Philippine Clinical Practice Guidelines for Cervical Cancer Prevention and the Treatment of Premalignant Lesions of the Cervix

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Commissioned by the Department of Health to
Dr. Jose R. Reyes Memorial Medical Center

Disclaimer and Contact Information

This clinical practice guideline (CPG) is intended to be used by all frontline healthcare professionals attending to women, including obstetrician-gynecologists, family physicians, general practitioners, nurses, nurse-midwives and midwives. Although adherence to this guideline is encouraged by the Department of Health (DOH), it should not restrict clinicians in using their clinical judgment and considering a patient's values, needs and preferences while handling individual cases. Clinicians and relevant stakeholders (e.g., Philippine Health Insurance Corporation [PHIC], health maintenance organizations [HMOs] and nongovernmental organizations [NGOs]) using this document must always exercise sound clinical decision-making as the individual patient's history, current physical status and responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules from which to base legal action.

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Participating Societies, Organizations, Agencies and/or Institutions

Association of Positive Women Advocates Inc.	Cancer Coalition Philippines
Department of Health, Republic of the Philippines	Integrated Midwives Association of the Philippines, Inc.
Pediatric Infectious Disease Society of the Philippines	Philippine Cancer Society Cancer Commission
Philippine Infectious Diseases Society for Obstetrics and Gynecology	Philippine Medical Association
Philippine Obstetrical and Gynecological Society	Philippine Oncology Nurses Association, Inc.
Philippine Society of Cervical Pathology and Colposcopy	Philippine Society of Hospice and Palliative Medicine
Philippine Society of Medical Oncology	Philippine Society of Oncology
Philippine Society of Pathology	Philippine Society of Public Health Physicians
Section of Gynecologic Oncology, Department of Obstetrics and Gynecology, Jose R. Reyes Memorial Medical Center	Society of Gynecologic Oncologists of the Philippines

List of Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ACS	American Cancer Society
AIDS	acquired immunodeficiency syndrome
ARR	absolute risk reduction
ART	antiretroviral therapy
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CP	Consensus Panel
CPG	clinical practice guideline
CVT	Costa Rica Vaccine Trial
DNA	deoxyribonucleic acid
DOH	Department of Health
ERE	Evidence Review Expert
Gavi	Gavi, the Vaccine Alliance
HIV	human immunodeficiency virus
HMO	health maintenance organization
HPV	human papilloma virus
hrHPV	high-risk human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
KEN SHE	Kenya Single-dose HPV-vaccine Efficacy Study
LEEP	loop electrosurgical excision procedure
LLETZ	large loop excision of the transformation zone
LMIC	low- and middle-income countries
NGO	nongovernmental organization
PHEX	Periodic Health Examination
PHIC	Philippine Health Insurance Corporation
POGS	Philippine Obstetrical and Gynecological Society
RCT	randomized controlled trial
RR	relative risk
RRR	relative risk reduction
SC	Steering Committee
SCJ	squamocolumnar junction
SUCCESS	Scale-up Cervical Cancer Elimination with Secondary prevention Strategy
TZ	transformation zone
UI	uncertainty interval
VAS	visual analog scale
VIA	visual inspection with acetic acid
VILI	visual inspection with Lugol’s iodine
WHO	World Health Organization

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Executive Summary

Table 1. Summary of recommendations for the screening, early detection and treatment of premalignant lesions of the cervix (see Chapter 4 for detailed discussion on each recommendation)

Recommendations	Strength of recommendations	Certainty of evidence
One-dose versus two-dose vaccination among young women		
Among young females aged 9 to 14 years, we recommend the use of one-dose HPV vaccination as an alternative to two doses to prevent cervical cancer.	Strong	Low
Self-collected versus provider-collected HPV DNA testing		
We suggest the use of self-collected HPV DNA sampling as an alternative to clinician-collected sampling for the detection of high-risk HPV infection among women.	Weak	Low
Screening of women living with HIV		
Among women living with HIV, we recommend early cervical cancer screening for the detection of cervical cancer.	Strong	Low
Appropriate screening for menopausal women		
Among menopausal women, we suggest AGAINST the use of VIA as a screening tool for cervical cancer screening.	Weak	Low
Thermal ablation versus cryotherapy in women with abnormal screening		
Among premenopausal women with a visible squamocolumnar junction with acetowhite lesions on VIA or a positive high-risk HPV DNA test, we recommend management using thermal ablation as an alternative to cryotherapy.	Strong	Low
Ablation versus excision in women with abnormal screening after previous treatment (persistent lesions)		
Among women with persistent acetowhite lesions or a positive high-risk HPV DNA test 12 months after treatment with ablation, we suggest excision (LEEP/LLETZ) over ablation (cryotherapy or thermal ablation).	Weak	Low
In settings where LEEP/LLETZ is unavailable or inaccessible, repeat ablation rather than no treatment should be done for women who test positive after prior ablation.	Strong	Low
Ablation versus excision in women with large acetowhite lesions		
Among premenopausal women with large acetowhite lesions, we suggest performing or referring for excisional therapy.	Weak	Low
In settings where excisional procedures or referral for additional treatment are not available, we suggest that women with large acetowhite lesions be treated with ablation.	Weak	Low

1. Introduction

Cervical cancer is a public health menace, being the fourth most frequent cancer in women globally.[1] There were an estimated 604,000 new cases of cervical cancer and 342,000 cervical cancer-related deaths in 2020. Of these deaths, 90% occurred in low- and middle-income countries (LMICs), such as the Philippines. In the country, cervical cancer is the second-leading cancer in women, with an estimated 7,277 new cases and 3,807 cervical cancer-related deaths every year.[2]

In 2018, the World Health Organization (WHO) launched a global agenda of eliminating cervical cancer as a public health burden by 2030.[3] To eliminate cervical cancer, all countries must reach and maintain an incidence rate of below 4 per 100,000 women. Achieving that goal rests on three key pillars and their corresponding targets: (a) to vaccinate 90% of females by 15 years of age against human papillomavirus (HPV); (b) to screen 70% of women by age 30 years and again by age 45 years using a high performance test; and (c) to treat 90% of pre-invasive cervical cancers and manage 90% of invasive cancers. The WHO Western Pacific Region Office also published an evidence-based, consultative framework for the prevention and control of cervical cancer in the region.[4] The Philippines is committed to achieving the WHO targets, and aims to adhere to the consultative framework to develop and strengthen the country's cervical cancer control program, ensuring sustainability towards achieving global targets.

In high-income countries, most women have access to HPV vaccination and regular screening for precancerous lesions. However, easy access to preventative measures in LMICs is often challenging, which prevents treatment of precancerous lesions before they become malignant. Furthermore, treatment of cancerous lesions may also be inaccessible, contributing to a higher mortality rate from cervical cancer.

Given the high but preventable burden of cervical cancer in the Philippines and the cost-effectiveness of various preventative measures, such as HPV vaccination, visual inspection with acetic acid (VIA) and high-performance HPV assay, and early treatment of premalignant lesions of the cervix, evidence-based clinical practice guidelines (CPG) are needed to ensure that the clinical benefits of these interventions are optimized and made equitable.

As scientific and technological advancements in cervical cancer diagnosis and treatment become part of standard of care, there is a need to make screening and treatment accessible to all women in the Philippines and to ensure that these advances have been evaluated in local CPG development. While there are local guidelines available on vaccination against HPV and the screening of premalignant cervical lesions or cervical cancer,[5] certain target populations are not yet included in currently available local guidelines. Additionally, there is a lack of standardized guidelines in the Philippines that address all frontline healthcare professionals attending to women, including obstetrician-gynecologists, family physicians, general practitioners, nurses, nurse-midwives and midwives. Expertise among healthcare professionals regarding screening is lacking, and infrastructure for implementation of cytology as a form of screening is poor. Hence, a CPG on screening, early detection and

management of abnormal screening and premalignant lesions would be an important source of information for healthcare professionals providing care to women. Additionally, a CPG that also clarifies recent developments in HPV vaccination, such as regimens potentially expanding the HPV coverage of young girls, would complement the outcome of screening and treatment. Finally, the CPG is intended to not only improve access to treatment by encouraging institutions to opt for the best evidence-based options for the prevention, diagnosis and treatment of cervical cancer, but also to provide alternatives to difficult-to-access interventions.

Reference:

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2. Objective, Scope, Target Population and Target Users

The CPG will focus on the primary and secondary prevention of cervical cancer.

The goal of the CPG is to provide guidance on selected clinical questions regarding the screening, early detection and treatment of premalignant lesions of the cervix, as well as to clarify the HPV vaccination dosing schedule.

Seven clinical questions are covered in this CPG.

- **On vaccination regimen**:
    - Clinical question 1: Among young females, is single-dose HPV vaccination as effective as two-dose HPV vaccination in preventing cervical cancer?
- **On screening:**
    - Clinical question 1: Among women undergoing HPV DNA testing, are self-collected HPV DNA tests an alternative to provider-collected tests for cervical cancer screening?
    - Clinical question 2: Among women living with HIV, should earlier cervical cancer screening be recommended over the screening age for the general population in preventing cervical cancer?
    - Clinical question 3: Among menopausal women, should VIA be recommended as a screening tool for cervical cancer screening?
- **On management of abnormal screening tests:**
    - Clinical question 1: Among premenopausal women with a visible squamo-columnar junction (SCJ) with acetowhite lesions on VIA or a positive high-risk HPV (hrHPV) DNA test, should thermal ablation be recommended over cryotherapy to achieve regression of acetowhite lesions or clearance of hrHPV infection?
    - Clinical question 2: Among women with a persistent acetowhite lesion or a positive hrHPV DNA test 12 months after treatment with an ablative procedure, should a repeat ablative procedure be recommended over an excision procedure to achieve clearance of acetowhite lesions or hrHPV infections?
    - Clinical question 3: Among premenopausal women with large acetowhite lesions, should an ablative procedure be recommended over an excision procedure to achieve regression of acetowhite lesions?

The CPG is designed: to align with the Implementing Rules and Regulations of the Universal Healthcare Act; to be practical and easily understood by general practitioners, in accordance with the global/WHO guidelines and contextually applicable to the Philippine situation, in line with the WHO global strategy and Sustainable Development Goals; and to be effective in decreasing the incidence of cervical cancer.

The target users of these guidelines are general practitioners, family physicians, obstetrician-gynecologists, nurses, nurse-midwives and midwives. Practitioners in lying-in clinics, rural

health units, local government units, levels I, II and II hospitals, regional and private hospitals, and medical centers are also targeted users. This CPG can be used by these healthcare providers as a directive when presented with options for cervical cancer vaccination, screening and treatment.

Although adherence to this guideline is encouraged by the Department of Health (DOH), the CPG should not restrict clinicians and other target users in using their clinical judgment and considering a patient's values, needs and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status and responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules from which to base legal action.

3. CPG Development Methodology

3.1 Organization of the Process

Following international standards, the DOH outlined the guideline development process into four phases, as stated in the Manual for CPG Development: (a) preparation and prioritization; (b) CPG generation; (c) CPG appraisal; and (d) implementation.[1]

In the preparation and prioritization phase, the Steering Committee (SC), which was composed of expert gynecological oncologists, set the CPG objectives, scope, target audience and clinical questions. The SC identified and formed the working groups involved in creating the evidence base and finalizing the recommendations for each clinical question.

The Evidence Review Experts (EREs), composed of practitioners of evidence-based medicine, and the Technical Working Group, which were composed of gynecological oncologists or cervical pathologists, were tasked to review existing CPGs, appraise and summarize the evidence, and draft the initial recommendations. The evidence summaries were then presented to the Consensus Panel (CP) members to finalize the recommendations.

The CP, comprised of multisectoral representatives involved in the delivery of healthcare in women at risk of or suffering from cervical cancer (Appendix I), were tasked to review the evidence summaries, evidence-to-decision summaries, and state their perspectives on the views and preferences of the target population using a survey form. The CP members also attended an en banc meeting to evaluate and develop final recommendations. During the meeting, they prioritized critical and important outcomes; discussed necessary considerations revolving around the recommendations including values, access and cost-effectiveness; and voted on each recommendation and its strength.

3.2 Evidence Summaries

The clinical questions were developed using the PICO (population, intervention, comparator and outcome) format. The EREs searched and appraised international practice guidelines related to the screening, early detection and treatment of premalignant lesions of the cervix. If the CPGs were of good quality and published within 5 years, the evidence summaries of the CPGs were adopted. The EREs also conducted a systematic search in electronic databases (MEDLINE via PubMed, CENTRAL and Google Scholar). Relevant local databases and websites of medical societies were also included in the search. Keywords were based on the PICO (MeSH and free text) set for each question. The EREs also contacted authors of related articles to verify details and identify other research studies for appraisal, if needed.

At least two reviewers worked on each PICO question. The EREs appraised the directness, methodological validity, results and applicability of each relevant article included. RevMan, STATA and GRADEPro were used for the quantitative synthesis of important clinical outcomes for each question. The ERE group generated evidence summaries for each of the seven questions. Each evidence summary included evidence on the burden of the problem, diagnostic performance, benefits, harm, and social and economic impact of the screening test/intervention. Evidence/information considered relevant to assessment (i.e., cost of screening test, cost-effectiveness studies, qualitative studies, etc.) were also included in the

evidence summaries. The quality of evidence was assessed using the GRADE approach (Table 2).[2]

Table 2. Basis for assessing the quality of the evidence using the GRADE approach [2]

Certainty of evidence	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Factors that lower quality of the evidence are: • Risk of bias • Important inconsistency of results • Some uncertainty about directness • High probability of reporting bias • Sparse data/imprecision • Publication bias Additional factors that may increase quality are: • All plausible residual confounding, if present, would reduce the observed effect • Evidence of a dose-response gradient • Large effect	

3.3 Formulation of the Recommendations

Draft recommendations were formulated based on the quality of evidence, trade-offs between benefit and harm, cost-effectiveness, applicability, feasibility, equity, resources and uncertainty due to research gaps. Prior to the series of online meetings, the CP received the draft recommendations together with evidence summaries based on the Evidence to Decision (EtD) framework shown in Table 3. These recommendations, together with the evidence summaries, were presented to the CP during the en banc meeting.

Table 3. Detailed considerations based on the EtD framework [3]

1. Problem: Is the problem a priority?
2. Desirable effects: How substantial are the desirable anticipated effects?
3. Undesirable effects: How substantial are the undesirable anticipated effects?
4. Certainty of effects: What is the overall certainty of the evidence of effects of the intervention?
5. Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?
6. Resources required: How large are the resource requirements (costs)?
7. Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?
8. Values: Is there important uncertainty about or variability in how much people value the main outcomes?
9. Equity: What would be the impact on health equity?
10. Acceptability: Is the intervention acceptable to key stakeholders?
11. Feasibility: Is the intervention feasible to implement?

The strength of each recommendation (i.e., strong or weak) was determined by the CP considering all the factors mentioned above. A “strong recommendation” meant that the panel is “confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects”; a “weak recommendation” meant that the “desirable effects of adherence to a recommendation probably outweigh the undesirable effect but is not confident.”[4]

The recommendation for each question and its strength was determined through voting. A consensus decision was reached if 75% of all CP members agreed.[2] If consensus was not reached in the first voting, questions and discussions were encouraged. Two further rounds of voting on an issue were conducted. Evidence-based draft recommendations were also revised based on input arrived at by consensus in the en banc discussions.

3.4 Managing Conflicts of Interest

The Central Executive Committee convened an Oversight Committee (OC) whose task was to thoroughly review the declaration of conflict of interest (DCOI) of each of the Task Force members, particularly the CP members, and make recommendations on how to manage the conflict of interest (COI). For TF members with potential significant COIs, an OC member conducted an additional investigation with due diligence to ensure the integrity of the CPG process and the final recommendations.

All task force members submitted a DCOI and their curriculum vitae prior to the initiation of guideline development process. The disclosure included a 4-year period of personal potential intellectual and/or financial COIs.

Management of the COIs of the CP, Technical Coordinators and Task Force Steering Committees were deliberated and decided by the OC, using the pre-agreed criteria. Individuals with significant potential COIs were not allowed to join the roster of CP members.

The funding body did not influence the development of these guidelines.

3.5 Planning for Dissemination and Implementation

The SC discussed with relevant stakeholders such as DOH and PHIC to prepare a dissemination plan that will actively promote the adoption of this guideline, with strategies for copyrights. Suggestions included making guidelines available on websites, press conferences, social media sites, professional society conventions and journal publications. Other plans for implementation include the development of summary documents, checklists, algorithms, and operation manuals, and integration of the recommendations of these CPGs to current key performance indicators of the DOH. These plan will be finetuned depending on the priorities and available resources of the Department of Health.

3.6 External Review

The CPGs were reviewed by independent stakeholders, who were not members of the Task Force. They were also presented in conferences and to relevant societies for their comments and suggestions, which were incorporated in the final manuscript.

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4. Recommendation and Evidence Summaries

4.1 Vaccination

4.1.1 CQ1: One-dose versus two-dose vaccination among young women

RECOMMENDATION

Among young females aged 9 to 14 years, we recommend the use of one-dose HPV vaccination as an alternative to two doses to prevent cervical cancer.

(strong recommendation, low certainty evidence)

Considerations

The panel considered several factors:

- The benefits of single-dose HPV vaccination, especially its protective benefits against persistent HPV infection
- The impact of the recommendation on vaccination reach and coverage, real-world implementation of vaccination programs and the cost-effectiveness of the interventions.

Remarks

- Despite the single-dose HPV vaccination showing lower serologic titers compared with those associated with two doses, the rate of persistent HPV infection (an important precancerous phase in the pathogenesis of cervical cancer) were similar between the two regimens.
- The use of single-dose HPV vaccination may potentially double the number of young females fully immunized against cervical cancer in terms of cost. This may substantially increase the cost-effectiveness of HPV vaccination to prevent cervical cancer.
- Other factors such as the high rate of dropouts after the first HPV vaccine dose, the high dropout rate among young females from school (which would exclude them from school immunization programs), the reduced manhours demanded from public health professionals and other logistical requirements needed to fully immunize a young female were also considered.
- Because of the aforementioned factors, the panel voted strongly in favor of single-dose HPV vaccination as an alternative to two-dose vaccination, considering the effectivity of single-dose vaccination and its potential to improve the accessibility of vaccine protection against cervical cancer in the Philippines.

4.1.1.1 Burden of disease

The Philippines currently ranks last in terms of HPV vaccine program coverage among LMICs, with only 23% of the target female population receiving the first dose and 5%, the final dose.[1] This was partly attributed to the high cost of the vaccines: a quadrivalent vaccine dose costs PHP 695 (via government procurement), whereas in the private sector, a bivalent dose costs PHP 2,000; a quadrivalent dose, PHP 2,362; and a nonavalent dose, PHP 5,411. At present, the Philippines is not eligible for Gavi, the Vaccine Alliance (Gavi), which deprives the country of the opportunity to acquire bivalent HPV vaccines at a lower cost.[2]

In 2013, the Philippine DOH aligned with the WHO initiative to start two-dose HPV vaccination among female school children.[3] However, in the December 2022 WHO Position on HPV vaccines, WHO recommended giving a one-dose schedule among girls and young women aged 9 to 20 years old.[4] Adopting a one-dose schedule may potentially double the number of girls who could receive vaccination at the same cost and would also simplify the vaccination schedule. A landscaping analysis also found that a two-dose schedule may limit vaccine coverage and promotes vaccine wastage from expiration because the program has to set aside the second dose, which may be wasted due to poor compliance (personal correspondence with Dr. Anthony Calibo).

4.1.1.2 Benefits and harms

One randomized controlled trial (RCT) and two cohort studies were included in the analysis. Findings from resulting cohort studies from the original randomized groups were also reported.[5-10]

The first study included was DoRIS, a randomized, open-label, noninferiority trial conducted in Tanzania. The 930 female participants aged 9 to 14 years old were randomized to one, two or three doses of HPV bivalent or nonavalent vaccines.[5]

The second study was originally a multicenter, cluster, randomized trial that compared two versus three doses of quadrivalent vaccines in girls aged 10 to 18 years old in India. After 4 years, recruitment and randomization were stopped due to unrelated regulatory requirements. At the time, 4,348 patients received three doses, 4,980 patients received two doses, and 4,949 patients received only one dose by default. These treatment groups were followed up as scheduled in the protocol and analyzed at 4 years until 10 years from vaccination as cohort studies.[6,7]

The Costa Rica Vaccine Trial (CVT) was a 4-year community-based, double-blind, randomized trial that aimed to determine the efficacy of three doses of bivalent HPV vaccine with three doses of hepatitis A vaccine as a control. The study included women aged 18 to 25 years. Due to early termination of the study, 422 women received only two doses and 196 received only one dose of HPV vaccine. Outcomes were assessed every 6 months to annually, and analyzed at 4, 7 and 10 years after vaccination as cohort studies.[8-10]

Overall, the three studies included data from 11,167 female participants. Immunogenicity studies from the three studies showed that antibody titers were significantly higher in the two-dose vaccine cohorts compared with the one-dose cohort. This difference persisted up to 10 years. Based on the ERE analysis, the effect size between groups for the HPV 16 titers was -137.90 (95% confidence interval [CI] -180.05 to -100.89) at 4 years and 113.87 (95% CI -180.24 to -47.51) at 10 years, both in favor of two doses. The effect size between groups for HPV 18 antibody titers was -66 (95% CI -90.16 to -43.30) at 4 years and -73.06 (95% CI -87.04 to -59.09) at 10 years, also both in favor of two doses.

Despite these immunogenicity results, the two long-term cohort studies found no difference between the two schedules in terms of the number of incident HPV 16/18 infections at 4 years (relative risk [RR] 0.59, 95% CI 0.2–0.76) and 10 years (RR 1.19, 95% CI 0.86–1.66).[6-10] This

may be partly explained by the fact that there is no established minimum protective level for neutralizing antibodies (measured by the antibody titer/immunogenicity) with HPV vaccination, and that despite a follow-up of up to 10 years, the levels of antibodies remained stable in the one-dose regimen albeit at a lower level compared with two doses.

One cervical intraepithelial neoplasia (CIN) 3+ case was detected in a participant who received one dose but tested negative to both HPV DNA 16 and 18. Furthermore, there was no difference in the seropositivity rates of patients receiving one dose compared with two doses for HPV 16 (RR 0.12, 95% CI 0.01–1.29) at 4 years. There were more who had HPV 18 seropositivity at RR 0.03 (95% CI 0.01–0.13) in the one dose compared with two doses. Persistent HPV 16/18 infections 10 to 12 months from the time of the first positive HPV DNA test was numerically higher among participants receiving one dose, but the difference was not statistically significant with a wide CI (RR 1.78, 95% CI 0.29–11.01). Similar trends were observed with regard to the risk of CIN 3+ (RR 2.25, 95% CI 0.09–55.24).

The overall certainty of evidence with all the considered outcomes was low because of the observational nature of the analyses.

A meta-analysis from six randomized controlled trials conducted in China showed that the risk of serious adverse events after HPV vaccination was similar to the control groups (RR 1.04, 95% CI 0.64–1.71, I2=0%).[11]

Finally, the KENya Single-dose HPV-vaccine Efficacy (KEN SHE) Study is a clinical trial that investigated if one dose of HPV vaccine was effective in preventing HPV infection in adolescents. This randomized, multicenter, double-blind, controlled trial compared single-dose nonavalent HPV vaccine, bivalent HPV vaccine or meningococcal vaccination (non-HPV vaccine control) among Kenyan women aged 15 to 20 years. The study found that by month 18, both the nonavalent and bivalent vaccines had a 97.5% vaccine efficacy in preventing incident persistent HPV infection compared with non-HPV controls.[12]

Table 4. GRADE summary of findings for Clinical Question 1

Critical outcomes	Basis (no and type of studies, total participants)	Effect size	95% CI	Interpretation	Certainty of evidence
DoRIS (2 years)					
HPV 16 antibody titers	1 RCT n=575	-124.91	-153.09, -96.73	Favors 2 doses	⊕⊕⊕⊕
HPV 18 antibody titers	1 RCT n=549	-31.45	-47.91, -14.99	Favors 2 doses	⊕⊕⊕⊕
Seropositivity HPV 16	1 RCT n=575	0.34	0.04, 3.33	Does not favor any dose	⊕⊕⊕⊕
Seropositivity HPV 18	1 RCT n=553	0.17	0.02, 1.39	Does not favor any dose	⊕⊕⊕⊕
2–4 years after vaccination					
Incident HPV infection	2 cohort n=2,014	0,59	0.2, 1.76	Does not favor any dose	Very low ⊕◯◯◯

HPV 16 antibody titers	2 cohort n=1,153	-217.4	-529.2, -94.4	Favors 2 doses	Very low ⊕◯◯◯
HPV 18 antibody titers	2 cohort n=1,149	-140.8	-315.3, -33.7	Favors 2-doses	Very low ⊕◯◯◯
Seropositivity HPV 16	1 RCT, 2 cohort n=1,495	0.12	0.01, 1.29	Does not favor any dose	Very low ⊕◯◯◯
Seropositivity HPV 18	1 RCT, 2 cohort n=1,490	0.04	0.01, 0.19	Favors 2 doses	Very low ⊕◯◯◯
10 years after vaccination					
Persistent	2 cohort n=3,819	0.56	0.08, 3.89	Does not favor any dose	Very low ⊕◯◯◯
Incident	2 cohort n=5,198	1.21	0.87, 1.69	Does not favor any dose	Very low ⊕◯◯◯
HPV 16 antibody titers	2 cohort n=962	-113. 87	-180.24, -47.51	Favors 2 doses	Very low ⊕◯◯◯
HPV 18 antibody titers	2 cohort n=962	-73.06	-87.03, -59.09	Favors 2 doses	Very low ⊕◯◯◯
CIN 2+/3	8 cohort studies	1.05	0.79, 1.40	Does not favor any dose	Very low ⊕◯◯◯

4.1.1.3 Cost implications

There were no cost-effectiveness studies identified in the Philippines.

Burger et al (2018) used a three-tiered hybrid modeling approach to demonstrate the cost-effectiveness of one- and two-dose schedules in Uganda, a Gavi-eligible country. The analysis found that one-dose HPV vaccination resulted in cost savings compared with no vaccination and could be cost-effective compared with two-dose vaccination if the former strategy provided longstanding protection and improved coverage.[13] The DoRIS trial also showed that in Tanzania, the financial cost for each fully immunized girl was USD 5.17 and the economic cost was USD 23.34. These costs were reduced to USD 2.51 and USD 12.18, respectively, using the one-dose schedule.[14] Finally, a comparative modelling analysis of the global impact and cost-effectiveness of one-dose versus two-dose HPV vaccination found that the single-dose strategy had similar health benefits to a two-dose regimen while simplifying vaccine delivery, reducing costs and lowering constraints in vaccine supply. The second dose may become more cost-effective in settings where vaccine and vaccination delivery costs can be reduced and the burden of cervical cancer is high.[15]

4.1.1.4 Ethical, social and health systems impact (equity, acceptability and feasibility)

A self-administered survey among 435 adult women in central Visayas showed that over half (54%) were accepting of HPV vaccination at a low price, but only 30% and 31% were accepting at a moderate and a high price, respectively.[16]

The panel also emphasized that the use of a one-dose schedule can double the number of females vaccinated at the same cost. Furthermore, this schedule simplifies vaccination implementation, especially by the Philippine DOH, as the one-dose regimen removes the need for a second visit, eliminates dropouts for a second dose and may potentially minimize vaccine wastage.

4.1.1.5 Recommendations from other groups

Table 5. Recommendations from other groups regarding Clinical Question 1

Group/Agency	Recommendations
WHO Strategic Advisory Group of Experts on Immunization (SAGE 2022)[4]	1- or 2-dose schedule for the primary target of girls aged 9–14 years 1- or 2-dose schedule for young women aged 15–20 years 2 doses with a 6-month interval for women older than 21 years
Philippine Pediatric Society (PPS)/Pediatric Infectious Disease Society of the Philippines (PIDSP)/Philippine Foundation for Vaccination (PFV) (2023)[17]	2-dose schedule from 9–14 years old 3-dose schedule for 15–18 years old
Philippine Society for Microbiology and Infectious Diseases (PSMID 2018)[18]	3-dose schedule until 26 years old
US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP)[19]/The American College of Obstetricians and Gynecologists (ACOG)[20]	2 doses for 9–14 years old 3 doses for 15 years old and above
UK Joint Committee on Vaccination and Immunisation (JCVI 2022)[21]	1 dose for girls up to and including 14 years

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4.2 Screening

4.2.1 CQ2: Self-collected versus provider-collected HPV DNA testing

RECOMMENDATION

We suggest the use of self-collected HPV DNA testing as an alternative to clinician-collected HPV DNA testing for the detection of high-risk HPV infection among women.

(weak recommendation, low certainty evidence)

Considerations

The panel considered several factors:

- The impact of the two sampling methods on diagnostic accuracy
- The cost associated with each sampling method
- Patient preference and its impact on testing rates

Remarks

- The evidence showed that clinician-collected sampling had higher sensitivity compared with self-collected sampling. The specificity rates were similar.
- Self-collected sampling was highly acceptable for women and the majority of them preferred self-collection over clinician-collected testing. Hence, the panel agreed that despite the lower sensitivity of self-collected sampling, more cases of hrHPV infection may be detected if self-collected sampling would substantially increase the number of women participating in cervical cancer screening.

4.2.1.1 Burden of disease

Cervical cancer affects 7,897 Filipinos yearly and causes 4,052 deaths.[1] One of the three pillars recommended by WHO to eliminate cervical cancer by 2030 is to screen 70% of women at age 30 years and again by age 45 years using a high-performance test.[2] Cervical cancer screening using HPV DNA has been recommended by WHO, the American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society (ACS) and the Philippine Guidelines on Periodic Health Examination (PHEX), and adopted by the Philippine Obstetrical and Gynecological Society (POGS).[3-7] According to the PHEX, HPV DNA testing every 5 years is recommended among women aged 30 to 65 years.[7]

Self-collected sampling for HPV DNA testing has been advocated in both developed and developing countries to increase participation in cervical cancer screening to reach the 70% target.[8,9] Self-collected sampling removes the need for a pelvic exam, the clinic setting and a trained clinician.[10] The principle of sample collection between the two strategies are essentially the same, with both strategies using a device (i.e., a cervical brush for clinician-collected testing and a brush, swab or tampon for self-collected testing) and a preservative solution for transporting the sample.[10]

4.2.1.2 Benefits and harms

The diagnostic accuracy of self-collected sampling compared with clinician-collected sampling was assessed in a 2014 meta-analysis.[11] Only studies on primary screening were included and studies of follow-up patients undergoing HPV DNA testing were excluded. Participants

were healthy women aged 15 to 85 years. For the outcome on accuracy in detecting hrHPV infection (patients with high-grade squamous intraepithelial lesions [HSIL] or CIN 2+ lesions), 12 cross-sectional studies were included (n=52,890). Eight studies used brushes (n=28,712), four studies used swabs (n=12,064), while one study used tampons (n=12,114). The pooled sensitivity rates in detecting HSIL or CIN 2+ lesions were 76% (95% CI 69–82%) for self-collected sampling and 91% (95% CI 87–94%) for clinician-collected samples. Meanwhile, the pooled specificity rates were 86% (95% CI 83–89%) for self-collected samples and 88% (95% CI 85–91%) for clinician-collected samples.[11]

The meta-analysis was assessed as high quality using AMSTAR 2. Certainty of evidence was downgraded to "very low" due to inconsistency (high heterogeneity) and moderate risk of bias. Reporting and execution of tests were unclear in several studies; attrition bias was evident and unexplained in two studies. The majority of studies included were observational studies and quasi-RCTs.[11]

4.2.1.3 Cost implications

According to a WHO cost-analysis modelling, a HPV DNA self-collection test costs USD 8.15 (~PHP 465) for the test alone, and USD 15.09 (~PHP 860) when additional overhead expenses are considered.[3] Commercial test kits cost around USD 49 to 89 per kit (~PHP 2,800 to 5,100).[12] Clinician-collected HPV DNA testing costs PHP 4,800 to 6,000 per test in diagnostic centers and outpatient clinics.[13] A recent study on the cost-effectiveness of HPV self-collection compared with usual care among underscreened women in the US showed that HPV DNA self-collection costed less with higher cervical screening uptake, and lower costs per additional persons screened.[14] Another cost-effectiveness analysis on home-based HPV DNA self-collection testing in El Salvador showed that self-collection of HPV DNA was projected to reduce population of cervical cancer risk by 14%, with a USD 1,210 per life-year saved compared with no screening.[15] Finally, a 2017 systematic review that reviewed cost-effectiveness studies of cervical cancer screening methods in LMICs showed that the direct medical cost of self-collected sampling was USD 7.50 compared with USD 13.27 for clinician-collected sampling.[16]

HPV DNA clinician-collected testing is available in various hospitals and diagnostic centers in the Philippines, but self-testing kits are not yet readily available locally. Given our recommendations, self-collection kits for HPV DNA testing should be made more readily available as an alternative to clinician-collected sampling.

4.2.1.4 Ethical, social and health systems impact (equity, acceptability and feasibility)

A meta-analysis pooled the results of 55 studies comprising 20,553 participants to assess the acceptability of self-collected sampling compared with clinician-sampling for HPV DNA testing.[17] Three studies were RCTs (n=919), nine were quasi-experimental studies (n=1,783) and 43 were cross-sectional studies (n=17,851). Participants were women aged 18 to 70 years old and undergoing primary screening. Twenty-two studies used brushes as the self-collecting device (n=6,547), 26 studies used swabs (10,626), two studies used lavages (n=917), two used tampons (n=334) and three studies did not report the device used.[17]

The analysis showed a pooled estimate of 95% acceptability (95% CI 94–97%) among participants (with high heterogeneity with I^2>95%).[16] Subgroup analysis by type of device

used showed acceptability rates of 93% (95% CI 90–96%) for brushes, 96% (95% CI 93–98%) for swabs, 95% (95% CI 95–100%) for lavages, and 97% (95% CI 92–100%) for tampons, with no observed significant difference between groups (p=0.420).[17]

In terms of preference, the same meta-analysis included 82 studies comprising 63,117 participants.[16] Nine studies were RCTs (n=12,624), 22 were quasi-experimental studies (n=9,549) and 51 were cross-sectional studies (n=41,004). Women were aged 24 to 70 years old and undergoing primary screening. Thirty-eight studies used brushes (n=34,422), 35 studies used swabs (n=26,643), 11 studies used lavages (n=11,329), three used tampons (n=362) and two studies did not report the device used.[17]

Pooled results showed that 66% (95% CI 62–70%) of women preferred self-collected sampling over clinician-collected sampling.[16] Subgroup analysis by type of device used showed that compared with clinician-collected sampling, 67% (96% CI 58–74%) preferred brushes, 65% (95% CI 59–70%) preferred swabs, 68% (95% CI 60–76%) preferred lavages, and 77% (95% CI 31–100%) preferred tampons. No significant difference was found in terms of device type (p=0.850) and heterogeneity was high (I^2>95%).[17]

With these results showing high acceptability and preference over clinician-collected sampling, the panel underscores that self-collected sampling may increase the number of women participating in cervical cancer screening and improve the detection (and potentially early treatment) of hrHPV infection.

4.2.1.5 Recommendations from other groups

Table 6. Recommendations from other groups regarding Clinical Question 2

Group/Agency	Recommendations
Philippine Guidelines on PHEX (2021)[7]	For 30–65 years, screening for cervical cancer every 3 years with cervical cytology alone or every 5 years with hrHPV testing alone *(Strong recommendation, low certainty evidence)* *No specific recommendation for self-sampling*
WHO (2021)[3]	Use of HPV DNA detection as the primary screening test *(Strong recommendation, moderate certainty of evidence)* When providing HPV DNA testing, suggest using either samples taken by a healthcare provider or self-collected samples among both the general population of women and women living with HIV *(Conditional, low certainty of evidence)*
ACOG (2021)[4]	FDA approved HPV DNA testing alone or as co-testing with cytology every 5 years for women aged 30–65 years *No specific recommendation for self-sampling*
ACS (2021)[5]	FDA approved HPV DNA testing is the preferred test for cervical cancer screening for people 25–65 years of age *No specific recommendation for self-sampling*
Cancer Council Australia (2022)[18]	Choice of self-collected versus clinician collected sample among women 25–74 years who have been sexually active

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4.2.2 CQ3: Screening of women living with HIV

RECOMMENDATION

Among women living with HIV, we recommend early cervical cancer screening for the detection of cervical cancer.

(strong recommendation, low certainty evidence)

Considerations

The panel considered several factors:

- The high risk of developing cervical cancer among women living with HIV
- The benefits and harms of cervical cancer in women living with HIV
- The impact of delayed cervical diagnosis on women in this at-risk, marginalized subpopulation

Remarks

- The panel emphasized that women living with HIV have a 6-fold increase in the risk of cervical cancer.
- The panel noted that even though there is low certainty of evidence, cervical cancer screening is feasible and sufficiently reliable among women living with HIV in settings similar to the Philippine setting.
- The panel recognized that women living with HIV have poor access to health care and are not routinely screened for cervical cancer as part of their routine care. They also have larger cervical lesions upon diagnosis, suggesting an earlier onset of cervical precancer. Hence, women living with HIV would need earlier screening to aid detection of precancerous lesions and initiation of curative treatment.
- The panel did not identify substantial harm in screening for cervical cancer earlier among women living with HIV.

4.2.2.1 Burden of disease

Persistent, chronic infection with hrHPV is a prerequisite for the development of precancerous intraepithelial lesions and cervical cancer.[1] HPV infection is common among women younger than 30 years old, particularly in those aged 20 to 24 years. HPV infection usually clears up in 2 to 4 years because of the development of natural immunity; women should test negative by age 30 years. However, a subgroup of women will have persistent, chronic HPV infection. When women test positive at age 30 or older, their risk for developing CIN is greater. Diminished immune response is believed to be a factor related to persistent chronic infection.[2]

HPV and HIV are both sexually transmitted infections and share common risk factors. Women living with HIV are at high risk of acquiring an HPV infection and have an elevated incidence of cervical precancer and cancer compared with the general population.[3] Aside from the shared risk factors, this increased incidence may be from suppression of the immune system, which fails to clear the HPV infection.[4] A meta-analysis of 24 studies comprising 236,127 women living with HIV showed that the pooled risk of cervical cancer was increased 6-fold (RR 6.07, 95% CI 4.40–8.37).[5] This is of particular concern in the Philippines, reportedly with the fastest-growing HIV epidemic in the Western Pacific region, increasing from 1 case per

day in 2008 to 28 cases per day in 2022.[4] Cervical cancer is also one of the AIDS-defining illnesses and the most common cancer among women living with HIV globally.[6] While antiretroviral therapy (ART) has been successful in prolonging the life of women living with HIV, it does not prevent the development of cervical cancer. This underscores the need for screening even in women receiving ART.

According to the 2021 WHO guideline for screening and treatment of cervical precancer lesions for cervical cancer prevention, women living with HIV may start regular cervical cancer screening at the age of 25 years (conditional recommendation, low certainty of evidence).[7] This applicability of this strategy in the Philippines was explored in the development of this CPG. It is highly relevant given that data from the Scale-up Cervical Cancer Elimination with Secondary prevention Strategy (SUCCESS) project [8] found that while the hrHPV positivity rate among the general population was 9%, the positivity rate ranged from 27% to 32% among women living with HIV in the Philippines. Furthermore, the current care for women living with HIV in the Philippines does not include routine cervical cancer screening.

4.2.2.2 Benefits and harms

There are no studies comparing the outcomes for early cervical cancer screening at 25 years versus regular screening at 30 years for women living with HIV. The evidence is limited and the number of publications that present results by age at first screening are scarce.

For this evaluation, one cohort study, four cross-sectional studies and one RCT were identified.[9-14] Most of the studies were conducted in LMICs, particularly Africa. The age bracket of screening varied from 18 to 65 years. Two of the studies also assessed cervical cancer screening methods among HIV-negative women.[12,14] One study assessed the utility of screening after treatment with cryotherapy (the screen-and-treat approach).[14] Outcome measures were evaluated for 6 to 36 months. These included CIN 2+ or HSIL, positive VIA and HPV DNA. Some studies included atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions.

Overall, the studies reported that cervical screening was started for women living with HIV from age 18 to 65 years, although the 2021 WHO cervical cancer screening guidelines (2nd edition) recommended screening starting at age 25 years.[7] Most studies recognize that women living with HIV are considered at high risk of pre-invasive cervical lesions and cervical cancer.

The evaluated studies found that cervical cancer screening was feasible in women living with HIV. However, there were differences in the diagnostic accuracy of various screening methods. One cohort study noted that three methods had comparable measures of accuracy in women living with HIV: sensitivity of VIA, conventional cytology at HSIL threshold and HPV DNA was 80%, 64% and 80%, respectively; specificity was 68.42%, 98.12% and 70.68%; and positive predictive value (PPV) was 19.23%, 76.19% and 22%.[9] A cross-sectional study found that women living with HIV had increased specificity but reduced sensitivity and diagnostic accuracy by both primary and triage testing approaches.[10] Another cross-sectional study found that VIA had a PPV of 35.2% compared with 38.2% with VIA followed immediately by visual inspection with Lugol's iodine (VILI) in women with a positive VIA result.[11] The third cross-sectional study found that 4.5% of women living with HIV were VIA positive, but VIA

showed a low sensitivity compared to HPV-testing for detection of HSIL+.[12] The fourth cross-sectional study found that for CIN 2+, the sensitivity, specificity and positive and negative predictive value estimates of VIA were 80%, 82.6%, 47.6% and 95.4%, respectively, and 20.9%, 96.0%, 50.0% and 86.3% for HSIL+.[13]

The diagnostic accuracy of these four studies is summarized in the tables below.

Table 7. Summary of diagnostic accuracy results for studies on cervical cancer screening for women living with HIV

Pimple et al[9]	**Cytology**	**VIA**	**HPV DNA**
Sensitivity	64 (42.52–82.03)	80 (59.3–93.17)	80 (68.78–97.45)
Specificity	98.12 (95.67–99.39)	68.42 (62.46–73.96)	70.68 (64.81–76.08)
PPV	76.19 (56.13–88.89)	19.23 (15.46–23.67)	22 (18.22–26.32)
Njue et al[10]	**Pap smear**	**VIA**	**HPV DNA**
Sensitivity	97.2	88.9	97.2
Specificity	66.4	76	72.8
PPV	45.5	51.6	50.7
Huchko et al[11]	**VIA**	**VIA-VILI**	
Screening positivity rate	26.4	21.7 (p=0.003)	
Prevalence of CIN 2+ detected in a single screening round	90 (87.2–93.8)	58.2 (p=0.271)	
PPV	35.2	38.2 (p=0.409)	
Dartell et al[12]	**VIA**	**HPV DNA**	
Sensitivity	50 (31.5–68.5)	100	
Specificity	90 (87.2–93.8)	58.2 (52.6–63.7)	
PPV	32.6	17.9	
Sahasrabuddhe et al[13]	**VIA**	**Cytology (HSIL)**	
Sensitivity	80 (66.3–90)	20.9 (10–36)	
Specificity	82.6 (77.4–87.1)	96 (92.5–98.1)	
PPV	47.6 (36.6–58.9)	50 (26–74)	

One RCT showed that screen-and-treat using HPV DNA was highly effective in reducing the risk of CIN 2+ by 36 months after treatment with cryotherapy among both HIV-positive (RR 0.20, 95% CI 0.06–0.69) and HIV-negative women (RR 0.31, 95% CI 0.2–0.5). The VIA-and-treat reached statistical significance only in HIV-positive women (RR 0.51, 95% CI 0.29–0.89).[14]

Overall, the level of evidence is very low due to the indirectness of the data, heterogeneity of studies and some inconsistencies in the study findings.

None of the studies evaluated harms associated with screening for cervical cancer. The panel also did not identify any substantial harm with earlier cervical cancer screening over conventional screening among women living with HIV.

4.2.2.3 Cost implications

There were no studies that analyzed the cost of early screening versus conventional screening among women living with HIV.

4.2.2.4 Ethical, social and health systems impact (equity, acceptability and feasibility)

The panel recognized that women living with HIV have poor access to health care due to various challenges, including stigma and low awareness among healthcare professionals on the proper care of women living with HIV. Furthermore, the panel highlighted that women living with HIV tended to have larger cervical lesions upon diagnosis and a higher risk of invasive cancer.[15] These reasons underscore the need to improve healthcare access to this marginalized population of women at risk. Global guidelines routinely recommend cervical cancer screening for women living with HIV; however, the Philippine Guidelines on PHEX does not yet include this recommendation for this at-risk group.[2,7]

4.2.2.5 Recommendations from other groups

Table 8. Recommendations from other groups regarding Clinical Question 3

Group/Agency	Recommendations
Philippine Guidelines on PHEX (2021)[2]	Among women aged 30–65 years, screening for cervical cancer every 3 years with cervical cytology alone or every 5 years with hrHPV testing alone Among women aged 21–29 years, recommendation against screening for cervical cancer or any alternative screening tests
WHO (2021)[7]	Use of HPV DNA detection as the primary screening test rather than VIA or cytology in screening and treatment approaches among both the general population of women living with HIV Suggestion to start regular cervical cancer screening at the age of 25 years among women living with HIV*

**The WHO's recommendation of an earlier age of screening for women living with HIV was based on three studies using the category CIN 2/3. Based on data from two studies, the pooled prevalence of CIN2/3 was 11.2% in women living with HIV below the age of 30 and 11.5% in women living with HIV above the age of 30. Only one study analyzed women aged older or younger than 25 years, and showed a prevalence of CIN 2/3 of 6.7% in women living with HIV younger than 25 years of age, and 9.9% in women living with HIV older than 25 years of age.[7]*

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4.2.3 CQ4: Appropriate screening for menopausal women

RECOMMENDATION

Among menopausal women, we suggest AGAINST the use of VIA as a screening tool for cervical cancer screening.

(weak recommendation, low certainty evidence)

Considerations

The panel considered several factors:

- The technical requirements for valid VIA procedure for cervical cancer screening
- The evidence on diagnostic accuracy of VIA as a screening tool among menopausal women
- The cost-effectiveness of the test in menopausal women

Remarks

- The panel recognized that because the SCJ recedes into the endocervical canal in perimenopausal and postmenopausal women, it becomes partially visible or not visible. This makes VIA difficult – if not invalid – in these women.
- The low pooled sensitivity of VIA in menopausal women diminished its utility as a screening tool for cervical cancer in this subgroup.
- While VIA is considered widely available and a low-cost option in the Philippines, the low sensitivity of this test in menopausal women may reduce its cost-efficiency.
- The Philippine Guidelines on PHEX recommends the use of cervical cytology (every years) or hrHPV testing (every 5 years) as the preferred modes of screening until 65 years of age. These screening tests should be used instead of VIA, given the limitations of the latter test in menopausal women.

4.2.3.1 Burden of disease

In the 2021 Philippine Guidelines on PHEX, the Task Force strongly recommended that women aged 30 to 65 years should be screened for cervical cancer every 3 years with cervical cytology alone or every 5 years with hrHPV testing alone.[1] Furthermore, the guidelines strongly recommended VIA as an alternative to Pap smear.[1]

VIA is a low-cost and simple method for detecting cervical precancerous lesions and early invasive cancer, and is widely used in LMICs as it enables a single-visit, screen-and-treat protocol.[2,3] However, for VIA, it is necessary to be able to visualize the SCJ as a condition for fully assessing the cervix. Almost all of the dysplastic changes are found at or are close to the SCJ. Because the SCJ recedes into the endocervical canal in perimenopausal and postmenopausal women, it is only partially visible or not visible, making VIA difficult – if not invalid – in these women.[4] Hence, the validity of VIA as an alternative to Pap smear in menopausal women needs to be confirmed.

4.2.3.2 Benefits and harms

Studies from three cross-sectional studies were included in this review. All three studies assessed the diagnostic accuracy of VIA and were conducted in LMICs.[4-6] The study by Holt

et al (2017) was based on a pooled analysis of individual patient data from 30,371 women enrolled in 17 cross-sectional population-based studies in China. Of these women, 2,757 had known menopausal status.[4] The study by Raifu et al (2017) was undertaken in the Democratic Republic of Congo. They compared the accuracy of VIA by examiner (nurse and physician) among women aged 30 years or older, of which 498 were menopausal.[5] The study by Cremer et al (2011) evaluated the adequacy of VIA (visibility of the SCJ) from four communities in El Salvador among women 50 years old and older, as well as the test accuracy (n=588).[6]

The combination of colposcopy and histology/biopsy was used as a reference standard in all studies. In the Cremer et al study, the final diagnosis was established by colposcopy, biopsy and endocervical curettage.[6] In the other two studies, a biopsy was performed if colposcopy was abnormal. When no colposcopic abnormalities were detected, colposcopy alone was used for proof of absence of disease [4,5]. All studies used CIN 2+ as the threshold for disease status.

Based on the three studies (n=4,325), the ERE group determined that the pooled sensitivity was 0.53 (95% CI 0.26–0.78) and the pooled specificity was 0.88 (95% CI 0.76–0.94) (Table 9).[4-6] While the pooled specificity of VIA was high, its sensitivity to detect patients with CIN 2+ was low.

Table 9. Summary of findings for VIA for the detection of CIN 2+

Outcome	Basis	Pooled estimate	95% CI	Certainty of evidence
Sensitivity	3 studies n=4,325	53.1%	26.0–78.5%	Very low
Specificity	3 studies n=4,325	88.1%	76.3–94.4%	Low

The risk of bias was deemed high for two studies [4,5] and low for one study.[6] Some issues reduced the quality of studies, such as verification bias in the Holt et al study, and the Raifu et al study did not report what happened to all participants.[4,5] Statistically significant heterogeneity was observed for sensitivity and specificity of all studies included in the analysis. Wide CIs were also observed for sensitivity estimates. Hence, the certainty of evidence for this review was very low.

No study was found discussing the harms of performing VIA among menopausal women.

4.2.3.3 Cost implications

There were no studies identified that examined the cost of VIA among menopausal women. In 2017, a systematic review on cost-effectiveness studies of cervical cancer screening methods in LMICs was conducted.[7] The screening methods assessed included two-visit self-collected HPV testing (screening + results and treatment if positive), two-visit provider-collected HPV testing (screening + results and treatment if positive), three-visit cytology (screening + results and colposcopy/biopsy if positive + treatment) and one-visit VIA (screening immediately followed by results and treatment if positive). The review found that

cost-effectiveness depended on parameter assumptions, including sensitivity of the test, cost and loss to follow-up. Cytology was the least efficient screening method as it was found to have a low sensitivity (between 46% and 80%), greater loss to follow-up (as it required three visits to complete a cytology screening course) and high cost. Direct medical cost of cytology was higher (USD 6.60) compared with VIA (USD 2.07) but lower than self-collected (USD 7.50) and provider-collected (USD 13.27) HPV testing.[7] Furthermore, the review found that HPV testing tended to be more efficient when VIA test sensitivity was poor or required a similar number of visits.[7]

In the Philippines, VIA is commonly conducted for free as part of social programs organized by private organizations and the government. It requires supplies that are locally attainable and inexpensive. Its results are immediately known, thus treatment could be offered to patients during the same visit.

4.2.3.4 Ethical, social and health systems impact (equity, acceptability and feasibility)

In the Philippines, as well in other Asian countries, life expectancy is increasing, averaging 73.3 years in 2019 compared with 68.8 years in 2000, with women outliving men more by 5 years.[8] As such, the number of postmenopausal women worldwide is expected to reach 1.1 billion by 2025.[9] Western guidelines recommend discontinuing cervical cancer screening at age 50 years (WHO) or 65 years (USA), based on a lower incidence of cervical cancer in women aged ≥65 years who have undergone continuous medical examination.[10,11] However, in other countries, particularly in Asia, the incidence of cervical cancer remains high among elderly women.[12] Hence, the need for screening in menopausal women remains in the Philippines.[1]

No study was found discussing preferences, acceptability or feasibility of performing VIA among menopausal women.

4.2.3.5 Recommendations from other groups

Table 10. Recommendations from other groups regarding Clinical Question 4

Group/Agency	Recommendations
Philippine Guidelines on PHEX (2021)[1]	Screening with Pap smear every 3 years for asymptomatic women aged 21–65 years of age Screening with VIA as an alternative to Pap smear for asymptomatic women aged 21–65 years of age
WHO (2021)[10]	HPV DNA testing is the primary screening test rather than VIA or cytology in the general population of women, starting at age of 30 years Testing recommended to be stopped at the age of 50 years after two consecutive negative screening results
ACOG (2021)[13]	Adopted USPSTF recommendations
American Society of Colposcopy and Cervical Pathology (ASCCP 2021)[14]	Adopted USPSTF and ACS recommendations
ACS (2020)[11]	Screening at age 25 years and undergo primary HPV testing every 5 years through age 65 years (preferred)

	If primary HPV testing is not available, individuals aged 25–65 years old should be screened with cotesting (HPV testing in combination with cytology) every 5 years or cytology alone every 3 years (acceptable)
US Preventive Services Task Force (USPSTF 2018)[15]	Screening with hrHPV testing every 5 years as one of the options for women 30–65 years of age OR Screening with cervical cytology alone every 3 years OR Screening with hrHPV testing and cytology every 5 years

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4.3 Management of abnormal screening

4.3.1 CQ5: Thermal ablation versus cryotherapy in women with abnormal screening

RECOMMENDATION

Among premenopausal women with a visible squamocolumnar junction with acetowhite lesions on VIA or a positive high-risk HPV DNA test, we recommend management using thermal ablation as an alternative to cryotherapy.

(strong recommendation, low certainty evidence)

Considerations

The panel considered several factors:

- The benefits and harm of the compared procedures
- The cost and availability of the procedures

Remarks

- Based on the review evidence, the panel agreed that thermal ablation is an effective treatment for cervical precancerous lesions and may be considered just as effective as cryotherapy. While the recurrence rate of thermal ablation exceeded 10%, the certainty of evidence for this outcome was very low.
- Safety data comparing the two procedures also suggested equivalence and that serious adverse events were not common.
- Thermal ablation had a lower cost compared with cryotherapy.
- Acceptability was similar between the two procedures and satisfaction from thermal ablation was considered high.

4.3.1.1 Burden of disease

Thermal ablation, also known as thermocoagulation or cold coagulation, is a method that uses electricity to heat a thermoprobe to 100–120°C to destroy abnormal cells of the cervix. This procedure is indicated for women of any age with CIN grades 1 to 3. It is ideal for when the transformation zone is visible and not previously treated and when there is no suspicion for endocervical involvement, or micro-invasive, invasive or glandular disease.[1] This procedure only takes a few seconds. The machine is battery-operated, portable and uses electricity to recharge the battery, making it an attractive alternative in resource-limited and/or geographically isolated settings.[2]

In 2019, WHO suggested that women who screened positive with hrHPV or VIA receive either thermal ablation or cryotherapy. This was an update from the 2012 and 2014 guidelines that recommended cryotherapy for the screen-and-treat approach in low-resource settings.[3-5]

Cryotherapy uses either nitrous oxide or carbon dioxide gas as cryogens to ablate abnormal tissues of the cervix and has high cure rates for CIN 1–3.[1] However, the use of cryotherapy is limited by its convenient access, prohibitive cost and logistical requirements for transport and storage of the cryogenic gas and its gas cylinders.[2]

As recent studies have shown effectiveness of thermal ablation for the management of cervical precancers, its efficacy compared with cryotherapy should be evaluated.

4.3.1.2 Benefits and harms

Five RCTs compared thermal ablation and cryotherapy in the management of cervical precancers. Two of the RCTs (one from India and one from Nigeria) included women who had a positive VIA test while the other three RCTs (one from China, one from Singapore and another from India) randomized the women to either thermal ablation or cryotherapy after positive cytology or positive hrHPV.[2,6-9] All five studies measured the proportion of patients with successful treatment or cure rate, measured by negative VIA or negative cytology. Four of the RCTs are recent studies (published from 2020 to 2022) and have not yet been included in two meta-analyses on thermal ablation for cervical precancer.[1,10]

Eight observational studies were also identified that assessed the effectiveness of thermal ablation alone in the real-world setting for cervical precancers.[11-18] Four were retrospective reviews.[11-14] Two studies were from the UK, one was from Ireland and one from Brazil. All patients were screened through cytology without VIA. The other four studies were prospective cohorts (two from Africa, one from the UK and one from Brazil.[15-18] Only one study was from Africa,[17] which used VIA or VILI for screening, while the others used cytology. Treatment success was defined as negative cytology, VIA, VILI or HPV after 6 months to 1 year of having an initial positive test.

Results of a pooled analysis by the EREs showed that, based on the five RCTs [2,6-9], thermal ablation had slightly fewer treatment failures compared with cryotherapy (RR 0.76, 95% CI 0.59–0.99). Although the difference was statistically significant, the 0.99 upper limit of the CI denoted equivalence. Of the 771 patients who received thermal ablation, 87 patients (11.3%) were considered treatment failures at 6 months posttreatment. Of the 750 patients who received cryotherapy, 111 patients (14.8%) were treatment failures. The pooled total of treatment failures of thermal ablation versus cryotherapy (11.3% vs. 14.8%) showed that thermal ablation was noninferior to cryotherapy.

From the eight observational studies, seven studies had a success rate (>80%) while the other study had a 59% success rate (possibly owing to overtreatment and a large number of participants lost to follow-up).[11-18]

The common side effects noted for thermal ablation and cryotherapy included pain, vaginal bleeding and vaginal discharge. Five RCTs showed no statistically significant difference in terms of participants reporting pain between thermal ablation and cryotherapy (RR 1.22, 95% CI 0.99–1.51).[2,6,9,19,20] In one RCT, the median visual analog scale (VAS) score was 2.5/10 for thermal ablation and 3.33/10 for cryotherapy.[6] Findings were comparable in another RCT, with a VAS of 3±2.4 for thermal ablation and VAS 2.2±1.3 for cryotherapy.[7] Three RCTs showed a statistically significant increase in vaginal bleeding with thermal ablation (RR 1.78, 95% CI 1.4–2.27) compared with cryotherapy [2,7,19]. However, four RCTs showed that there were significantly fewer participants with vaginal discharge in the thermal ablation group (RR 0.58, 95% CI 0.53–0.64) compared with the cryotherapy group. Vaginal discharge persisted for a mean of 7 days.[23]

Other serious adverse events noted included three cases of cervical infection after thermal ablation, all of which resolved after systemic antibiotics.[6,7,13] Other adverse events

included vasovagal response in 1 of 52 (1.9%) patients (100%)[13] and vaginal burning in 1 of 318 (0.3%) patients.[23]

Table 11. GRADE summary of findings for Clinical Question 5

Critical outcomes	Basis (no and type of studies, total participants)	Treatment arm: thermal ablation	Comparator/control arm: cryotherapy	Effect size	95% CI	Interpretation	Certainty of evidence
Treatment failures (measure of efficacy)	5 RCTs n=1,521	87/771 (11.3%)	111/750 (14.8%)	RR 0.76	0.59, 0.99	Benefit	Moderate
Pain	5 RCTs n=2,561	171/1287 (13.3%)	138/1274 (10.8%)	RR 1.22	0.99, 1.51	Equivalent	Moderate
Vaginal bleeding	3 RCTs n=1,696	161/895 (18.0%)	90/801 (11.2%)	RR 1.78	1.4, 2.27	Harm	High
Vaginal discharge	4 RCTs n=1,854	344/929 (37.0%)	59/925 (63.9%)	RR 0.58	0.53, 0.64	Benefit	Low
Acceptability	2 RCTs n=769	378/378 (100.0%)	388/391 (99.2%)	RR 0.15	0.01,2.85	Equivalent	Moderate

The five RCTs included to measure efficacy had an overall low risk of bias, although there was some uncertainty as patients could not be blinded to treatment. In addition, it was unclear in four of the five studies whether the outcome assessors were blinded to the treatment assignment, making them at risk for detection bias. Hence, the overall certainty of evidence was moderate.

For the eight observational effectiveness trials, certainty assessment was very low because of their observational study design, inconsistency with the screening tests used in the studies, and indirectness from having only one treatment arm.

The overall certainty of evidence for all adverse events (pain, vaginal bleeding and discharge) taken together was low. Taken separately, certainty of evidence was high for vaginal bleeding, moderate for pain, and low for vaginal discharge. Due to inconsistency in the measurement across the studies and imprecision in rating pain, a subjective complaint, the certainty of evidence was lower. The more serious adverse events after thermal ablation, such cervical infection and vaginal burn, were based on individual reports.

An unpublished 2023 meta-analysis of RCTs by Nevado-Gammad and Santiago showed similar findings in terms of efficacy, vaginal bleeding and acceptability of thermal ablation versus cryotherapy.[24] However, the meta-analysis showed benefit of thermal ablation with regard to pain (low certainty of evidence) and equivalence with regard to vaginal discharge (moderate certainty of evidence). These differences could be due to the inclusion of observational studies in the present review.

Three observational studies assessed the recurrence of CIN after thermal ablation.[25-27] Of 1,214 total patients, the recurrence rate was 18.8%. Two of the studies reported a high rate of loss to follow-up.[25,26]

4.3.1.3 Cost implications

No economic evaluations were found in the literature. Cost comparison was mentioned in a study from Nigeria. [2] The mean cost for treatment with thermal ablation was ~PHP 63.08±5.35, which is about a fourth of the mean cost for treatment with cryotherapy (~PHP 309.16±30.16).

4.3.1.4 Ethical, social and health systems impact (equity, acceptability and feasibility)

The overall acceptability of both thermal ablation and cryotherapy was high, as measured by a "yes" response to whether participants would recommend the same procedure to a friend or relative. Two RCTs showed no significant difference in the acceptability between thermal ablation and cryotherapy (RR 0.15, 95% CI 0.01–2.85).[9,20]

One RCT showed 99.3% of women gave a high level of satisfaction (score of 7–9 over 9) with thermal ablation versus 98.0% with cryotherapy. One participant gave a score of 1–3 over 9 in the thermal ablation group and three participants gave a score of 4–6 over 9 in the cryotherapy group.[9] In another RCT, 100% in the thermal ablation group versus 99.2% in the cryotherapy group were highly satisfied with the procedure. Only one participant in the cryotherapy group gave a score of 4–6 over 9.[20]

4.3.1.5 Recommendations from other groups

Table 12. Recommendations from other groups regarding Clinical Question 5

Group/Agency	Recommendations
ASCO (September 2022)[28]	For basic settings, if primary screening is VIA and results are positive, then treatment should be offered with thermal ablation and/or loop electrosurgical excision procedure, depending on the size and location of the lesion *(Moderate strength of recommendation; intermediate quality of evidence)*
Federation of Obstetrics and Gynaecologic Societies of India (FOGSI) (February 2018)[29]	In limited resource settings, all grades of CIN fulfilling the criteria for ablation should undergo cryotherapy or thermal ablation. Criteria: • Lesion should be entirely visible and not occupy more than two quadrants of cervix • The entire lesion should be located on ectocervix without any vaginal or endocervical extension, • Lesion should be entirely covered by largest cryotherapy probe available • No suspicion of invasive disease • Contraindicated in cases with postcoital or postmenopausal bleeding, obvious cervical growth, irregular surface or bleeds on touch
WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions (2019)[3]	Either thermal ablation or cryotherapy to women screened positive with hrHPV or VIA OR hrHPV followed by VIA and who are eligible for ablative treatment OR LLETZ when the woman is not eligible for cryotherapy or thermal ablation *(Conditional recommendation; very low certainty in evidence of effects)*

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4.3.2 CQ6: Ablation versus excision in women with abnormal screening after previous treatment (persistent lesions)

RECOMMENDATION

Among women with persistent acetowhite lesions or a positive hrHPV DNA test 12 months after treatment with ablation, we suggest excision (LEEP/LLETZ) over ablation (cryotherapy or thermal ablation).
(weak recommendation, low certainty evidence)

In settings where LEEP/LLETZ is unavailable or inaccessible, repeat ablation rather than no treatment should be done for women who test positive after prior ablation.
(strong recommendation, low certainty evidence)

Considerations

The panel considered several factors:

- Cure rates of various treatment modalities for patients with persistent abnormal screening tests after prior ablation
- Accessibility of treatment modalities

Remarks

- The panel underscores that due to the lack of evidence, the WHO recommendations, where loop electrosurgical excision procedure (LEEP)/large loop excision of the transformation zone (LLETZ) is preferred over thermal ablation or cryotherapy to treat women who test positive after prior ablative therapy, may be applied to the local setting.
- The 74% to 85% cure rates reported with ablative therapies to treat women with persistent abnormal screening were acceptable compared with no treatment in women with no access to excision procedures.

4.3.2.1 Burden of disease

Screening for cervical cancer followed by treatment (or the screen-and-treat approach) in primary care settings has been endorsed by WHO as one of the most cost-effective strategies for cancer prevention.[1] An ablative procedure, usually cryotherapy, is done as part of the screen-and-treat approach. Cryotherapy is considered the most suitable option because of its low cost, the lack of requirement for anesthesia or electricity, and its low complication rate. Aside from cryotherapy, other treatment modalities are available, such as thermal ablation and excision procedures (e.g., LEEP or LLETZ).

Persistence or recurrence of cervical lesions after initial treatment has been described in 1% to 20% of cases.[2] Hence, there is a need to determine the most appropriate treatment modality (ablation or excision) for persistent acetowhite lesions or positive hrHPV DNA test after a woman has undergone an ablative procedure.

4.3.2.2 Benefits and harms

There were no studies identified that directly compared the outcomes of ablative (thermal ablation or cryotherapy) or excision (LLETZ/LEEP) procedure for the treatment of persistent acetowhite lesions or a positive hrHPV DNA test after an initial ablative procedure.

A few studies reported outcomes in women with histologically confirmed CIN 2+ who tested positive after 4 months to 2 years.[3] The study found that when treated with thermal ablation, 85% (95% CI 74–96%) were cured. Furthermore, about 74% of women previously treated with cryotherapy who were retreated with cryotherapy were cured. The cure rate after conization was 92%.

No studies measured safety/adverse events when retreating with ablation versus excision procedures.

4.3.2.3 Cost implications

No economic evaluation studies were found in the literature. Cost comparison was mentioned in a study from Nigeria.[2] The mean cost of treatment with thermal ablation was ~PHP 63.08±5.35, which is about a fourth of the mean cost of treatment with cryotherapy (PHP 309.16±30.16).

In contrast, LEEP/LLETZ can cost from PHP 15,000 to PHP 90,000 in the Philippines (inclusive of professional fees of the operator).

4.3.2.4 Ethical, social and health systems impact (equity, acceptability and feasibility)

There were no studies found that evaluated equity, acceptability and feasibility of treatment strategies for patients with persistent abnormal screening after a previous treatment.

The panel recognized that ablative treatments such as thermal ablation and cryotherapy are more readily available than excision procedures. The latter procedures are mostly available in larger medical centers and are not easily accessible to women who live in remote areas with limited mobility. In contrast, ablative treatments such as cryotherapy or thermal ablation are easy to transport.

4.3.2.5 Recommendations from other groups

Table 13. Recommendations from other groups regarding Clinical Question 6

Group/Agency	Recommendations
WHO (2019)[4]	LLETZ – rather than thermal ablation or cryotherapy – was the recommended treatment for women who test positive after prior thermal ablation or cryotherapy (conditional recommendation, very low certainty in evidence of effects). Thermal ablation or cryotherapy was recommended only when LLETZ was unavailable or inaccessible. The evidence was uncertain about the effects of retreatment with thermal ablation, cryotherapy or excision in women who test positive after previous treatment with ablative procedure.

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4. WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions. Geneva: World Health Organization; 2019.

4.3.3 CQ7: Ablation versus excision in women with large acetowhite lesions

RECOMMENDATION

Among premenopausal women with large acetowhite lesions, we suggest performing or referring for excisional therapy.
(weak recommendation, low certainty evidence)

In settings where excisional procedures or referral for additional treatment are not available, we suggest that women with large acetowhite lesions be treated with ablation.
(weak recommendation, low certainty evidence)

Considerations

The panel considered several factors:

- The effectiveness and drawbacks of ablation versus excision in women with large acetowhite lesions.
- The cost of treatments
- The availability of resources in marginalized settings

Remarks

- There are no studies that directly compared outcomes for large acetowhite lesions managed by ablation versus excision. There is some indirect evidence that for large acetowhite lesions and those with endocervical extension, recurrence rates after cryotherapy are higher.
- There is evidence that cervical ablation decreases the risk of cervical cancer compared with no treatment.
- There is no difference in the severity of pain, perioperative blood loss and hemorrhage rates between ablation and excision. The risk of infection after 24 hours is slightly higher with ablation and the risk of preterm birth is higher with LLETZ compared with ablative procedures.
- The management of patients with large acetowhite lesions does not only entail excisional therapy but also more frequent follow-up visits and examinations.

4.3.3.1 Burden of disease

The screen-and-treat protocol is preferred in resource-limited settings, where economic and infrastructure limitations limit the application of standard screening strategies. In this approach, only a single visit is required.[1] WHO recommends ablative therapy (either thermal ablation or cryotherapy) in women with no suspicion of invasive and glandular disease and those with lesions that are fully visible and do not extend into the endocervix.[2,3] The recommendation for lesions that cover more than 75% of the ectocervix or extend into the endocervical canal is referral for excision.

Hence, there is a need to confirm whether or not ablative therapy may be performed on large acetowhite lesions (on VIA) that cover more than 75% of the ectocervix and/or encroach into the endocervical canal.

4.3.3.2 Benefits and harms

There were no studies identified that directly compared the use of ablative therapy with excisional procedures to treat large acetowhite lesions that cover more than 75% of the ectocervix or extend into the cervical canal. The presence of large aceto-whitening and lesions with endocervical extension are excluded in most trials of ablative therapy and these patients are referred for excisional procedures, in line with WHO recommendations, supposedly for an increased risk of treatment failure or recurrence in large lesions.

Recurrence rates in large lesions treated with ablation

Indirect evidence on the recurrence and persistence rate with cryotherapy or thermal ablation has been reported. Based on 23 observational studies, large lesions are associated with recurrence rates of 180 per 1,000 (95% CI 130–230)[4-8], whereas small lesions had recurrence rates of 60 per 1,000 (95% CI 50–70)[4,6,8-12], and for medium lesions, 70 per 1,000 (95% CI 60–80).[5,8,11-14]

Based on 42 observational studies, recurrence rates are higher in women with endocervical extension. According to a pooled analysis by EREs, the recurrence rate for those with positive endocervical extension is 16% (95% CI 13–20%)[5,8,15-22], compared with only 6% (95% CI 5–6%) for those with no endocervical extension.[4,5,8,10-17,20,21,23-42]

In an RCT that included 390 women with CIN who underwent cryotherapy, laser vaporization and LEEP, lesion size of greater that two thirds of the cervix was associated with an adjusted RR of persistence of 18.9 (95% CI 3.23–110.6) compared with the reference lesion that only covered less than a third of the cervix.[35]

Based on these studies, the recurrence rate and persistence rate are higher in patients with large lesions and those with endocervical extension treated with ablative therapy.

Ablation versus no therapy

The panel also examined evidence on patients treated with ablation compared with no therapy. Based on retrieved evidence, the recurrence rate of CIN 1–3 was 6% after ablative treatment and the absolute risk reduction (ARR) for cervical cancer after cryotherapy was calculated as 18% over 30 years for a baseline risk of 1%.

The ARR was calculated by the EREs as follows: It was assumed from observational studies with no independent control that the RR reduction (RRR) with cryotherapy was 86%, but with a spontaneous regression of 28%. This indicates a 61% RRR with cryotherapy [86% - (28% × 86%)]. Using 1% baseline risk without cryotherapy, the ARR with cryotherapy is 0.61% over 1 year or 18% over 30 years.[2]

Progression to cervical cancer

In a large cohort study of 37,142 women treated for CIN 1–3 using cryotherapy, LEEP/LLETZ, laser ablation or cold knife conization, cryotherapy was associated with the highest rate of progression within 10 years, with an adjusted odds ratio (OR) of 2.98 (95% CI 2.09–4.60) for invasive cervical cancer.[34]

Safety outcomes

Four clinical trials (three RCTs and one quasi-RCT) that provided a head-to-head comparison between ablation and excision showed no statistical difference between cryotherapy and LEEP/LLETZ for the severity of pain, perioperative blood loss and secondary hemorrhage.[43]

A systematic review of RCTs on women with CIN treated with cryotherapy, cold knife or thermocoagulation compared with LEEP/LLETZ showed that there was no difference in minor bleeding during the first 24 hours, pain after 24 hours posttreatment and cervical stenosis. There was increased infection after 24 hours with cryotherapy.[44]

A recent network meta-analysis that included 29 studies (including 2 randomized trials) with 68,817 participants compared the rates of preterm birth after excision and ablation. LEEP/LLETZ increased the rate of preterm birth with an RR of 1.37 (95% CI 1.16–1.62) while no differences were found for ablative methods. The evidence was based on mostly observation studies and had a high risk of bias.[45]

The most common side effects associated with excision included: intraoperative bleeding and delayed hemorrhage (usually 1 to 2 weeks postoperatively). Ablation was associated with posttreatment bleeding and infection and prolonged watery vaginal discharge.

4.3.3.3 Cost implications

There were no published local studies identified on the cost-effectiveness of ablative and excisional procedures. A 2018 cost-effectiveness analysis that compared cryotherapy with LEEP/LLETZ in South Africa found that on average, cryotherapy was less costly per patient at USD 118.00 (uncertainty interval [UI] 113.91–122.10), and per case "cured" at USD 140.90 (UI 136.01–145.79). LEEP/LLETZ costs USD 162.56 (UI 157.90–167.22) per patient and USD 205.59 (UI 199.70–211.49) per case cured.[46]

4.3.3.4 Ethical, social and health systems impact (equity, acceptability and feasibility)

According to the results of two RCTs that compared excision with ablation, both procedures were acceptable to patients. In Chirenje et al (2001), 400 women were randomized to either cryotherapy or LEEP/LLETZ. Participants from both treatment groups reported that they found the treatment modalities highly acceptable (cryotherapy, 91.2%; LEEP, 95.7%).[47] In Gunasekera et al (1990), LEEP/LLETZ was significantly more acceptable to patients compared with laser ablation. Laser ablation is not being used currently in the Philippines.[48]

Because thermal ablation is a relatively recent technology, studies on patient preference are mostly observational or single-arm studies. Three observational studies with 678 participants investigated patient acceptability with thermal ablation by asking about patient satisfaction and willingness to recommend treatment to others. Based on data, there was a 99% satisfaction rate and 100% willingness to recommend treatment to others.[49-51]

In low-resource settings, accessibility of equipment and supplies, ease of training and necessary provider skills are all important considerations. Currently, cryotherapy is standard practice for treating patients with cervical precancer in the screen-and-treat programs. Compared with excision methods such as LEEP/LLETZ, cryotherapy with its relative simplicity makes it possible to train mid-level providers to perform the procedure.

In remote areas in the Philippines where access to an experienced LEEP/LLETZ provider may be difficult and patients may be lost to follow-up, the accessibility of ablative therapy may provide a therapeutic option to improve outcomes compared with no treatment.

4.3.3.5 Recommendations from other groups

Table 14. Recommendations from other groups regarding Clinical Question 7

Group/Agency	Recommendations
WHO guidelines: Use of cryotherapy for cervical intraepithelial neoplasia (2011)[2]	In settings where LEEP is available and accessible, treatment with LEEP over cryotherapy is suggested Cryotherapy over no treatment is recommended Among women with CIN lesions covering more than 75% of the ectocervix, or with lesions extending beyond the cryo tip being used, performing or referring for excisional therapy is suggested In settings where LEEP is available and accessible, and women present with CIN lesions extending into the cervical canal, treatment with LEEP over cryotherapy is suggested In settings where excisional procedures (e.g., LEEP, laser or cold knife cone) or referral to additional treatment are not available, it was suggested that women with lesions extending into the endocervical canal be treated with cryotherapy
WHO guidelines for the use of thermal ablation for cervical precancer lesions (2019)[3]	Suggested providing either thermal ablation or cryotherapy to women screened positive with hrHPV or VIA; or hrHPV followed by VIA and who are eligible for ablative treatment, or providing LLETZ when the woman is not eligible for cryotherapy or thermal ablation Women who screen positive, but there is no suspicion of invasive or glandular disease (i.e., adenocarcinoma or adenocarcinoma in situ) are eligible for ablative therapy if: • the transformation zone (TZ) is fully visible, the whole lesion is visible and it does not extend into the endocervix, OR • the lesion is type 1 TZ (completely ectocervical and is therefore fully visible) OR • the lesion is type 2 TZ where the probe tip will achieve complete ablation of the SCJ epithelium Suggested either LLETZ, or cryotherapy or thermal ablation to treat all women who have histologically confirmed CIN 2+ disease and who are eligible for thermal ablation or cryotherapy *(The choice of LLETZ, or cryotherapy or thermal ablation depends on the expertise, training, equipment and consumables available, infrastructure and resources in a program)*

In exceptional conditions when LLETZ is not available for women who have histologically confirmed CIN 2+ disease and are not eligible for cryotherapy or thermal ablation, an alternative treatment was recommended; the choice of alternative treatment will be dependent on the skills and resources available and referral to a higher level of care where a cone biopsy, trachelectomy or hysterectomy can be performed

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5. Research Implications/Gaps

As mentioned, the literature review identified several gaps in literature regarding the screening and treatment approach for cervical cancer prevention, which may be opportunities for future research. These could include well-designed studies on the long-term impact on clinical outcomes of self-collected versus clinician-collected sampling and early screening on women living with HIV. The long-term efficacy and harms of ablation directly compared with excision in patients with persistent lesions and large lesions could also be further investigated. Finally, the cost-effectiveness and the values of patients with regard to these interventions are also subjects for further research.

6. Dissemination and Implementation

A full copy of this document will be sent to the DOH for transmittal and publication. The Disease Prevention and Control Bureau will transmit copies of this CPG to the PHIC, HMOs and NGOs involved in cervical cancer prevention and management. The recommendations and the evidence summaries will be posted in the DOH website.

All strong recommendations in this guideline can be used for monitoring and auditing practices in institutions. These could be converted to key performance indicators and be used in creating clinical pathways.

7. Applicability Issues

The Task Force accentuates some caveats of this CPG using equity and applicability lenses. Evaluating risk factors for a disease and the probability of developing diseases, history of serious adverse events towards vaccines and financial accessibility are essential factors when considering vaccination. This CPG does not necessarily supersede the consumers' (i.e., health professionals, hospital administrators, employers, payors and patients) values, settings and circumstances.

Although this CPG intends to influence the direction of health policies for the general population, it should not be the sole basis for recreating or abolishing practices that aim to improve the health conditions of many Filipinos, particularly those part of the workforce.

8. Updating of the Guidelines

The recommendations herein shall hold until such time that new evidence on screening, diagnosing or managing various risk factors and diseases emerges and contingencies dictate updating this CPG. The CPG will be updated every 3 to 5 years or earlier if new significant evidence becomes available.

9. Appendices

APPENDIX A

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APPENDIX B

Declaration of conflicts of interest

Name	COI based on Oversight Committee	Remarks
Steering Committee		
Dr. Lilli May T. Cole	No constraints	
Dr. Cecilia L. Llave	No constraints	
Dr. Enriquito Lu	No constraints	
Voting consensus panel members		
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Dr. Sybil Bravo (PIDSOG)	No constraints	
Dr. Catherine Teh (PCS CanCom)	Manageable with minor constraint	Been a member of a private organization or advocacy group with an interest in the subject of this CPG
Dr. Gonzalo Banuelos (PSO)		
Ms. Carmen Auste (Patient Advocate)	Manageable with minor constraint	Been involved in a project or program with an interest in the subject of the CPG topic
Dr. Joseph Tiu (PSHPM)	No constraints	
Ms. Rowena Yumang (IMAP)	No constraints	
Ms. Edilaida Garcia (PONA)	No constraints	
Dr. Maria Minerva Calimag (PMA)	No constraints	
Dr. Melody Tolentino (PIDSP)	No constraints	
Dr. James de la Cruz (PSPHP)	No constraints	
Ms. Elena Felix (APWAI)	No constraints	
Non-voting consensus panel members		
Dr. Jan Aura Laurelle Llevado (DOH)	Major restriction – disallow voting	Representative of DOH
Dr. Vincent Sumergido (DOH)	Major restriction – disallow voting	Representative of DOH
Dr. Julieta Germar (SGOP)	Major restriction – disallow voting	Principal author or co-author of a published paper related to the CPG Topic; Editor-in-chief POGS Consensus Bulletin; been involved in cervical cancer screening workshops; had an official function as technical adviser Cervical Cancer Z Package; member of SGOP PSCPC; made public statements, given lectures, appeared in ads, or provided expert

		testimony on issues related to the subject of the CPG.
Dr. Carolyn Zalameda-Castro (PSCPC)	Major restriction – disallow voting	Received benefits or kind from educational activities for an entity with a financial or commercial interest that may be affected by the CPG, and is has editorial position in a journal, book or manuscript related to the CPG topic and had been involved in a project or program with an interest in the subject of the CPG. Incoming president of a private organization or advocacy group with an interest in the subject of this CPG.
Dr Christia Padolina (AOFOG)	Major restriction – disallow voting	Declared to have been involved in any project or program with an interest in the subject of the CPG topic and have been/is a member of a private organization or advocacy group with an interest in the subject of this CPG, and has a spouse/partner, sibling or offspring that have been involved in such projects or programs. Hence, participation is allowed with major restriction, i.e., will not be allowed to vote.
Dr. John Paolo Vergara (PSMO)	Major restriction – disallow voting	Part of the Speakers Bureau of Astra Zeneca since 2020, which involves speakership in round table discussion for breast cancer products and lung cancer products (fulvestrant, olaparib, osimertinib), as well as making slide decks for use by the company's commercial unit for client presentation. Current Chair of the CPG (ad hoc) of the PSMO
Technical working group and adviser		
Dr. Jericho Thaddeus Luna	No constraints	
Dr. Aretha Ann G. Liwag	No constraints	
Dr. Gia Anna Bervano	No constraints	
Dr. Carmela Augusta F. Dayrit-Castro	No constraints	
Dr. Patricia Ann Factor	No constraints	
Dr. Mariel Nevado-Gammad	No constraints	Has made prior public statements about the latest cervical cancer guidelines of WHO. A critical appraisal of one journal article used in the recommendation.
Dr. Patricia Orduña	No constraints	
Dr. Andrea Santiago	No constraints	

Dr. Alice Sun-Cua	No constraints	
Mr. Regin George Miguel Kua	No constraints	
Dr. Joan Kristel B. Abrenica	No constraints	
Dr. Ivan Noel Olegario	No constraints	
Dr. Anna de Guzman	No constraints	
Oversight Committee Members		
Dr. Rey H. delos Reyes	Manageable with minor constraint	Authorship of a published paper related to the CPG topic.
Dr. Arnold P. Liwag	Manageable with minor constraint	Implementor of the SUCCESS Program of the DOH; member of SGOP; made public statements, given lectures, appeared in ads, or provided expert testimony on issues related to the subject of the CPG (scientific symposium and lectures in colleges of medicine regarding cervical cancer).

APPENDIX C

One-dose vs two-dose vaccination among young women

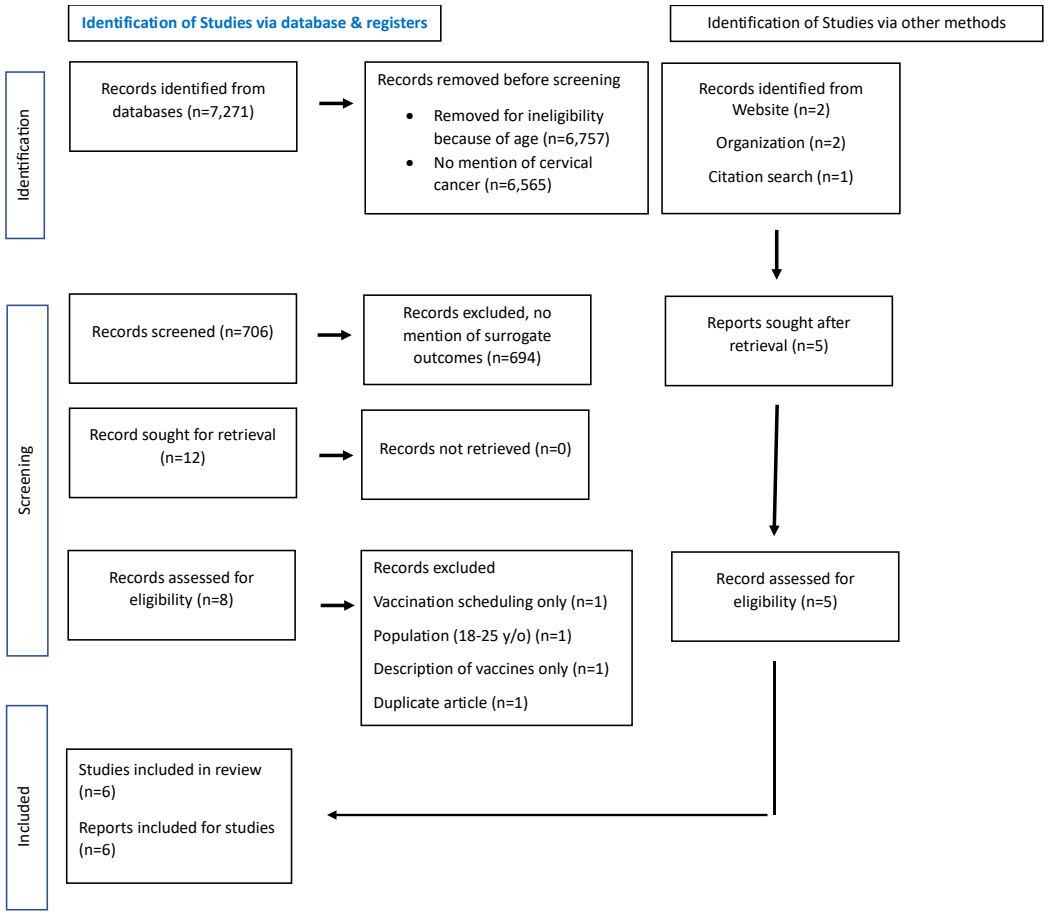
Author(s): Alice Sun-Cua, MD, MSc; Aretha Gacutan-Liwag, MD, MSc ;

Question: 1-dose compared to 2-doses HPV vaccination among young females to prevent cervical cancer

Setting: Outpatient, community, in low and middle income countries

SEARCH STRATEGY:
A systematic search was done from the date of last search December 1, 2022 until March 7, 2023 using PubMed and Cochrane Library, Google Scholar with a combined MeSH and free text search using the terms: One dose HPV Vaccine OR Two dose HPV Vaccine OR Three dose HPV Vaccine. Filters applied were: Abstract, Free full text, Clinical trial, Meta-analysis, Randomized Controlled Trial, Systematic Review and 5 years (2018 to 2022). 7,271 articles were obtained. After excluding articles for ineligibility because the population's ages were not applicable to our Research Question, and with no mention of cervical cancer, only 706 articles remained. Again, records were excluded because there was no mention of surrogate outcomes for cervical cancer. Records sought for retrieval were 12. Four were excluded because the articles were about vaccination schedules only (n=1), the population was not for our study (n=1), the article only described the vaccines (n=1), and a duplicate article (n=1). Eight were assessed for eligibility and were reviewed. A total of six (6) studies were included in the analysis.
Also reviewed were Clinical Practice Guidelines from the Periodic Health Examination of the (PHEX) Department of Health (DoH) Vaccination Guidelines, American College of Gynecologist (ACOG), European Society of Medical Oncologists (ESMO), the Center for Disease Control and Prevention (CDC) on HPV Vaccination[16] and the Cochrane Summary Response

PRISMA Flow Diagram


Identification of Studies via database & registers
Identification of Studies via other methods
Identification
Records identified from databases (n=7,271)
Records removed before screening
Removed for ineligibility because of age (n=6,757)
No mention of cervical cancer (n=6,565)
Records identified from Website (n=2)
Organization (n=2)
Citation search (n=1)
Screening
Records screened (n=706)
Records excluded, no mention of surrogate outcomes (n=694)
Reports sought after retrieval (n=5)
Record sought for retrieval (n=12)
Records not retrieved (n=0)
Records assessed for eligibility (n=8)
Records excluded
Vaccination scheduling only (n=1)
Population (18-25 y/o) (n=1)
Description of vaccines only (n=1)
Duplicate article (n=1)
Record assessed for eligibility (n=5)
Included
Studies included in review (n=6)
Reports included for studies (n=6)

Characteristics of included studies

Title/Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two of three doses in Tanzanian girls (DoRIS) Watson-Jones D, et al	Randomized, open-label, non-inferiority trial.	Tanzania	922 females 9- 14 years old	Tanzanian women	Six sets of treatment groups: -One dose of bivalent HPV vacc. - Two doses of bivalent HPV vacc. -Three doses of bivalent HPV vacc.	One dose of nonavalent HPV vacc. -Two doses of nonavalent HPV vacc. -Three doses of nonavalent HPV vacc.	HPV 16 & HPV 18 IgG antibodies for seropositivity
Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. Basu, P, et al	RCT, post hoc analysis	India	17,729 Unmarried females 10-18 years old	Indian females	4348 participants were included in the three-dose cohort, 4980 in the two-dose cohort, 3452 in the two-dose default cohort, 4949 in the single-dose default cohort,	Unvaccinated women matched by age and site of recruitment 5,172 unvaccinated cohort	Persistent oncogenic HPV infection
Immunogenicity and HPV infection after one, two and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study Sangkaranarayanan, R (2016)	Multi center, cluster-Randomized trial, to 3 versus 2- dose HPV vaccine, Cohort for (post hoc)	India	4348 participants were included in the three-dose cohort, 4980 in the two-dose cohort, 3452 in the two-dose default cohort,	Unmarried girls ages 10-18	2 doses (by default and 2 doses cohort) 1 dose by default	3 doses	Immune response antibody titers (GMT at 7,18,36,48 months Persistent oncogenic HPV infection Detection of CIN2+ (annually, baseline

			4950 in the single-dose default cohort				until 4 years)
Durable Antibody Responses Following One Dose of the Bivalent Human Papillomavirus L1 Virus-like Particle Vaccine in the Costa Rica Vaccine Trial (CVT) Safaeian (2013)	Community based, randomized phase III CVT 2004-2005 Post-hoc analysis 4 years	Costa Rica Total population 2 doses = 422/928 1 dose – 196/549	Included data from women with serum available for all visits One dose = 78 Two doses (142+52)	Females 18-25	3 doses HPV vaccination	Hepatitis vaccination	Immune response, Persistent oncogenic HPV infection Detection of CIN2+
Durability of Protection Afforded by Fewer Doses of the HPV16/18 Vaccine: The CVT Trial Safaeian 2018	Cohort For 7 years						Immune response, Persistent oncogenic HPV infection Detection of CIN2+
Evaluation of durability of a single dose of the bivalent HPV Vaccine: The CVT Trial (post hoc analysis) Kreimer A., et al	Community-based, randomized phase III Clinical Trial 4 years, cohort for 11 years	Costa Rica		Females 18-25 years old	1,2,3 doses of HPV vaccines		Incident HPV 16/18 infections Persistent HPV 16/18 infections Vaccine efficacy (seropositivity)

GRADE EVIDENCE PROFILE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1-dose HPV vaccine	2-doses HPV Vaccine	Relative (95% CI)	Absolute (95% CI)		
HPV 16 antibody titers 2-4 years after vaccination (follow-up: range 2 years to 4 years; assessed with: GMC)												

3	randomised trials	serious 1,2, a,b	not serious	not serious	not serious		881	612	-	MD 112.34 lower (123.78 lower to 100.89 lower)	⨁⨁⨁◯-	

HPV 18 Antibody titers 2-4 years after vaccination (follow-up: range 2 years to 4 years; assessed with: GMC)

3	randomised trials	serious[a,b]	not serious	not serious	not serious		606	865	-	MD **32.37 lower** (36.4 lower to 28.35 lower)	⨁◯-	

Seropositivity HPV 16 (follow-up: range 2 years to 4 years)

3	randomised trials	serious[a,b]	not serious	not serious	not serious		641/847 (75.7%)	682/648 (105.2%)	**OR 0.15** (0.08 to 0.29)	**445 more per 1,000** (from 155 more to 1,000 more)	-	

Incident HPV 16/18 infection after 2-4 years (follow-up: range 2 years to 4 years)

2	randomised trials	serious[a,b]	not serious	not serious	not serious		4/722 (0.6%)	13/1292 (1.0%)	**RR 0.59** (0.20 to 1.76)	**4 fewer per 1,000** (from 8 fewer to 8 more)	-	

Seropositivity HPV 18 (follow-up: range 2 years to 4 years)

3	randomised trials	serious[a,b]	not serious[a,b]	not serious	not serious		641/847 (75.7%)	682/648 (105.2%)	**RR 0.59** (0.30 to 1.18)	**432 fewer per 1,000** (from 737 fewer to 189 more)	-	

Explanations

a. Attrition rate per group is more than 20%

b. The study started as an RCT comparing 1-, 2-, and 3-bivalent HPV doses against no vaccination, converted to a cohort study with default 1-dose group

OUTCOMES 10 years after vaccination
Incident infection HPV 16/18 (follow-up: range 9 years to 11; assessed with: DNA testing)

2	observational studies	serious[a]	not serious	not serious[b]	not serious	none	94/2920 (3.2%)	60/2278 (2.6%)	**OR 1.21** (0.87 to 1.09)	**5 more per 1,000** (from 3 fewer to 2 more)	⊕◯◯◯ Very low
Persistent infection (follow-up: 10 years; assessed with: HPV DNA test or cytology)											
2	observational studies	serious[a]	not serious	not serious	not serious[a,c]	none	3/2197 (0.1%)	2/1564 (0.1%)	**OR 1.78** (0.29 to 11.01)	**1 more per 1,000** (from 1 fewer to 13 more)	⊕◯◯◯ Very low
HPV 16 antibody after 10 years (follow-up: range 9 years to 10 years; assessed with: GMC)											
2	observational studies	serious[1,2,a,d]	not serious	not serious	not serious		881	612	-	mean **112.34 lower** (123.78 lower to 100.89 lower)	-	
HPV 18 antibody titers atfter 10 years (follow-up: mean 10 years; assessed with: GMC)											
2	observational studies	serious[3,4,a]	not serious	not serious	not serious		390	572	-	mean **32.37 lower** (36.4 lower to 28.35 lower)	-	
CIN3 (follow-up: mean 10 years; assessed with: Cytology/ biopsy)											
2	observational studies	serious[a,d]	not serious	not serious	not serious		1/2920 (0.0%)	0/2254 (0.0%)	**RR 2.25** (0.09 to 55.24)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	-	

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Attrition rate per group is more than 20%

b. The clinical question involves adolescents (9-14 years old) , however, this study recruited women 18-25 years of age.

c. There was uneven number of participants per group.

d. The study started as an RCT comparing 1-, 2-, and 3-bivalent HPV doses against no vaccination, converted to a cohort study with default 1-dose group

APPENDIX D

Self-collected vs provider-collected HPV DNA testing

Author(s): Dr. Patricia Orduña, Dr. Gia Anna Bervano

Question: Among women undergoing HPV DNA testing, is self-collected HPV DNA test an alternative to provider-collected for cervical cancer screening?

Setting: Outpatient, community, in low and middle income countries

Search Strategy

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE OF LAST SEARCH	RESULTS	
			Yield	Eligible
Pubmed	[HPV OR HPV DNA OR human papilloma virus OR cervical cancer OR cervical neoplasm OR cervical intraepithelial neoplasia OR CIN OR HSIL OR high grade squamous intraepithelial lesion] AND [screening OR cancer screening OR cervical cancer screening OR high-risk HPV] AND [self-collection OR self-testing OR home testing OR self-collection kit] AND [clinician OR gynecologist OR healthcare provider OR doctor OR clinician-collected OR provider-collected OR clinic testing] AND [accuracy OR sensitivity OR specificity] AND preference AND acceptability Filters: RCT, systematic review and meta-analysis	6 May 2023	76	2 SRMA
Cochrane Reviews	[HPV OR HPV DNA OR human papilloma virus OR cervical cancer OR cervical neoplasm OR cervical intraepithelial neoplasia OR CIN OR HSIL OR high grade squamous intraepithelial lesion] AND [screening OR cancer screening OR cervical cancer screening OR high-risk HPV] AND [self-collection OR self-testing OR home testing OR self-collection kit] AND [clinician OR gynecologist OR healthcare provider OR doctor OR clinician-collected OR provider-collected OR clinic testing] AND [accuracy OR sensitivity OR specificity] AND preference AND acceptability	6 May 2023	0	0
Google Scholar	HPV OR CIN OR HSIL OR cervical cancer AND screening AND self-collection AND clinician OR gynecologist OR healthcare provider OR doctor-collected	6 May 2023	1030	3 SRMA
Clinicaltrials.gov	HPV OR CIN OR HSIL OR cervical cancer AND screening AND self-collection AND clinician OR gynecologist OR healthcare provider OR doctor-collected	6 May 2023	2	2

Medxriv.com	HPV OR CIN OR HSIL OR cervical cancer AND screening AND self-collection AND clinician OR gynecologist OR healthcare provider OR doctor-collected	6 May 2023	25	0

Characteristics of Included Systematic Reviews

Title/Author	Study design	Population Characteristics	Outcomes
Arbyn et al. 2014 Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: A meta-analysis	34 studies Between Jan 1, 1990, and June 3, 2013 N in total = 154,556	Age: 15 to 85 years old Primary screening, high-risk and follow-up screening included Index test 1: Self-collected HPV DNA sample Index test 2: Clinician-collected HPV DNA sample Reference test: Colposcopy and biopsy Subgroups By device type: Brush, swab, tampon	Sensitivity Specificity
Di Gennaro et al. 2022 Does self-sampling for human papilloma virus testing have the potential to increase cervical cancer screening? An updated meta-analysis of observational studies and randomized clinical trials	154 studies Until May 2022 N in total = 482,271	Age: 18 to 70 years old Self-sampling and clinician-sampling Subgroups By device type: Brush, swab, tampon	CCS uptake Secondary outcomes: Acceptability Preference

Study Appraisal

AMSTAR 2

Items	Arbyn 2014	Gennaro 2022
1. Did the research question and inclusion criteria for this review include the components of PICO?	Yes	Yes
2. Did the report contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No

11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of ROB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes
13. Did the review authors account for ROB in primary studies when interpreting or discussing the results of the review?	Yes	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of any heterogeneity observed in the results of the review?	Yes	Yes
15. If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received?	Yes	Yes
Overall assessment	High	High

GRADE Evidence Profile

Author(s):
Question: Self-collected sample compared to clinician-collected sample for screening high risk HPV infection in women
Setting: Ouptatient

Question: Should self-collected sample be used to screen for high risk HPV infection in women?

Sensitivity	0.76 (95% CI: 0.69 to 0.82)
Specificity	0.86 (95% CI: 0.83 to 0.89)

Prevalences	7.7%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 7.7%	
True positives (patients with high risk HPV infection)	12 studies 52890 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none	59 (53 to 63)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly								18 (14 to 24)	

classified as not having high risk HPV infection)									
True negatives (patients without high risk HPV infection)	12 studies 52890 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none	794 (766 to 821)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having high risk HPV infection)								129 (102 to 157)	

Explanations

a. Reporting and execution of tests unclear 3 studies; delay between self-sampling, clinician sampling, and verification with the reference standard was unreported in 2 studies; withdrawal of patients not adequately explained in 2 studies; In most studies, uninterpretable results were poorly reported

Question: Should clinician-collected sample be used to screen for high-risk HPV infection in women?

Sensitivity	0.91 (95% CI: 0.87 to 0.94)
Specificity	0.88 (95% CI: 0.85 to 0.91)

Prevalences	7.7%	0%	0%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of7.7%	pre-test probability of0%	pre-test probability of0%	
True positives (patients with high risk HPV infection)	12 studies 52890 patients	cross-sectional (cohort type accuracy study)	serious[a]	not serious	not serious	not serious	none	70 (67 to 72)	0 (0 to 0)	0 (0 to 0)	⨁⨁⨁◯ Moderate

False negatives (patients incorrectly classified as not having high risk HPV infection)								7 (5 to 10)	0 (0 to 0)	0 (0 to 0)	
True negatives (patients without high risk HPV infection)	12 studies 52890 patients	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	not serious	none	812 (785 to 840)	880 (850 to 910)	880 (850 to 910)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having high risk HPV infection)								111 (83 to 138)	120 (90 to 150)	120 (90 to 150)	

Explanations

a. Reporting and execution of tests unclear 3 studies; delay between self-sampling, clinician sampling, and verification with the reference standard was unreported in 2 studies; withdrawal of patients not adequately explained in 2 studies; In most studies, uninterpretable results were poorly reported

Certainty assessment							**№ of patients**		**Effect**		**Certainty**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**self-collected sample**	**clinician-collected sample**	**Relative (95% CI)**	**Absolute (95% CI)**		
Acceptability												
43	observational studies	not serious	not serious	not serious	not serious	none	95% acceptability for self-collection HPV DNA testing (95% CI 0.94 to 0.97)				⨁⨁◯◯ Low	CRITICAL
New outcome												
51	observational studies	not serious	not serious	not serious	not serious	none	66% prefer self-collection HPV DNA testing (95% CI 0.94 to 0.97)				⨁⨁◯◯ Low	CRITICAL

CI: confidence interval

Forest Plots and SROC Graph

Study	TP	FP	FN	TN	Type of device	Sensitivity (95% CI)	Specificity (95% CI)
Belinson 2001	71	269	15	1642	swab	0.83 [0.73, 0.90]	0.86 [0.84, 0.87]
Belinson 2012	58	548	23	3644	brush	0.72 [0.60, 0.81]	0.87 [0.86, 0.88]
Belinson 2012 (b)	74	509	7	3688	brush	0.91 [0.83, 0.96]	0.88 [0.87, 0.89]
Girianelli 2006	27	219	8	1521	brush	0.77 [0.60, 0.90]	0.87 [0.86, 0.89]
Guan 2013	7	8	2	45	brush	0.78 [0.40, 0.97]	0.85 [0.72, 0.93]
Holanda 2006	8	289	1	580	brush	0.89 [0.52, 1.00]	0.67 [0.64, 0.70]
Longatto 2012	100	1641	75	9835	tampon	0.57 [0.49, 0.65]	0.86 [0.85, 0.86]
Nieves 2013	10	143	6	1890	brush	0.63 [0.35, 0.85]	0.93 [0.92, 0.94]
Nieves 2013 (b)	10	193	6	1840	brush	0.63 [0.35, 0.85]	0.91 [0.89, 0.92]
Quiao 2008	57	408	13	1910	brush	0.81 [0.70, 0.90]	0.82 [0.81, 0.84]
Salmeron 2003	108	787	79	6758	swab	0.58 [0.50, 0.65]	0.90 [0.89, 0.90]
Szarewski 2007	17	160	4	739	swab	0.81 [0.58, 0.95]	0.82 [0.80, 0.85]
Wright 2000	63	217	33	1052	swab	0.66 [0.55, 0.75]	0.83 [0.81, 0.85]
Zhao 2012	437	2411	70	10086	brush	0.86 [0.83, 0.89]	0.81 [0.80, 0.81]

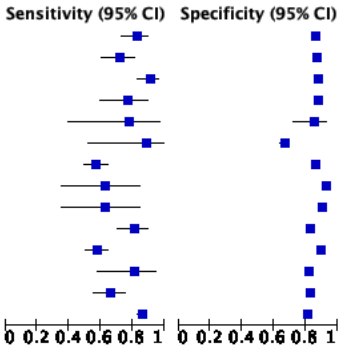


Figure 1. Sensitivity and specificity of self-collected HPV DNA sampling against reference standard

Study	TP	FP	FN	TN	Type of device	Sensitivity (95% CI)	Specificity (95% CI)
Belinson 2001	71	269	15	1642	swab	0.83 [0.73, 0.90]	0.86 [0.84, 0.87]
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Longatto 2012	100	1641	75	9835	tampon	0.57 [0.49, 0.65]	0.86 [0.85, 0.86]
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Nieves 2013 (b)	10	193	6	1840	brush	0.63 [0.35, 0.85]	0.91 [0.89, 0.92]
Quiao 2008	57	408	13	1910	brush	0.81 [0.70, 0.90]	0.82 [0.81, 0.84]
Salmeron 2003	108	787	79	6758	swab	0.58 [0.50, 0.65]	0.90 [0.89, 0.90]
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Zhao 2012	437	2411	70	10086	brush	0.86 [0.83, 0.89]	0.81 [0.80, 0.81]

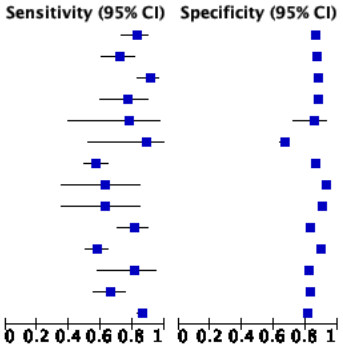


Figure 2. Sensitivity and specificity of clinician-collected HPV DNA sampling against reference standard

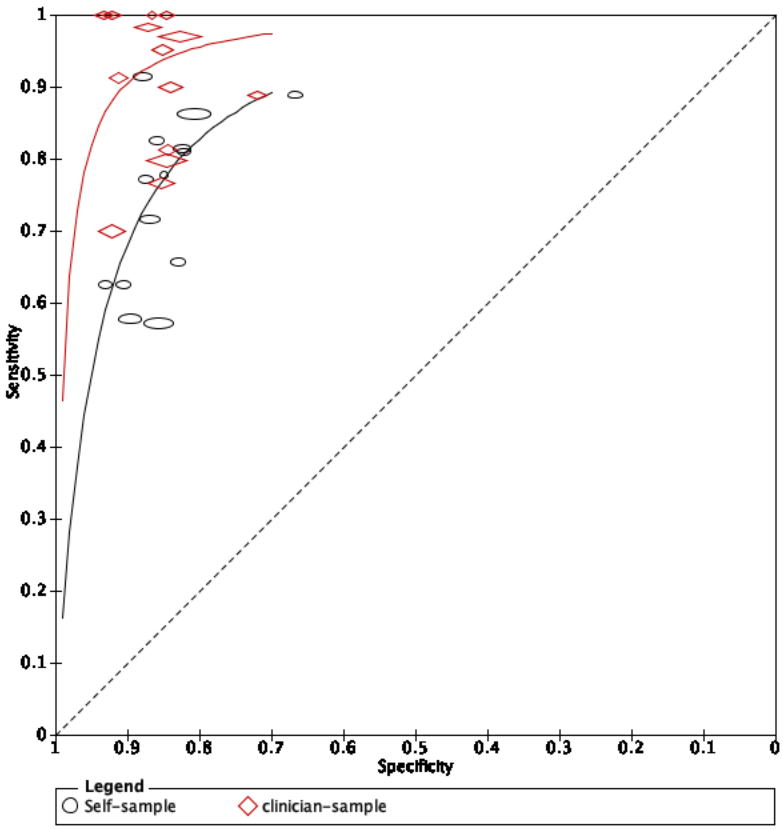


Figure 3. SROC plot of sensitivity and specificity of self-collected vs clinician-collected HPV DNA samples

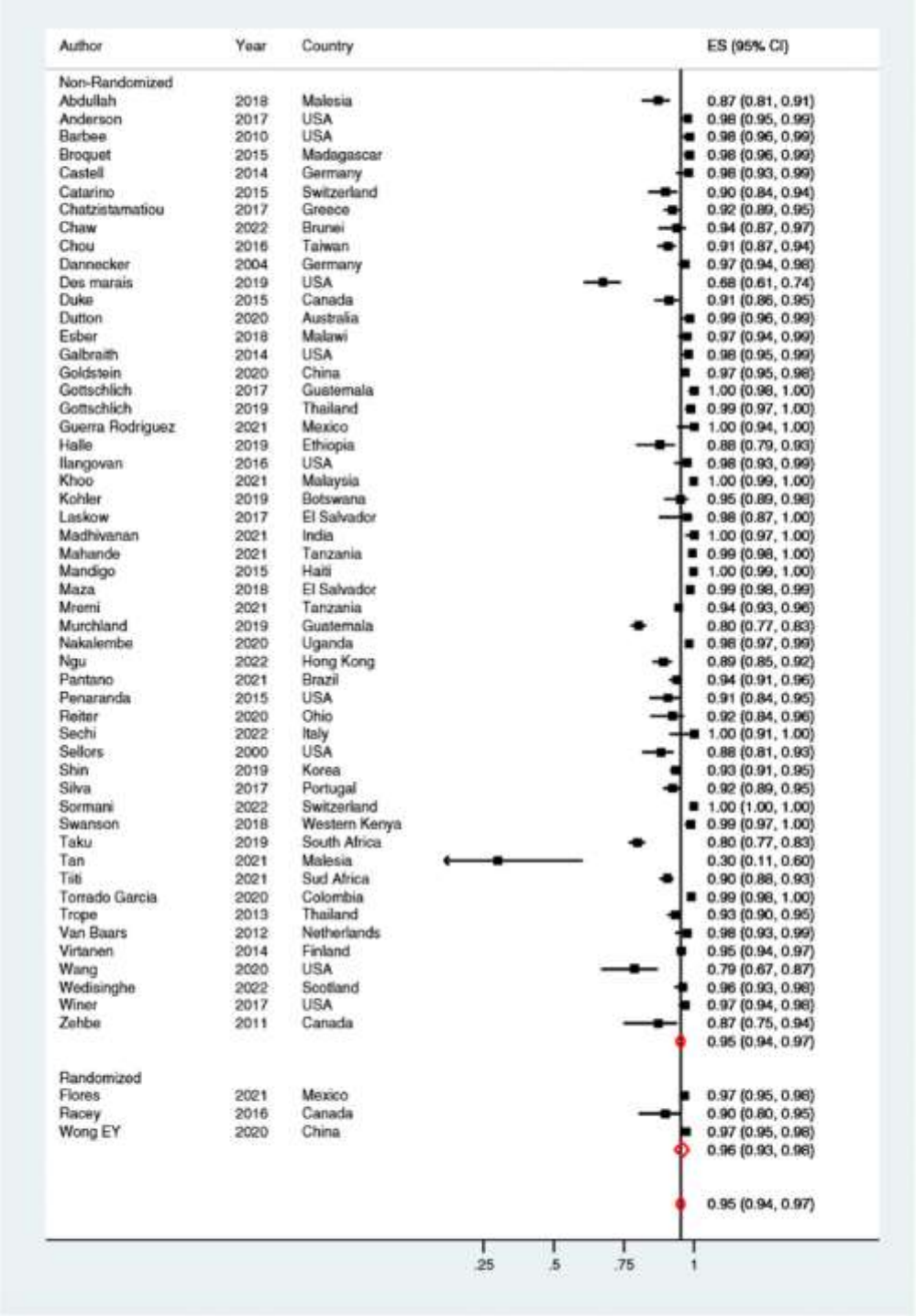


Figure 4. Pooled estimate for acceptability among women undergoing self-collected HPV DNA testing (adopted from Di Gennaro et al. 2022)

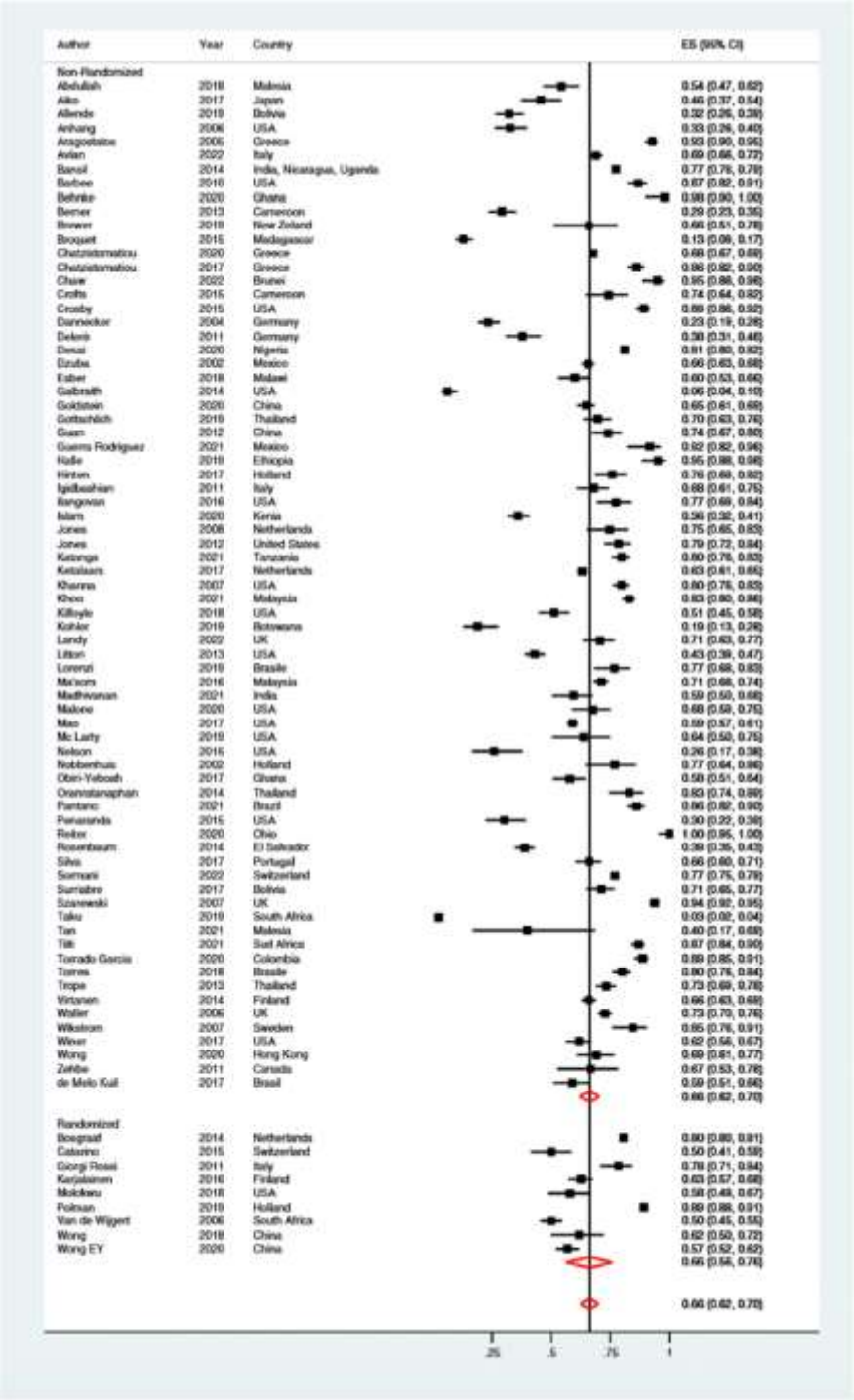


Figure 5. Pooled estimate for preference among women undergoing self-collected HPV DNA testing (adopted from Di Gennaro et al. 2022)

APPENDIX E

Screening of women living with HIV

Author(s): Dr. Mariel Nevado-Gammad; Dr. Andrea Santiago

Question: Among women undergoing HPV DNA testing, is self-collected HPV DNA test an alternative to provider-collected for cervical cancer screening?

Setting: Outpatient, community, in low and middle income countries

Characteristics of In Studies

Author, Year	Population Setting	Intervention Group(s)	Outcomes	Study Design	Comments
Pimple, 2022	>/= 21 India Tertiary Cancer Center May 2010-June 2015 291	VIA (+): well-defined dense acetowhite area abutting or touching the squamocolumnar junction in the transformation zone CIN 2/3 invasive cancer cytology HPV DNA	high-risk HPV infection CIN screening test positivity accuracy Sn, Sp, PPV, NPV CIN2+ prevalence: 8.6%	Retrospective cohort	age started screening: 21 Molecular high-risk HPV detection is much less dependent on the quality of the sample and on human judgement than are cytology and visual inspection With the gold standard of diagnostic colposcopy, with or without biopsy, our results indicate that VIA, HPV testing, and Pap cytology (LSIL+) have higher sensitivity in detecting high-grade CIN 2 and above lesions
Njue, 2022	18-46 Kenya January 2018-December 2019 N= 317 HIV(+) n= 161 HIV(-) n= 156	VIA Cytology HPV DNA	ASCUS LSIL HSIL invasive cancer cervicitis candidiasis	Comparative Cross-sectional study	Age was significantly associated with HIV status: more women aged below 35 years had a higher HIV infection rate than those aged over 35 years (p=0.016) A significantly higher HPV infection, positive VIA test, abnormal cytology, and histology rate were established among HIV-infected than non-infected women
Dartell, 2014	<25 to >60 Tanzania	VIA HPV	HPV types: normal,	Cross sectional	HSIL higher in HIV positive women

	February 2008-March 2009 N= 3603 (334 HIV positive) HIV(+) n= 334 HIV(-) n= 3005 not tested n= 264	cytology as gold standard	ASCUS, LSIL, HSIL		
Sahasrabuddhe, 2012	~30 India September 2006-February 2007 N=303	VIA Cytology	CIN 2+	cross-sectional	
Kuhn, 2010	35-65 yrs South Africa Health Clinics in Cape Town January 2000-December 2002 N=956	VIA HPV (screen and treat) control group	CIN 2+ at 36 mos Relative Risk: HPV DNA 0.2 (0.06-0.69) VIA 0.51 (0.29-0.89)	Randomized clinical trial	Screen-and-treat using HPV testing is a simple and effective method to reduce high-grade cervical cancer precursors

APPENDIX F

Appropriate screening for peri- and postmenopausal women aged 50 years old and above

Author(s): Dr. Gia Anna Bervano; Dr. Patricia Orduña

Question: Among peri- and postmenopausal women, what is the most effective screening tool for cervical cancer screening?

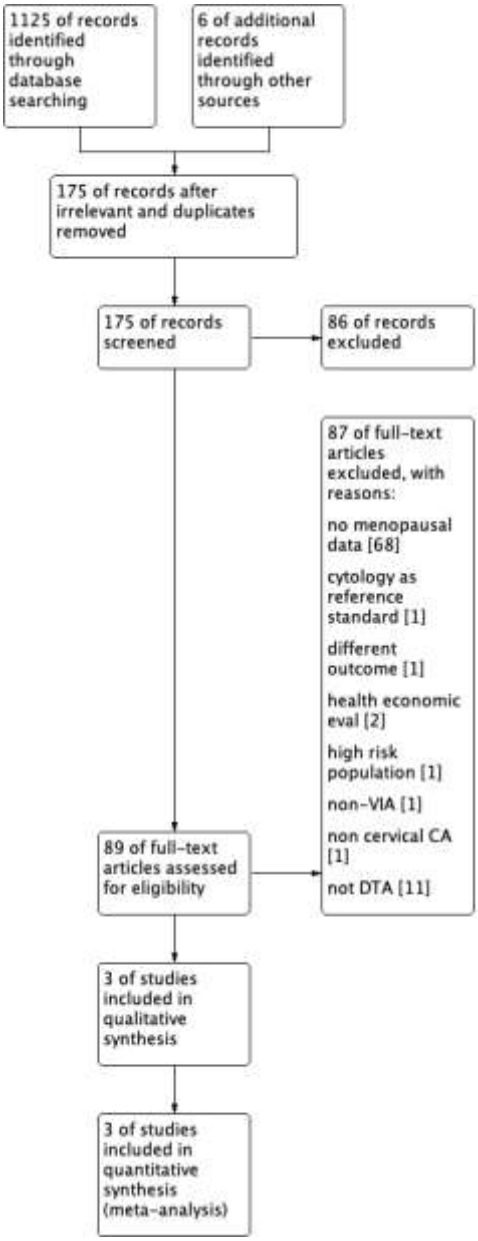
Setting: Outpatient, community, in low and middle income countries

SEARCH STRATEGY

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	(((((((uterine cervical neoplasm[MeSH Terms]) OR (uterine cervical dysplasia[MeSH Terms])) OR (cervical intraepithelial neoplasia[MeSH Terms])) OR ((((((cancer[Text Word]) OR (carcinoma[Text Word])) OR (adenocarcinoma[Text Word])) OR (neoplas*[Text Word])) OR (dysplasia*[Text Word])) AND (((cervix[Text Word]) OR (cervical[Text Word])) OR (cervico*[Text Word])))) OR (((((((CIN[Text Word]) OR (CIN2*[Text Word])) OR (CIN II[Text Word])) OR (CIN3*[Text Word])) OR (CIN III[Text Word])) OR (HSIL[Text Word])) OR (H-SIL[Text Word])))) AND ((VIA[Text Word]) OR ((((visual screening[Text Word]) OR (visual inspection[Text Word])) OR (cervicoscopy[Text Word])) AND (acetic acid)))) AND (((((cancer screening[MeSH Terms]) OR (sensitiv*[Text Word])) OR (specific*[Text Word])) OR (specificity)) OR (sensitivity))) AND (((((menopause[Text Word]) OR (menopaus*[Text Word])) OR (postmenopause[Text Word])) OR (elderly[Text Word])) OR (advanced age))	June 30 12:54AM	707	2
CENTRAL	ID Search Hits #1 (VIA):ti,ab,kw OR (visual):ti,ab,kw OR (visual inspection): ti,ab,kw #2 (visual):ti,ab,kw AND (acetic acid): ti,ab,kw #3 #1 OR #2 #4 MeSH descriptor: [Uterine Cervical Neoplasms] explode all trees #5 MeSH descriptor: [Uterine Cervical Dysplasia] explode all trees	July 1 8:51 PM	123	0

	#6 (cervical intraepithelial neoplasia):ti,ab,kw OR (CIN):ti,ab,kw OR (CIN 2):ti,ab,kw OR (CIN II):ti,ab,kw OR (CIN 3):ti,ab,kw #7 (CIN III):ti,ab,kw #8 #4 OR #5 OR #6 OR #7 #9 (sensitivity):ti,ab,kw OR (specificity):ti,ab,kw OR (accuracy):ti,ab,kw OR (diagnostic accuracy):ti,ab,kw #10 MeSH Descriptor: [Early Detection of Cancer] explode all trees #11 #9 OR #10 #12 #3 AND #8 AND #11			
Google Scholar	"visual inspection with acetic acid" AND ("menopause" OR "postmenopausal" OR "elderly" "advanced age") AND ("screening" OR "accuracy")	July 2 8:00PM	295	1
Clinicaltrials.gov	"visual inspection with acetic acid" AND "uterine cervical neoplasms" OR "cervical intraepithelial neoplasia 2/3" AND "accuracy" OR "screening"	July 2 10:05 PM	0	0

PRISMA FLOW DIAGRAM



CHARACTERISTICS OF INCLUDED STUDIES

	Study ID	Setting	Index Test	Purpose	Index Test Specimen	Screener	Population	Sample Size	Reference Standard	Reference Standard Specimen
1	Cremer 2011	Primary screening; Community-based (El Salvador)	VIA (acetowhite lesions) Conventional Cytology	Compare adequacy and performance of VIA	Cervical	Gynecologists, trained nurses & residents (4th year)	>= 50 year old, healthy women	588	Colposcopy with biopsy & ECC	Cervical (CIN 2+)
2	Holt 2016	Primary screening; Community-based (China)	VIA (acetowhite lesions) HPV DNA Liquid based cytology	Compare performance of VIA, cytology, HPV DNA	Cervical	Gynecologists	46 to 59 year old, healthy women (mean menopausal age = 46.7)	2757	Colposcopy with or without biopsy	Cervical (CIN 2+, CIN 3+)
3	Raifu 2017	Primary screening; Community-based (Republic of Congo)	VIA (acetowhite lesions) Conventional Cytology HPV DNA	Compare performance of VIA, cytology, HPV DNA	Cervical	Trained Nurses/ Gynecologists	30 to 85 year old, healthy women	498 are menopausal	Colposcopy with or without biopsy	Cervical (CIN 2+)

GRADE EVIDENCE PROFILE

Author(s): Gia Anna Bervano, MD

Question: Should visual inspection with acetic acid be used to screen for cervical cancer in menopausal women?

Bibliography:

1. Cremer M, Conlisk E, Maza M, Bullard K, Peralta E, Siedhoff M, et al. Adequacy of visual inspection with acetic acid in women of advancing age. Int J Gynaecol Obstet. 2011 Apr;113(1):68-71. doi: 10.1016/j.ijgo.2010.10.018. Epub 2011 Jan 26. PMID: 21272884.
2. Holt HK, Zhang L, Zhao FH, Hu SY, Zhao XL, Zhang X, et al. Evaluation of multiple primary and combination screening strategies in postmenopausal women for detection of cervical cancer in China. International Journal of Cancer. 2017 Feb 1;140(3):544-554. doi: 10.1002/ijc.30468. Epub 2016 Oct 31. PMID: 27727464.
3. Raifu AO, El-Zein M, Sangwa-Lugoma G, Ramanakumar A, Walter SD, Franco EL; Congo Screening Study Group. Determinants of Cervical Cancer Screening Accuracy for Visual Inspection with Acetic Acid (VIA) and Lugol's Iodine (VILI) Performed by Nurse and Physician. PLoS One. 2017 Jan 20;12(1):e0170631. doi: 10.1371/journal.pone.0170631. PMID: 28107486; PMCID: PMC5249231.

Sensitivity	0.53 (95% CI: 0.26 to 0.79)

Prevalences	2.7%	3%	2.1%

Specificity	0.88 (95% CI: 0.76 to 0.94)

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of2.7%	pre-test probability of3%	pre-test probability of2.1%	
True positives (patients with cervical cancer)	3 studies 4325 patients	cross-sectional (cohort type accuracy study)	serious[a,b]	not serious	serious[c]	serious[d]	none	14 (7 to 21)	16 (8 to 24)	11 (5 to 16)	⨁◯◯◯ Very low
False negatives (patients incorrectly classified as not having cervical cancer)								13 (6 to 20)	14 (6 to 22)	10 (5 to 16)	
True negatives (patients without cervical cancer)	3 studies 4325 patients	cross-sectional (cohort type accuracy study)	serious[a,b]	not serious	serious[c]	not serious	none	857 (742 to 919)	855 (740 to 916)	862 (747 to 924)	⨁⨁◯◯ Low
False positives (patients incorrectly classifi								116 (54 to 231)	115 (54 to 230)	117 (55 to 232)	

ed as having cervical cancer)											

Explanations

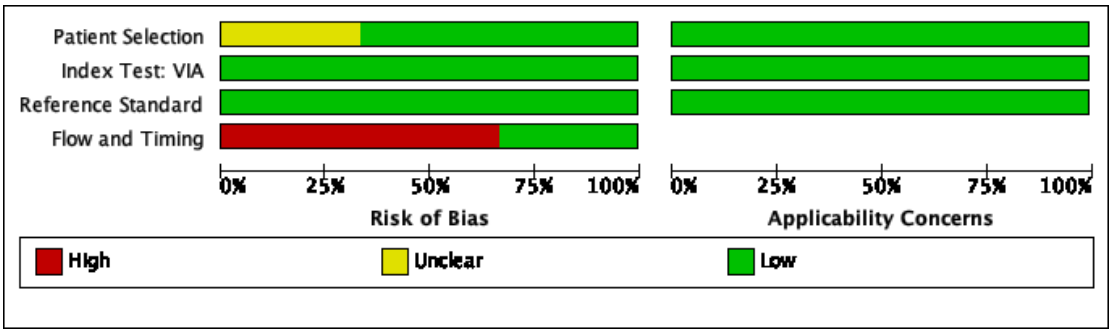
a. Reference standard used was colposcopy with or without biopsy not applied to all women who were screening test negative; used a different criteria to establish disease status

b. Not clear what happened to all participants who entered the study including withdrawals.

c. There was statistically significant heterogeneity of results for sensitivity (the proportion of patients with CIN 2+ with a positive VIA test) and specificity (the proportion of patients with negative CIN 2+ with a negative VIA test)

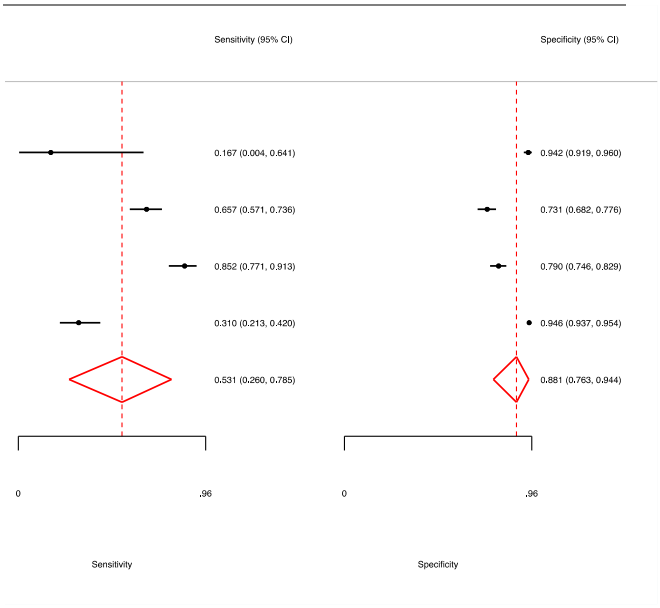
d. Wide confidence intervals for sensitivity estimates

RISK OF BIAS AND APPLICABILITY CONCERNS SUMMARY



FOREST PLOTS

	TP	FN	FP	TN	SN	SP
Cremer 2011	1	5	33	533	16.7	94.2
Raifu 2017a	90	47	97	264	65.7	73.1
Holt 2016	92	16	82	308	85.2	79.0
Cremer 2011	26	58	144	2529	30.95	94.61
Pooled					53.1	88.1



APPENDIX G

Thermal ablation vs cryotherapy in women with abnormal screening

Author(s): Dr. Carmela Augusta F. Dayrit-Castro; Dr. Alice Sun-Cua

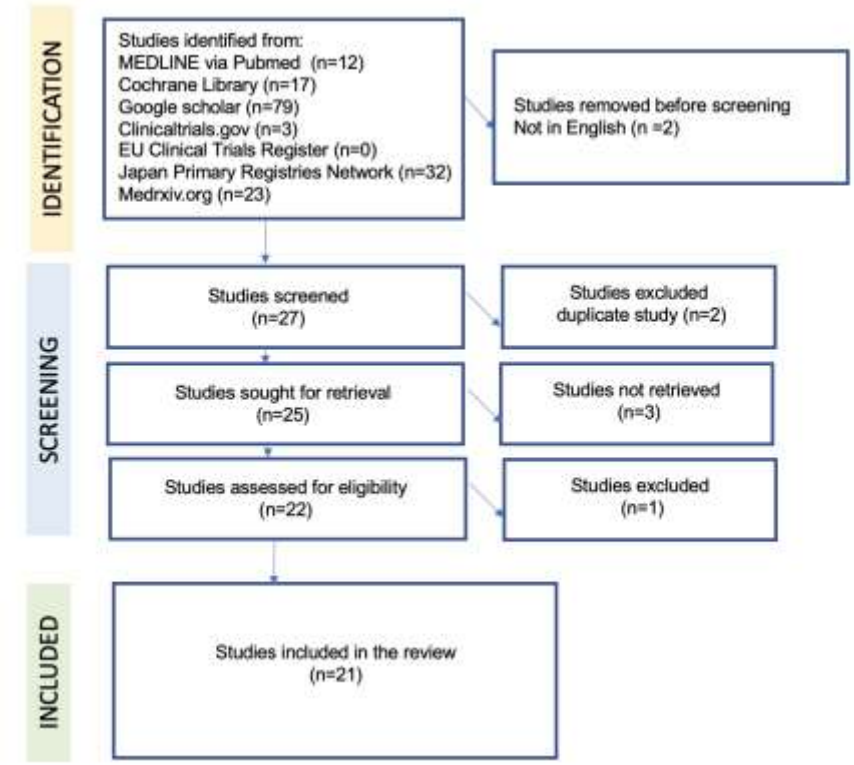
Question: Among premenopausal women with visible squamo-columnar junction with acetowhite lesion on VIA or positive high-risk HPV DNA test, should thermal ablation be recommended over cryotherapy to achieve regression of acetowhite lesion or high-risk HPV infection?

Setting: Outpatient, community, in low and middle income countries

Search Strategy

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	Free text: [thermal ablation] OR [thermocoagulation] OR MeSH Terms [cold coagulation] AND MeSH Terms [cervical precancer] OR [cervical intraepithelial neoplasia] AND MeSH Terms [cryotherapy]	April 4, 2023, 11:30PM	12	6
CENTRAL	Search manager, MeSH: [thermal ablation] OR [cold coagulation] AND MeSH; [cervical intraepithelial neoplasia] No other limits	April 6, 2023 3:00PM	17	4
Google Scholar	"thermal ablation" AND "cervical intraepithelial neoplasia" AND "cryotherapy" AND "clinical trial" Custom range: 2012-2023	April 7, 2023 10:00AM	79	8
ClinicalTrials.gov	Cervical intraepithelial neoplasia and thermal ablation	April 8, 2023 7:00PM	3	0
EU Clinical Trials Register	Cervical intraepithelial neoplasia and thermal ablation	April 8, 2023 7:05 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Cervical intraepithelial neoplasia	April 8, 2023 7:15 PM	32	0
Medrxiv.org	Cervical intraepithelial neoplasia and thermal ablation	April 8, 2023 7:45 PM	23	0

Prisma Flow Diagram



3.1.3. Table of Study Characteristics

Studies comparing efficacy of thermal ablation with cryotherapy

Author, year	Country	Study year	Study design	Age of recipient	Treatment at 1st visit (screen and treat)	Duration of follow-up	Number of women treated	Number of women followed-up	Cure definition	Other outcomes
Verma, 2022	India	Sept 2018-Aug 2019	RCT: TA vs. cryo	30-50 years old	Yes	6 months	TA=32 Cryo=34	TA=31 Cryo=31	(-) VIA	Immediate pain score (VAS 1-10), and at 6 weeks, safety
Chigbu, 2019	Nigeria	2014-2018	RCT: TA vs. cryo	Mean age 47	Yes	6 months	TA=511 Cryo=512	TA=476 Cryo=444	(-) VIA	Patient satisfaction, duration of treatment, cost, side effects
Duan, 2021	China	May 2017-May 2018	RCT: TA vs. cryo	20-49 years old	No	4 months 8 months	TA=74 Cryo=71	TA=67 Cryo=68 TA=65 Cryo=62	(-) cytology, (-) CIN2+	Pain, discharge, duration of treatment

Singh, 1988	Singapore	Sept 1983-Feb 1988	RCT: TA vs. cryo	20-53 years old	No	3 months 6 months	TA = 90 Cryo = 68	TA = 89 Cryo = 65	normal cytology and colposcopic exam	Side effects
Banerjee, 2020	India	Feb 2016-July 2017	RCT: TA vs. cryo	30-60 years old	Yes	12 months	TA= 136 Cryo = 150	TA=75 Cryo=80	(-) biopsy of CIN 2/3	Acceptability: Pain intensity and level of satisfaction

Title/Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Control	Outcomes
Studies on effectiveness of thermal ablation							
Parry-Smith et al, 2014	Clinical report (Retro-spective analysis)	UK	557	Colposcopy Department, Shrewsbury and Telford NHS Trust, United Kingdom: women undergoing cold coagulation for the treatment of CIN between 2001 and 2011, with cytologic follow-up until December 2012	TA	n/a	Success rate: post-treatment cytology
Mcarthy et al, 2016	Clinical report (Retro-spective analysis)	Ireland	89	Large tertiary referral hospital: women who underwent TA for CIN from January 2009 until January 2010	TA	n/a	Success rate: post-treatment cytology
Naud et al, 2015	Clinical report (Retro-spective analysis)	Brazil	52	Hospital: hospital records of women with high-grade CIN (CIN2/3) who were treated by thermocoagulation between March 6, 2012, and October 29	TA	n/a	Success rate: (-) VIA and cytology
Loobuyck et al, 1993	Clinical report (Retro-spective analysis)	UK	1165	Colposcopy Clinic, Ninewells Hospital, Dundee: women with CIN 1/2 and treated between January 1978 and December 1990.	TA	n/a	Success rate: (-) cytology
Tran, et al, 2017	Clinical report	Africa	17	Community: women aged 30–49 years in	TA	n/a	Cure rate: percentag

	(Effectiveness study)			Dschang, Cameroon, (+) hrHPV, (+) VIA/VILI			e of women with no evidence of persistent disease at 12 months
Campbell, et al, 2016	Clinical report (Screen and treat)	Africa	234	Health care clinics (Nkhoma Hospital, Kasina and Nathenje Health Centres), women with (+) VIA	TA	n/a	number of patients considered healed
Gordon et al, 1991	Clinical report	UK	1628	Ninewells Clinic: 2 smears showing mild Dyskaryosis/atypia or 1 smear showing Moderate-severe dyskaryosis, (+VIA)	TA	n/a	Effectiveness: normal cytology on follow-up
Williams et al, 1993	Clinical report (Effectiveness study)	UK	116	Genitourinary medicine colposcopy clinic: CIN 1/2	TA	n/a	Effectiveness: normal cytology on follow-up
Other outcomes							
Soler et al, 2022	RCT	El Salvador, China, Columbia	1152	Hospital 1° de Mayo of the Instituto del Seguro Social in San Salvador, El Salvador; Hospital Universitario San Ignacio in Bogotá, Colombia; and the Shanxi Bethune Hospital in Taiyuan, Shanxi Province, China: CIN2+	TA	Cryo, CO2	Pain VAS 1-10, side effects
Pinder et al, 2020	RCT	Zambia	750	Primary health clinic in Lusaka, Zambia, 295-49 years old with (+) VIA	TA	Cryo, LLETZ	Acceptability
Sandoval et al, 2019	Clinical report (Accept-ability and safety)	Hondurias	90	4 government health facilities: positive HPV screening test over a period of five months. Women were eligible to participate if they were as follows: aged 30–49 years, not pregnant, HPV and	TA	n/a	Acceptability, pain

				visual inspection with acetic acid (VIA) positive, and eligible for ablative treatment per the following WHO guidelines			
Metaxas, et al, 2022	Clinical report (Accept-ability and Safety)	Africa	232	Dschang Health District: Asymptomatic women aged 30–49 years old	TA	n/a	Acceptability, side effects
Goodman et al, 1991	Clinical report (Patient Acceptability)	London	78	Teaching hospital in London: HPV+ or CIN1/2/3	TA	laser	Side effects (bleeding, discharge), time taken to complete the treatment; VAS for pain experienced
Oga et al, 2016	Retro-spective cross-sectional	Africa	177	6 hospitals: National Hospital Abuja (NHA), University of Abuja Teaching Hospital (UATH), Garki Hospital Abuja (GHA), Federal Medical Centre Keffi (FMCK), Aminu Kano Teaching Hospital (AKTH) and Mother and Child Hospital, Ondo (MCHO): patients with (+) VIA/VILI	TA	n/a	Recurrence and potential risk factors for recurrence
Armstrong, et al, 2022	Retro-spective cross-sectional	UK	909	Colposcopy unit in hospital: women (CIN2 or CIN3) , had TA or LLETZ, failed cure: (+) hr-HPV (+) cytology or both	TA	LLETZ	Rate of recurrence
Slakovsky et al, 2020	Clinical report (Effectiveness study)	Honduras	128	4 government health facilities in Honduras: all HPV and VIA (+)	TA	n/a	Treatment outcomes after 1 year

Cryo: Cryotherapy; LLETZ: Large Loop Excision of Transition Zone; TA: thermal ablation; VIA: Visual Inspection with Acetic Acid

3.1.4. GRADE Evidence Profile

Author(s): Carmela Augusta F. Dayrit-Castro, M.D.
Question: Thermal ablation compared to cryotherapy for cervical precancer
Setting: Community
Bibliography:

TREATMENT FAILURE (EFFICACY)

1. Chigbu CO, Onwudiwe EN, Onyebuchi AK. Thermo-coagulation versus cryotherapy for treatment of cervical precancers: A prospective analytical study in a low-resource African setting. J Obstet Gynaecol Res. 2020 Jan;46(1):147-152.
2. Verma ML, Singh U, Kumari R, Sachan R, Sankhwar PL, Solanki V. Randomized controlled study for comparison of efficacy and safety between thermocoagulation and cryotherapy in visual inspection with acetic acid positive cervical lesions. J Cancer Res Ther. 2022 Apr-Jun;18(3):603-611.
3. Duan L, Du H, Belinson JL, Liu Z, Xiao A, Liu S, Zhao L, Wang C, Qu X, Wu R. Thermocoagulation versus cryotherapy for the treatment of cervical precancers. J Obstet Gynaecol Res. 2021 Jan;47(1):279-286. doi: 10.1111/jog.14520.
4. Singh, P., Loke, K. L., Hii, J. H. C., Sabaratnam, A., Lim-Tan, S. K., Sen, D. K., Kitchener, H. C., Arunachalam, I., & Ratnam, S. S. (1988). Cold Coagulation Versus Cryotherapy for Treatment of Cervical Intraepithelial Neoplasia: Results of a Prospective Randomized Trial. Colposcopy and Gynecologic Laser Surgery, 4(4), 211-221.
5. Banerjee D, Mandal R, Mandal A, Ghosh I, Mittal S, Muwonge R, Lucas E, Basu P. A Prospective Randomized Trial to Compare Safety, Acceptability and Efficacy of Thermal Ablation and Cryotherapy in a Screen and Treat Setting. Asian Pac J Cancer Prev. 2020 May 1;21(5):1391-1398.

PAIN/BLEEDING/DISCHARGE

1. Chigbu CO, Onwudiwe EN, Onyebuchi AK. Thermo-coagulation versus cryotherapy for treatment of cervical precancers: A prospective analytical study in a low-resource African setting. J Obstet Gynaecol Res. 2020 Jan;46(1):147-152.
2. Verma ML, Singh U, Kumari R, Sachan R, Sankhwar PL, Solanki V. Randomized controlled study for comparison of efficacy and safety between thermocoagulation and cryotherapy in visual inspection with acetic acid positive cervical lesions. J Cancer Res Ther. 2022 Apr-Jun;18(3):603-611.
3. Banerjee D, Mandal R, Mandal A, Ghosh I, Mittal S, Muwonge R, Lucas E, Basu P. A Prospective Randomized Trial to Compare Safety, Acceptability and Efficacy of Thermal Ablation and Cryotherapy in a Screen and Treat Setting. Asian Pac J Cancer Prev. 2020 May 1;21(5):1391-1398.
4. Soler, Montserrat, et al. "Safety and Acceptability of Three Ablation Treatments for High-Grade Cervical Precancer: Early Data From a Randomized Noninferiority Clinical Trial." JCO Global Oncology 8 (2022): e2200112.
5. Pinder LF, Parham GP, Basu P, Muwonge R, Lucas E, Nyambe N, Sauvaget C, Mwanahamuntu MH, Sankaranarayanan R, Prendiville W. Thermal ablation versus cryotherapy or loop excision to treat women positive for cervical precancer on visual inspection with acetic acid test: pilot phase of a randomised controlled trial. Lancet Oncol. 2020 Jan;21(1):175-184.
6. Duan L, Du H, Belinson JL, Liu Z, Xiao A, Liu S, Zhao L, Wang C, Qu X, Wu R. Thermocoagulation versus cryotherapy for the treatment of cervical precancers. J Obstet Gynaecol Res. 2021 Jan;47(1):279-286. doi: 10.1111/jog.14520.

ACCEPTABILITY

1. Banerjee D, Mandal R, Mandal A, Ghosh I, Mittal S, Muwonge R, Lucas E, Basu P. A Prospective Randomized Trial to Compare Safety, Acceptability and Efficacy of Thermal Ablation and Cryotherapy in a Screen and Treat Setting. Asian Pac J Cancer Prev. 2020 May 1;21(5):1391-1398.
2. Pinder LF, Parham GP, Basu P, Muwonge R, Lucas E, Nyambe N, Sauvaget C, Mwanahamuntu MH, Sankaranarayanan R, Prendiville W. Thermal ablation versus cryotherapy or loop excision to treat women positive for cervical precancer on visual inspection with acetic acid test: pilot phase of a randomised controlled trial. Lancet Oncol. 2020 Jan;21(1):175-184.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**thermal ablation**	**cryotherapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Treatment failure (follow-up: median 6 months; assessed with: persistent (+) VIA, (+) HPV, abnormal cytology)												
5	randomised trials	serious[a]	not serious	not serious	not serious	none	87/771 (11.3%)	111/750 (14.8%)	**RR 0.76** (0.59 to 0.99)	**36 fewer per 1,000** (from 61 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Pain (assessed with: patient report)												
5	randomised trials	serious[b]	serious[c]	not serious	serious[d]	all plausible residual confounding would suggest spurious effect, while no effect was observed dose response gradient	171/1287 (13.3%)	138/1274 (10.8%)	**RR 1.22** (0.99 to 1.51)	**24 more per 1,000** (from 1 fewer to 55 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Vaginal Bleeding (assessed with: patient/provider report)												
3	randomised trials	not serious	serious[e]	not serious	not serious	all plausible residual confounding would suggest spurious effect,	161/895 (18.0%)	90/801 (11.2%)	**RR 1.78** (1.40 to 2.27)	**88 more per 1,000** (from 45 more to 143 more)	⨁⨁⨁⨁ High	IMPORTANT

						while no effect was observed						
Vaginal discharge (assessed with: patient/provider report)												
4	randomised trials	not serious	serious [f]	not serious	very serious [g]	dose response gradient	344/929 (37.0%)	591/925 (63.9%)	**RR 0.58** (0.53 to 0.64)	**268 fewer per 1,000** (from 300 fewer to 230 fewer)	⊕⊕◯◯ Low	IMPORTANT
Acceptability (assessed with: would recommend to others: yes/no)												
2	randomised trials	serious [h]	not serious	not serious	very serious [i]	all plausible residual confounding would reduce the demonstrated effect dose response gradient	378/378 (100.0%)	388/391 (99.2%)	**RR 0.15** (0.01 to 2.85)	**843 fewer per 1,000** (from 982 fewer to 1,000 more)	⊕⊕⊕◯ Moderate	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations
a. unclear risk for performance bias and detection bias in majority of the studies since there was no mention that the patients and outcome assessors were blinded to treatment group (see risk of bias summary)
b. the patients could not be blinded to the procedure they received (TA vs. cryo) in all studies: Verma, 2022; Chigbu, 2019; Banerjee, 2020; Pinder 2020
c. inconsistency in measurement of pain: presence or absence of pain (Verma, 2022; Chigbu, 2019; Banerjee, 2020) or qualified as moderate-severe pain (Pinder, 2020)
d. some studies noted presence or absence of pain (Verma, 2022; Chigbu, 2019), VAS rating may be imprecise depending on patient characteristics (Banerjee, 2020; Pinder, 2020)
e. 2 studies (Chigbu, 2019; Duan, 2021) reported mild post-procedure bleeding while in 1 study (Verma, 2022) reported after 6 weeks
f. variation in amount/character of vaginal discharge that would be reportable
g. 1 study differentiated between watery and malodorous discharge (Soler, 2022) while the others did not include malodorous discharge
h. risk for reporting bias in all studies
i. only took into account if patient would recommend the procedure to others but did not take into account level of satisfaction due to differences in measurement scales

Risk of Bias Tables and Summary

Figure 1. Risk of Bias Graph for Studies on Treatment Failure of Thermal Ablation vs. Cryotherapy

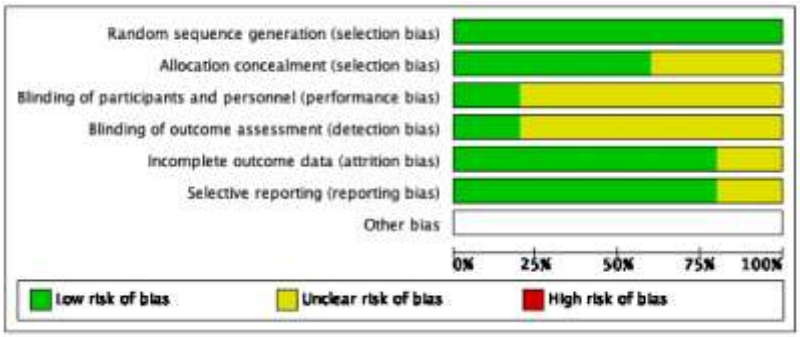


Figure 2. Risk of Bias Summary for Studies on Treatment Failure of Thermal Ablation vs. Cryotherapy

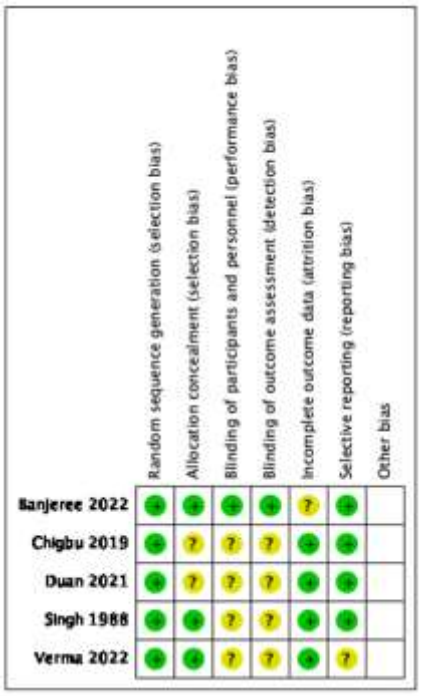


Figure 3. Risk of Bias Graph for Studies on Efficacy and Effectiveness

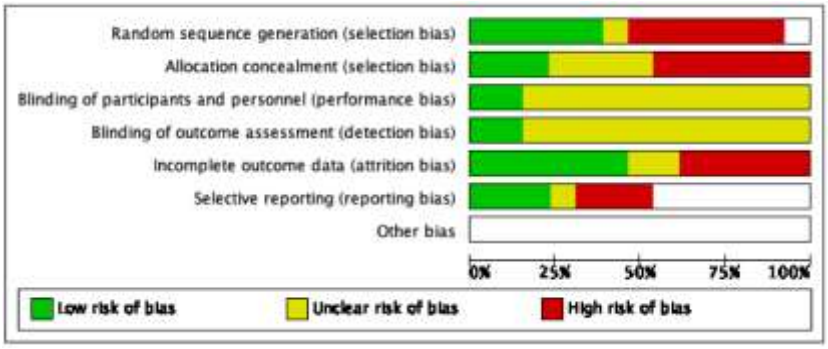
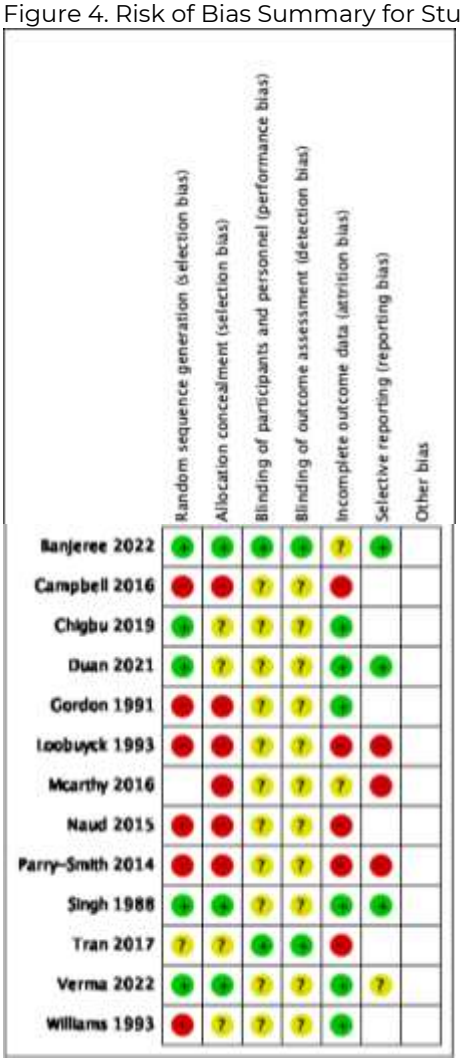


Figure 4. Risk of Bias Summary for Studies on Efficacy and Effectiveness



Forest Plots

Figure 1: Treatment failures with thermal ablation vs. cryotherapy

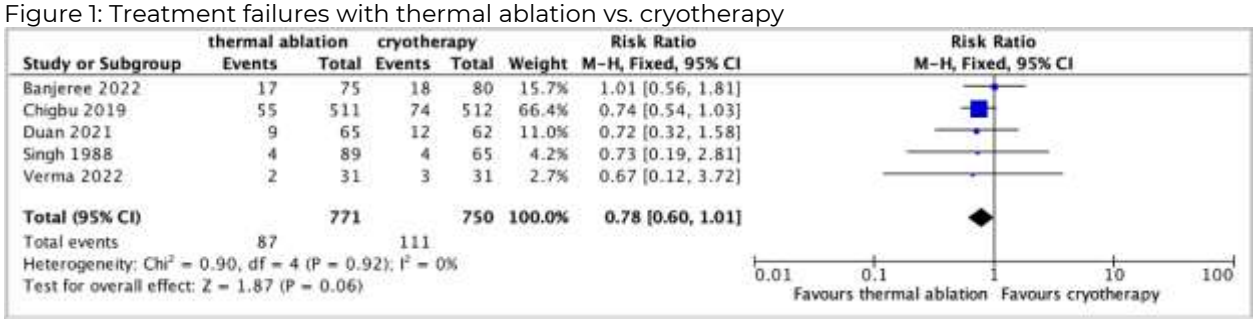


Figure 2: Pain after thermal ablation vs. cryotherapy

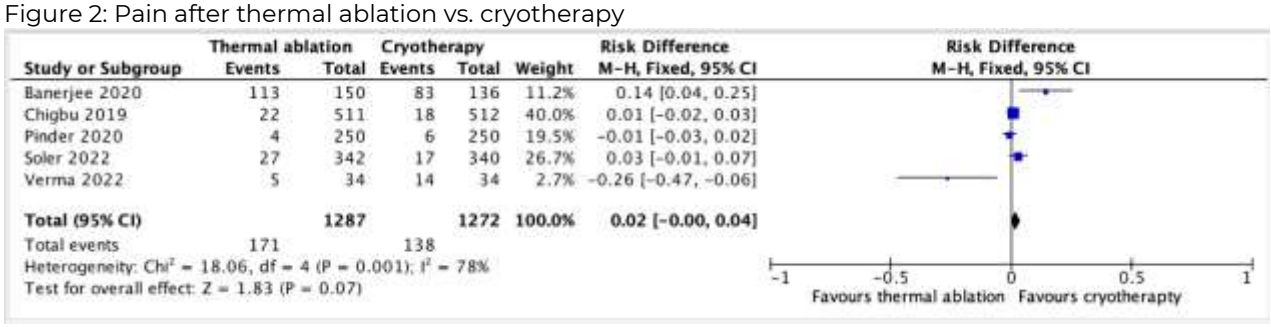


Figure 3: Vaginal bleeding with thermal ablation vs. cryotherapy

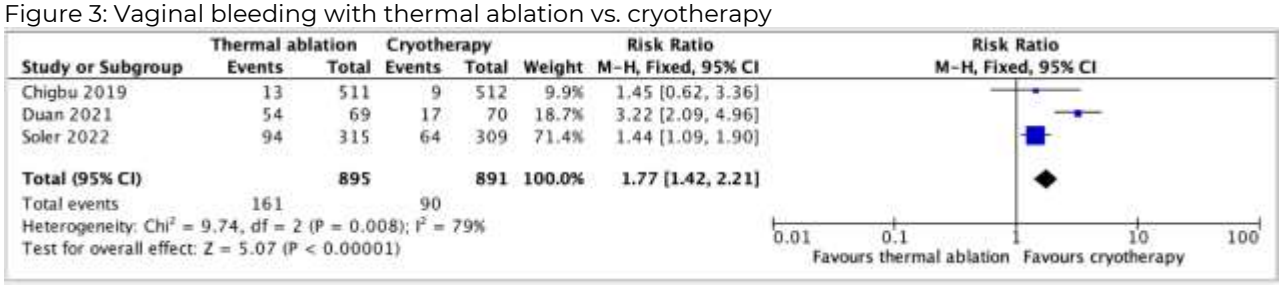


Figure 4: Vaginal discharge with thermal ablation vs. cryotherapy

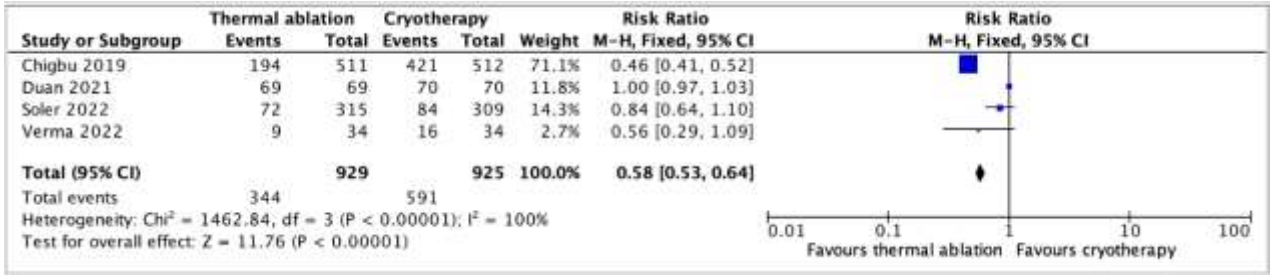
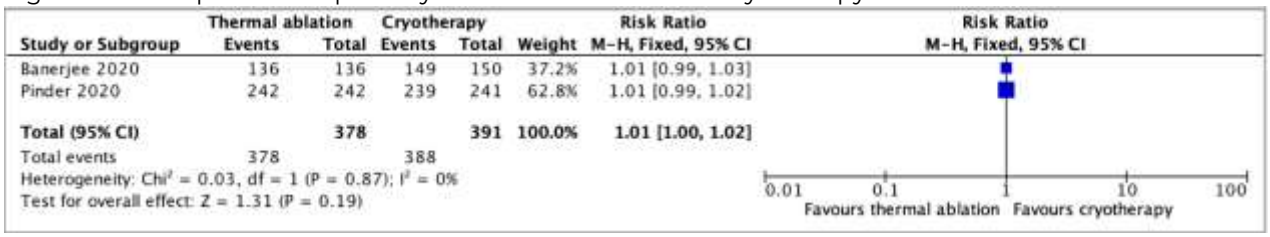


Figure 5: Forest plot of acceptability for thermal ablation vs. cryotherapy



APPENDIX H

Ablation vs excision in women with abnormal screening after previous treatment (persistent lesions)

Author(s): Dr. Andrea Santiago; Dr. Mariel Nevado-Gammad

Question: Among women with persistent acetowhite lesion or positive high-risk HPV DNA test 12 months after treatment with ablative procedure, should a repeat ablative procedure be recommended over excision procedure to achieve clearance of acetowhite lesion or high-risk HPV infection?

Setting: Outpatient, community, in low and middle income countries

REVIEW METHODS

A systematic search was done from December 15, 2022 to March 8, 2023 using Medline, Cochrane Library, and Google Scholar with combined MeSH and free text search using the terms: thermal ablation, cold coagulation, thermocoagulation, cryotherapy, cryosurgery, ablative procedure, large loop electrosurgical excision of the transformation zone (LLETZ), loop electrosurgical excision procedure (LEEP), persistent acetowhite lesions, positive high-risk HPV DNA, cervical intraepithelial neoplasia, high grade squamous intraepithelial lesions, cervical dysplasia, precancer cervix, preinvasive lesions and atypical squamous cells of the cervix.

Ongoing studies in the NIH clinicaltrials.gov and preprints from Medrxiv were also searched. Randomized controlled trials and observational studies were included in the review. Outcomes of interest included: cure rate, safety, and patient acceptability.

RESULTS

No direct studies were found comparing the effects of ablation with excision for women with persistent acetowhite lesions or positive high-risk HPV DNA test after an ablative procedure.

Data from the WHO guidelines for the use of cryotherapy for cervical intraepithelial neoplasia in 2011 showed that cure rates after retreatment were: 74% (after cryotherapy) and 92% (after conization).

Recommendation 10. Should cryotherapy versus conization be used for treatment failures diagnosed > 12 months after first cryotherapy treatment?

Quality assessment							**No. of patients**		**Effect**			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy	Conization	Relative (95% CI)	Absolute	Quality	Importance
12	Observational studies	No serious limitations	No serious inconsistency	Serious[1]	Serious[2]	None	26/99 (26.3%)	6/76 (7.9%) 30%[3]	OR 2.35 (0.82 to 6.7)	- 202 more per 1000 (from 40 fewer to	⨁◯◯◯ Very low	CRITICAL

										442 more)		

[1] Follow-up after first cryotherapy treatment and diagnosis of CIN/retreatment often not reported in studies. [2] Few participants and events with confidence intervals including no difference or lower recurrence rates with cryotherapy versus conization. Recurrence rates with conization ranged from 0-50%.

In a meta-analysis by Randall, (and as reported in the WHO guidelines for the use of thermal ablation for cervical precancer lesions in 2019[6]), out of 40 women with histologically confirmed CIN2+ disease who screened positive after 4 months to 2 years, 34 (85%, 95% CI 74-96%) were cured when retreated with thermal ablation.

	Follow-up and screened positive	**Number retreated with thermal ablation**	**Number cured after retreatment**
Singh 1988	Up to 2 years	8	6
Hussein 1985	At 4 months	6	6
Gordon 1991	Approx. 18 months	26	22

No studies reported on adverse events/safety and acceptability when retreating with ablation versus excision.

APPENDIX I

Ablation vs excision in women with large acetowhite lesions

Author(s): Dr. Patricia Factor; Dr. Carmela Augusta F. Dayrit-Castro

Question: Among premenopausal women with large acetowhite lesions, should ablative procedure be recommended over excision procedure to achieve regression of acetowhite lesions?

Setting: Outpatient, community, in low and middle income countries

SEARCH STRATEGY

Database	Search Strategy	Date and Time	Results Yield	Results Eligible
Medline	((("acetowhite"[All Fields] OR "acetowhiteness"[All Fields]) AND ("lesion"[All Fields] OR "lesion s"[All Fields] OR "lesional"[All Fields] OR "lesions"[All Fields])) OR ("uterine cervical dysplasia"[MeSH Terms] OR ("uterine"[All Fields] AND "cervical"[All Fields] AND "dysplasia"[All Fields]) OR "uterine cervical dysplasia"[All Fields] OR ("cervical"[All Fields] AND "intraepithelial"[All Fields] AND "neoplasia"[All Fields]) OR "cervical intraepithelial neoplasia"[All Fields])) AND ((("thermal"[All Fields] OR "thermalization"[All Fields] OR "thermalize"[All Fields] OR "thermalized"[All Fields] OR "thermalizes"[All Fields] OR "thermalizing"[All Fields] OR "thermally"[All Fields] OR "thermals"[All Fields]) AND ("ablate"[All Fields] OR "ablated"[All Fields] OR "ablates"[All Fields] OR "ablating"[All Fields] OR "ablation"[All Fields] OR "ablational"[All Fields] OR "ablations"[All Fields])) OR ("cryotherapy"[MeSH Terms] OR "cryotherapy"[All Fields] OR "cryotherapies"[All Fields])) AND ("regression, psychology"[MeSH Terms] OR ("regression"[All Fields] AND "psychology"[All Fields]) OR "psychology regression"[All Fields] OR "regression"[All Fields] OR "regressions"[All Fields] OR ("cure"[All Fields] AND ("j rehabil assist technol eng"[Journal] OR "rate"[All Fields])) OR ("clearance"[All Fields] OR "clearances"[All Fields]))	January 23, 2023	49	22
Cochrane Library	Cervical intraepithelial neoplasia AND excision AND ablation	January 24, 2023	26	5
Clinicaltrials.gov	Cervical intraepithelial neoplasia, excision, ablation	January 24, 2023	6	0
EU Clinical Trials Register	Cervical intraepithelial neoplasia AND excision AND ablation	March 12, 2023	0	
Chinarxiv.org	"cervical intraepithelial neoplasia" (match all words) and abstract or title "excision ablation" (match all words)	March 18, 2023	0	

Medrxiv.org	"cervical intraepithelial neoplasia" (match all words) and abstract or title "excision ablation" (match all words)	March 18, 2023	0	

SUMMARY OF FINDINGS TABLE

1. RECURRENCE RATES BASED ON LESION SIZE

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Recurrence in Small Lesions	7 observational studies (1705 patients)	60 per 1000	50 to 70	HARM Recurrence is higher in large lesions after cryotherapy	Very low
Recurrence in Medium Lesions	11 observational studies (2211 patients)	70 per 1000	60 to 80		Very low
Recurrence in Large Lesions	5 observational studies (246 patients)	180 per 1000	130 to 230		Very low

2. RECURRENCE RATES BASED ON ENDOCERVICAL EXTENSION

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Recurrence in Lesions that extend into the endocervical canal	9 observational studies (302 patients)	160 per 1000	130-200	HARM Recurrence is higher in lesions that extend into the endocervical canal	Very low
Recurrence in Lesions that DOES NOT extend into the endocervical canal	33 observational studies (10901 patients)	60 per 1000	50-60		Very low

3. PROGRESSION TO CERVICAL CA WITH CRYOTHERAPY

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
Progression to Cervical CA with cryotherapy	1 longitudinal cohort study (37 142 women)	OR 2.98	2.09-4.60	HARM	Very low

4. ADVERSE EVENTS/COMPLICATIONS

Outcomes	No of Participants (Studies)	Absolute Effects Excision Risk	Anticipated Ablation Risk Risk	Relative Effect (96% CI)	Interpretation	Certainty of Evidence
Minor bleeding during 1st 24 hours	669 2 ECAs	15 per 1000	4 per 1000 (90-229)	RR 0.27 (0.04 to 1.62)	NO DIFFERENCE	Very low
Minor bleeding after 1st 24 hours	625 2 ECAs	484 per 1000	237 per 1000 (194 to 286)	RR 0.49 (0.40 to 0.59)	BENEFIT	Moderate
Pain after 24h post treatment	625 2 ECAs	275 per 1000	256 per 1000 (200-322)	RR 0.93 (0.74 to 1.17)	NO DIFFERENCE	Very Low

Outcomes	No of Participants (Studies)	Absolute Effects Excision Risk	Anticipated Ablation Risk	Relative Effect (96% CI)	Interpretation	Certainty of Evidence
Cervical Stenosis	596 2 ECAs	3 per 1000	6 per 1000 (1-68)	RR 01.87 (0.17 to 20.38)	NO DIFFERENCE	Very low
Infection after 24h	625 2 ECAs	465 per 1000	544 per 1000 (502 to 595)	RR 1.17 (1.08 to 1.28)	HARM	Very Low
Pre-term birth	68817 2 RCT 27 observational	RR 1.37 (95% CI 1.16-1.62)	RR 1.01 (95% CI 0.35-2.92)		HARM with Excision	Very Low