for HPV: Overall agreement = 54.6% (95% CI = NR) κ = 0.35 (95% CI = NR)	• "Detection of HPV was significantly less common with the s-FTA method relative to the s-DRY or [physician-collected sampling using specimen transport medium], using the same test for HPV detection." (p.9) • "The FTA method is inappropriate for use in low-resource settings and may only be slightly appealing for self-HPV testing in developed countries, because of a pleasing modern design that may help reassure women and motivate them to perform self-sampling at home." (p.11)
Latiff, 2015[23]	
Concordance of SC cervical and CC cervical samples for HPV DNA detection: HPV detected: 86.20% (95% CI = NR); κ = 0.6 (95% CI = 0.5-0.7) HR HPV: 85.40% (95% CI = NR); κ = 0.5 (95% CI = 0.4-0.6) LR HPV: 93.70% (95% CI = NR); κ = 0.3 (95% CI = 0.0- 0.6) HPV 16: 93.00% (95% CI = NR); κ = 0.3 (95% CI = 0.1-0.5) HPV 18: 86.00% (95% CI = NR); κ = 0.3 (95% CI = 0.2-0.5) HPV 31: 98.60% (95% CI = NR); κ = NR HPV 33: 99.00% (95% CI = NR); κ = NR HPV 45: 99.00% (95% CI = NR); κ = NR HPV 11: 93.70% (95% CI = NR); κ = 0.3 (95% CI = 0.0-0.6)	• "There was good agreement between self-sampling and physician obtained sampling in terms of […] HPV DNA detection for cervical cancer screening in rural or low resource setting in Malaysia." (p.8500)

Table A8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Latiff, 2015[16]	
Agreement between SC cervical and CC cervical samples for detection of high risk DNA genotypes: Overall agreement = NR κ = 0.71 (95% CI = 0.44-0.98) Agreement between SC cervical and CC cervical samples for detection of low risk DNA genotypes: Overall agreement = NR κ = 0.71 (95% CI = 0.5-0.92)	• "The results of this study revealed good agreement between self-sampling and physician obtained sampling in terms of high risk and low risk HPV detection." (p.563)
Economic Evaluations	
Blake, 2015[24]	
Base-case results, HCP perspective **eSTI strategy:** Total cost = $96,088 STI detected (n) = 75 Cost per STI detected = $1,281 **Clinic referral strategy:** Total cost = $71,668 STI detected (n) = 45 Cost per STI detected = $1,593 Base-case results, clinical trial perspective **eSTI strategy:** Total cost = $94,938 STI detected (n) = 75 Cost per STI detected = $1,266 **Clinic referral strategy:** Total cost = $87,367 STI detected (n) = 45 Cost per STI detected = $1,941	• "eSTI is likely to be more effective and cost less per infection detected than clinic referral for STI screening in the context of a clinical trial as well as for clinical care." (p.8)
Huang, 2011[25]	
Base-case results, HCP perspective **Internet-based screening strategy:** Total cost = $860,000 Positive chlamydia cases detected (n) = 303 **Clinic screening strategy:** Total cost = $902,000 Positive chlamydia cases detected (n) = 232 Internet-based screening strategy was **dominant** (less costly, more effective) over the clinic screening strategy	• "Our model demonstrated that an internet-based, self-swab strategy is cost-effective compared with the traditional, clinic-based screening strategy." (p.7)

CC = clinician-collected; CI = confidence interval; HCP = health care payer; HPV = human papillomavirus; κ = kappa statistic; NPV = negative predicitbe value; NR = not reported; PPV = positive predictive value; SC = self-collected; s-DRY = self-collected samples using dry sw ab without transport medium; s-FTA = self-collected samples using a cytobrush applied to an FTA cartridge; SN = sensitivity; SP = specificity

APPENDIX 5: Additional References of Potential Interest

CADTH Rapid Response Reports

Screening for sexually transmitted infections: a review of guidelines [Internet]. Ottawa: CADTH; 2013 Apr [cited 2016 Jun 22]. (Rapid response report: summary with critical appraisal). Available from: https://www.cadth.ca/sites/default/files/pdf/htis/may-2013/RC0447%20-%20STI%20algorithms%20Final.pdf

Systematic Reviews and Meta-analyses

Arbyn M, Verdoodt F, Snijders PJ, Verhoef VM, Suonio E, Dillner L, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. Lancet Oncol. 2014 Feb;15(2):172-83.

Note: Women undergoing HPV testing for primary cervical cancer screening (comparative accuracy of sampling methods evaluated in terms of cytological outcomes)

Fajardo-Bernal L, Aponte-Gonzalez J, Vigil P, Angel-Muller E, Rincon C, Gaitan HG, et al. Home-based versus clinic-based specimen collection in the management of Chlamydia trachomatis and Neisseria gonorrhoeae infections. Cochrane Database Syst Rev. 2015 Sep 29;(9):CD011317.

Note: Men and women undergoing STI screening for chlamydia and gonorrhea (subgroup analysis based on sex not reported)

Snijders PJ, Verhoef VM, Arbyn M, Ogilvie G, Minozzi S, Banzi R, et al. High-risk HPV testing on self-sampled versus clinician-collected specimens: a review on the clinical accuracy and impact on population attendance in cervical cancer screening. Int J Cancer. 2013 May 15;132(10):2223-36.

Note: Women undergoing HPV testing for primary cervical cancer screening (comparative accuracy of sampling methods evaluated in terms of cytological outcomes)

Verdoodt F, Jentschke M, Hillemanns P, Racey CS, Snijders PJ, Arbyn M. Reaching women who do not participate in the regular cervical cancer screening programme by offering self-sampling kits: a systematic review and meta-analysis of randomised trials. Eur J Cancer. 2015 Nov;51(16):2375-85.

Note: Women undergoing HPV testing for primary cervical cancer screening (comparative accuracy of sampling methods evaluated in terms of cytological outcomes)

Economic Evaluations

Flores YN, Bishai DM, Lorincz A, Shah KV, Lazcano-Ponce E, Hernandez M, et al. HPV testing for cervical cancer screening appears more cost-effective than Papanicolau cytology in Mexico. Cancer Causes Control [Internet]. 2011 Feb [cited 2016 Jun 22];22(2):261-72. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3025113

Note: Women undergoing HPV testing for primary cervical cancer screening

Ostensson E, Hellstrom AC, Hellman K, Gustavsson I, Gyllensten U, Wilander E, et al. Projected cost-effectiveness of repeat high-risk human papillomavirus testing using self-collected vaginal samples in the Swedish cervical cancer screening program. Acta Obstet Gynecol Scand. 2013 Jul;92(7):830-40.

Note: Women undergoing HPV testing for primary cervical cancer screening

Rozemeijer K, de Kok IM, Naber SK, van Kemenade FJ, Penning C, van Rosmalen J, et al. Offering self-sampling to non-attendees of organized primary HPV screening: when do harms outweigh the benefits? Cancer Epidemiol Biomarkers Prev. 2015 May;24(5):773-82.

Note: Women undergoing HPV testing for primary cervical cancer screening

Evidence-based Guidelines

Canadian guidelines on sexually transmitted infections [Internet]. Ottawa: Public Health Agency of Canada; 2010 Jan [cited 2016 Jun 22]. Available from: http://www.phac-aspc.gc.ca/std-mts/sti-its/index-eng.php

Note: Publication date outside of literature search timeframe