World Health Organization

WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions

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ABBREVIATION AND ACRONYMS

C4GEP	WHO Comprehensive cervical cancer control: a guide to essential practice
CIN	Cervical intraepithelial neoplasia
CKC	Cold knife conization
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
LEEP	Loop electro excision procedure
LLETZ	Large loop excision of the transformation zone
LMIC	Low- and middle-income countries
LSIL	Low-grade squamous intraepithelial lesion
PICO	Population, intervention, comparison and outcome framework
SCJ	Squamocolumnar junction
TZ	Transformation zone
VIA	Visual inspection with acetic acid
WHO	World Health Organization

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Executive summary

INTRODUCTION

It is estimated that more than 311 000 women die of cervical cancer each year. Of these deaths, 91% occur in low- and middle-income countries. Demographic changes and a lack of action mean that the number of deaths per year is projected to reach 460 000 by 2040.

Screening programmes have dramatically reduced cervical cancer rates in high-income countries. Screening using a cytology-based method and histological confirmation of cervical intraepithelial neoplasia (CIN) is typically followed by treatment such as cryotherapy, large loop excision of the transformation zone (LLETZ), and cold knife conization (CKC). However, in low- and middle-income countries, it has not been possible to obtain high population coverage with cytology-based screening, and other tests are being used to screen, including visual inspection with acetic acid (VIA) and more recently, DNA/RNA tests for human papillomavirus (HPV). Screen-and-treat algorithms, where women who are positive for a screening test are treated with ablative treatment (destruction of the cervical transformation zone including the lesion), have been implemented.

Cryotherapy is a World Health Organization (WHO) recommended ablative treatment, but one major disadvantage is the need for a refrigerant gas (N_2O or CO_2). The gas containers are bulky and heavy to transport and some areas of low- and middle-income countries (LMICs) may have supply issues. In addition, frequent refilling of freezing gas can be costly. Thermal ablation, also called "cold coagulation" or thermocoagulation, is another ablative treatment for CIN. The equipment is simple, lightweight (devices can weigh much less than 2 kg), and is easily portable to LMIC field clinics. Treatment is based on a 20–40 second application (multiple if needed) of a reusable metallic probe that is electrically heated to approximately 100 °C, leading to epithelial and stromal destruction. Like cryotherapy, thermal ablation is provided by a variety of health care personnel, including primary health care workers, and typically performed without anesthesia.

RATIONAL FOR THE GUIDELINES

Thermal ablation is not included in the latest version of the WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ, nor in the *WHO Comprehensive cervical cancer control: a guide to essential practice* (C4GEP) manual, but evidence is accumulating to support its inclusion, and there were requests from countries and WHO partners to issue recommendations on the use of thermal ablation for the treatment of cervical precancer lesions.

OBJECTIVES

The objectives of these guidelines are

- to provide evidence-based guidance on the use of thermal ablation to treat cervical precancer; and
- to support countries to update their national guidelines for the use of thermal ablation for cervical precancer.

METHODS

These guidelines were developed using the *WHO Handbook for guideline development*. A Guideline Development Group (GDG) was established that included experts, clinicians and researchers in cervical cancer prevention and treatment, health programme directors, and methodologists. Conflicts of interests were managed according to WHO rules. An independent systematic review team and methodologist synthesized the evidence and produced evidence summaries following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. GRADE evidence profiles and evidence-to-decision frameworks were created and used by the Guideline Development Group to make recommendations. This guideline was peer reviewed by an external group and approved by the WHO Guidelines Review Committee.

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RECOMMENDATIONS

These guidelines provide recommendations for the use of thermal ablation for the treatment of precancerous cervical lesions. These recommendations are applicable for women who have histologically confirmed CIN2-3 or for women who have been screened positive in a screen-and-treat strategy. These recommendations expand on the treatment for screen-and-treat strategies as provided in the WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.

In these recommendations, the GDG decided to use the term thermal ablation instead of cold coagulation or thermocoagulation, to reflect the fact that it is an ablative treatment. The GDG decided that in these guidelines, as well as in future WHO publications, the term LLETZ will be used to represent a therapeutic intervention to excise the transformation zone (TZ). LLETZ is the original terminology used for excision of the TZ. The C4GEP manual, as well as some countries, use the term LEEP (Loop Electro Excision Procedure) and the two terms (LLETZ and LEEP) are often used interchangeably. The term LEEP also refers to a diagnostic procedure, requiring up to 2 cm of tissue to be excised from the cervix for the pathologist to make an accurate diagnosis.

ELIGIBILITY FOR THERMAL ABLATION AND CRYOTHERAPY

Eligibility for treatment should be assessed by colposcopy (if available) or by naked eye examination of cervix after applying 3–5% acetic acid for 1 minute.

Clinicians usually describe what they see when performing visual inspection (for example, if the TZ is fully visible; if the whole lesion is visible; if the lesion extends into the endocervix), and then consider if the probe can reach the whole lesion. Clinicians can consider using the International Federation for Cervical Pathology and Colposcopy's classification of three types of Transformation Zone, characterised by the size and site:

- A type 1 TZ is completely ectocervical and is therefore fully visible.
- A type 2 TZ is partially endocervical but is still fully visible. It may be shallow and within range of an ablative probe or may extend beyond reach of an ablative probe.
- A type 3 TZ extends out of view up the endocervical canal, i.e., the squamocolumnar junction (SCJ), and is not fully visible.

Following assessment as described above, 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 TZ is fully visible, the whole lesion is visible and it does not extend into the endocervix, or
- the lesion is type 1 TZ; or
- the lesion is type 2 TZ where the probe tip will achieve complete ablation of the SCJ epithelium, i.e., where it can reach the upper limit of the TZ. Sometimes the SCJ can be seen high in the canal but a probe tip would not reach it.

Women who screen positive are not eligible for ablative therapy if there is any suspicion of invasive or glandular disease, (i.e. adenocarcinoma or adenocarcinoma in situ), and:

- the TZ is not fully visible because it is endocervical (Type 3 TZ); or
- it is a Type 2 TZ where the SCJ is out of reach of the probe tip.

INTERVALS FOR FOLLOW-UP

Intervals for follow-up should be conducted according to the WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ[1], and the WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention[2]. According to those recommendations, all women who have received treatment should receive post-treatment follow-up at 1 year to ensure effectiveness of treatment. Post treatment follow-up is critical, in particular for women living with HIV or women of unknown HIV status in areas with high endemic HIV infection.

[1] http://apps.who.int/iris/bitstream/10665/104174/1/9789241506779_eng.pdf?ua=1
[2] https://www.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf?ua=1

Recommendations	Strength of recommendation and certainty of evidence
Recommendation 1.a WHO suggests either LLETZ, or cryotherapy or thermal ablation to treat all women who have histologically confirmed CIN2+ disease and who are eligible for thermal ablation or cryotherapy. ***Remarks:*** The choice of LLETZ, or cryotherapy or thermal ablation depends on the expertise, training, equipment and consumables available, infrastructure and resources in a programme. This recommendation applies to all women, including women living with HIV. See Figure 1.	Conditional recommendation, moderate certainty in evidence of effects
Recommendation 1.b WHO suggests thermal ablation be provided at a minimum of 100 °C for 20–30 seconds using as many applications as needed to cover the entire transformation zone in overlapping fields.	Conditional recommendation, very low certainty in evidence of effects
Recommendation 2 In exceptional conditions when LLETZ is not available for women who have histologically confirmed CIN2+ disease and are not eligible for cryotherapy or thermal ablation, the GDG recommends an alternative treatment. 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. ***Remarks:*** This recommendation applies to all women including women living with HIV. See Figure 1.	Strong recommendation, very low certainty in evidence of effects
Recommendation 3 WHO suggests providing either thermal ablation or cryotherapy to women screened positive with hrHPV or visual inspection with acetic acid (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. ***Remarks:*** This recommendation applies to all women, including women living with HIV. The choice of screening tests is based on WHO recommendations for screening and treatment. See Figure 2.	Conditional recommendation, very low certainty in evidence of effects
Recommendation 4 WHO suggests that prophylactic antibiotics are not used when providing thermal ablation.	Conditional recommendation, very low certainty in evidence of effects
Recommendation 5 WHO suggests that trained nurses, midwives or health care workers as well as physicians may perform thermal ablation in order to ensure the availability and accessibility of treatment.	Conditional recommendation, very low certainty in evidence of effects
Recommendation 6 In settings where LLETZ is available and accessible, WHO suggests LLETZ rather than thermal ablation or cryotherapy for women who test positive for cervical cancer after prior thermal ablation or cryotherapy. In settings where LLETZ is unavailable or inaccessible, the WHO recommends thermal ablation or cryotherapy rather than no treatment for women who test positive after prior thermal ablation or cryotherapy. ***Remarks:*** This recommendation is consistent with the recommendation to provide LLETZ after prior cryotherapy.	Conditional recommendation, very low certainty in evidence of effects Strong recommendation, very low certainty in evidence of effects

Figure 1a: Flowchart for histologically confirmed CIN2+

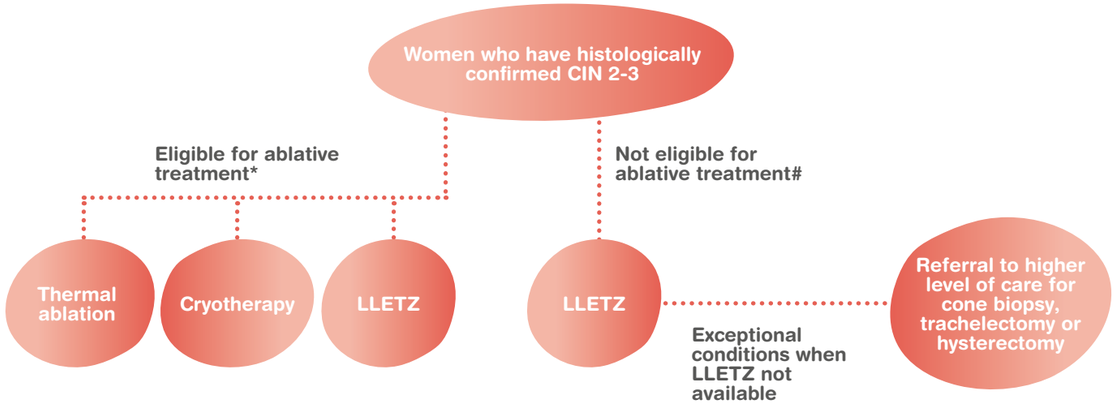
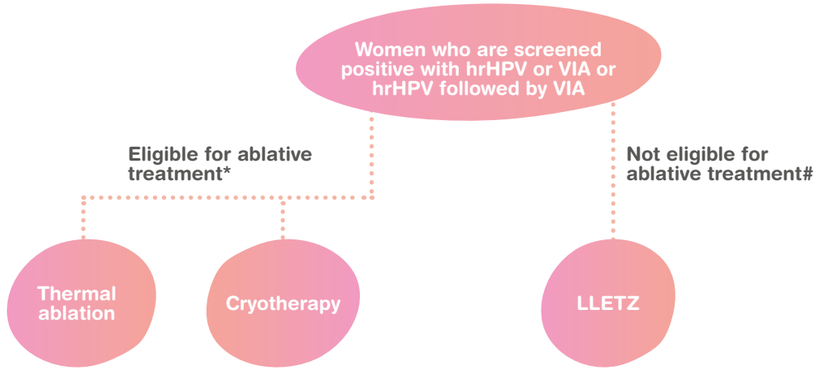


Figure 1b: Flowchart for screen positive with hrHPV or VIA or hrHPV followed by VIA



* 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 TZ is fully visible, the whole lesion is visible and it does not extend into the endocervix, or
- the lesion is type 1 TZ, or
- the lesion is type 2 TZ where the probe tip will achieve complete ablation of the SCI epithelium, i.e., where it can reach the upper limit of the TZ. Sometimes the SCJ can be seen high in the canal but a probe tip would not reach it.

\# Women who screen positive are not eligible for ablative therapy if there is any suspicion of invasive or glandular disease, (i.e. adenocarcinoma or adenocarcinoma in situ), and

- the TZ is not fully visible because is endocervical (Type 3TZ), or
- is a Type 2 TZ where the SCJ is out of reach the probe tip.

1. INTRODUCTION

1.1 BACKGROUND

It is estimated that more than 311 000 women die of cervical cancer each year, and that 91% of these deaths occur in low- and middle-income parts of the world *(1)*. Demographic changes, ageing and lack of action mean that the number of deaths per year is projected to reach 460 000 by 2040 *(2)*. The highest burden is found in sub-Saharan Africa, Central and South America, East Africa, South and South-East Asia, and the Western Pacific.[3]

Screening programmes have dramatically reduced cervical cancer rates in high-income countries. In the United States of America (USA), for example, mortality has been reduced by 80% in 50 years thanks to screening by the Papanicolaou (PAP) smear test and treatment of confirmed precancerous cervical intraepithelial lesions grade 2 or more (CIN2+ *(2)*. Screening using the same cytology-based method and histological confirmation of lesions has not been so successful in low- and middle-income countries (LMIC), mainly because of high costs and logistical considerations specific to the PAP smear test, general lack of colposcopy and histology services, and inadequate access to treatment of precancerous lesions in these regions *(3)*.

Alternative tests have been introduced - first the visual inspection with acetic acid (VIA), and more recently, a nucleic acid test for human papillomavirus (HPV). Due to the lack of services for diagnostic confirmation, the first edition of the *WHO Comprehensive cervical cancer control: a guide to essential practice* (C4GEP) in 2006 recommends the implementation of screen-and–treat algorithms where women who are positive for a screening test are treated with ablative treatment (destruction of the cervical transformation zone, including the lesion). More recently, WHO has endorsed the use of cryotherapy through an evidence-based review in 2011 and in 2014 *(4,5)*, and in the WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention and the updated C4-GEP review of 2014 *(6,7)*. Cryotherapy was found to have similar efficacy compared to excision of the CIN2+ lesion by large loop excision of the transformation zone (LLETZ). WHO also published a technical specifications document for cryosurgical equipment *(8)*.

One major disadvantage of cryotherapy is the need for a refrigerant gas (N_2O or CO_2). The gas containers are bulky and heavy transport and the gas is not always easily available in low- and middle-income countries (LMICs) *(9)*. In addition, cryotherapy can be costly: the purchase of can be expensive, alongside the purchase or rental of the tank. It has been reported that this can lead to delay and even lack of treatment after a positive screening test, which undermines prevention through a screen-and-treat approach. Novel ablative treatment methods have been developed since the last update of the C4GEP (9), for which member countries and key stakeholders have approached WHO for guidance on their use. To overcome the need for cryo-gas, companies have developed portable devices that use electricity to cool the treatment probe to freezing point. This technology is used in some new devices like the CryoPenTM (by Cryopen Inc.). The system consists of a hand-held copper tip that is inserted into a refrigeration unit, and reusable tips. The entire system weighs about 10 kg. There is also a device (Cryopop) that uses gas more efficiently by converting the gas into a solid in order to freeze tissue. It will be established whether these devices comply with the WHO technical specifications for cryotherapy equipment *(8)*.

Thermal ablation is another novel ablative treatment for CIN, and is sometimes called “cold coagulation” or “thermocoagulation”. WHO and the Guideline Development group decided to use the term thermal ablation, as it describes most closely what the treatment is. The equipment is fairly simple and treatment is based on a 20–30 second application of a reusable metallic probe that is electrically heated to approximately 100 °C, leading to epithelial and stromal destruction of the lesion. Conventional desktop devices weigh about 5 kg and are reasonably portable. Newer handheld, battery-operated devices weigh less than 2 kg, and are compact enough to carry in a backpack which makes for easy implementation in LMIC. The treatment time is shorter with thermal ablation. As in the case of cryotherapy,

[3] Globocan 2019

thermal ablation is provided by a variety of qualified health care personnel, including primary health care workers, and no anesthesia is required.

1.2 RATIONALE FOR RECOMMENDATIONS

Thermal ablation is currently not included in the latest version of the WHO guidelines for screening and treatment of precancerous lesions for cervical cancer, or WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ *(5,6)*. Although the technique was used quite frequently in the UK in the 1980s and early 1990s, there were few reports on its use. Hence WHO concluded at that time that there were insufficient efficacy and safety data to develop recommendations on its use at the time of the last revision of the C4GEP. However, evidence is now accumulating and has been synthesized in a meta-analysis that has now been updated *(10)*.

1.3 OBJECTIVES

The objectives of these guidelines are

- to provide evidence-based guidance on the use of thermal ablation for cervical precancer; and,
- to support countries in updating their national guidelines for the use of thermal ablation for cervical precancer.

1.4 TARGET AUDIENCE

This document is intended primarily for policy-makers, managers, programme officers, and other professionals in the health sector who have responsibility for choosing strategies for cervical cancer prevention and control, at country, regional, and district levels. Individuals working in reproductive health care programmes, particularly programmes for prevention of sexually transmitted infections including HIV/AIDS and for family planning, at the district and primary health care levels, should also consult this document to understand how recommendations are developed and why it is vitally important to select and implement evidence-based strategies to prevent cervical cancer. Technical terms used in the document are defined in the Glossary.

This document is intended primarily for policymakers, managers, programme officers, and other professionals in the health sector

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2. METHODS

These guidelines were developed following the methods outlined in the 2014 edition of the *WHO handbook for guideline development (11)*.

2.1 GUIDELINE DEVELOPMENT GROUP (GDG)

The GDG was established with 35 members who brought varied expertise in technical and societal aspects of screening and treatment of precancerous lesions (Annex A). Members were from the African Region, Region of the Americas, South-East Asia Region, European Region, and the Western Pacific Region. The GDG participated in in-person meetings and teleconferences to identify and prioritize questions to be addressed in this guideline, to discuss the evidence reviews, and to make recommendations. The GDG reviewed and approved the final version of this guideline.

2.2 QUESTIONS AND OUTCOMES

In April 2017, the GDG discussed the approach to develop the questions for this review based on the population, intervention, comparison and outcome framework (PICO). It was proposed to follow a similar set of recommendation questions from the 2011 cryotherapy guidelines *(4)*. The GDG agreed that recommendations should be made about the use of thermal ablation for the treatment of precancerous cervical lesions and about its use in screen-and-treat strategies. The group also agreed that evidence would be needed to inform the specific application of thermal ablation in practice, for example, in key populations, by specific health care professionals, and with specific modalities of use. PICO questions specific to thermal ablation were then prepared by the WHO secretariat in collaboration with the systematic review team and shared with the GDG. A final list of PICO questions was agreed upon during a teleconference with the GDG in September 2017 (Annex B).

The outcomes previously identified for the guidelines for treatment of precancerous lesions and screen-and-treat strategies to prevent cervical cancer *(5, 6)* were used as a basis for discussion by the GDG. The thermal ablation GDG reviewed and agreed upon the outcomes to use in this guideline via email and a teleconference call. The outcomes are included in the PICO questions in Annex B.

2.3 REVIEWS OF THE EVIDENCE

We used a hierarchical approach to search for evidence to make recommendations. We searched for systematic reviews, then primary studies when no systematic reviews were available. We used the evidence from a recently published systematic review and meta-analysis for the benefits and harms of thermal ablation that included studies in which at least one group of women received thermal ablation *(10)*. Randall and colleagues *(10)* conducted a comprehensive search of multiple databases up to December 2017 and reviewed references of included studies. We also searched for information about patient values and preferences, resources, acceptability, equity and feasibility related to thermal ablation from 1997 up to January 2018. We updated the search for the systematic reviews conducted for the WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ for cryotherapy for studies greater than 300 people since it was unlikely that studies of fewer than 300 people would change the previously calculated pooled proportions *(12)*. The search was conducted from 2012 to January 2018, but no new studies meeting the eligibility criteria were identified. We obtained preliminary data from the GDG for four ongoing or completed, but not yet published, studies in India, Peru and El Salvador, Zambia, South Africa. We also used the test accuracy data from the systematic review and meta-analysis for the WHO guidelines for screen-and-treat strategies to prevent cervical cancer by Mustafa and colleagues *(13)*. This search was conducted up to September 2012 and was not updated. The results were compared to field accuracy of the screening tests.

When there was little evidence available, we systematically obtained the observations of the GDG using a survey (www.surveymonkey.com). Questions in the survey were related to the modality of thermal ablation used, such as

timing of application, shape of probe, and temperature of probes (Annex C).

Two members of the systematic review team screened studies independently, and extracted and assessed the risk of bias of the individual studies using a tool specific to the study design (e.g. Cochrane Risk of Bias Tool for randomized controlled trials (www.handbook-5-1.cochrane.org) or used the risk of bias assessment in the published systematic reviews when available. We used the pooled analyses from systematic reviews when available. However, when not available, one member of the team synthesized the data quantitatively in RevMan 5.2 (https://community.cochrane.org/help/tools-and-software/revman-5) or narratively, and another member of the team verified the analyses. For dichotomous outcomes, we calculated a risk ratio with 95% confidence intervals by pooling results from randomized studies or pooling results from non-randomized studies with two groups using the random effects model. Effects were converted to absolute effects using the calculated relative effect and a representative baseline risk, typically the pooled proportion of the event without the treatment across studies. When studies with one group receiving an intervention were included (e.g., case series), a pooled proportion of an event (and confidence intervals) was calculated across the studies using the generic inverse variance. For continuous outcomes, a mean difference or a standardized mean difference (when studies used different scales to measure an outcome) was calculated.

For screen-and-treat recommendations, outcome data were not available from randomized or non-randomized studies. We therefore used the same model that was developed to make the recommendations for screen-and-treat strategies to prevent cervical cancer *(6)*. We used an Excel spreadsheet to calculate outcomes based on the sensitivity and specificity of the tests *(13)*, the natural progression of CIN, and treatment of CIN *(12)*.

The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (https://gdt.gradepro.org/app/handbook/handbook.html). The evidence is presented in GRADE evidence profiles and in evidence-to-decision frameworks that were created using GRADEpro (www.gradepro.org) (Annex D).

The certainty of the evidence is assessed at four levels in the GRADE approach:

- 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 the effect.

2.4 MAKING RECOMMENDATIONS

Recommendations were developed during four teleconference meetings with the GDG. The methodologist presented the evidence-to-decision frameworks during the meetings (completed evidence-to-decision frameworks are in Annex D and the evidence reviews are in Annex E). When formulating the recommendations, the GDG considered and discussed the desirable and undesirable effects of the interventions, the value placed on the outcomes, the associated costs and use of resources, the acceptability of the interventions to all stakeholders, the impact on health equity, and the feasibility of implementation. Judgements were made for each criterion above, and guideline recommendations were agreed. The goal was to reach consensus across the GDG. Disagreements among the GDG members were noted in the evidence-to-decision framework for each judgement. In the case of failure to reach consensus for a recommendation, the planned procedure was for the GDG to take a vote and record the results. However, no votes were taken because the GDG reached consensus during discussion for all of the recommendations. The recommendations were discussed via teleconference, reviewed and revised again by a core group of the GDG, and then final approval was obtained from all GDG members electronically. These guidelines were subsequently written up in full and peer reviewed by an External Review Group that approved the methods and agreed with the recommendations made by the GDG (members are listed in Annex A).

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Table 1. Implications of strong and conditional recommendations

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

According to the GRADE approach, the strength of each recommendation was rated as either strong or conditional. Strong recommendations were made when all the desirable consequences of treatment outweighed the undesirable consequences, and are presented using the wording "recommends". Conditional recommendations were made when the desirable consequences probably outweighed the undesirable consequences, and are worded as "suggests". The implications of the different strengths of recommendations for patients, clinicians and policy-makers are explained in detail in Table 1.

2.5 MANAGEMENT OF CONFLICTS OF INTEREST

We followed the WHO guidelines for declaration of interests (DOI) *(14)*. We obtained DOI statements from all GDG members prior to the guideline meetings, and members had to disclose any changes to their interests at the beginning of each meeting. We also updated their DOI statements before the publication of these guidelines. Three experts of the GDG participated in clinical trials on ablative treatment, but it was not assessed as a barrier to participating in the meetings and discussions. The WHO Secretariat concluded that there were no significant conflicts of interest that would exclude any member from participating fully in the guideline development process (see Annex A). Therefore, options for conditional participation, partial or total exclusion of any GDG member were not necessary.

3. DISSEMINATION, IMPLEMENTATION, EVALUATION AND UPDATING OF GUIDELINES

These guidelines are available as a printed publication, as a download on the website of the WHO Department of Reproductive Health and Research (with links to all supporting documentation), and in the WHO Reproductive Health Library (RHL). The guidelines will be announced in the next edition of the RHL newsletter and in the Reproductive Health and Research departmental newsletter, and other relevant organizations will be requested to copy the announcement in their respective newsletters.

WHO headquarters will work with WHO's regional offices and country offices to ensure that countries receive support in the adaptation, implementation and monitoring of these guidelines using the WHO Department of Reproductive Health and Research guidance on Introducing WHO's reproductive health guidelines and tools into national programmes.[4] These guidelines will also be disseminated at major conferences related to reproductive health, cancers, cervical cancer and HIV, and the aforementioned programme areas.

In the context of the Cervical Cancer Elimination Initiative, WHO and partners are working with a number of specific countries that will scale-up screening and treatment.[5] As part of the Initiative that aims at strengthening health systems to eliminate cervical cancer, monitoring systems will be particularly reviewed. In particular the following indicators will be measured: 1) process indicators as screening coverage and treatment coverage with cryotherapy or thermal ablation; 2) impact indicators with morbidity and mortality of cervical cancer through population-based cancer registries; and 3) quality and safety of services indicators. These will measure the use of this guideline and others, as well as the uptake of policies regarding cervical cancer control.

A system of monitoring relevant new evidence and updating the recommendations as new findings become available will be established within a year of implementing the guidelines. An electronic follow-up survey of key end-users of these guidelines will be conducted after the release of the guidelines.

The results of the survey will be used to identify challenges and barriers to the uptake of the guidelines, to evaluate their usefulness for improving service delivery, and to identify topics or gaps in treatment that need to be addressed in future editions.

In the context of the Cervical Cancer Elimination Initiative, WHO and partners are working with a number of specific countries that will scale-up screening and treatment

[4] http://whqlibdoc.who.int/hq/2007/WHO_RHR_07.9_eng.pdf?ua=1
[5] https://www.who.int/ncds/un-task-force/un-joint-action-cervical-cancer-leaflet.pdf

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4. RECOMMENDATIONS

These guidelines provide recommendations for the use of thermal ablation for the treatment of precancerous cervical lesions. These recommendations are applicable for women who have histologically confirmed CIN2+ or for women who have been screened positive in a screen-and-treat strategy. These recommendations expand on the treatment for screen-and-treat strategies as provided in the WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention (6).

In these recommendations the term LLETZ (Large Loop Excision of the Transformation Zone) is used for excision of the transformation zone (TZ) and represents a therapeutic intervention. LLETZ is the original terminology used for excision of the TZ, however in some countries this terminology was changed to LEEP (Loop Electro Excision Procedure) and the two terms are often used interchangeably. The term LEEP has also been used to refer to a diagnostic procedure, requiring the excision of up to 2 cm of tissue from the cervix for the pathologist to make an accurate diagnosis. These guidelines therefore use LLETZ to represent a therapeutic intervention to excise the TZ.

Box 1: Terminology for thermal ablation and LLETZ

Thermal ablation is also referred to as "thermocoagulation" and "cold coagulation". This guideline uses "thermal ablation" for the application of a reusable metallic probe that is electrically heated to approximately 100 °C, leading to epithelial and stromal destruction of the lesion.

The terms ***LLETZ*** (Large Loop Excision of the Transformation Zone) and LEEP (Loop Electro Excision Procedure) are often used interchangeably. This guideline uses LLETZ for the excision of the transformation zone (TZ) and represents a therapeutic intervention.

Eligibility for thermal ablation and cryotherapy

Eligibility for treatment requires a visual assessment ((visual assessment for treatment; VAT) which includes: colposcopy (if available) or naked eye examination of cervix after applying 3–5% acetic acid for 1 minute.

Clinicians usually describe what they see when performing visual inspection (for example, if the TZ is fully visible; if the whole lesion is visible; if the lesion extends into the endocervix), and then consider if the probe can reach the whole lesion. Clinicians can also consider the following classification from the International Federation for Cervical Pathology and Colposcopy according to the visibility of the TZ *(15)*.

- A type 1 TZ is completely ectocervical and is therefore fully visible.
- A type 2 TZ is partially endocervical but is still fully visible. It may be shallow and within range of an ablative probe or may extend beyond reach of an ablative probe.
- A type 3 TZ extends out of view up the endocervical canal, i.e., the squamocolumnar junction (SCJ) is not fully visible.

Following assessment as described above, women who screen positive are eligible for ablative therapy if there is no suspicion of invasive or glandular disease, and if:

- the TZ is fully visible, the whole lesion is visible and it does not extend into the endocervix; or
- the lesion is type 1 TZ; or
- the lesion is type 2 TZ where the probe tip will achieve complete ablation of the SCJ epithelium, i.e., where it can reach the upper limit of the TZ. Sometimes the SCJ can be seen high in the canal but a probe tip would not reach it.

Women who screen positive are not eligible for ablative therapy if there is any suspicion of invasive or glandular disease (i.e., adenocarcinoma or adenocarcinoma in situ), and:

- the TZ is not fully visible because it is endocervical (Type 3 TZ), or
- it is a type 2 TZ where the SCJ is out of reach of the probe tip.

Intervals for follow-up

Intervals for follow-up should be conducted according to the WHO guidelines *(5,6)*. According to those recommendations, all women who have received treatment should receive post-treatment follow-up at 1 year to ensure effectiveness of treatment. Post treatment follow-up is critical in particular for women living with HIV or women of unknown HIV status in areas with high endemic HIV infection.

RECOMMENDATION 1.A.

WHO suggests either LLETZ, or cryotherapy or thermal ablation to treat all women who have histologically confirmed CIN2+ disease and who are eligible for thermal ablation or cryotherapy.

(Conditional recommendation, moderate certainty in evidence of effects)

Remarks: The choice of LLETZ, cryotherapy or thermal ablation depends on the expertise, training, equipment and consumables available, infrastructure and resources in a programme. This recommendation applies to all women, including women living with HIV. See Figure 1.

RECOMMENDATION 1.B.

WHO suggests thermal ablation be provided at a minimum of 100 °C for 20–30 seconds using as many applications as needed to cover the entire transformation zone in overlapping fields.

(Conditional recommendation, very low certainty in evidence of effects)

Summary of the evidence

This recommendation is based on a previous recommendation that suggests either cryotherapy or LLETZ for the treatment of women with histologically confirmed CIN 2–3. That evidence showed that the benefits of LLETZ may be greater than cryotherapy, but the harms may be similar. When comparing the effects of thermal ablation to cryotherapy, there is moderate certainty evidence that there are trivial differences in the benefits and harms of these two treatments. Systematic reviews of randomized and non-randomized studies found evidence that there may be little to no difference between the proportion of women who are cured when treated with thermal ablation (91%) or cryotherapy (90%). A 2-probe method, in which treatment of the visible glandular epithelium with a small conical probe followed by treatment of the ectocervix with a flat probe, was used in some studies, and a one-probe method in others. Direct comparisons of probe methods within a study were not available, and the probe method used was often not reported by the author, and therefore assumptions were based on country setting and may not be accurate. Evidence showed that more women may be cured with a 2-probe method (95%; 95%CI, 93–98%) than a one-probe method (85%; 95%CI, 80–90%), but there is very low certainty in this evidence and more research is needed. The temperature of the probe typically used in studies was 100 oC, and subgroup analysis by 100 oC versus greater than 100 oC (up to 120 oC) did not show differences in curative effects. In most studies, the probe was applied for 20–30 seconds, and there was very low certainty evidence showing fewer cures with applications longer than 30 seconds. Multiple applications up to 5 times were used in most studies in order to cover the entire transformation zone. Very few studies compared these different modalities of thermal ablation, and therefore it is very uncertain which methods of application (temperature, type of probe, number of applications) result in more benefits and less harm.

Although rare, there was low certainty evidence for little to no difference in the number of major infections between the thermal ablation and cryotherapy. For major bleeds, there were inconsistent results from randomized controlled trials and non-comparative studies: low certainty evidence found that thermal ablation may result in slightly fewer major bleeds compared to cryotherapy, 6 fewer bleeds per 1000 women (from 11 to 0 fewer). Five small non-comparative studies found that there may be little to no difference in the number of women having premature deliveries after thermal ablation compared to the general population, but the evidence is uncertain. Based on moderate certainty evidence from randomized controlled trials, the acceptability of both thermal ablation and cryotherapy is likely similar. Though anaesthesia is typically not provided to women for either procedure, moderate certainty evidence showed that it is likely that slightly fewer women (5% fewer – from 16% fewer to 10% more) would have pain with thermal ablation compared with cryotherapy. The GDG agreed that women would probably value cure and the acceptability of the treatments (including pain) over other outcomes.

There are no comparative studies evaluating the benefits and harms of thermal ablation compared to other treatment methods or no treatment in women living with HIV with histologically confirmed CIN 2-3. There are very few studies evaluating cure or other outcomes with thermal ablation in women living with HIV. From the few studies, the proportion of cures in women living with HIV who were treated with thermal ablation was within the range of cures in women not living with HIV. The GDG agreed that given the benefits and harms are similar between thermal ablation and cryotherapy in women not living with HIV, then the benefits and harms between the two treatments in women living with HIV are likely similar. Since cure is typically lower in women living with HIV compared to women not living with HIV, follow-up is important, especially after ablative treatment.

The GDG agreed that the initial cost of thermal ablation and cryotherapy units is often similar, but for cryotherapy the maintenance costs are likely greater and there is the additional cost of gas and transport of gas tanks. The latter made cryotherapy less feasible in some settings and therefore could delay prompt treatment. Thermal ablation requires electricity to charge the batteries for battery-driven devices, or solar power for some models. The GDG also considered that many health care providers may find thermal ablation more acceptable to provide because it takes less time to perform, is easy to perform, and in some settings, is perceived to cause less pain.

Overall, the differences between benefits and harms of thermal ablation and cryotherapy are trivial, but there are likely large resource savings with the use of thermal ablation. Thermal ablation is also probably more acceptable to providers, more available, and therefore more feasible to implement than cryotherapy in some settings. Therefore, the choice between thermal ablation or cryotherapy will be based on expertise, training, equipment and consumables, and infrastructure and resources in a programme. Since a previous recommendation suggests either cryotherapy or LLETZ, and there are trivial differences between cryotherapy and thermal ablation, this recommendation suggests the use of thermal ablation, cryotherapy or LLETZ. This recommendation is also consistent with remarks in previous recommendations to base the choice of which treatment to use on available resources. See Annex D for evidence-to-decision frameworks and evidence reviews.

RECOMMENDATION 2

In exceptional conditions when LLETZ is not available for women who have histologically confirmed CIN2+ disease or are not eligible for cryotherapy or thermal ablation, WHO recommends an alternative treatment. 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. See Figure 1.

(Strong recommendation, very low certainty in evidence of effects)

Remarks: This recommendation applies to all women, including women living with HIV.

Summary of the evidence

We found no evidence comparing the use of ablative treatments with excisional procedures to treat transformation zone or lesions extending into the cervical canal or covering more than 75% of the ectocervix. When reported, non-comparative studies evaluating thermal ablation (and other ablative therapies) exclude these women, or refer them to excisional procedures. The GDG agreed that it is likely that thermal ablation tips will not reach or cover these lesions, resulting in failed treatment or recurrence which can lead to cervical cancer. It is also essential to perform excisional therapy in order to not inadvertently miss an invasive lesion. For these reasons, the GDG agreed that when LLETZ is not available to a women who is not eligible for

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cryotherapy or thermal ablation, other excisional therapies should be provided, including cone biopsy, trachelectomy or hysterectomy. The type of excision therapy provided will be based on the resources available and skills of the providers. See Annex D for evidence-to-decision frameworks and evidence reviews in Annex E.

RECOMMENDATION 3

WHO suggests providing either thermal ablation or cryotherapy to women screened positive with hrHPV or VIA or hrHPV followed by VIA, with no histological confirmation and who are eligible for ablative treatment, or providing LLETZ when the woman is not eligible for cryotherapy or thermal ablation.

(Conditional recommendation, very low certainty in evidence of effects)

Remarks: This recommendation applies to all women, including women living with HIV. The choice of screening tests is based on WHO recommendations for screening and treatment. See Figure 2.

Summary of the evidence

The evidence comparing the effects of treatment with thermal ablation to cryotherapy was used to model the effects of providing either treatment after screening with hrHPV, VIA or HPV followed by VIA. The evidence for the effects of treating women with confirmed CIN2+ lesions from a systematic review of randomized and non-randomized studies was used in the model (see Recommendation 1, Summary of evidence). The test accuracy of hrHPV (95% sensitivity, 84% specificity) and VIA (60% sensitivity, 84% specificity) from a systematic review of evidence and the field were used.

In 1 million women being treated, there may be slightly fewer CIN2+ recurrences when providing thermal ablation rather than cryotherapy (200–400 fewer), as well as fewer cervical cancers (6–9 fewer) and fewer deaths (1–4 fewer). There may be slightly fewer major bleeds (300–1200) or major infections (40–180 fewer) with thermal ablation. The number of women experiencing pain may be lower (1700–7000 fewer). The GDG agreed that women would probably value cure and the acceptability of the treatments (including pain) over other outcomes. The differences were similar to the benefits and harms found when modelled for women living with HIV.

The GDG agreed that better resource use, feasibility, and accessibility seen with programmes in which CIN2-3 lesions are histologically confirmed would be applicable to screen-and-treat programmes. This may mean that thermal ablation may lead to more immediate treatment within screen-and-treat programmes compared to cryotherapy in some settings.

Overall, the differences between benefits and harms of providing thermal ablation and cryotherapy in a screen-and-treat programme are small, but there are likely large resource savings with the use of thermal ablation. Thermal ablation is also probably more acceptable to providers, does not require a renewable resource such as gas, is more portable than cryotherapy, and therefore more feasible to provide than cryotherapy as part of a screen-and-treat programme in some settings. See Annex D for evidence-to-decision frameworks and Annex E evidence reviews.

RECOMMENDATION 4

WHO suggests that prophylactic antibiotics are not used when providing thermal ablation.

(Conditional recommendation, very low certainty in evidence of effects)

Summary of the evidence

There are no randomized or non-randomized studies that compare the benefits or harms of providing antibiotics or not when women receive thermal ablation. Instead, the pooled proportion of infections requiring treatment was 0.09% (2/1407) across studies where antibiotic use was confirmed, and 0.14% (15/2675) in studies that did not report use (but not confirmed). The GDG agreed that although there may be fewer infections requiring treatment when antibiotics are provided prophylactically, there is a risk of increased antimicrobial resistance and allergic reactions. There was no information about women's preferences or cost of taking antibiotics, but costs are likely greater with antibiotic use. Overall, the potential harms and additional resources probably outweigh any benefits. See Annex D for evidence-to-decision frameworks and evidence reviews.

RECOMMENDATION 5

WHO suggests that trained nurses, midwives or health care workers as well as physicians may perform thermal ablation in order to ensure the availability and accessibility of treatment.

(Conditional recommendation, very low certainty in evidence of effects)

Summary of the evidence

There is very low certainty of evidence for differences in the benefits and harms when different health care professionals provide thermal ablation, and there are no trials comparing the consequences of thermal ablation between different health care professionals. Therefore, the proportion of women cured when receiving thermal ablation by colposcopists, gynaecologists, physicians, or non-physicians (including nurses or other health care workers) across individual studies was calculated. The review found that there may be little to no difference in the proportion of women with biopsy confirmed CIN 2-3 who are cured. There is also little to no difference in major bleeding or infections requiring treatment, but this is very uncertain as the analysis included few studies in which a non-physician provided thermal ablation. Major bleeding occurred in 0.1% when provided by physician and 0% by non-physician, and infections occurred in 0.08% when provided by physician and 0% by non-physician. The evidence suggests that fewer women experience pain when a non-physician provides thermal ablation – approximately 50% compared to 70% when provided by a physician. There were no data for premature deliveries. The GDG agreed that women would probably value cure and the acceptability of the treatments (including pain) over other outcomes.

The GDG agreed that if trained nurses or other health care workers provided thermal ablation, the costs would be lower than if physicians performed thermal ablation. Training non-physicians may also increase the availability and accessibility of thermal ablation, and reduce delays in treatment.

Overall, the differences between benefits and harms between different health care providers performing thermal ablation are trivial, with the exception of pain, which favours non-physicians performing thermal ablation. When non-physicians perform thermal ablation the costs are likely lower, and it may increase availability and accessibility of thermal ablation which may increase the benefits of treatment. See Annex D for evidence-to-decision frameworks and evidence reviews.

RECOMMENDATION 6

In settings where LLETZ is available and accessible, WHO suggests LLETZ rather than thermal ablation or cryotherapy for women who test positive after prior thermal ablation or cryotherapy.

(Conditional recommendation, very low certainty in evidence of effects)

In settings where LLETZ is unavailable or inaccessible, the GDG recommends thermal ablation or cryotherapy rather than no treatment for women who test positive after prior thermal ablation or cryotherapy.

(Strong recommendation, very low certainty in evidence of effects)

Remarks: This recommendation is consistent with the recommendation to provide LLETZ after prior cryotherapy.

Summary of the evidence

We found no studies that directly compared the number of women who were cured after retreatment with thermal ablation or cryotherapy or LLETZ. Three studies reported that 34/40 women with histologically confirmed CIN2+ disease who screened positive after 4 months to 2 years were cured when retreated with thermal ablation (85% (CI 95%, from 74 to 96%). In comparison, a review of studies found that approximately 74% of women previously treated with cryotherapy who were retreated with cryotherapy were cured, and 92% of women retreated with conization were cured. No studies measured adverse effects when retreating with thermal ablation versus other treatments.

Overall, the evidence is uncertain about the effects of retreatment with thermal ablation, cryotherapy, LLETZ or conization in women who test positive after previous treatment with thermal ablation. Given the paucity of evidence, the GDG agreed that the recommendation for LLETZ would be consistent with a previously published recommendation to provide LLETZ for women who screen positive after prior treatment with cryotherapy. See Annex D for evidence-to-decision frameworks and evidence reviews.

This guidelines is based on the best available evidence for the benefits and harms of thermal ablation and consideration of issues related to patient values and preferences, acceptability, feasibility, equity, and resources.

5. RESEARCH IMPLICATIONS

The WHO guidelines are based on the best available evidence for the benefits and harms of thermal ablation compared to other treatments to prevent cervical cancer, and on the consideration of issues related to patient values and preferences, acceptability, feasibility, equity, and resources. The evidence in this area continues to grow, and we provide guidance about the conduct of future research that may have an impact on the recommendations or strength of the recommendations in the next update of this guideline. For this guideline, a comprehensive and up-to-date systematic review and meta-analysis was used to inform most of these recommendations for thermal ablation *(10)* and additional systematic reviews were conducted.

However, few studies compared thermal ablation to other treatments for histologically confirmed precancerous cervical lesions. Instead, studies that followed a single group of women who received thermal ablation were used and these results were indirectly compared to evidence from studies that followed a single group of women receiving the other treatments. For many recommendations, this indirect evidence resulted in recommendations based on low or very low certainty evidence. Although the GDG was able to also use preliminary results from small ongoing trials comparing thermal ablation to other treatments, more comparative studies are needed. The need for comparative studies is urgent, particularly in women living with HIV, where there is little information about cures with thermal ablation, and no information about other important outcomes, such as HIV shedding or risk of transmission after treatment. The search for evidence also found few studies in which thermal ablation was used in a screen-and-treat strategy when CIN is not histologically confirmed.

There were also few studies that reported on outcomes after treatment of women who screened positive for precancerous lesions after prior treatment with thermal ablation. Additional studies assessing health delivery models of screen-and-treat strategies which include thermal ablation are needed. Studies evaluating delivery in rural health facilities or mobile outreach services could be compared to models in fixed referral sites and the use of centralized or decentralized testing. Studies should follow these women from screen-and-treat programmes and report their outcomes. Future research should also include not just outcomes for cure and major complications, but also for outcomes that the GDG identified as important to women, such as fertility and reproductive outcomes.

There is also little information about the best methods to apply thermal ablation in practice. There were no published studies that compared different modalities, such as one- or two-probe methods, different temperatures of the probes, or timing and number of applications. The GDG did not recommend one modality over another for this reason, but there was much discussion in particular about the one- or two-probe methods. While it is thought that the practice in the UK is the two-probe method, little could be concluded from studies in that setting as the studies did not adequately describe the method. In future, studies should clearly report the method of thermal ablation used, and studies comparing different modalities should be conducted.

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REFERENCES

1. IARC/WHO. GLOBOCAN 2019: Estimated cancer incidence, mortality and prevalence worldwide in .2019. Cervical Cancer Fact Sheet. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-Uteri-fact-sheet.pdf.

2. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study. Lancet Oncol. 2019 Mar;20(3):394-407. doi: 10.1016/ S1470-2045(18)30836-2. Epub 2019 Feb 19.

3. Denny L, Kuhn L, Hu CC, Tsai WY, Wright TC Jr. Human papillomavirus-based cervical cancer prevention: long-term results of a randomized screening trial. J Natl Cancer Inst. 2010;102(20):1557–67. https://pdfs.semanticscholar.org/8b2f/227630d7c8cd5f623c11ef3a5aa567aaf987.pdf https://bmjopen.bmj.com › content by F Pesola - 2019 - Lönnberg S, Anttila A, Luostarinen T, Nieminen P. Age-specific effectiveness of the Finnish cervical cancer screening programme. Cancer Epidemiol Biomarkers Prev 2012; 21: 1354–61. https://www.ncbi.nlm.nih.gov/pubmed/22665576.
Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, Wiener H, Herbert A, von Karsa L. European guidelines for quality assurance in cervical cancer screening. Second edition – summary document. Ann Oncol. 2010; 21: 448–58. https://www.ncbi.nlm.nih.gov/pubmed/20176693.

4. WHO guidelines – use of cryotherapy for cervical intraepithelial neoplasia. Geneva: World Health Organization; 2011 (http://www.who.int/reproductivehealth/publications/cancers/9789241502856/en/, accessed 20 June 2019).

5. WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ: cryotherapy, large loop excision of the transformation zone, and cold knife conization. Geneva: World Health Organization, 2014 (https://www.who.int/reproductivehealth/publications/cancers/treatment_CIN_2-3/en/, accessed 20 June 2019).

6. WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva: World Health Organization; 2013 https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/, accessed 20 June 2019).

7. WHO – Comprehensive cervical cancer control: a guide to essential practice. 2nd edition. Geneva: World Health Organization; 2014 (http://www.who.int/reproductivehealth/publications/cancers/cervical-cancer-guide/en/, accessed 20 June 2019).

8. WHO technical specifications: cryosurgical equipment for the treatment of precancerous cervical lesions and prevention of cervical cancer. Geneva: World Health Organization; 2012 (http://www.who.int/reproductivehealth/publications/cancers/9789241504560/en/, accessed 20 June 2019).

9. Paul P, Winkler JL, Bartolini RM, Penny ME, Huong TT, Nga lT, et al. Screen-and-treat approach to cervical cancer prevention using visual inspection with acetic acid and cryotherapy: experiences, perceptions, and beliefs from demonstration projects in Peru, Uganda, and Vietnam. Oncologist. 2013;18(12):1278-1284.

10. Randall TC, Sauvaget C, Muwonge R, Trimble EL, Jeronimo J. Worthy of further consideration: An updated meta-analysis to address the feasibility, acceptability, safety and efficacy of thermal ablation in the treatment of cervical cancer precursor lesions. Prev Med. 2019;Jan;118:81–91.

11. WHO handbook for guideline development, 2nd edition. Geneva: World Health Organization; 2014 (http://www.who.int/kms/handbook_2nd_ed.pdf, accessed 6 September 2016).

12. Santesso N, Mustafa RA, Wiercioch W, Kehar R, Gandhi S, Chen Y, et al. Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. Int J Gynaecol Obstet. 2016;Mar;132(3):266–71.

13. Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, et al. Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. Int J Gynaecol Obstet. 2016;132(3):259–65.

14. WHO guidelines for declaration of interests (WHO experts). Geneva: World Health Organization; 2014.

15. Bornstein J, Bentley J, Bosze P, Girardi F, Haefner H, Menton M, et al. 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol. 2012 Jul:120(1):166–72.

GLOSSARY

Cervical intraepithelial neoplasia (CIN): a precancerous condition involving the covering layer (epithelium) of the cervix. It can be diagnosed using a microscope. The condition is graded as CIN1, 2 or 3, according to the thickness of the abnormal epithelium (one third, two thirds or the entire thickness)

Cold knife conization (CKC): the removal of a cone-shaped area from the cervix, including portions of the outer (ectocervix) and inner cervix (endocervix), usually done in a hospital; the amount of tissue removed will depend on the size of the lesion and the likelihood of finding invasive cancer

Colposcopy: the examination of the cervix, vagina and vulva with an instrument that provides strong light and magnifies a field, allowing specific patterns in the epithelial (surface) layer and surrounding blood vessels to be examined

Cryotherapy: by applying a highly cooled metal disc (cryoprobe) to the cervix and freezing the abnormal areas (along with normal areas) covered by it, cryotherapy eliminates precancerous areas on the cervix by freezing (i.e. It is an ablative method)

Cytology: the study of the structure of cells under the microscope; abnormal findings are usually confirmed by biopsy

Epithelium (plural – epithelia): a covering or lining, comprising one or more layers of cells; usually protective of the organ it covers

Histologically: the study of the microscopic structure of tissues; a histological examination uses thin slices of stained tissue to determine the presence or absence of disease

Hysterectomy: surgery to remove the uterus and, sometimes, the cervix (when the uterus and the cervix are removed, it is called a total hysterectomy; when only the uterus is removed, it is called a partial hysterectomy)

Neoplasia: process of new growth or tumour formation, sometimes malignant

Screening: a public health intervention provided to an asymptomatic target population; it is not undertaken to diagnose a disease, but to identify individuals with increased probability of having either the disease itself or a precursor of the disease

Sensitivity: the proportion of people who have a condition who are identified correctly by a test (true positives).

Specificity: the proportion of people who do not have a condition who are correctly identified by a test (true negatives)

Trachelectomy: surgical removal of the uterine cervix, without removal of the uterine fundus

ANNEXES

ANNEX A

MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP (GDG)

Name	Region	Country	Institution	Declarations of conflicts of interest				Meeting restriction
				Involved in related academic work	Declared any related commercial financial interest	Declared any indirectly related commercial financial interest	Declared related non-commercial interest or grants	
Claire Judith Ikaté Achieng	Africa	Uganda	Cancer Society, Uganda	No	No	No	No	No
Pierre Marie Tebeu	Africa	Cameroon	Centre Hospitalier Universitaire, Yaoundé	Yes	Yes but no explanation	No information	No	No: did not preclude participation
Lynette Denny	Africa	South Africa	University of Cape Town	Yes	No	No	No	No
Mamadou Diop	Africa	Senegal	Joliot Curie Cancer Institute, Dakar	Yes	No	No	No	No
Michael Chung	Africa	Kenya	Aga Khan University of Nairobi	Yes	No	No	No	No
Motshedisi Sebitloane	Africa	South Africa	University of Kwazulu-Natal, Durban	Yes: study on screen-and-treat algorithms describing side-effects of cryotherapy and thermal ablation. No salary support	No	No	No	No
Maribel Almonte	Europe	France	International Agency for Research on Cancer, Lyon	Yes	No	No	No	No

Name	Region	Country	Institution	Declarations of conflicts of interest				Meeting restriction
				Involved in related academic work	Declared any related commercial financial interest	Declared any indirectly related commercial financial interest	Declared related non-commercial interest or grants	
Marc Arbyn	Europe	Belgium	Belgian Cancer Centre / Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels	No	No	No	Yes: contribution to conduct a meta-analysis on the accuracy of margin status vs HPV testing to predict outcome of treatment of CIN. European Federation of Colposcopy, 2016	No
Béatrice Lauby-Secretan	Europe	France	International Agency for Research on Cancer, Lyon	No	No	No	No	No
Rolando Herrero	Europe	France	International Agency for Research on Cancer, Lyon	Yes	No	No	No	No
Walter Prendiville	Europe	Ireland	International Agency for Research on Cancer, Lyon	Yes: ongoing grant to IARC to develop and evaluate a new hand-held thermal coagulator. Senior Visiting Scientist & project Manager for this study	Yes: advised Liger redesign of a thermal coagulator (no payment). Received royalties from Utah Med. for a loop used in the USA (<US$ 1000)	No	No	No
Partha Basu	Europe	France	International Agency for Research on Cancer, Lyon	Yes	No	No	No	No
Patrick Petignat	Europe	Switzerland	Hôpitaux Universitaires de Genève	Yes	No	No	No	No
Wendy McMullen	Europe	Scotland	NHS Tayside, Dundee	Yes	No	No	No	No
Thomas Randall	Americas	USA	Harvard Medical School, Boston	Yes	No	No	No	No

Name	Region	Country	Institution	Declarations of conflicts of interest				Meeting restriction
				Involved in related academic work	Declared any related commercial financial interest	Declared any indirectly related commercial financial interest	Declared related non-commercial interest or grants	
Miriam Cremer	Americas	USA	Basic Health International, New York	Yes	No	No	Yes: PI NIH grant to develop and test the CryoPen for use in LMIC. No money received from WiSAP or from Cryopen for work nor will benefit directly if the devices are successful. Salary support given regardless of trial results	No
Vivien Tsu	Americas	USA	PATH, Seattle	Yes				
Philip E Castle	Americas	USA	Albert Einstein College of Medicine, New York	Yes	No	No	No	No
Silvia de Sanjose	Americas	USA	PATH Seattle	Yes	No	Yes: agreement and provision of free vaccines for a European FP7 project	Yes: Merck grant for analysis of data impact of Gardasil 9, 9-valend HPV vaccine	No
Julia Gage	Americas	USA	National Cancer Institute, Bethesda	Yes	No	No	No	No
Isabelle Heard	Americas	France	Hôpital Tenon, Paris	No	No	No	No	No
Jose Jeronimo	Americas	USA	Global Coalition Against Cervical Cancer, New York	Yes	No	No	Yes: 2 thermo coagulator devices were donated to PATH, the entity where he used to work, for additional testing	No
Silvana Luciani	Americas	USA	Pan American Health Organization, Washington	No	No	No	No	No

Name	Region	Country	Institution	Declarations of conflicts of interest				Meeting restriction
				Involved in related academic work	Declared any related commercial financial interest	Declared any indirectly related commercial financial interest	Declared related non-commercial interest or grants	
Mauricio Maza	Americas	El Savador	Basic Health International, Salvador	Yes	No	No	Yes: Innovative Treatment for Cervical Precancer (UH3) grant with NCI. Salary allocation received for current year	No
Raul Murillo	Americas	Colombia	Centro Oncológico Javeriano, Bogota	No	No	No	No	No
Srabani Mittal	South-East Asia	India	Child In Need Institute, Kolkata	No	No	No	No	No
Swee Chong Quek	South-East Asia	Singapore	ASC Clinic for Women, Singapore	Yes: member of advisory committee on cervical cancer prevention	No	Yes: honoraria for giving lectures related to HPV vaccines (GSK Merck)	No	No
Ugyen Tshomo	South-East Asia	Bhutan	Jigme Dorji Wangchuck National Referral Hospital, Thimphu	No	No	No	No	No
Smita Joshi	South-East Asia	India	Department of Preventive Oncology, Prayas and HCJMRI, Pune	No	No	No	No	No
Ashrafunnessa	South-East Asia	Bangladesh	Bangabandhu Sheikh Mujib Medical University, Shahbag	No	No	No	No	No
You-lin Qiao	Western Pacific	China	Cancer Foundation of China	Yes	No	No	No	No
Fanghui Zhao	Western Pacific	China	National Cancer Center and Cancer Hospital, Beijing	Yes	No	No	No	No

Name	Region	Country	Institution	Declarations of conflicts of interest				Meeting restriction
				Involved in related academic work	Declared any related commercial financial interest	Declared any indirectly related commercial financial interest	Declared related non-commercial interest or grants	
John Kaldor	Western Pacific	Australia	The Kirby Institute UNSW, Sydney	Yes: Cepheid has provided loan of genexpert platforms with no involvement in research design, conduct, analysis or interpretation.	No	No	No	No
Enriquito R Lu	Americas	USA	JHPIEGO	Yes: patent for the CryoPop, a cryotherapy device using solid carbon dioxide (dry Ice). Ultimately, the university holds all the intellectual rights to this device	No	No	No	No: did not preclude participation as CryoPop not discussed

MEMBERS OF THE EXTERNAL REVIEW GROUP (ERG)

Name	Region	Country	Institution	Declarations of conflicts of interest				Meeting restriction
				Involved in related academic work	Declared any related commercial financial interest	Declared any indirectly related commercial financial interest	Declared related non-commercial interest or grants	
Silvina Arrossi		Argentina	CEDES	Yes	No	No	No	No
Neerja Bhatla	South-East Asia	India	All India Institute of Medical Sciences	Yes	No	No	5a. No 5b. Yes Chairperson, Gynecologic oncology Committee, Federation of Obstetrics and Gynecological societies of India (FOGSI), 2015–17 Chairperson, Gynecologic oncology Committee, International Federation of Obstetrics and Gynecology (FIGO), 2015–18	No
Mike Chirenje	Africa	Zimbabwe	University of Zimbabwe	Yes	No	No	No	No

Name	Region	Country	Institution	Declarations of conflicts of interest				Meeting restriction
				Involved in related academic work	Declared any related commercial financial interest	Declared any indirectly related commercial financial interest	Declared related non-commercial interest or grants	
Heather A Cubie	Europe	Scotland	University of Edinburgh, Scotland	Yes	No	2a No Honorarium; Chaired User's HPV meeting, November 2015; Abbott Molecular; Income £ 1000 2b Yes Provision of 2 GeneXpert platforms (each 4 cartridges) and discounted HPV cartridges for Scottish Government-funded project in Nkhoma Hospital, Malawi; Cepheid Inc;	1b Yes Consultancy fee related to PQDx 0085-028-00, August 2015; WHO; Income EUR 1500 5a Yes I was asked as an expert on HPV tests to assess dossier submitted by Qiagen to WHO for pre-qualification of careHPV (PQDx0085-028-00). I have never used nor had access to careHPV. This work was completed August	No

Name	Region	Country	Institution	Declarations of conflicts of interest				Meeting restriction
				Involved in related academic work	Declared any related commercial financial interest	Declared any indirectly related commercial financial interest	Declared related non-commercial interest or grants	
						Equipment owned by Cepheid but loaned to Nkhoma Hospital, Malawi; Income: Unknown value, discount on kits probably around 30%; project completed but equipment still at Nkhoma Hospital	2015 and I was paid EUR 1500 through University of Edinburgh. See also 1b. I was associated with the collection of careHPV samples in Nkhoma Hospital Malawi which were sent to Scottish HPV Reference Laboratory in Edinburgh for testing The only link to the current DOI is that the HPV work in Nkhoma Hospital was associated with an ongoing, same-day screen-and-treat service which uses thermoablation. I have no responsibility for that service, although I was the lead for the Scottish Government grant (MW01 2013–2016) which led to the introduction by others of thermoablation at Nkhoma	

Name	Region	Country	Institution	Declarations of conflicts of interest				Meeting restriction
				Involved in related academic work	Declared any related commercial financial interest	Declared any indirectly related commercial financial interest	Declared related non-commercial interest or grants	
Chandoni Anoma Jayathilaka	South-East Asia	India	WHO, South-East Asia Region	No	No	No	No	No
Akintade Oluwasanmi	Africa	Lesotho	Elizabeth Glaser Pediatrics Aids Fondation	No	No	No	No	No
Edward Trimble	Americas	USA	US National Cancer Institute	Yes	No	No	No	No
Andrew Vallely	Western Pacific	Australia	Kirby Institute, UNSW Sydney, Australia	No	No	No	No	No

WHO SECRETARIAT

Members	Department and Team
Nathalie Broutet	Department of Reproductive Health and Research Human Reproduction Team
Meg Doherty	Department of HIV/AIDS
Hugo De Vuyst	Department of Reproductive Health and Research Human Reproduction Team / IARC Prevention and Implementation group
Elena Fidarova	Department of Management of Non-communicable Diseases
James Kiarie	Department of Reproductive Health and Research Human Reproduction Team
Andre Ilbawi	Department of Management of Non-communicable Diseases
Morkor Newman Owiredu	Intercountry Support Team, Family and Reproductive Health Cluster
Cherian Varghese	Department of Management of Non-communicable Diseases
Adriana Velazquez	Department of Innovation, Access and Use

SYSTEMATIC REVIEW TEAM: Angela Barbara, Housne Begum, Laura Fullerton, Holger Schünemann (Principal Investigator), The Michael G. DeGroote Cochrane Canada Centre, McMaster University
METHODOLOGIST: Nancy Santesso, The Michael G. DeGroote Cochrane Canada Centre, McMaster University

ANNEX B
Additional methods for guideline development

Final PICO questions

1.a. Should thermal ablation versus cryotherapy be used in women with histologically confirmed CIN?
1.b. Should thermal ablation versus LLETZ be used in women with histologically confirmed CIN2/3/AIS?

Subgroups for question 1:
Women with different lesion size
Women with endocervical involvement
Women who are HIV-positive
Women at different age groups

2. Should thermal ablation or versus cryotherapy or LEEP or cold knife conisation be used in a screen-and-treat algorithm being hrHPV+, VIA+, or positive by cytology (LSIL of HSIL cut off)?

3. Should one modality of thermal ablation be used versus another modality?
Differences in modalities include temperature, number applications, duration, shape and size of probes and treatment procedure.

4. After thermal ablation, Sshould antibiotics be provided prophylactically after thermal ablation or not?

5. Should thermal ablation be provided by a non-physician versus physician?

6. Should thermal ablation versus LLETZ or cold knife conisation be used for treatment failures diagnosed >12 months after first thermal ablation treatment?

Outcomes

Residual and recurrent CIN2+ (if assessed histologically, by degree of CIN) (long term if available: cervical cancer, mortality); pain, bleeding, infections (+/- antibiotics), and obstetrical effects.

ANNEX C
Survey to collect systematic observations of the Guideline Development Group

Evidence for the implementation of thermal ablation

This is not a survey. It is a form to systematically gather your observations about the implementation and feasibility of thermal ablation so that the World Health Organization can make recommendations.

In order to make recommendations, we need to systematically gather evidence from published literature and unpublished literature. To date, there is little literature about the implementation and feasibility of using thermal ablation. The information you provide about the screen-and-treat programme or practice will be the evidence upon which we will make the recommendations. The information should not be your opinion based on what you have heard or read, it is your experiences and observations.

Please note that you can answer the questions from the perspective of the whole programme or your own practice. The information you provide will be summarized with other information. It will not be presented in connection with a specific programme or clinic or your practice.

Please complete these questions before [date]….

1. Are you a member of the WHO Guideline Development Group for making recommendations for thermal ablation in women with CIN?

Yes [ ] No [ ]

2. Do you currently have or participate in a screen and treat programme for cervical cancer screening?

No [ ] Yes, please provide the programme/clinic name and location [ ]

3. How many years has this programme or practice been in place?

4. How many screening clinics are included?

5. Approximately how many women are screened each day?

6. What percentage of women do you estimate to be HIV positive?

WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions - Annexes

7. Do you treat women at the screening clinic or do you refer them?

[ ] All women are treated on site
[ ] Some women are referred and some women are treated on site
[ ] All women are referred

8. How many women are treated at the clinic each week?

9. Does the programme provide thermal ablation?

Yes [ ] No, please provide reason(s) for not providing [ ]

10. What percentage of the screened positive women are treated with thermal ablation?

11. Approximately how many years has the programme offered thermal ablation?

12. Are/were there any barriers to providing thermal ablation?

13. Are/were there any factors that made providing thermal ablation easier compared to cryotherapy?

14. Please describe any resources or costs of providing thermal ablation that are different from other techniques:

15. What temperature is typically used?

16. How many seconds do you apply the heated probe?

17. What is the maximum number of times you would apply the probe?

18. What shape and size of probes are used? Select all that you provide.

[ ] Flat probe
[ ] Probe with nipple
[ ] Cone-shaped

19. How is the equipment sterilized? Please describe.

20. Which equipment do you use? Please select all that are used.

[ ] Standard electricity powered
[ ] Hand-held battery operated

21. Does the programme provide cryotherapy?

No [ ] Yes, please provide percentage of women receiving cryotherapy [ ]

22. Would your choice of either cryotherapy or thermal ablation be influenced by any of the following criteria? Please indicate your choice of treatment or whether it does not influence choice.

	Preferred choice is cryotherapy	Preferred choice is thermal ablation	No preference for cryotheraphy or thermal ablation
Bigger lesion	[ ]	[ ]	[ ]
Endocervical involvement of lesion	[ ]	[ ]	[ ]
Non/partial visible junction	[ ]	[ ]	[ ]
Older woman	[ ]	[ ]	[ ]
HIV positive status woman	[ ]	[ ]	[ ]
Woman contemplating pregnancy	[ ]	[ ]	[ ]

Comments:

23. Does the programme provide LEEP/LLETZ?

No [ ] Yes. Please provide percentage of women receiving LEEP/LLLETZ. [ ]

24. Does the programme provide other techniques? Please list and indicate percentage of women receiving the other techniques.

25. Based on your experiences in your programme, choose which of the techniques would have a HIGHER chance of the outcome. This is based on your experiences, not what you have read or heard.

If you do not provide one of the techniques do not consider it in your rankings, but please indicate the technique at the end of the question.

	Thermal ablation	Cryotherapy	LEEP/LLETZ	Don't know
More recurrence of CIN	[ ]	[ ]	[ ]	[ ]
More minor bleeding	[ ]	[ ]	[ ]	[ ]
More major bleeding	[ ]	[ ]	[ ]	[ ]
More minor infections	[ ]	[ ]	[ ]	[ ]
More major infections	[ ]	[ ]	[ ]	[ ]
More pain	[ ]	[ ]	[ ]	[ ]
Higher risk of poor pregnancy/fertility outcomes	[ ]	[ ]	[ ]	[ ]
More acceptable to women	[ ]	[ ]	[ ]	[ ]
More acceptable to clinician providing technique	[ ]	[ ]	[ ]	[ ]

I did not consider the following technique in my ranking:

ANNEX D
Evidence to decision frameworks

Should thermal ablation versus cryotherapy be used for women with histologically confirmed CIN 2-3? (Recommendations 1 and 2)

POPULATION:	women with histologically confirmed CIN 2-3
INTERVENTION:	thermal ablation
COMPARISON:	cryotherapy
MAIN OUTCOMES:	cure; pain; major bleeding; infection (including fever); premature delivery; acceptability
SETTING:	outpatient
PERSPECTIVE:	population
BACKGROUND:	Thermal ablation is another ablative treatment for CIN, also called "cold coagulation". Treatment is based on a 20–40 second application of a reusable metallic probe that is electrically heated to 100 °C, leading to epithelial and stromal destruction of the lesion. Cryotherapy eliminates precancerous areas on the cervix by freezing (an ablative method). It involves applying a highly cooled metal disc (cryoprobe) to the cervix and freezing the abnormal areas (along with normal areas) covered by it. The supercooling of the cryoprobe is accomplished using a tank with compressed carbon dioxide (CO_2) or nitrous oxide (N_2O) gas. Companies have developed hand-held devices that use electricity to cool the treatment probe to freezing temperatures. This technology is used in some new devices like the CryoPenTM (by Cryopen Inc.). The system consists of hand-held freeze modules, a lightweight refrigeration unit, and reusable tips.
CONFLICT OF INTERESTS:	See Annex A

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [ ] Probably yes [✓] **Yes** [ ] Varies [ ] Don't know	Thermal ablation is not covered in the WHO guidelines for the treatment of CIN2-3. Current WHO recommendations for women with any CIN grade recommend: 1. Use cryotherapy over no treatment. Very low evidence 2. Use loop electrosurgical excision procedure (LEEP) over no treatment. Low evidence 3. Use either cryotherapy or LEEP in women for whom either cryotherapy or LEEP is appropriate to use and available. Very low evidence	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[✓] **Trivial** [ ] Small [ ] Moderate [ ] Large [ ] Varies [ ] Don't know	**See Annex E** **Systematic review** Randall TC, Sauvaget C, Muwonge R, Trimble EL, Jeronimo J. Worthy of further consideration: An updated meta-analysis to address the feasibility, acceptability, safety and efficacy of thermal ablation in the treatment of cervical cancer precursor lesions. Prev Med. 2019;Jan:118:81–91. **Unpublished data** Basu et al. Randomized controlled trial of the Liger Thermal Coagulator vs Cryo and vs LLETZ to prevent cervical neoplasia in VIA positive women in Zambia. Results for side effects, acceptability (would recommend procedure), pain, satisfaction. Zambia 2018. Basu et al. Thermal ablation and cryotherapy in India. 286 women screened and treated with cryotherapy or thermal ablation (some with CIN confirmed).Results for side effects, adverse events, and satisfaction. India 2018 De Vuyst and Forestier et al. Thermal ablation and cryotherapy in Durban. 46 women. Results for side effects and pain. Durban; 2018. Cremer, Maza et al. Current RCT of 65 women comparing CryoPen, CO2 cryotherapy, and thermal ablation (WiSAP) with flat tip for 40s at 120 degrees in Lima Peru; and in El Salvador. Pain and acceptability measured. 2018.	The WHO GDG agreed that cures were likely similar with thermal ablation or cryotherapy. Studies were identified by use of two probe or one probe by country location, but many assumptions were made as authors did not report probe method used or shape of probe or size. The two-probe method appeared better for cure. There was also no clear information about applications or overlapping applications. For HIV-positive women there were very few studies. The WHO GDG noted that cure rates are lower in HIV-positive women (similar to failed HPV clearance in immunocompromised women). It was unclear whether the relative benefits would be different between the treatments. Since not known, the WHO GDG agreed that they could not recommend thermal ablation similarly to cryotherapy.

Summary of Findings Table

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Risk with cryotherapy	Risk with thermal ablation	Difference with thermal ablation	
Cure № of participants: 85 (1 RCT)	RR 1.14 (0.89 to 1.46)	Moderate			Moderate
		90.0%	100.0% (80.1 to 100.0)	12.6% more (9.9 fewer to 41.4 more)	
Cure № of participants: 157 (1 observational study)	RR 1.01 (0.89 to 1.14)	Moderate			Very low
		90.0%	90.9% (80.1 to 100.0)	0.9% more (9.9 fewer to 12.6 more)	
Cure № of participants: (23 case series)	not estimable	Moderate			Low
		90.0% (87 to 93)	92% (90 to 95) 2 probe: 95 (93 to 98) Not 2 probe: 85 (80 to 90)		
Pain immediately № of participants: 413 (4 RCTs)	RR 0.93 (0.76 to 1.15)	65.4%	60.8% (49.7 to 75.2)	4.6% fewer (15.7 fewer to 9.8 more)	Moderate
Pain immediately № of participants: (case series)	not estimable	Moderate			Low
		30.0% (19 to 41)	63% (42 to 83)	33% more	
Major bleeding № of participants: 817 (6 RCTs)	RR 0.62 (0.37 to 1.02)	1.7%	1.0% (0.6 to 1.7)	0.6% fewer (1.1 fewer to 0 fewer)	Moderate
Major bleeding № of participants: (case series)	not estimable	4 / 9941	9 / 4634		Low
Infection (including fever) № of participants: 816 (6 RCTs)	RR 0.81 (0.10 to 6.33)	0.3%	0.2% (0.0 to 1.6)	0.0% fewer (0.2 fewer to 1.3 more)	Moderate
Infections (including fever) (45 case series)	not estimable	60 / 8674	17 / 4082		Low
Acceptability – whether they would recommend it № of participants: 631 (3 RCTs)	Acceptability is likely not different between thermal ablation and cryotherapy. Risk Ratio 1.01 (0.99 to 1.02)				Moderate
Premature delivery № of participants: 204 (5 case series)	In total, across 5 studies there were 3 premature deliveries in 204 pregnant women (1.5%). In women without cervical lesions (typical population) premature delivery occurs in 5.5% of women.				Very low

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Systematic observations from GDG	

Temperature	≤ 100 C	≥ 100 C
Proportion of use in GDG	12/13	1/13

Probe size and shape	Conical probe	Flat probe	With nipple
Proportion of use in GDG	4/12	11/12	8/12

Timing of application	20 to 30 seconds	40 to 45 seconds
Proportion of use in GDG	7/13	6/13

Number of applications	
Proportion of use in GDG (maximum)	
5 to 6 times	4/13
3 times	4/13
4 times	2/13
2 times	1/13
No maximum	1/13

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Large [ ] Moderate [ ] Small [✓] **Trivial** [ ] Varies [ ] Don't know		Various measures of pain are available (e.g., yes/no or intensity). Important to consider also whether pain led to stopping of treatment, as pain could include cramping or discomfort. The WHO GDG agreed that slightly fewer women had pain with thermal ablation than cryotherapy. Major bleeding and major infections are rare in both groups. Major bleeding may be lower with thermal ablation, but occurrence of major infections is similar.

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Very low [ ] Low [✓] **Moderate** [ ] High [ ] No included studies	For most outcomes, the evidence from comparative studies was of low certainty. However, there was information from case series including over 3000 people that assessed either thermal ablation or cryotherapy that supported the comparative evidence. Therefore, the overall evidence was moderate certainty for similar effects.	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Important uncertainty or variability [ ] Possibly important uncertainty or variability [✓] **Probably no important uncertainty or variability** [ ] No important uncertainty or variability	The WHO GDG identified critical outcomes as cure; pain; major bleeding; infection (including fever); premature delivery; and acceptability. Higher value was placed on cures and acceptability.	

Balance of effects
Does the balance between desirable and undesirable effects favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Favours the comparison [ ] Probably favours the comparison [✓] **Does not favour either the intervention or the comparison** [ ] Probably favours the intervention [ ] Favours the intervention [ ] Varies [ ] Don't know		The WHO GDG agreed that there is probably little to no difference between the two treatments.

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Large costs [ ] Moderate costs [ ] Negligible costs and savings [ ] Moderate savings ☑ **Large savings** [ ] Varies [ ] Don't know	We performed a literature review searching comprehensively for resource use and thermal ablation, and reviewed included studies from the systematic review published by Randall 2018. Joshi 2013: The authors describe the challenges in maintaining cryotherapy services due to the high-cost refrigerant gas. Campbell 2016: Cost-effectiveness was not measured, however they estimated in Malawi that after initial purchase of equipment, cost savings could be made after 80–90 women were treated with thermal ablation. Viviano 2017: Cost of thermal ablation unit similar to cost of cryotherapy unit. Costs estimated in Campos 2016 (no thermal ablation data) **Based on the observations of the WHO GDG (collected systematically)** Maintenance costs appear lower with thermal ablation compared to cryotherapy, although electricity needs to be reliably maintained or battery power used (gas transport and costs appear higher), disinfection products, probe replacement similar; LLETZ is more expensive with more resources needed. From experiences in Dundee, non-battery operated thermal ablation, required replacement of a probe due to issues with the Teflon after 1000–2000 uses, but there were no recurrent costs. Initial costs of machines appear similar between thermal and cryotherapy (although some reported thermal ablation was more expensive) Standard electricity powered cost €3150 (including shipping) Battery powered cost €1900 (including shipping) Liger Thermal Coagulator cost US$ 1500	The WHO GDG agreed that the costs of different thermal ablation equipment is similar. The WHO GDG also agreed that the consumable costs are higher with cryotherapy. There are higher maintenance costs with higher numbers of women (3 months of use, 50 applications - need maintenance). Costs are generally incurred because countries have money to procure but little money to maintain.

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
☑ **Very low** [ ] Low [ ] Moderate [ ] High [ ] No included studies		

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Favors the comparison [ ] Probably favors the comparison [ ] Does not favor either the intervention or the comparison ☑ **Probably favors the intervention** [ ] Favors the intervention [ ] Varies [ ] No included studies		The WHO GDG agreed that the benefits and harms are trivial between the treatments but costs are lower for use and for the consequences of thermal ablation. Therefore cost-effectiveness probably favoured thermal ablation.

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Reduced [ ] Probably reduced [ ] Probably no impact ☑ **Probably increased** [ ] Increased [ ] Varies [ ] Don't know	**From the review of the literature:** *Patients* Campbell 2016: A higher percentage of women received same-day treatment at an urban hospital in Malawi (89%) than in two semi-urban health centres (68% and 64%) where thermos coagulators and trained staff were not always available. Ibrahim 2012: An Irish study accessing the need to change the cervical cancer screening age for women <25 years found biopsy-proven cervical abnormalities in 43% of women <25 years who were referred to a Limerick colposcopy clinic.	Many areas (e.g. urban) receive gas easily – although some rural areas cannot receive gas easily. Therefore with thermal ablation equity is probably increased for rural areas and even some urban areas. The WHO GDG agreed thermal ablation would increase accessibility – it is portable.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [✓] **Probably yes** [ ] Yes [ ] Varies [ ] Don't know	We performed a literature review searching comprehensively for acceptability and thermal ablation, and reviewed included studies from Randall 2018. **Participants** In addition to the acceptability measured in comparative studies (see Summary of Findings table above), Duncan 1984 reported that a treatment temperature of 100 oC is insufficient to produce charring. Subsequent absence of smoke and smell contribute to high acceptability to patient and physicians; extremely short duration of treatment renders the associated discomfort tolerable for most patients, for whom anesthesia in unnecessary. Singh 1988: much shorter treatment time, seldom exceeding 80 seconds for 3 applications per patient compared to 20–30 minutes for cryotherapy. **Providers** Campbell 2016: In a Malawian screen-and-treat study, six local providers reported satisfaction with the training received in ablative techniques, and high perceived patient acceptability of thermal ablation treatment. The four providers with experience using both cryotherapy and thermal ablation reported faster treatment times, fewer treatment sequelae, and greater perceived patient acceptability with thermal ablation. Paul 2013: Training for use of cryotherapy was well received. Systematic observations from the WHO GDG The WHO GDG indicated that 6/13 thought thermal ablation would be easy to use by clinicians and therefore more acceptable than cryotherapy or LLETZ, and indicated thermal ablation is more acceptable to women likely because is a faster treatment.	The WHO GDG agreed that acceptability would increase if more information about the procedures and follow-up was provided. The WHO GDG agreed that more data should be collected to determine any differences in acceptability in women who are younger or nonparous or multiparous. The WHO GDG also suggested that acceptability may be higher because it is more readily available than cryotherapy.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [ ] Probably yes [✓] **Yes** [ ] Varies [ ] Don't know	We searched for feasibility issues related to thermal ablation, and reviewed included studies from Randall 2018. Duncan 1984: The advantages of thermal ablation included: • Runs conveniently and inexpensively on mains electricity. • Portable (small and light) and silent operation. The disadvantages of thermal ablation included: • Thermosounds cannot be repaired and two commonly used ones in the author's institution have had to be replaced. Paul 2013: In interviews with providers and women in Peru, Uganda and Vietnam, challenges of cryotherapy included ensuring supply of gas, as long delays for obtaining gas occurred in Uganda and Peru. Difficulties arose when the cryotherapy machine stopped working and could not be repaired by the local technician. Singh 1988: Thermal ablation versus cryotherapy: • Conveniently and inexpensively works on readily available, simple main electoral power, obviating the need for gas. • Convenient portability of the small device, so can be transported to other locations with electrical power. • Simple to wash in tap water between procedures. • Automatic self-sterilization activated by turning on switch between uses. • Silent mode of operation. • Needs only simple electrical power for thermal ablation and does not need gas or gas cylinders (which are costly and difficult to handle). Viviano 2017: In a screen-and-treat programme in Cameroon, 91% of women (110/121) screened positive were eligible for thermal ablation. Following evaluation of thermal ablation, the authors concluded that it is a valuable option due to its high availability, efficiency, simplicity, light weight and ease of transportation to remote areas that have electricity. **Systematic observations from the WHO GDG** 7/13 - no barriers to use of thermal ablation; but 3/12 thought electricity supply a barrier. 6/13 – thermal ablation machine portable and small. 9/13 - more reliable equipment and available. Equipment used by the WHO GDG: Standard electricity-powered 10/12 Hand-held battery-operated 9/12	The WHO GDG noted that when centres run out of gas then women are not treated which result in delays and then women often do not return for treatment. Maintenance is much less with thermal ablation - however, we do not have much information in LMICs (although we have info in Scotland). could obtain some information There may be some delay in delivery of thermal ablation units, so important to ensure that there is availability and accessibility of units The WHO GDG also noted that provider time with cryotherapy is 10 to 20 mins; and with thermal ablation it is less than 10. It has been very important in campaigns for screening and treatment to have the shorter time. Battery-operated units would negate need for electricity. The WHO GDG agreed that multiple areas already provide thermal ablation.

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	**Conditional recommendation for either the intervention or the comparison**	**Conditional recommendation for the intervention**	**Strong recommendation for the intervention**
[ ]	[ ]	[x]	[ ]	[ ]

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CONCLUSIONS

RECOMMENDATION

Recommendation 1.a
The WHO GDG suggests either LLETZ, or cryotherapy or thermal ablation to treat all women who have histologically confirmed CIN2+ disease and who are eligible for thermal ablation or cryotherapy.

(Conditional recommendation, moderate certainty in evidence of effects)

Remarks: The choice of LLETZ, or cryotherapy or thermal ablation depends on the expertise, training, equipment and consumables available, infrastructure and resources in a programme. This recommendation applies to all women, including women living with HIV.

Recommendation 1.b
The WHO GDG suggests thermal ablation be provided at a minimum of 100 °C for 20–30 seconds using as many applications as needed to cover the entire transformation zone in overlapping fields.

(Conditional recommendation, very low certainty in evidence of effects)

Recommendation 2
In exceptional conditions when LLETZ is not available for women who have histologically confirmed CIN2+ disease and are not eligible for cryotherapy or thermal ablation, the WHO GDG recommends an alternative treatment. 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.

(Strong recommendation, very low certainty in evidence of effects)

Remarks: This recommendation applies to all women including women living with HIV.

JUSTIFICATION

This recommendation is based on a previous recommendation that suggests either cryotherapy or LLETZ to treat women with histologically confirmed CIN 2-3. That evidence showed that the benefits of LLETZ may be greater than cryotherapy, but the harms may be similar. When comparing the effects of thermal ablation to cryotherapy, there is moderate certainty evidence that there are trivial differences in the benefits and harms of these two treatments. Systematic reviews of randomized and non-randomized studies found evidence that there may be little to no difference between the proportion of women who are cured when treated with thermal ablation (91%) or cryotherapy (90%). A two-probe method, in which treatment of the visible glandular epithelium with a small conical probe followed by treatment of the ectocervix with a flat probe was used in some studies, and a one-probe method in others. Direct comparisons of probe methods within a study were not available, and the probe method used was often not reported by the author, and therefore assumptions were based on country setting and may not be accurate.

Evidence showed that more women may be cured with a two-probe method (95%; 95%CI, 93–98%) than a one-probe method (85%; 95%CI, 80–90%), but there is very low certainty in this evidence and more research is needed. The temperature of the probe typically used in studies was 100oC, and subgroup analysis by 100 oC versus greater than 100 oC (up to 120 oC) did not show differences in curative effects. In most studies, the probe was applied for 20–30 seconds, and there was very low certainty evidence showing fewer cures with applications longer than 30 seconds. Multiple applications up to five times were used in most studies in order to cover the entire transformation zone. Very few studies compared these different modalities of thermal ablation, and therefore it is very uncertain which methods of application (temperature, type of probes, number of applications) result in more benefits and less harm.

Although rare, there was low certainty evidence for little to no difference in the number of major infections between the thermal ablation and cryotherapy. For major bleeds, there were inconsistent results from randomized controlled trials and non-comparative studies: low certainty evidence found that thermal ablation may result in slightly fewer major bleeds compared to cryotherapy, six fewer bleeds per 1000 women (from 11 to 0 fewer). Five small non-comparative studies found that there

may be little to no difference in the number of women having premature deliveries after thermal ablation compared to the general population, but the evidence is uncertain. Based on moderate certainty evidence from randomized controlled trials, the acceptability of both thermal ablation and cryotherapy is likely similar. Though anaesthesia is typically not provided to women for either procedure, moderate certainty evidence showed that it is likely that slightly fewer women (5% fewer (from 16% fewer to 10% more) would have pain with thermal ablation compared to cryotherapy. The WHO GDG agreed that women would probably value cure and the acceptability of the treatments (including pain) over other outcomes.

There are no comparative studies evaluating the benefits and harms of thermal ablation compared to other treatment methods or no treatment in women living with HIV with histologically confirmed CIN 2-3. There are very few studies evaluating cure or other outcomes with thermal ablation in women living with HIV. From the few studies that do exist, the proportion of cures in women living with HIV who were treated with thermal ablation was within the range of cures in women not living with HIV. The WHO GDG agreed that given the benefits and harms are similar between thermal ablation and cryotherapy in women not living with HIV, then the benefits and harms between the two treatments in women living with HIV are likely similar. Since cure is typically lower in women living with HIV compared to women not living with HIV, follow-up is important, especially after ablative treatment.

The WHO GDG agreed that the initial cost of thermal ablation and cryotherapy units are often similar, but for cryotherapy the maintenance costs are likely greater and there is the additional cost of gas and transportation of gas tanks. The latter made cryotherapy less feasible in some settings and therefore could delay prompt treatment. Thermal ablation requires electricity to charge batteries for battery-driven devices, or solar power for some models. The WHO GDG also considered that many health care providers may find thermal ablation more acceptable to provide because it takes less time to perform, is easy to perform, and in some settings, is perceived to cause less pain.

Overall, the differences between the benefits and harms of thermal ablation and cryotherapy are trivial, but there are likely large resource savings with the use of thermal ablation. Thermal ablation is also probably more acceptable to providers, more available, and therefore more feasible to implement than cryotherapy in some settings. Therefore, the choice between thermal ablation or cryotherapy will be based on expertise, training, equipment and consumables, and infrastructure and resources in a programme. Since a previous recommendation suggests either cryotherapy or LLETZ, and there are trivial differences between cryotherapy and thermal ablation, this recommendation suggests the use of thermal ablation, cryotherapy or LLETZ. This recommendation is also consistent with remarks in previous recommendations to base the choice of which treatment to useon available resources.

We found no evidence comparing the use of ablative treatments with excisional procedures to treat transformation zone or lesions extending into the cervical canal or covering more than 75% of the ectocervix. When reported, non-comparative studies evaluating thermal ablation (and other ablative therapies) exclude these women, or refer them to excisional procedures. The WHO GDG agreed that it is likely that thermal ablation tips will not reach or cover these lesions, resulting in failed treatment or recurrence which can lead to cervical cancer. It is also essential to perform excisional therapy in order to not inadvertently miss an invasive lesion. For these reasons, the WHO GDG agreed that when LLETZ is not available to women who are not eligible for cryotherapy or thermal ablation, other excisional therapies should be provided, including cone biopsy, trachelectomy or hysterectomy. The type of excision therapy provided will be based on the resources available and skills of the providers.

IMPLEMENTATION, MONITORING AND EVALUATION

Proper techniques for sterilization of equipment should follow manufacturers' instructions. Thermal ablation should be monitored in practice and information collected about facilitators and barriers to implementation, as well as outcomes. Information about whether some women cannot have ablative methods should be gathered. For women who cannot receive ablation, infrastructure to access excisional methods needs to be available.

RESEARCH PRIORITIES

More data are needed about maintenance costs and the logistics of use of thermal ablation, as well as information the reasons why women cannot use from ablative methods; measures of pain when a biopsy is done or not done before thermal ablation; and research into abstinence (e.g., in women of HIV-positive status).

WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions - Annexes

Should thermal ablation versus cryotherapy be used in a screen-and-treat algorithm when screened hrHPV+ or VIA+? (Recommendation 3)	
POPULATION:	women screened hrHPV+ or VIA+
INTERVENTION:	thermal ablation
COMPARISON:	cryotherapy
MAIN OUTCOMES:	Mortality, Cervical Cancer, CIN2-3 recurrence, Major bleeding, Minor bleeding, Pain, Major infections, Minor infections
SETTING:	outpatient
PERSPECTIVE:	population
BACKGROUND:	Women may be screened and treated for pre-cancerous cervical lesions based on various strategies including HPV test, visual inspection with acetic acid, or cytology . Treatments for women screened positive can be cryotherapy, or LLETZ. LLETZ is provided for women not eligible for cryotherapy. One of the objectives of screen and treat algorithms is to ensure screening is followed by treatment (e.g., screen and treat in a single visit).
CONFLICT OF INTERESTS:	See Annex A

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [ ] Probably yes [✓] **Yes** [ ] Varies [ ] Don't know	Current WHO guidelines for screen-and-treat strategies do not include treatment with thermal ablation. The WHO guidelines recommend against the use of CKC as a treatment in a screen-and-treat strategy. Therefore, all screen-and-treat strategies below involve treatment with cryotherapy, or LLETZ when the patient is not eligible for cryotherapy. Conditional recommendation for: • HPV test followed by VIA and treat, or a strategy of screen with an HPV test and treat. • HPV test followed by VIA and treat, over a strategy of screen with VIA and treat. • HPV test and treat, over a strategy of screen with VIA and treat. Or if hrHPV not available use VIA. • HPV test and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat. Or if cytology in place, use cytology. • HPV test followed by VIA and treat, over a strategy of screen with cytology followed by colposcopy.	

Desirable Effects
How substantial are the desirable anticipated

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[✓] **Trivial** [ ] Small [ ] Moderate [ ] Large [ ] Varies [ ] Don't know	See Annex E. We did not find studies that followed and reported on all women who were screened and did not or did receive thermal ablation or cryotherapy. We therefore modelled outcomes based on reviews of sensitivity and specificity of various screening tests and reviews of non-randomized studies comparing thermal ablation to cryotherapy. **Systematic reviews** See data from Recommendation 1 and 2. Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, et al. Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. Int J Gynaecol Obstet. 2016;132(3):259–65. Santesso N, Mustafa RA, Wiercioch W, Kehar R, Gandhi S, Chen Y, et al. Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. Int J Gynaecol Obstet. 2016;132(3):266–71. **Risks when treated with thermal ablation or cryotherapy** • Baseline risk of CIN 2-3 is 2% • 30% of CIN 2-3 will regress according to natural progress of disease. • 2.5% of people with CIN 2-3 will progress to cervical cancer • 71% of people with cervical cancer will die **Notes about assumption for cervical recurrence, cancer and mortality [references available]**	We do not have data for women who are HIV positive. It is unclear whether the progression to cancer would be more rapid, or whether the assumed regression is similar in HIV-negative versus HIV-positive women. There was some discussion but no agreement about whether outcomes would be further improved with thermal ablation because the screen-and-treat strategy including thermal ablation could reach more people than with cryotherapy.

	Risk to use in model for cryotherapy	Risk to use in model for thermal ablation
CIN 2-3 recurrence in women with confirmed CIN 2-3	0.10	0.08
Major bleeding	0.017	0.01
Infections	0.003	0.002
Pain (mild to severe) [comparative]	0.654	0.608

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Large [ ] Moderate [ ] Small [✓] **Trivial** [ ] Varies [ ] Don't know	**Outcomes per 1 000 000 women screened**	

	HPV sensitivity: 95% specificity: 84%		VIA sensitivity: 60%* specificity: 84%*		HPV then VIA	
	Cryotherapy	Thermal ablation	Cryotherapy	Thermal ablation	Cryotherapy	Thermal ablation
Women treated (TP, FP)	175 800		168 800		36 500	
Women over-treated (FP)	156 800		156 800		25 100	
Missed cases (FN)	1 000		8 000		8 600	
Mortality	46	40	121	117	128	124
Cervical Cancer	65	56	170	164	179	173
CIN2-3 recurrence	2600	2 200	6800	6 560	7 160	6 932
Major bleeding	2 989	1758	2870	1 688	620	365
Pain	114 973	106 886	110 395	102 630	23 863	22 185
Major infections	527	352	506	338	109	73

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[✓] **Very low** [ ] Low [ ] Moderate [ ] High [ ] No included studies		

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Important uncertainty or variability [ ] Possibly important uncertainty or variability [✓] **Probably no important uncertainty or variability** [ ] No important uncertainty or variability		We placed more value on cervical cancer and mortality.

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Favors the comparison [ ] Probably favors the comparison [x] **Does not favor either the intervention or the comparison** [ ] Probably favors the intervention [ ] Favors the intervention [ ] Varies [ ] Don't know		

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Large costs [ ] Moderate costs [ ] Negligible costs and savings [ ] Moderate savings [x] **Large savings** [ ] Varies [ ] Don't know	Research evidence similar to that of recommendations 1, 2 and 3 was considered.	The WHO GDG agreed that the costs are likely similar to procure equipment, but maintenance is more costly for cryotherapy and therefore large savings with thermal ablation could be achieved. There may be even greater savings with the use of thermal ablation if uptake of the screen-and-treat strategy is greater (but this data was not modelled).

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[x] **Very low** [ ] Low [ ] Moderate [ ] High [ ] No included studies		

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Favors the comparison [ ] Probably favors the comparison [ ] Does not favor either the intervention or the comparison [x] **Probably favors the intervention** [ ] Favors the intervention [ ] Varies [ ] No included studies		

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Reduced [ ] Probably reduced [ ] Probably no impact [x] **Probably increased** [ ] Increased [ ] Varies [ ] Don't know	Evidence is similar to recommendations 1,2,3.	The WHO GDG agreed that thermal ablation may improve accessibility of screen-and-treat programmes in rural areas and some urban areas.

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [x] **Probably yes** [ ] Yes [ ] Varies [ ] Don't know	Evidence is similar to that of recommendations 1,2,3.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [✓] **Probably yes** [ ] Yes [ ] Varies [ ] Don't know	Evidence is similar to that of recommendations 1, 2 and 3.	The WHO GDG noted that when centres run out of gas, women are not treated, which results in delays women often not returning for treatment. The greatest impact could be realized in single visit strategies with thermal ablation. It is also possible there would greater portability for outreach with thermal ablation (which may not be as great when a more portable version of cryotherapy is available). It is unclear what the impact of battery-operated thermal ablation will be given that there may be issues with disinfection of equipment (as battery operated equipment cannot go into autoclave).

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	**Large savings**	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
[ ]	[ ]	[✓]	[ ]	[ ]

CONCLUSIONS

RECOMMENDATION

Recommendation 3.
The WHO GDG suggests providing either thermal ablation or cryotherapy to women screened positive with hrHPV or VIA, or hrHPV followed by VIA with no histological confirmation who are eligible for ablative treatment, or providing LLETZ when the woman is not eligible for cryotherapy or thermal ablation.
(Conditional recommendation, very low certainty in evidence of effects)

Remarks: This recommendation applies to all women, including women living with HIV. The choice of screening tests is based on WHO recommendations for screening and treatment.

JUSTIFICATION

The evidence comparing the effects of treatment with thermal ablation to cryotherapy was used to model the effects of providing either treatment after screening with hrHPV, VIA or hrHPV followed by VIA. The evidence for the effects of treating women with confirmed CIN2+ lesions from a systematic review of randomized and non-randomized studies was used in the model (see Recommendation 1 summary of evidence). The test accuracy of hrHPV (95% sensitivity, 84% specificity) and VIA (60% sensitivity, 84% specificity) from a systematic review of evidence and the field were used.

In 1 million women being treated, there may be slightly fewer CIN2+ recurrences when providing thermal ablation rather than cryotherapy (200–400 fewer), as well as fewer cervical cancers (6–9 fewer) and fewer deaths (1–4 fewer). There may be slightly fewer major bleeds (300–1200) or major infections (40–180 fewer) with thermal ablation. The number of women experiencing pain may be lower (1700–7000 fewer). The WHO GDG agreed that women would probably value cure and the acceptability of the treatments (including pain) over other outcomes. The differences were similar to the benefits and harms found when modelled for women living with HIV.

The WHO GDG agreed that better resource use, feasibility and accessibility seen with programmes in which CIN2-3 lesions are histologically confirmed would be applicable to screen-and-treat programmes. This may mean that thermal ablation may lead to more immediate treatment within screen-and-treat programmes compared to cryotherapy in some settings.

Overall, the differences between benefits and harms of providing thermal ablation and cryotherapy in a screen-and-treat programme are small, but there are likely large resource savings with the use of thermal ablation. Thermal ablation is also probably more acceptable to providers, does not require a renewable resource such as gas, is more portable than cryotherapy, and therefore more feasible to provide than cryotherapy as part of a screen-and-treat programme in some settings.

IMPLEMENTATION, MONITORING AND EVALUATION

Note that choosing the appropriate screen strategy should be based on the WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention, 2013 (https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/).

Proper techniques for sterilization of equipment should follow manufacturers' instructions. Thermal ablation should be monitored in practice and information collected about facilitators and barriers to implementation, as well as outcomes. Information about whether some women cannot have ablative methods should be gathered. For women, who cannot receive ablation then infrastructure to access excisional methods need to be available.

RESEARCH PRIORITIES

In addition to research priorities described in Recommendations 1, 2 and 3, information about differences in uptake of screen-and-treat programmes with the use of thermal ablation or cryotherapy should be collected.

Should prophylactic antibiotics versus no prophylaxis be used for the application of thermal ablation? (Recommendation 4	
POPULATION:	Women treated with thermal ablation
INTERVENTION:	prophylactic antibiotics
COMPARISON:	no prophylaxis
MAIN OUTCOMES:	Major and minor infections
SETTING:	out-patient
PERSPECTIVE:	population
BACKGROUND:	The use of prophylactic antibiotics with thermal ablation is not consistent.
CONFLICT OF INTERESTS:	See Annex A

ASSESSMENT

Problem **Is the problem a priority?**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
[ ] No [ ] Probably no [ ] Probably yes [✓] **Yes** [ ] Varies [ ] Don't know	The current WHO recommendation for cryotherapy suggests that prophylactic antibiotics should not be used when providing cryotherapy (conditional recommendation, very low quality evidence)	

Desirable Effects **How substantial are the desirable anticipated**		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
[✓] **Trivial** [ ] Small [ ] Moderate [ ] Large [ ] Varies [ ] Don't know	See Annex E. We did not find studies comparing women taking or not taking antibiotics with thermal ablation, or studies comparing antibiotic use with different treatments (e.g. LEEP, LLETZ, cryotherapy or CKC compared to thermal ablation). We instead reviewed studies identified in Randall 2018 for antibiotic use and infections (major or minor). It was assumed that when not reported in the study, antibiotics had not been used.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Large [ ] Moderate [ ] Small [✓] **Trivial** [ ] Varies [ ] Don't know	Number of major and minor infections with thermal ablation: Total 17/4082 = 0.000681 (-0.000698, 0.002059) = 0.07% With antibiotic use 2/1407 = 0.000868 (-0.001439, 0.003175) =0.09% Without antibiotic use 15/2675 = 0.001352 (-0.001839, 0.004544) = 0.14% **Note**: Basu (2018, unpublished data, Zambia) reported no serious adverse events related to the thermal ablation (including infections). Basu (2018, unpublished data, India) did not report infections. Indirect evidence from the use of antibiotics with cryotherapy was reported from Recommendation 7 in the WHO guidelines - use of cryotherapy for cervical intraepithelial neoplasia, 2011 (http://www.who.int/reproductivehealth/publications/cancers/9789241502856/en/)	Information about increasing antibiotic microbial resistance is not available specific to the use of antibiotics for thermal ablation, however, it is a risk with any use. Although the incidence is not high, there is a risk of allergic reactions with any drug.

Recommendation 7. **Should antibiotics be provided prophylactically with cryotherapy in women with histologically confirmed CIN?**

Quality assessment							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy with antibiotics	No antibiotics	Relative (95% CI)	Absolute	Quality	Importance
Major infection (follow-up 12 months; requiring hospitalization or blood transfusion)												
16	observational studies	serious limitations[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	0/1600 (0%)	10/4573 (0.22%)	–	0 per 1000[3]	⊕◯◯◯	IMPORTANT
All severe adverse events (follow-up 12 months; (major infections and bleeding, pelvic inflammatory disease, stenosis, etc)												
17	observational studies	serious limitations[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	0/1705 (0%)	22/5142 (0.43%)	–	0 per 1000[3]	⊕◯◯◯	IMPORTANT
Minor infections (follow-up 12 months)												
10	observational studies	serious limitations[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	50/1600 (3.1%)	107/2337 (4.6%)	–	30 fewer per 1000 (from 40 to 20 fewer)	⊕◯◯◯	IMPORTANT

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[✓] **Very low** [ ] Low [ ] Moderate [ ] High [ ] No included studies		

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Important uncertainty or variability [ ] Possibly important uncertainty or variability [✓] **Probably no important uncertainty or variability** [ ] No important uncertainty or variability		

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Favors the comparison [ ] Probably favors the comparison [✓] **Does not favor either the intervention or the comparison** [ ] Probably favors the intervention [ ] Favors the intervention [ ] Varies [ ] Don't know		

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Large costs [✓] **Moderate costs** [ ] Negligible costs and savings [ ] Moderate savings [ ] Large savings [ ] Varies [ ] Don't know	Additional costs of antibiotics.	

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Very low [ ] Low [ ] Moderate [ ] High [✓] **No included studies**		

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Favors the comparison [ ] Probably favors the comparison [✓] **Does not favor either the intervention or the comparison** [ ] Probably favors the intervention [ ] Favors the intervention [ ] Varies [ ] No included studies	No research evidence available specific to use with thermal ablation.	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Reduced [ ] Probably reduced [✓] **Probably no impact** [ ] Probably increased [ ] Increased [ ] Varies [ ] Don't know	No research evidence available specific to use with thermal ablation.	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [✓] **Probably yes** [ ] Yes [ ] Varies [ ] Don't know	No research evidence available specific to use with thermal ablation.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [ ] Probably yes [✓] **Yes** [ ] Varies [ ] Don't know	No research evidence available specific to use with thermal ablation.	

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
[ ]	[ ]	[x]	[ ]	[ ]

CONCLUSIONS

RECOMMENDATION

Recommendation 4.
The WHO GDG suggests that prophylactic antibiotics are not used when providing thermal ablation.
(Conditional recommendation, very low certainty in evidence of effects)

JUSTIFICATION

There are no randomized or non-randomized studies that compare the benefits or harms of providing antibiotics or not when women receive thermal ablation. Instead, the pooled proportion of infections requiring treatment was 0.09% (2/1407) across studies where antibiotic use was confirmed, and 0.14% (15/2675) in studies that did not report use (but not confirmed). The WHO GDG agreed that although there may be fewer infections requiring treatment when antibiotics are provided prophylactically, there is a risk of increased antimicrobial resistance and allergic reactions. There was no information about women's preferences or burden of taking antibiotics, but resources are likely greater with antibiotic use. Overall, the potential harms and additional resources probably outweigh any benefits.

Should other trained providers versus physicians provide thermal ablation? (Recommendation 5)

POPULATION:	Women treated with thermal ablation
INTERVENTION:	Other trained providers
COMPARISON:	physicians
MAIN OUTCOMES:	cure; pain; major bleeding; infection (including fever); premature delivery; acceptability
SETTING:	out-patient
PERSPECTIVE:	population
BACKGROUND:	Both physicians, including colposcopists and specialists and trained providers provide thermal ablation in many countries.
CONFLICT OF INTERESTS:	See Annex A

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [ ] Probably yes [✓] **Yes** [ ] Varies [ ] Don't know	*WHO guidelines – use of cryotherapy for cervical intraepithelial neoplasia* (2011) suggests that trained nurses or trained midwives rather than physicians may perform cryotherapy. Guidance is needed for thermal ablation.	

Desirable Effects
How substantial are the desirable anticipated

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[✓] **Trivial** [ ] Small [ ] Moderate [ ] Large [ ] Varies [ ] Don't know	See Annex E. We did not find studies comparing the effects of different health care providers providing thermal ablation. We instead reviewed studies identified in Randall 2018 for thermal ablation provided by different providers and data not yet published from Zambia, India, Peru and El Salvador. Results of studies with one group receiving thermal ablation by physicians were thus compared to studies with one group receiving thermal ablation by trained non-physicians.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Large [ ] Moderate [ ] Small [✓] **Trivial** [ ] Varies [ ] Don't know	**Thermal ablation provided by physician versus trained non-physicians for women with histologically confirmed CIN 2-3**	The WHO GDG agreed that there may little difference in number of women cured, or in major harms. However, fewer women may experience pain when a non-physician provides thermal ablation

Outcome (studies)	Risk with physician	Risk with trained non-physicians	Certainty
Cure (CIN 2-3 diagnosis and cure) (12 case series)	91 to 94%	91%	Very low
Number of women experiencing pain (8 case series)	72% (53 to 92%)	47% (25 to 69%)	Very low
Pain on 0-10 scale (4 case series)	Mean score 2.97 (1.96 to 3.98)	Mean score 2.10 (1.90 to 2.30)	Very low
Major bleeding (17 case series)	4 / 4218 (0.1%)	0 / 416 (0%)	Very low
Infection (including fever) (6 RCTs)	17/3958 (0.08%)	0/124 (0%)	Very low
Premature delivery	at 4 months		-

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[✓] **Very low** [ ] Low [ ] Moderate [ ] High [ ] No included studies		

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Important uncertainty or variability [ ] Possibly important uncertainty or variability [✓] **Probably no important uncertainty or variability** [ ] No important uncertainty or variability	The WHO GDG identified critical outcomes as cure; pain; major bleeding; infection (including fever); premature delivery; and acceptability. Higher value was placed on cures and acceptability.	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Favors the comparison [ ] Probably favors the comparison [✓] **Does not favor either the intervention or the comparison** [ ] Probably favors the intervention [ ] Favors the intervention [ ] Varies [ ] Don't know		

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Large costs [ ] Moderate costs [ ] Negligible costs and savings [✓] **Moderate savings** [ ] Large savings [ ] Varies [ ] Don't know	No research evidence available.	The WHO GDG agreed that the costs would be reduced if trained non-physicians provided thermal ablation.

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Very low [ ] Low [ ] Moderate [ ] High [✓] **No included studies**		

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Favors the comparison [ ] Probably favors the comparison [ ] Does not favor either the intervention or the comparison [✓] **Probably favors the intervention** [ ] Favors the intervention [ ] Varies [ ] No included studies	No research evidence available.	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Reduced [ ] Probably reduced [ ] Probably no impact [✓] **Probably increased** [ ] Increased [ ] Varies [ ] Don't know	No research evidence available.	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [✓] **Probably yes** [ ] Yes [ ] Varies [ ] Don't know	No research evidence available.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [✓] **Probably yes** [ ] Yes [ ] Varies [ ] Don't know	No research evidence available.	The WHO GDG agreed that increasing the range of professionals that can provide thermal ablation may increase its availability and therefore its accessibility. It may also reduce delays in treatment.

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
[ ]	[ ]	[ ]	[✓]	[ ]

CONCLUSIONS

RECOMMENDATION

Recommendation 5.
WHO suggests that trained nurses, midwives or health care workers as well as physicians may perform thermal ablation in order to ensure the availability and accessibility of treatment.
(Conditional recommendation, very low certainty in evidence of effects)

JUSTIFICATION

There is very low certainty of evidence for differences in the benefits and harms when different health care professionals provide thermal ablation. There are no trials comparing the consequences of thermal ablation between different health care professionals. Therefore, the proportion of women cured when receiving thermal ablation by colposcopists, gynaecologists, physicians, or non-physicians (including nurses or other health care workers) across individual studies was calculated. The review found that there may be little to no difference in the proportion of women with biopsy-confirmed CIN 2-3 who are cured. There is also little to no difference in major bleeding or infections requiring treatment, but this is very uncertain as the analysis included few studies in which a non-physician provided thermal ablation. Major bleeding occurred in 0.1% of cases when provided by a physician and 0% by a non-physician, and infections occurred in 0.08% of cases when provided by a physician and 0% by a non-physician. The evidence suggests that fewer women experience pain when a non-physician provides thermal ablation – approximately 50% compared to 70% when provided by a physician. There was no data for premature deliveries. The WHO GDG agreed that women would probably value cure and the acceptability of the treatments (including pain) over other outcomes.

The WHO GDG agreed that if trained nurses or other health care workers provided thermal ablation, the costs would be lower than if physicians performed thermal ablation. Training non-physicians may also increase the availability and accessibility of thermal ablation, and reduce delays in treatment.

Overall, the differences between benefits and harms between different health care providers performing thermal ablation are trivial, with the exception of pain which favours non-physicians performing thermal ablation. When non-physicians perform thermal ablation the costs are likely lower, and it may increase availability and accessibility of thermal ablation, which may increase the benefits of treatment.

Should women who screen positive after prior treatment with thermal ablation receive a different treatment or repeat treatment with thermal ablation? (Recommendation 6)	
POPULATION:	Women who screen positive after prior treatment with thermal ablation
INTERVENTION:	Other treatment (e.g., cryotherapy, LLETZ, CKC)
COMPARISON:	Repeat thermal ablation
MAIN OUTCOMES:	cure; pain; major bleeding; infection (including fever); premature delivery; acceptability
SETTING:	out-patient
PERSPECTIVE:	population
BACKGROUND:	*The WHO guidelines for the use of cryotherapy for cervical intraepithelial neoplasia* (2011) recommends cryotherapy over no treatment for women who screen positive after prior cryotherapy treatment; and suggests treatment with LEEP over cryotherapy for women who screen positive after prior cryotherapy treatment in settings where LEEP is available and accessible.
CONFLICT OF INTERESTS:	See Annex E

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [ ] Probably yes [✓] **Yes** [ ] Varies [ ] Don't know		

Desirable Effects
How substantial are the desirable anticipated

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Trivial [ ] Small [✓] **Moderate** [ ] Large [ ] Varies [ ] Don't know	See Annex E. We did not find studies comparing the effects of different treatments for women who screen positive after prior treatment with thermal ablation. We instead reviewed studies identified in Randall 2018 for repeat thermal ablation.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Large [ ] Moderate [✓] **Small** [ ] Trivial [ ] Varies [ ] Don't know	Data from Recommendation 10 in the WHO guidelines for the use of cryotherapy for cervical intraepithelial neoplasia (2011) were reported as recurrence. Cures were 74% with cryotherapy and 92% with conization. Adverse events were not reported with retreatment. From the thermal ablation studies of women with CIN 2-3 diagnosis and CIN 2-3 at follow-up, there were 40 women retreated with thermal ablation and 34 were cured = 85%. There were no studies that reported on LLETZ or CKC after prior treatment with thermal ablation (i.e., numbers were not reported or not possible to pull out). Studies reported in Randall 2019.	Adverse events with retreatment was not reported. However, adverse events typically greater with conisation/excision methods. The WHO GDG agreed that there were greater cures with conisation/excision methods.

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
Recurrence all CIN												
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 442 more)	⊕◯◯◯	CRITICAL

[1] Follow-up interval 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. [3] Recurrence rate with conization ranged from 0 to 50%.

	Follow-up and screened positive	Number retreated with thermal ablation	Number cured after retreatment
Singh 1988	up to 2 years	8	6
Nessa 2017		not reported	
Naud 2016		not reported	
Joshi 2013		not reported	
Javaheri 1981		not reported	
Hussein 1985	at 4 months	6	6
Gordon 1991	approx 18 months	26	22
Rogstad 1992		not reported	
Williams 1993		failures not treated	
Loobuyck 1993		could not calculate	
Hirae 2015		not reported	
Staland 1978		none	

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[✓] **Very low** [ ] Low [ ] Moderate [ ] High [ ] No included studies		

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Important uncertainty or variability [ ] Possibly important uncertainty or variability [✓] **Probably no important uncertainty or variability** [ ] No important uncertainty or variability	The WHO GDG identified critical outcomes as cure; pain; major bleeding; infection (including fever); premature delivery; and acceptability. Higher value was placed on cures and acceptability.	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Favors the comparison [ ] Probably favors the comparison [ ] Does not favor either the intervention or the comparison [✓] **Probably favors the intervention** [ ] Favors the intervention [ ] Varies [ ] Don't know		Given greater cures, conization is favoured.

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Large costs [✓] **Moderate costs** [ ] Negligible costs and savings [ ] Moderate savings [ ] Large savings [ ] Varies [ ] Don't know	No research evidence available.	Fewer resources are required to provide thermal ablation compared to LLETZ, and even fewer for thermal ablation when compared to conization. Therefore if methods other than thermal ablation are provided there would be moderate costs.

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Very low [ ] Low [ ] Moderate [ ] High [✓] **No included studies**		

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Favors the comparison [ ] Probably favors the comparison [ ] Does not favor either the intervention or the comparison [✓] **Probably favors the intervention** [ ] Favors the intervention [ ] Varies [ ] No included studies	No research evidence available.	Although costs are higher with conization methods, there are greater cures.

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] Reduced [ ] Probably reduced [✓] **Probably no impact** [ ] Probably increased [ ] Increased [ ] Varies [ ] Don't know	No research evidence available.	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [✓] **Probably yes** [ ] Yes [ ] Varies [ ] Don't know	No research evidence available.	LLETZ is available and acceptable to providers and women.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
[ ] No [ ] Probably no [✓] **Probably yes** [ ] Yes [ ] Varies [ ] Don't know	No research evidence available.	LLETZ is currently provided as treatment for women who are not eligible for cryotherapy or thermal ablation.

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
[ ]	[ ]	[ ]	[✓]	[ ]

CONCLUSIONS

RECOMMENDATION

Recommendation 6.
In settings where LLETZ is available and accessible, the WHO GDG suggests LLETZ rather than thermal ablation or cryotherapy for women who test positive after prior thermal ablation or cryotherapy.
(Conditional recommendation, very low certainty in evidence of effects)

In settings where LLETZ is unavailable or inaccessible, the WHO GDG recommends thermal ablation or cryotherapy rather than no treatment for women who test positive after prior thermal ablation or cryotherapy.
(Strong recommendation, very low certainty in evidence of effects)

Remarks: This recommendation is consistent with the recommendation to provide LLETZ after prior cryotherapy.

JUSTIFICATION

We did not find studies that directly compared the number of women who were cured after retreatment with thermal ablation or cryotherapy or LLETZ. Three studies reported that 34/40 women with histologically confirmed CIN2-3 who screened positive after 4 months to 2 years were cured when retreated with thermal ablation (85% (CI 95%, from 74 to 96%). In comparison, a review of studies found that approximately 74% of women previously treated with cryotherapy who were retreated with cryotherapy were cured, and 92% of women retreated with conization were cured. No studies measured adverse effects when retreating with thermal ablation versus other treatments.

Overall, the evidence is uncertain about the effects of retreatment with thermal ablation, cryotherapy, LLETZ or conization in women who test positive after previous treatment with thermal ablation. Given the paucity of evidence, the WHO GDG agreed that the recommendation for LLETZ would be consistent with a previously published recommendation to provide LLETZ for women who screen positive after prior treatment with cryotherapy.

ANNEX E
Evidence reviews

Final PICO questions

1.Should thermal ablation versus cryotherapy or LLETZ or cold knife conisation be used for women with histologically confirmed CIN 2-3?

Subgroups for question 1:
Women with different lesion size
Women with endocervical involvement
Women who are HIV-positive
Women in different age groups

2. Should one modality of thermal ablation be used versus another modality?
Differences in modalities include temperature, number applications, duration, shape and size of probes and treatment procedure.

3. Should thermal ablation versus cryotherapy be used in a screen-and-treat algorithm when women are screened hrHPV+ or VIA+?

4. Should prophylactic antibiotics versus no prophylaxis be provided after thermal ablation?

5. Should thermal ablation be provided by other trained providers versus physicians?

6. Should women who screen positive after prior treatment with thermal ablation receive a different treatment or repeat treatment with thermal ablation?

Outcomes

Residual and recurrent CIN2+ (if assessed histologically, by degree of CIN) (long term if available: cervical cancer, mortality); pain, bleeding, infections (+/- antibiotics), and obstetrical effects.

7. What are the related patient values and preferences, acceptability, feasibility, equity and resource issues related to thermal ablation versus other treatments?

We conducted a search for previously published and current systematic reviews of any study design relevant to the PICOs. We found three systematic reviews: Randall 2019, Santesso 2016 and Mustafa 2016. All included randomized and/or non-randomized studies.

Santesso 2016 searched Medline, Embase, and other databases to February 2012 for benefits, and to July 2012 for harms. Randomized and non-randomized studies of non-pregnant women aged 18 years or older not previously treated for CIN 2-3 were included. We updated the search up to 2018 January for data for cryotherapy, LEEP/LLETZ or CKC using the same search strategy. See Box 1 for the search strategy and results.

Box 1: Search strategy to update Santesso 2016

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

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1 cervical intraepithelial neoplasia/ (15839)
2 uterine cervical dysplasia/ (6681)
3 uterine cervical neoplasms/ (77891)
4 ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw. (162552)
5 (cin or cin2* or cin3* or cin1).tw. (24817)
6 1or2or3or4or5(200874)
7 (co or ae or su or th).fs. (10637617)
8 6 and 7 (53742)
9 (cone or coni?ation).tw. (80689)
10 (biopsy or knife or cold).tw. (903057)
11 9 and 10 (4211)
12 cold knife.tw. (1547)
13 conization/ (3466)
14 11 or 12 or 13 (7110)
15 8 and 14 (2418)
16 (leep or lletz).tw. (2269)
17 electrosurgery.sh. (9627)
18 loop.tw. (258342)
19 or/16-18 (267360)
20 8 and 19 (2201)
21 cryotherapy.tw. (15323)
22 cryosurgery/ (22031)
23 21 or 22 (33966)
24 8 and 23 (955)25 15 or 20 or 24 (4494)
26 limit 25 to yr="2012 -Current" (1067)
29 remove duplicates from 26 (737)

Database: Embase <1974 to 2018 January 23>

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1 exp uterine cervix disease/ (109593)
2 ((precancer* or pre-cancer* or neoplas* or dysplasia or lesion* or premalignan* or malignan* or cancer* or carcinoma*) adj3 cervi*).tw. (91036)
3 (cin or cin1 or cin2* or cin3*).tw. (14598)
4 1or2or3(135486)
5 (co or dm or pc or si or su or th).fs. (5448423)
6 4 and 5 (40960)
7 (cone or coni?ation).tw. (43333)
8 (biopsy or knife or cold).tw. (533229)
9 7 and 8 (2484)
10 cold knife.tw. (922)
11 conization/ (2543)
12 9or10or11(4561)
13 (leep or lletz).tw. (1429)
14 electrosurgery.sh. (5430)
15 loop.tw. (138058)
16 or/13-15 (143279)
17 cryotherapy.tw. (8938)
18 cryosurgery/ (10052)
19 17 or 18 (17688)

We conducted a search of primary studies for PICO 7 from 1997 up to 2018 January, given that data about feasibility and other issues would not be applicable before 1997. See Box 2 for the search strategy and results.

Box 2: Search strategy for thermal ablation (feasibility, acceptability, equity, patient values and preferences)

Database: Embase <1974 to 2018 January 19>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

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1 exp electrocoagulation/ (22792)
2 exp thermocoagulation/ (12804)
3 exp ablation therapy/ (13688)
4 exp gynecologic electrocautery unit/ (4)
5 1or2or3or4 (37650)
6 exp cauterization/ (24282)
7 exp cold/ (95858)
8 6 and 7 (57)
9 cold coagulation.ti,ab. (160)
10 thermosurgery.ti,ab. (20)
11 thermal coagulation.ti,ab. (761)
12 thermocoagulation.ti,ab. (1985)
13 thermo coagulation.ti,ab. (117)
14 electrocautery.ti,ab. (7092)
15 electro cautery.ti,ab. (121)
16 semm.ti,ab. (268)
17 semms.ti,ab. (53)
18 electrocoagulation.ti,ab. (6199)
19 electro coagulation.ti,ab. (313)
20 ablative.ti,ab. (22486)
21 ablate.ti,ab. (7436)
22 ablation.ti,ab. (188724)
23 9or10or11or12or13or14or15or16or17or18or19or20or21or22 (224279)
24 exp uterine cervix carcinoma in situ/ (13681)
25 cervical intraepithelial neoplasia.ti,ab. (15382)
26 cervical intra epithelial neoplasia.ti,ab. (675)
27 cin.ti,ab. (21633)
28 24or25or26or27 (33435)
29 5 or 8 or 23 (242207)
30 28 and 29 (764)
31 limit 30 to yr="1997 -Current" (473)
32 remove duplicates from 31 (324)

The Mustafa 2016 review compared the test accuracy of the hrHPV test, cytology (cervical smear), and unaided visual inspection with acetic acid (VIA); and determined the test accuracy of HPV and colposcopy impression. Medline and Embase were searched up to September 2012; we did not update this search. Studies of at least 100 non-pregnant women (aged ≥18 years) not previously diagnosed with CIN were included. Twenty-three studies were included in the meta-analyses. The test accuracy for hrHPV, VIA, and hrHPV followed by HPV was used from Mustafa 2016 and then these numbers were confirmed by consulting with the Guideline Development Group and comparing them to the accuracy typically found in the field.

We did not update the review by Randall 2019. The authors conducted systematic searches of PubMed, Embase, Web of Science and regional databases for the years 2014 to 2017.

We contacted members of the Guideline Development Group and experts in the field to identify unpublished or in-progress studies.

Identification of studies, data abstraction and synthesis

Two investigators independently abstracted additional data from the studies included in the Randall 2019 review to identify information about important subgroups, different intervention modalities, and other outcomes. Data were compared and agreement was reached.

We included studies following the methods used by Santesso 2016. However, we only included recently published studies that involved over 300 women as we predicted that studies with fewer than 300 women would likely not have an impact on the previously synthesized evidence. Two investigators independently screened titles, abstracts, and the full text of relevant articles, and a third investigator resolved disagreements.

New data were incorporated into the synthesized evidence using Review Manager 5 (RevMan 5 https://community.cochrane.org/help/tools-and-software/revman-5). Relative risks (e.g. risk ratios – RRs – and odds ratios) were calculated by pooling results from RCTs and separately from non-randomized studies comparing interventions. When no direct comparisons between interventions within a study were available (e.g. cryotherapy versus thermal ablation), the risk of an event (or proportion) with an intervention in a study was calculated and then the proportions from each study weighted by the generic inverse variance were combined. The pooled proportion for each intervention was presented but we did not calculate a relative effect between the two interventions.

Modeling of outcomes for a screen-and-treat algorithm

To compare the benefits and harms of one screen-and-treat strategy to those of another, we used the mathematical model previously developed for the WHO guidelines for treatment of cervical intraepithelial neoplasia 2-3 and screen-and-treat strategies to prevent cervical cancer (Santesso 2016b). We used an excel spreadsheet to calculate the downstream consequences of treatment/no treatment after women screen positive or negative, such as cervical cancer, mortality, recurrence of CIN2–3, and adverse events of treatment (and overtreatment). The model includes data for CIN2-3 prevalence, natural progression, the pooled diagnostic test accuracy for the screening tests, and pooled effects of treatment for women of unknown and known HIV status.

Assessment of the certainty of the evidence

We used the risk of bias assessments provided by the authors in the previously conducted systematic reviews, and determined whether the risk of bias assessment would change with the addition of the new studies. We then assessed the certainty of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, and a third investigator helped to resolve any discrepancies. The certainty of the evidence in the results was assessed as high, moderate, low or very low. The certainty of the evidence for the model was based on the assessment originally conducted in the previous WHO guidelines (Santesso 2016b).

Summaries of the evidence

We summarized the evidence in GRADE Summary of Findings tables. We converted relative effects into absolute effects using the baseline risks identified in the non-randomized studies.

Results

Randall 2019

The authors reviewed 34 total reports including 10 995 patients. Twenty-three studies (one RCT and 22 non-randomized studies) with 6371 patients were included in the meta-analysis of pooled proportions. The primary outcome was cervical intraepithelial neoplasia grade 2 or higher (CIN2-3). The authors used results only from the group that received thermal ablation, there were no comparisons. For example, if the study compared thermal ablation to another surgical intervention, only the proportion of women with cure from the thermal ablation group was used in the meta-analysis.

Santesso 2016

We did not find additional studies for this review. Therefore, we used the results from the 167 studies (see Figure 3).

Mustafa 2016

This review was not updated.

Review of accessibility, feasibility, equity and costs

We found eight studies that provided information for accessibility, feasibility, equity and costs: Campbell 2016, Campos 2016, Duncan 1983, Ibrahim 2012, Joshi 2013, Paul 2013, Singh 1988, Viviano 2013 (see Figure 4).

Figure 3: PRISMA flowchart – cryotherapy, LEEP/LLETZ and CKC

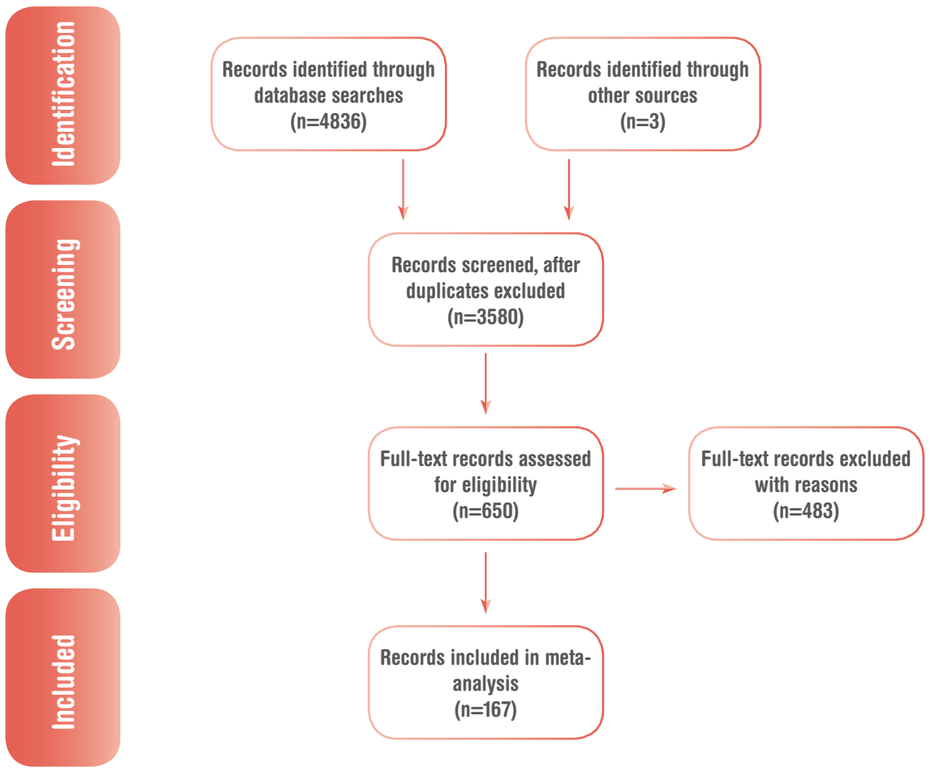
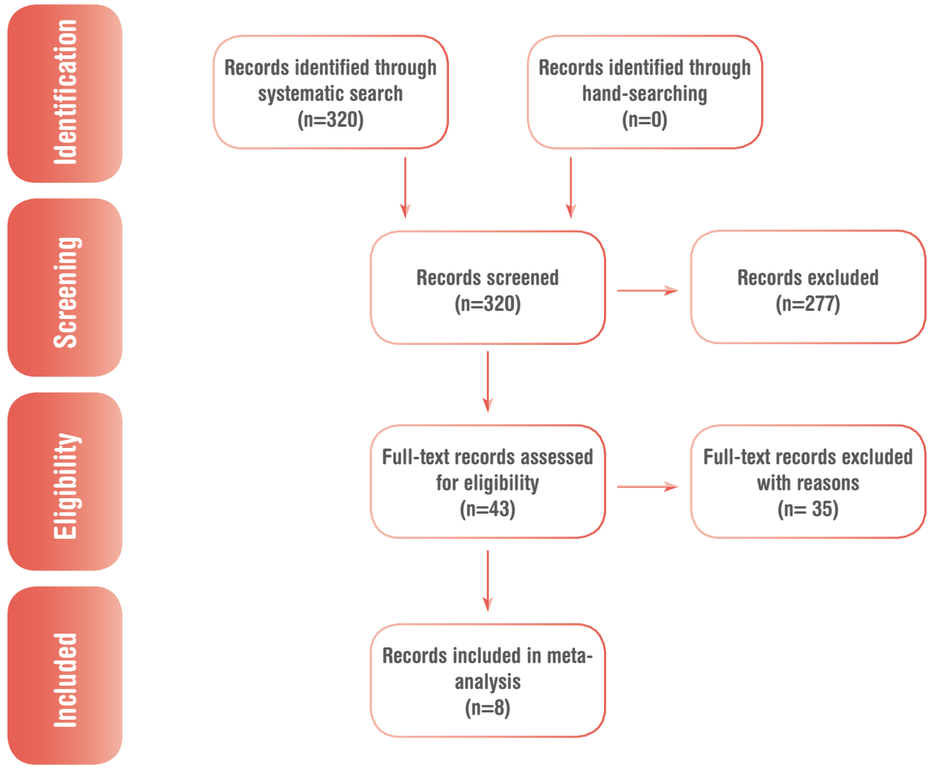


Figure 4: PRISMA flowchart – thermal ablation search on accessibility, feasibility, equity and costs



Should thermal ablation versus cryotherapy or LLETZ or conisation be used for women with histologically confirmed CIN2-3?

Should one modality of thermal ablation be used versus another modality?

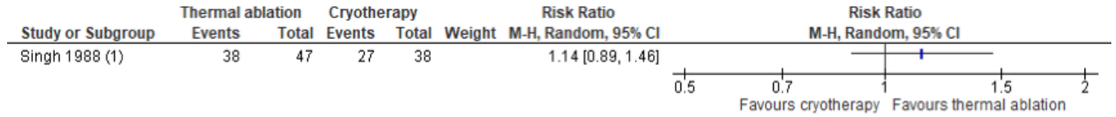
(PICO 1 and 2 – Recommendations 1 and 2)

GRADE TABLE

Outcome Nº of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Risk with cryotherapy	Risk with thermal ablation	Difference with thermal ablation	
Cure Nº of participants: 85 (1 RCT)	RR 1.14 (0.89 to 1.46)	Moderate 90.0%	100.0% (80.1 to 100.0)	12.6% more (9.9 fewer to 41.4 more)	Moderate
Cure Nº of participants: 157 (1 observational study)	RR 1.01 (0.89 to 1.14)	Moderate 90.0%	90.9% (80.1 to 100.0)	0.9% more (9.9 fewer to 12.6 more)	Very low
Cure Nº of participants: (23 case series)	not estimable	Moderate 90.0% (87 to 93)	92% (90 to 95) 2 probe: 95 (93 to 98) Not 2 probe: 85 (80 to 90)		Low
Pain immediately Nº of participants: 413 (4 RCTs)	RR 0.93 (0.76 to 1.15)	65.4%	60.8% (49.7 to 75.2)	4.6% fewer (15.7 fewer to 9.8 more)	Moderate
Pain immediately Nº of participants: (case series)	not estimable	Moderate 30.0% (19 to 41)	63% (42 to 83)	33% more	Low
Major bleeding Nº of participants: 817 (6 RCTs)	RR 0.62 (0.37 to 1.02)	1.7%	1.0% (0.6 to 1.7)	0.6% fewer (1.1 fewer to 0 fewer)	Moderate
Major bleeding Nº of participants: (case series)	not estimable	4 / 9941	9 / 4634		Low
Infection (including fever) Nº of participants: 816 (6 RCTs)	RR 0.81 (0.10 to 6.33)	0.3%	0.2% (0.0 to 1.6)	0.0% fewer (0.2 fewer to 1.3 more)	Moderate
Infections (including fever) (45 case series)	not estimable	60 / 8674	17 / 4082		Low
Acceptability – whether they would recommend it Nº of participants: 631 (3 RCTs)	Acceptability is likely not different between thermal ablation and cryotherapy. Risk Ratio 1.01 (0.99 to 1.02)				Moderate
Premature delivery Nº of participants: 204 (5 case series)	In total, across 5 studies there were 3 premature deliveries in 204 pregnant women (1.5%). In women without cervical lesions (typical population) premature delivery occurs in 5.5% of women.				Very low

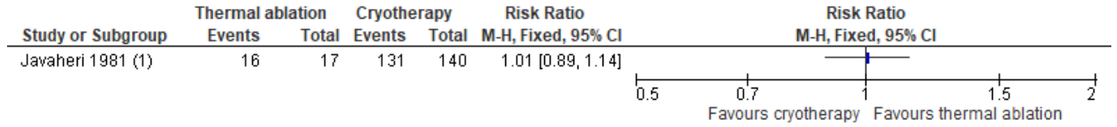
FOREST PLOTS

Cure, randomized studies



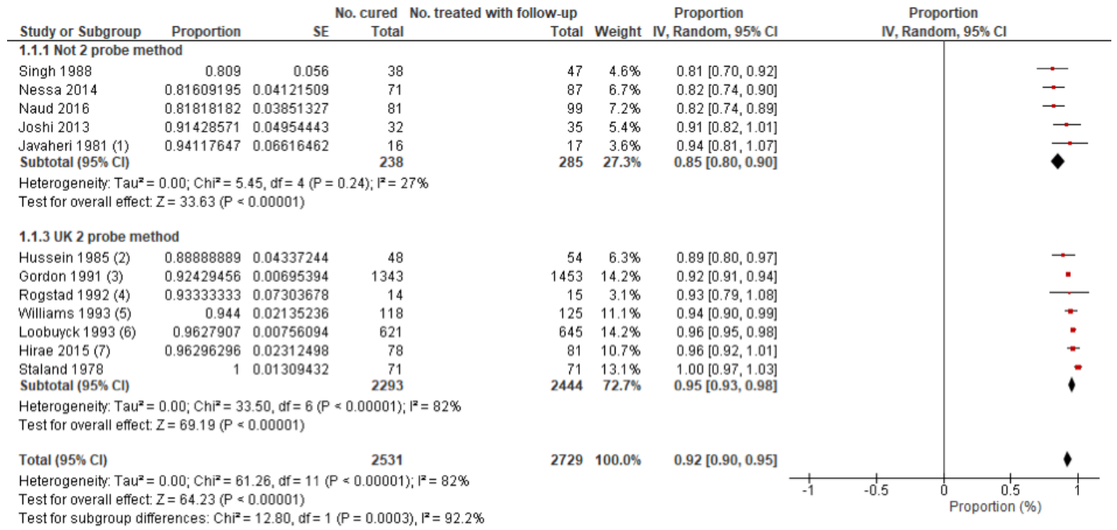
Footnotes
(1) 3 months - 2 years f/u; CIN 2-3 diag histologically confirmed; CIN 2+ cure

Cure, non-randomized studies



Footnotes
(1) CIN 2-3 diagnosis and CIN 2+ cures

Cure with thermal ablation, case series

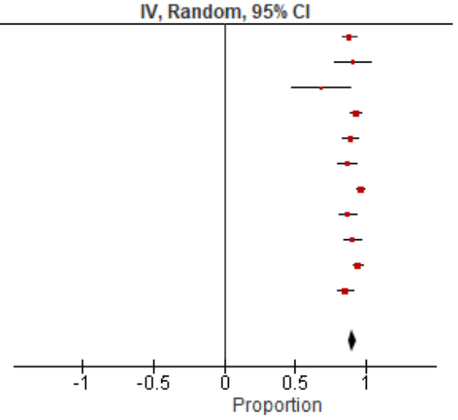


Footnotes
(1) temperature 70 to 90C
(2) Not clear, may not be 2 probe
(3) lower endocervix
(4) not clear if 2 probe method
(5) TZ and inner canal
(6) lower endocervix detroyed (could be 17 not 24 failures)
(7) not indicated, likely 2 probes used

Cure with cryotherapy, case series

Study or Subgroup	Proportions	SE	Weight	Proportions IV, Random, 95% CI
chirenje	0.882	0.025	10.8%	0.88 [0.83, 0.93]
doh	0.909	0.065	3.8%	0.91 [0.78, 1.04]
guijon	0.688	0.106	1.7%	0.69 [0.48, 0.90]
kaufman73	0.931	0.022	11.6%	0.93 [0.89, 0.97]
luciani (1)	0.893	0.027	10.2%	0.89 [0.84, 0.95]
nene	0.868	0.033	8.7%	0.87 [0.80, 0.93]
ostergard	0.964	0.015	13.6%	0.96 [0.93, 0.99]
sankar	0.873	0.033	8.7%	0.87 [0.81, 0.94]
schantz	0.905	0.033	8.7%	0.91 [0.84, 0.97]
selim	0.947	0.019	12.5%	0.95 [0.91, 0.98]
walton	0.855	0.029	9.7%	0.85 [0.80, 0.91]
Total (95% CI)			**100.0%**	**0.90 [0.87, 0.93]**

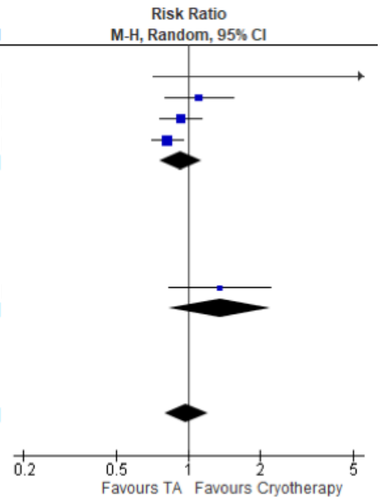
Heterogeneity: Tau² = 0.00; Chi² = 28.74, df = 10 (P = 0.001); I² = 65%
Test for overall effect: Z = 62.21 (P < 0.00001)



Footnotes
(1) VIA or cytology

Pain, randomized studies

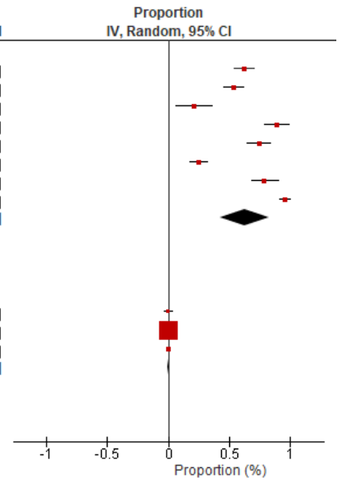
Study or Subgroup	Thermal ablation Events	Total	Cryotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Measured immediately						
Fergusson 1974	5	24	0	27	0.6%	12.32 [0.72, 211.79]
Forestier unpublished	32	36	8	10	21.1%	1.11 [0.80, 1.55]
basu zambia	82	153	84	146	30.6%	0.93 [0.76, 1.14]
Basu unpublished India (1)	86	136	116	150	34.6%	0.82 [0.70, 0.95]
Subtotal (95% CI)		**349**		**333**	**86.9%**	**0.93 [0.76, 1.15]**
Total events	205		208			
Heterogeneity: Tau² = 0.02; Chi² = 6.48, df = 3 (P = 0.09); I² = 54%						
Test for overall effect: Z = 0.67 (P = 0.50)						
1.4.2 Measuerd 6 week visit						
Cremer unpublished (2)	15	22	12	24	13.1%	1.36 [0.83, 2.23]
Subtotal (95% CI)		**22**		**24**	**13.1%**	**1.36 [0.83, 2.23]**
Total events	15		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.22)						
Total (95% CI)		**371**		**357**	**100.0%**	**0.99 [0.80, 1.22]**
Total events	220		220			
Heterogeneity: Tau² = 0.03; Chi² = 9.30, df = 4 (P = 0.05); I² = 57%						
Test for overall effect: Z = 0.13 (P = 0.89)						
Test for subgroup differences: Chi² = 1.96, df = 1 (P = 0.16), I² = 49.0%						



Footnotes
(1) no anaethesia
(2) cramping; measured at 6 week visit

Pain with thermal ablation, case series

Study or Subgroup	Proportion	SE	No. pain Total	No. treated with TA Total	Weight	Proportion IV, Random, 95% CI
2.3.1 Pain/cramps						
Basu unpublished India (1)	0.623	0.041	86	138	12.6%	0.62 [0.54, 0.70]
basu zambia (2)	0.536	0.04	82	153	12.6%	0.54 [0.46, 0.61]
Fergusson 1974 (3)	0.20833333	0.07691378	5	24	12.0%	0.21 [0.06, 0.36]
Forestier unpublished (4)	0.889	0.053	32	36	12.4%	0.89 [0.79, 0.99]
Goodman 1991 (5)	0.744	0.049	58	78	12.5%	0.74 [0.65, 0.84]
Joshi 2013 (6)	0.25	0.038	31	124	12.6%	0.25 [0.18, 0.32]
Naud 2016 (7)	0.788	0.056	41	52	12.4%	0.79 [0.68, 0.90]
Viviano 2017 (8)	0.955	0.021	105	110	12.8%	0.95 [0.91, 1.00]
Subtotal (95% CI)			**440**	**715**	**100.0%**	**0.63 [0.42, 0.83]**
Heterogeneity: Tau² = 0.08; Chi² = 360.80, df = 7 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 6.01 (P < 0.00001)						
2.3.2 stopped treatment due to pain						
Hussein 1985 (9)	0	0.01694282	0	54	3.2%	0.00 [-0.03, 0.03]
Joshi 2015 (10)	0	0.00326839	0	296	84.6%	0.00 [-0.01, 0.01]
Viviano 2017 (11)	0	0.00860845	0	110	12.2%	0.00 [-0.02, 0.02]
Subtotal (95% CI)			**0**	**460**	**100.0%**	**0.00 [-0.01, 0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 2 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						

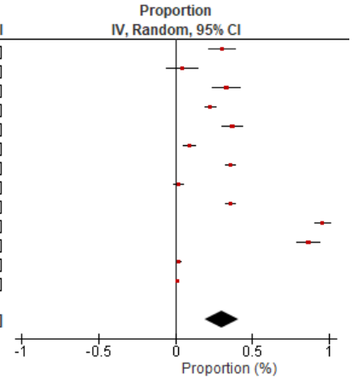


Test for subgroup differences: Chi² = 36.10, df = 1 (P < 0.00001), I² = 97.2%

Footnotes
(1) pain/cramps; no anaesthesia;
(2) pain/cramps; no anaesthesia????; 8 had moderate, 0 had severe
(3) 'pain'; use of anaethesia not reported
(4) cramps; no anaethesia???; 4 were moderate, 0 severe
(5) local anaesthesia; mean pain score was 2 (0-10, worse); people with any pain
(6) no anaesthesia; mild pain or cramps
(7) mild pain or cramps; no anaesthesia/analgesics
(8) no anaethesia; experienced pain that was a mean (SD) of 3.0 +/- 1.6
(9) no anaesthesia; abandoned treatment
(10) not 'well tolerated'; no anaesthesia
(11) no anaethesia; 0 interrupted treatment

Pain with cryotherapy, case series

Study or Subgroup	Proportion	SE	No. pain Total	No. cryotherapy Total	Weight	Proportion IV, Random, 95% CI
Acosta 1973	0.301	0.04452509	31	103	7.5%	0.30 [0.21, 0.39]
Adewole 1998 (1)	0.043	0.05158148	1	23	7.4%	0.04 [-0.06, 0.14]
Berget 1987 (2)	0.33	0.04625473	33	100	7.5%	0.33 [0.24, 0.42]
Blumenthal 2007	0.227	0.01618503	97	427	7.8%	0.23 [0.20, 0.26]
Chirenje 2001	0.37	0.034	74	200	7.6%	0.37 [0.30, 0.44]
Coffey 2005	0.08928571	0.01921901	20	224	7.8%	0.09 [0.05, 0.13]
Denny 2005	0.35721812	0.01552623	339	949	7.8%	0.36 [0.33, 0.39]
Doh 1999 (3)	0.01960784	0.01614816	2	102	7.8%	0.02 [-0.01, 0.05]
Gaffkin 2003	0.359	0.016	307	856	7.8%	0.36 [0.33, 0.39]
Harper 1997	0.95294118	0.02458903	81	85	7.7%	0.95 [0.90, 1.00]
Harper 1998	0.86206897	0.03701305	75	87	7.6%	0.86 [0.79, 0.93]
nene	0.024	0.007	14	574	7.8%	0.02 [0.01, 0.04]
Sankaranarayanan 2007	0.013	0.002	32	2513	7.9%	0.01 [0.01, 0.02]
Total (95% CI)			**1106**	**6243**	**100.0%**	**0.30 [0.19, 0.41]**
Heterogeneity: Tau² = 0.04; Chi² = 3179.74, df = 12 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 5.39 (P < 0.00001)						

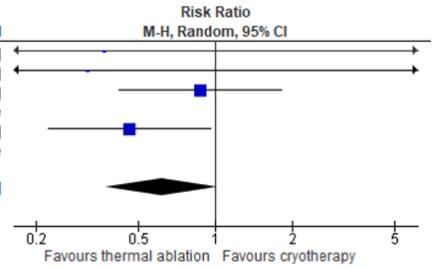


Footnotes
(1) no anaethesia
(2) no anaethesia
(3) no anaethesia

Major bleeding, randomized studies

Study or Subgroup	Thermal ablation Events	Total	Cryotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Basu unpublished India (1)	0	138	1	154	2.5%	0.37 [0.02, 9.05]
basu zambia (2)	0	153	1	146	2.5%	0.32 [0.01, 7.75]
Cremer unpublished (3)	8	22	10	24	47.7%	0.87 [0.42, 1.81]
Fergusson 1974 (4)	0	24	0	27		Not estimable
Forestier unpublished	10	36	6	10	47.3%	0.46 [0.22, 0.96]
Singh 1988	0	46	0	37		Not estimable
Total (95% CI)		**419**		**398**	**100.0%**	**0.62 [0.37, 1.02]**
Total events	18		18			

Heterogeneity: Tau² = 0.00; Chi² = 1.73, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.88 (P = 0.06)

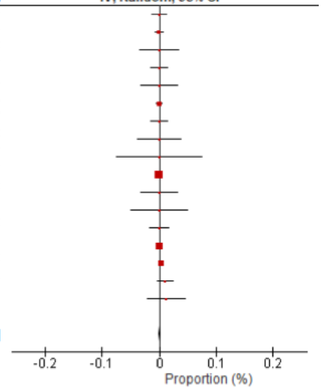


Footnotes
(1) bleeding is non-serious
(2) no major bleeding in either group
(3) measured 6 weeks after treatment
(4) no bleeding (however post coital bleeding is reported at 8 weeks)

Major bleeding with thermal ablation, case series

Study or Subgroup	Proportion	SE	No. major bleeding Total	No. treated with TA Total	Weight	Proportion IV, Random, 95% CI
basu zambia	0	0.006	0	154	1.7%	0.00 [-0.01, 0.01]
Joshi 2015	0	0.00326839	0	296	5.7%	0.00 [-0.01, 0.01]
Naud 2016	0	0.01754964	0	52	0.2%	0.00 [-0.03, 0.03]
Joshi 2013	0	0.00766574	0	124	1.0%	0.00 [-0.02, 0.02]
Hussein 1985	0	0.01694282	0	54	0.2%	0.00 [-0.03, 0.03]
Williams 1993 (1)	0	0.00255314	0	380	9.4%	0.00 [-0.01, 0.01]
Basu unpublished India	0	0.007	0	138	1.2%	0.00 [-0.01, 0.01]
Singh 1988	0	0.01927555	0	47	0.2%	0.00 [-0.04, 0.04]
Cremer unpublished (2)	0	0.038	0	22	0.0%	0.00 [-0.07, 0.07]
Zawislak 2003	0	0.0013446	0	725	33.9%	0.00 [-0.00, 0.00]
Javaheri 1981	0	0.01694282	0	54	0.2%	0.00 [-0.03, 0.03]
Forestier unpublished (3)	0	0.025	0	36	0.1%	0.00 [-0.05, 0.05]
Viviano 2017	0	0.00860845	0	110	0.8%	0.00 [-0.02, 0.02]
Cassidy 1987	0.00108225	0.00150862	1	924	26.9%	0.00 [-0.00, 0.00]
Loobuyck 1993 (4)	0.00343348	0.00190283	4	1165	16.9%	0.00 [-0.00, 0.01]
Allam 2005 (5)	0.01090909	0.00710739	3	275	1.2%	0.01 [-0.00, 0.02]
Goodman 1991 (6)	0.013	0.017	1	78	0.2%	0.01 [-0.02, 0.05]
Total (95% CI)			**9**	**4634**	**100.0%**	**0.00 [-0.00, 0.00]**

Heterogeneity: Tau² = 0.00; Chi² = 4.97, df = 16 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)

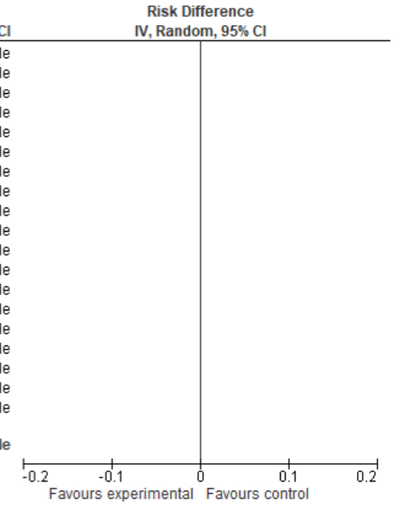


Footnotes
(1) Farquharson 1987 reported 2% of patients had bleeding requiring hospital atttention (no denominator given)
(2) reported mean type of bleeding was light to moderate, no major bleeding reported
(3) bleding reported immediately after treatment: 10/36 - not indicated as major.
(4) colposcpically directed biopsy
(5) cytology and histological confirmation
(6) diagnosis: biopsy proven malignant disease

Major bleeding with cryotherapy, case series

Study or Subgroup	Risk Difference	SE	cryotherapy Total	No control Total	Weight	Risk Difference IV, Random, 95% CI
Adewole 1998	0	0	0	23		Not estimable
benedet 1981	0	0	0	516		Not estimable
Bhatla 2009	0	0	0	43		Not estimable
Blumenthal 2007	0	0	0	427		Not estimable
chirenje	0	0	1	200		Not estimable
Denny 2005	0	0	1	949		Not estimable
einerth	0	0	0	54		Not estimable
Gaffkin 2003	0	0	0	756		Not estimable
Kayser 1973	0	0	0	218		Not estimable
Kohler 1983	0	0	2	102		Not estimable
Loizzi 1992	0	0	0	131		Not estimable
luciani	0	0	0	1398		Not estimable
mitchell	0	0	0	139		Not estimable
Moon 2012	0	0	0	221		Not estimable
muwonge 2010	0	0	0	276		Not estimable
nene	0	0	0	574		Not estimable
Phongsavan 2011	0	0	0	113		Not estimable
Sankaranarayanan 2007	0	0	0	2513		Not estimable
Sankaranarayanan 2007	0	0	0	1288		Not estimable
Total (95% CI)			**4**	**9941**		**Not estimable**

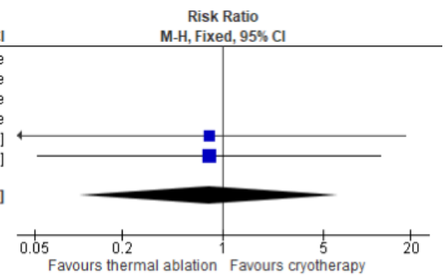
Heterogeneity: Not applicable
Test for overall effect: Not applicable



Infection (including fever), randomized studies

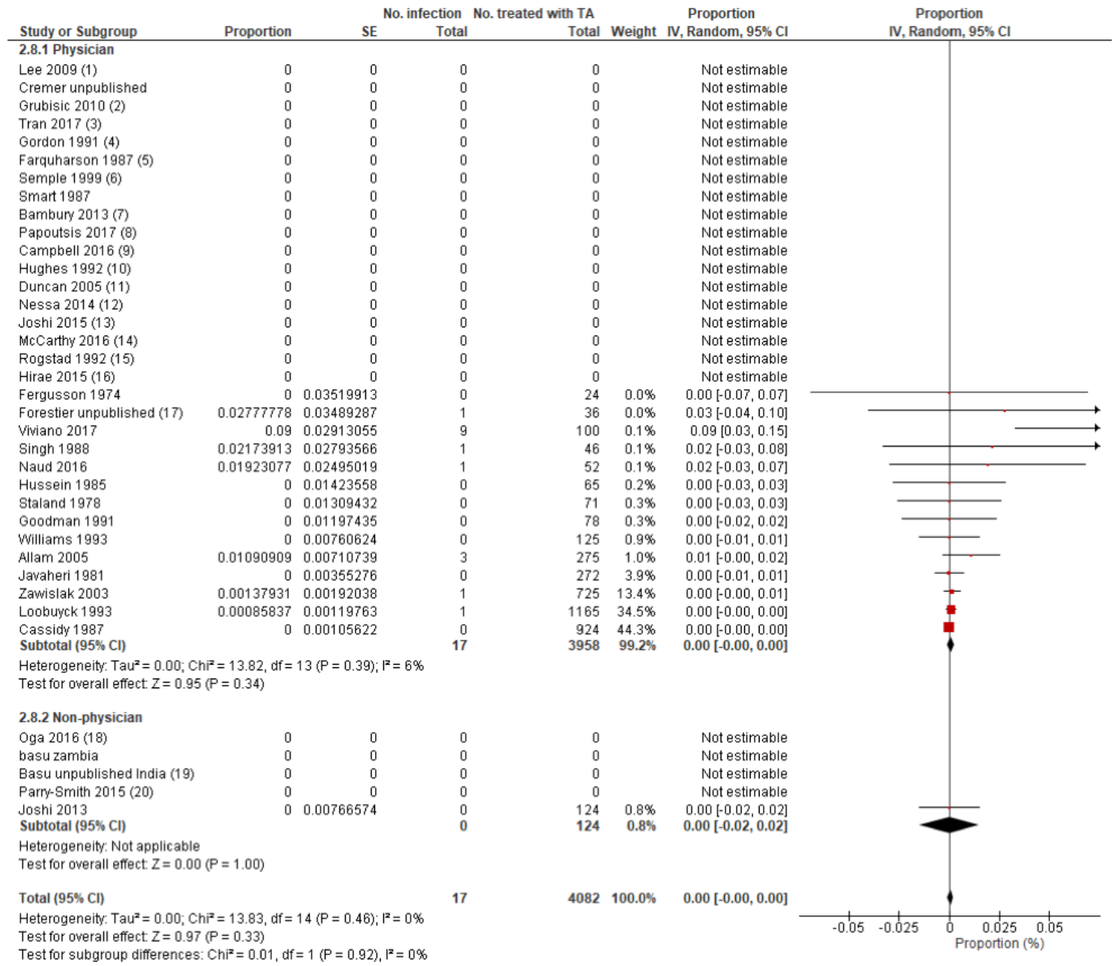
Study or Subgroup	Thermal ablation Events	Total	Cryotherapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Basu unpublished India (1)	0	138	0	154		Not estimable
basu zambia (2)	0	153	0	146		Not estimable
Cremer unpublished (3)	0	22	0	24		Not estimable
Fergusson 1974	0	24	0	27		Not estimable
Forestier unpublished	1	36	0	9	41.5%	0.81 [0.04, 18.43]
Singh 1988	1	46	1	37	58.5%	0.80 [0.05, 12.43]
Total (95% CI)		**419**		**397**	**100.0%**	**0.81 [0.10, 6.33]**
Total events	2		1			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



Footnotes
(1) not reported
(2) not measured
(3) not reported

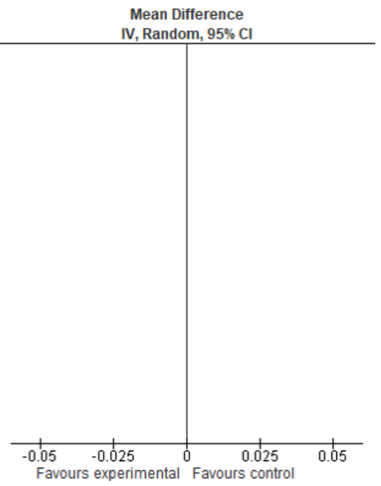
Infection (including fever) with thermal ablation, case series



Study or Subgroup	Proportion	SE	No. infection Total	No. treated with TA Total	Weight	Proportion IV, Random, 95% CI
2.8.1 Physician						
Lee 2009 (1)	0	0	0	0		Not estimable
Cremer unpublished	0	0	0	0		Not estimable
Grubisic 2010 (2)	0	0	0	0		Not estimable
Tran 2017 (3)	0	0	0	0		Not estimable
Gordon 1991 (4)	0	0	0	0		Not estimable
Farquharson 1987 (5)	0	0	0	0		Not estimable
Semple 1999 (6)	0	0	0	0		Not estimable
Smart 1987	0	0	0	0		Not estimable
Bambury 2013 (7)	0	0	0	0		Not estimable
Papoutsis 2017 (8)	0	0	0	0		Not estimable
Campbell 2016 (9)	0	0	0	0		Not estimable
Hughes 1992 (10)	0	0	0	0		Not estimable
Duncan 2005 (11)	0	0	0	0		Not estimable
Nessa 2014 (12)	0	0	0	0		Not estimable
Joshi 2015 (13)	0	0	0	0		Not estimable
McCarthy 2016 (14)	0	0	0	0		Not estimable
Rogstad 1992 (15)	0	0	0	0		Not estimable
Hirae 2015 (16)	0	0	0	0		Not estimable
Fergusson 1974	0	0.03519913	0	24	0.0%	0.00 [-0.07, 0.07]
Forestier unpublished (17)	0.02777778	0.03489287	1	36	0.0%	0.03 [-0.04, 0.10]
Viviano 2017	0.09	0.02913055	9	100	0.1%	0.09 [0.03, 0.15]
Singh 1988	0.02173913	0.02793566	1	46	0.1%	0.02 [-0.03, 0.08]
Naud 2016	0.01923077	0.02495019	1	52	0.1%	0.02 [-0.03, 0.07]
Hussein 1985	0	0.01423558	0	65	0.2%	0.00 [-0.03, 0.03]
Staland 1978	0	0.01309432	0	71	0.3%	0.00 [-0.03, 0.03]
Goodman 1991	0	0.01197435	0	78	0.3%	0.00 [-0.02, 0.02]
Williams 1993	0	0.00760624	0	125	0.9%	0.00 [-0.01, 0.01]
Allam 2005	0.01090909	0.00710739	3	275	1.0%	0.01 [-0.00, 0.02]
Javaheri 1981	0	0.00355276	0	272	3.9%	0.00 [-0.01, 0.01]
Zawislak 2003	0.00137931	0.00192038	1	725	13.4%	0.00 [-0.00, 0.01]
Loobuyck 1993	0.00085837	0.00119763	1	1165	34.5%	0.00 [-0.00, 0.00]
Cassidy 1987	0	0.00105622	0	924	44.3%	0.00 [-0.00, 0.00]
Subtotal (95% CI)			**17**	**3958**	**99.2%**	**0.00 [-0.00, 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 13.82, df = 13 (P = 0.39); I² = 6%						
Test for overall effect: Z = 0.95 (P = 0.34)						
2.8.2 Non-physician						
Oga 2016 (18)	0	0	0	0		Not estimable
basu zambia	0	0	0	0		Not estimable
Basu unpublished India (19)	0	0	0	0		Not estimable
Parry-Smith 2015 (20)	0	0	0	0		Not estimable
Joshi 2013	0	0.00766574	0	124	0.8%	0.00 [-0.02, 0.02]
Subtotal (95% CI)			**0**	**124**	**0.8%**	**0.00 [-0.02, 0.02]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)			**17**	**4082**	**100.0%**	**0.00 [-0.00, 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 13.83, df = 14 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						

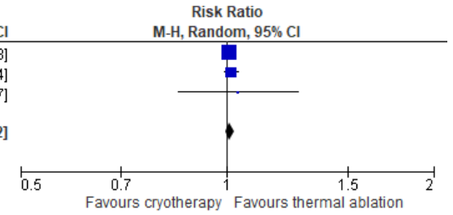
Footnotes
(1) not measured
(2) Not measured
(3) not measured
(4) not measured
(5) unclear reporting of treatment of discharge
(6) not measured
(7) not measured
(8) not measured
(9) not reported
(10) not measured
(11) not measured
(12) not measured
(13) not measured
(14) not measured
(15) not measured
(16) not measured
(17) fever
(18) not measured
(19) not measured
(20) not measured

Infection (including fever) with cryotherapy, case series



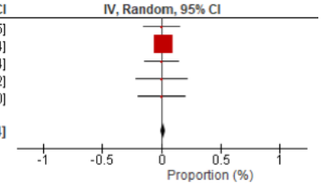
Study or Subgroup	Mean Difference	SE	cryotherapy Total	No control Total	Weight	Mean Difference IV, Random, 95% CI
Acosta 1973	0	0	2	103		Not estimable
Adefuye 2015	0	0	5	220		Not estimable
benedet 1981	0	0	1	516		Not estimable
berget	0	0	1	101		Not estimable
Bhatla 2009	0	0	0	43		Not estimable
Blumenthal 2007	0	0	0	427		Not estimable
chirenje	0	0	0	200		Not estimable
Creasman 1973	0	0	4	75		Not estimable
doh	0	0	2	102		Not estimable
einerth	0	0	0	54		Not estimable
Ferenczy 1985	0	0	1	1147		Not estimable
Gaffkin 2003	0	0	1	756		Not estimable
luciani	0	0	14	1398		Not estimable
mitchell	0	0	1	139		Not estimable
monaghan	0	0	1	204		Not estimable
nene	0	0	10	574		Not estimable
Sankaranarayanan 2007	0	0	16	2513		Not estimable
vanLent 1982	0	0	1	102		Not estimable
Total (95% CI)			**60**	**8674**		**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Acceptability, randomized studies



Study or Subgroup	thermal ablation Events	Total	cryotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Basu unpublished India	136	136	149	150	59.8%	1.01 [0.99, 1.03]
basu zambia	154	154	143	145	39.7%	1.01 [0.99, 1.04]
Cremer unpublished	20	22	21	24	0.5%	1.04 [0.85, 1.27]
Total (95% CI)		**312**		**319**	**100.0%**	**1.01 [0.99, 1.02]**
Total events	310		313			
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						

Premature delivery with thermal ablation, case series

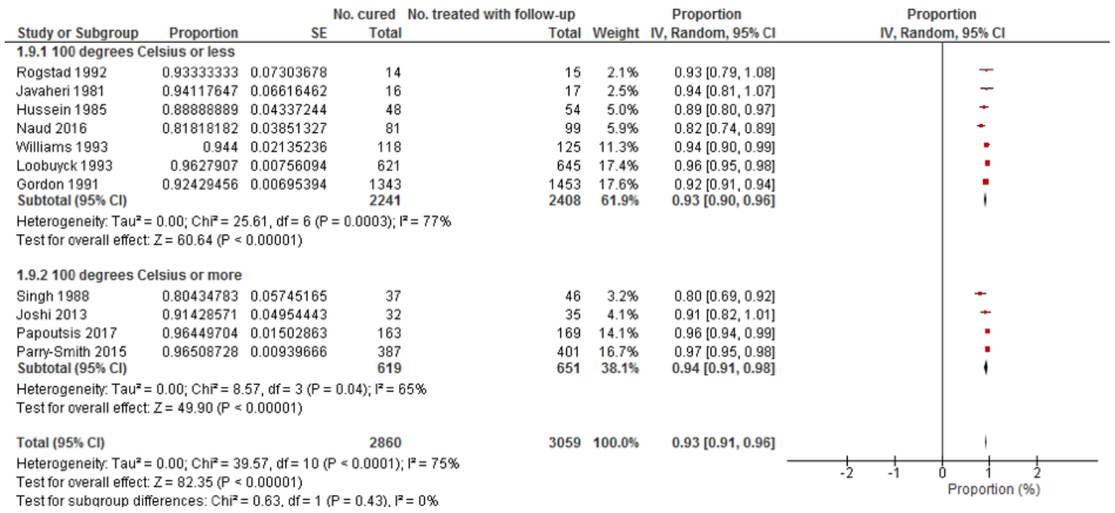


Study or Subgroup	Proportion	SE	No. premature deliveries Total	No. pregnant tx with TA Total	Weight	Proportion IV, Random, 95% CI
Cassidy 1987	0	0.07631448	0	9	1.9%	0.00 [-0.15, 0.15]
Gordon 1991 (1)	0.017	0.011	3	174	93.7%	0.02 [-0.00, 0.04]
Lee 2009	0	0.07080106	0	10	2.3%	0.00 [-0.14, 0.14]
Staland 1978	0	0.111	0	5	0.9%	0.00 [-0.22, 0.22]
Williams 1993	0	0.0995773	0	6	1.1%	0.00 [-0.20, 0.20]
Total (95% CI)			**3**	**204**	**100.0%**	**0.02 [-0.00, 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.50 (P = 0.13)						

Footnotes
(1) 94 of 101 women conceived within 2years after treatment

Evidence for one modality of thermal ablation versus another

Probe temperature	Duration of probe application	No. cured / no. treated with follow-up (rate)	Studies included in meta-analysis	Studies without data on cure rate
100 °C or less		2241 / 2408 (0.93)		
70–90 °C	30 seconds		Javaheri 1981	
100 °C	20 seconds		Hussein 1985 Gordon 1991 Rogstad 1992 Loobuyck 1993 Williams 1993 Naud 2016	Duncan 1983
100 °C	60 seconds			Tran 2017 Viviano 2017
100 °C	Not specified			Goodman 1991
100 °C or higher		619 / 651 (0.94)		
100–110 °C	20 seconds		Singh 1998	
105 °C	45 seconds		Joshi 2013	Joshi 2015
110–120 °C	Min. 20 seconds		Parry-Smith 2014 Papoutsis 2017	
120 °C	20 seconds			Smart 1987 Allam 2005
120 °C	30–40 seconds			Zawislak 2003
120 °C	30–60 seconds			Lee 2009
Temperature not specified				
	30 seconds		McCarthy 2016	



Unpublished data from Cremer et al. 2018. Thermal ablation data from three-arm and five-arm randomized controlled trials in Peru and El Salvador.

	n	Range	Mean (SD)	Fail to meet 3.5 mm benchmark (%)
120 0C, flat probe, 40 seconds	22	1.5–6.1	2.3 (1.3)	16 (72.7%)
100 0C, wide conical probe, 40 seconds	27	2.5–5.5	3.5 (0.9)	13 (48.1%)

Should thermal ablation versus cryotherapy be used in a screen-and-treat algorithm when women are screened hrHPV+ or VIA+? (PICO 3 – Recommendation 3)

Data for the effects of treatment were obtained from the analysis in PICO 1 and summarized below.

Risks when treated with thermal ablation or cryotherapy

	Risk to use in model for cryotherapy	Risk to use in model for thermal ablation
CIN 2-3 recurrence in women with confirmed CIN 2-3	0.10	0.08
Major bleeding	0.017	0.01
Infections	0.003	0.002
Pain (mild to severe) [comparative]	0.654	0.608

Notes about assumption for cervical recurrence, cancer and mortality [references available]

- Baseline risk of CIN 2-3 is 2%
- 30% of CIN 2-3 will regress according to natural progress of disease.
- 2.5% of people with CIN 2-3 will progress to cervical cancer
- 71% of people with cervical cancer will die

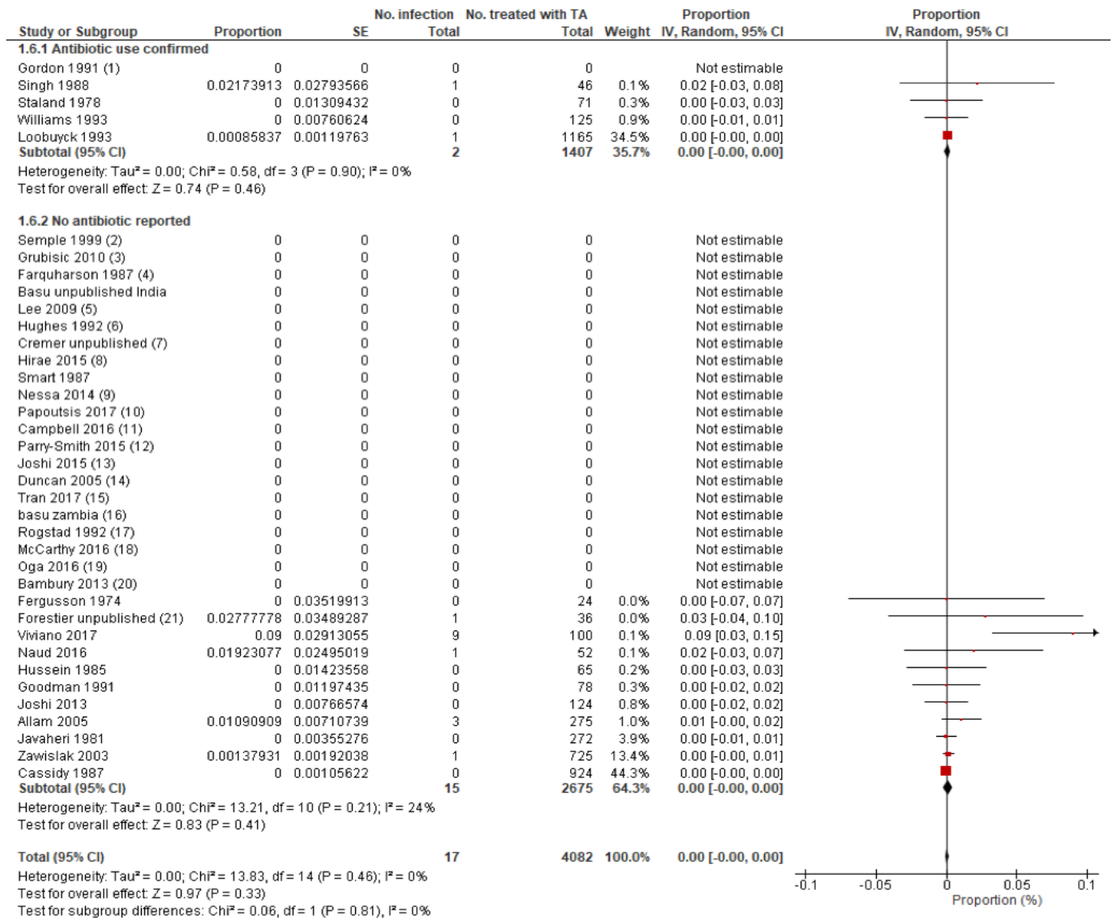
	HPV sensitivity: 95% specificity: 84%		VIA sensitivity: 60%* specificity: 84%*		HPV then VIA	
	Cryotherapy	Thermal ablation	Cryotherapy	Thermal ablation	Cryotherapy	Thermal ablation
Women treated (TP, FP)	175 800		168 800		36 500	
Women over-treated (FP)	156 800		156 800		25 100	
Missed cases (FN)	1 000		8 000		8 600	
Mortality	46	40	121	117	128	124
Cervical Cancer	65	56	170	164	179	173
CIN2-3 recurrence	2600	2 200	6800	6 560	7 160	6 932
Major bleeding	2 989	1758	2870	1 688	620	365
Pain	114 973	106 886	110 395	102 630	23 863	22 185
Major infections	527	352	506	338	109	73

Should prophylactic antibiotics versus no prophylaxis be provided after thermal ablation? (PICO 4 – Recommendation 4)

We did not find studies comparing women taking or not taking antibiotics with thermal ablation, or studies comparing antibiotic use with different treatments (e.g. LEEP, LLETZ, cryotherapy or CKC compared to thermal ablation).

We instead reviewed studies identified in Randall 2018 for antibiotic use and infections (major or minor). It was assumed that when not reported in the study that antibiotics were not used.

FOREST PLOTS



Note:

Basu (2018, unpublished data, Zambia) reported no serious adverse events related to the thermal ablation (including infections)

Basu (2018, unpublished data, India) did not report infections

Indirect evidence from the use of antibiotics with cryotherapy was reported from the WHO guidelines for the use of cryotherapy for cervical intraepithelial neoplasia, 2011 (http://www.who.int/reproductivehealth/publications/cancers/9789241502856/en/)

Recommendation 7. **Should antibiotics be provided prophylactically with cryotherapy in women with histologically confirmed CIN?**

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy with antibiotics	No antibiotics	Relative (95% CI)	Absolute		
Major infection (follow-up 12 months; requiring hospitalization or blood transfusion)												
16	observational studies	serious limitations[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	0/1600 (0%)	10/4573 (0.22%)	–	0 per 1000[3]	⊕◯◯◯	IMPORTANT
All severe adverse events (follow-up 12 months; (major infections and bleeding, pelvic inflammatory disease, stenosis, etc)												
17	observational studies	serious limitations[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	0/1705 (0%)	22/5142 (0.43%)	–	0 per 1000[3]	⊕◯◯◯	IMPORTANT
Minor infections (follow-up 12 months)												
10	observational studies	serious limitations[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	50/1600 (3.1%)	107/2337 (4.6%)	–	30 fewer per 1000 (from 40 to 20 fewer)	⊕◯◯◯	IMPORTANT

Should thermal ablation be provided by other trained providers versus physicians? (PICO 5 – Recommendation 5)

We did not find studies comparing the effects of different health care providers providing thermal ablation.
We instead reviewed studies identified in Randall 2018 for thermal ablation provided by different providers and data not yet published from Zambia, India, Peru and El Salvador. Results of studies with one group receiving thermal ablation by physicians were thus compared to studies with one group receiving thermal ablation by trained non-physicians.

GRADE TABLE

Thermal ablation provided by physician versus trained non-physicians for women with histologically confirmed CIN 2-3

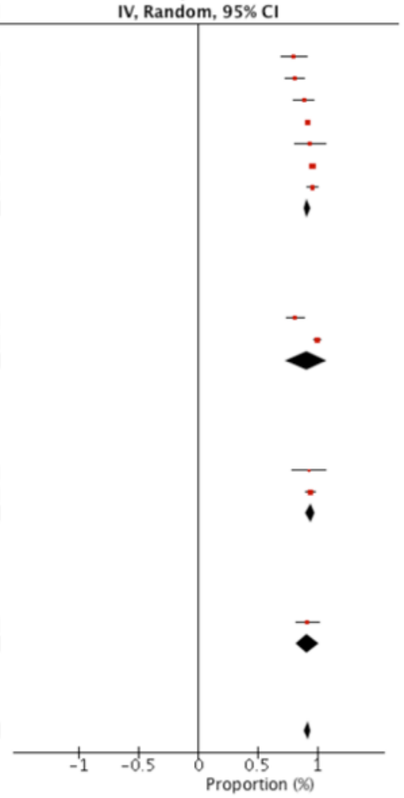
Outcome (studies)	Risk with physician	Risk with trained non-physicians	Certainty
Cure (CIN 2-3 diagnosis and cure) (12 case series)	91 to 94%	91%	Very low
Number of women experiencing pain (8 case series)	72% (53 to 92%)	47% (25 to 69%)	Very low
Pain on 0-10 scale (4 case series)	Mean score 2.97 (1.96 to 3.98)	Mean score 2.10 (1.90 to 2.30)	Very low
Major bleeding (17 case series)	4 / 4218 (0.1%)	0 / 416 (0%)	Very low
Infection (including fever) (6 RCTs)	17/3958 (0.08%)	0/124 (0%)	Very low
Premature delivery	at 4 months		-

FOREST PLOTS

Cure by provider, case series

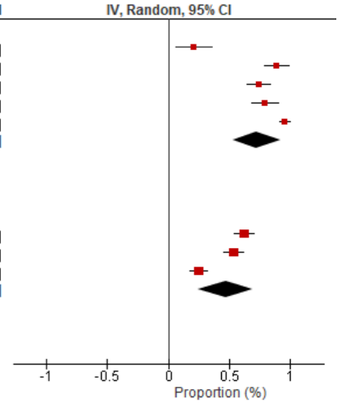
CIN 2-3 diagnosis and cure (cytology +/- biopsy confirmed)

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
1.9.1 Colposcopist				
Singh 1988	0.80434783	0.05745165	4.4%	0.80 [0.69, 0.92]
Nessa 2014	0.81609195	0.04121509	6.7%	0.82 [0.74, 0.90]
Hussein 1985	0.88888889	0.04337244	6.3%	0.89 [0.80, 0.97]
Gordon 1991	0.92429456	0.00695394	14.3%	0.92 [0.91, 0.94]
Javaheri 1981	0.94117647	0.06616462	3.6%	0.94 [0.81, 1.07]
Loobuyck 1993	0.9627907	0.00756094	14.2%	0.96 [0.95, 0.98]
Hirae 2015	0.96296296	0.02312498	10.7%	0.96 [0.92, 1.01]
Subtotal (95% CI)			**60.1%**	**0.92 [0.89, 0.95]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 31.16$, df = 6 ($P < 0.0001$); $I^2 = 81\%$				
Test for overall effect: $Z = 54.92$ ($P < 0.00001$)				
1.9.2 Gynecologist				
Naud 2016	0.81818182	0.03851327	7.2%	0.82 [0.74, 0.89]
Staland 1978	1	0.01309432	13.1%	1.00 [0.97, 1.03]
Subtotal (95% CI)			**20.3%**	**0.91 [0.73, 1.09]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 19.98$, df = 1 ($P < 0.00001$); $I^2 = 95\%$				
Test for overall effect: $Z = 10.05$ ($P < 0.00001$)				
1.9.3 Physician				
Rogstad 1992	0.93333333	0.07303678	3.1%	0.93 [0.79, 1.08]
Williams 1993	0.944	0.02135236	11.1%	0.94 [0.90, 0.99]
Subtotal (95% CI)			**14.2%**	**0.94 [0.90, 0.98]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 ($P = 0.89$); $I^2 = 0\%$				
Test for overall effect: $Z = 46.02$ ($P < 0.00001$)				
1.9.4 non-physician (nurse or health care workers)				
Joshi 2013	0.91428571	0.04954443	5.4%	0.91 [0.82, 1.01]
Subtotal (95% CI)			**5.4%**	**0.91 [0.82, 1.01]**
Heterogeneity: Not applicable				
Test for overall effect: $Z = 18.45$ ($P < 0.00001$)				
Total (95% CI)			**100.0%**	**0.92 [0.90, 0.95]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 61.35$, df = 11 ($P < 0.00001$); $I^2 = 82\%$				
Test for overall effect: $Z = 64.12$ ($P < 0.00001$)				
Test for subgroup differences: $Chi^2 = 0.90$, df = 3 ($P = 0.82$), $I^2 = 0\%$				



Number of women experiencing pain by provider, case series

Study or Subgroup	Proportion	SE	No. pain Total	No. treated with TA Total	Weight	Proportion IV, Random, 95% CI
2.6.1 Pain/cramps physician						
Fergusson 1974 (1)	0.20833333	0.07691378	5	24	18.9%	0.21 [0.06, 0.36]
Forestier unpublished (2)	0.889	0.053	32	36	20.0%	0.89 [0.79, 0.99]
Goodman 1991 (3)	0.744	0.049	58	78	20.2%	0.74 [0.65, 0.84]
Naud 2016 (4)	0.788	0.056	41	52	19.9%	0.79 [0.68, 0.90]
Viviano 2017 (5)	0.955	0.021	105	110	21.0%	0.95 [0.91, 1.00]
Subtotal (95% CI)			**241**	**300**	**100.0%**	**0.72 [0.53, 0.92]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 99.25$, df = 4 ($P < 0.00001$); $I^2 = 96\%$						
Test for overall effect: $Z = 7.12$ ($P < 0.00001$)						
2.6.2 Pain/cramps non-physician						
Basu unpublished India (6)	0.623	0.041	86	138	33.2%	0.62 [0.54, 0.70]
basu zambia (7)	0.536	0.04	82	153	33.3%	0.54 [0.46, 0.61]
Joshi 2013 (8)	0.25	0.038	31	124	33.4%	0.25 [0.18, 0.32]
Subtotal (95% CI)			**199**	**415**	**100.0%**	**0.47 [0.25, 0.69]**
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 49.96$, df = 2 ($P < 0.00001$); $I^2 = 96\%$						
Test for overall effect: $Z = 4.10$ ($P < 0.0001$)						



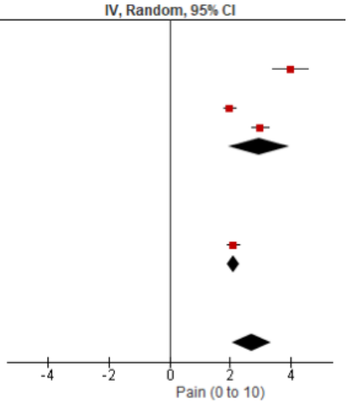
Test for subgroup differences: $Chi^2 = 2.79$, df = 1 ($P = 0.10$), $I^2 = 64.1\%$

Footnotes

(1) 'pain'; use of anaethesia not reported
(2) cramps; no anaethesia???; 4 were moderate, 0 severe
(3) local anaesthesia; mean pain score was 2 (0-10, worse); people with any pain
(4) mild pain or cramps; no anaesthesia/analgesics
(5) no anaethesia; experienced pain that was a mean (SD) of 3.0 +/- 1.6
(6) pain/cramps; no anaesthesia;
(7) pain/cramps; no anaesthesia????; 8 had moderate, 0 had severe
(8) no anaesthesia; mild pain or cramps

Pain on 0–10 scale by provider, case series

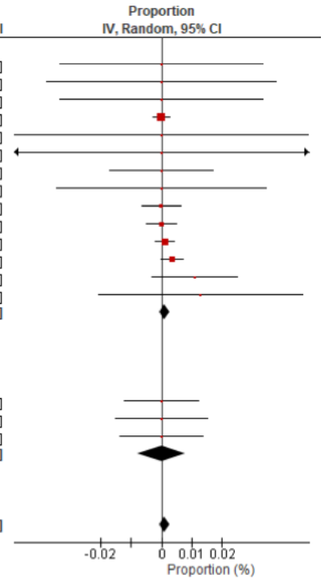
Study or Subgroup	mean	SE	not applicable Total	thermal ablation Total	Weight	mean IV, Random, 95% CI
2.7.1 Pain/cramps physician						
Cremer unpublished (1)	4	0.2017	0	130		Not estimable
Cremer unpublished (2)	4	0.3	0	98	21.9%	4.00 [3.41, 4.59]
Cremer unpublished (3)	3.1	0.2357	0	65		Not estimable
Goodman 1991 (4)	2	0.1022	0	78	26.3%	2.00 [1.80, 2.20]
Viviano 2017 (5)	3	0.1526	0	110	25.5%	3.00 [2.70, 3.30]
Subtotal (95% CI)			**0**	**286**	**73.7%**	**2.97 [1.96, 3.98]**
Heterogeneity: $Tau^2 = 0.76$; $Chi^2 = 59.04$, df = 2 ($P < 0.00001$); $I^2 = 97\%$						
Test for overall effect: $Z = 5.76$ ($P < 0.00001$)						
2.7.2 Pain/cramps non-physician						
Basu unpublished India (6)	2.1	0.1022	0	138	26.3%	2.10 [1.90, 2.30]
Subtotal (95% CI)			**0**	**138**	**26.3%**	**2.10 [1.90, 2.30]**
Heterogeneity: Not applicable						
Test for overall effect: $Z = 20.55$ ($P < 0.00001$)						
Total (95% CI)			**0**	**424**	**100.0%**	**2.72 [2.09, 3.35]**
Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 65.59$, df = 3 ($P < 0.00001$); $I^2 = 95\%$						
Test for overall effect: $Z = 8.44$ ($P < 0.00001$)						
Test for subgroup differences: $Chi^2 = 2.73$, df = 1 ($P = 0.10$), $I^2 = 63.4\%$						



Footnotes

(1) 5 arm trial; no anaethesia; scale 1-9
(2) Bogota; no anaethesia; scale 0-10
(3) 3 arm trial; no anaethesia; scale 1-6
(4) SE from basu; local anaesthesia used
(5) no anaethesia
(6) pain/cramps; no anaesthesia;

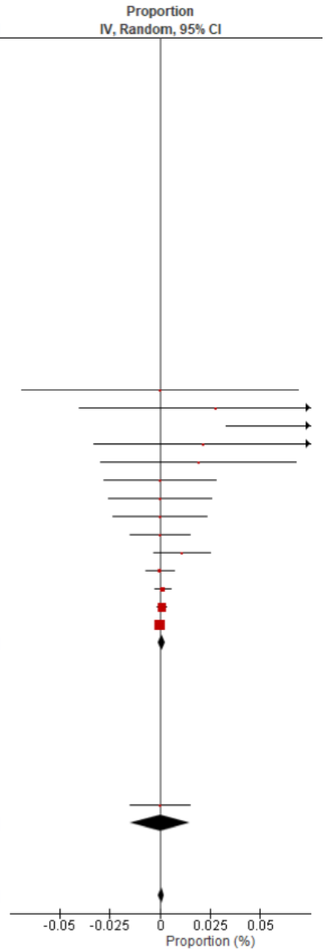
Major bleeding by provider, case series



Study or Subgroup	Proportion	SE	No. major bleeding Total	No. treated with TA Total	Weight	Proportion IV, Random, 95% CI
2.9.1 Physician						
Javaheri 1981	0	0.01694282	0	54	0.2%	0.00 [-0.03, 0.03]
Singh 1988	0	0.01927555	0	47	0.2%	0.00 [-0.04, 0.04]
Hussein 1985	0	0.01694282	0	54	0.2%	0.00 [-0.03, 0.03]
Zawislak 2003	0	0.0013446	0	725	33.9%	0.00 [-0.00, 0.00]
Forestier unpublished (1)	0	0.02459741	0	36	0.1%	0.00 [-0.05, 0.05]
Cremer unpublished (2)	0	0.03792335	0	22	0.0%	0.00 [-0.07, 0.07]
Viviano 2017	0	0.00860845	0	110	0.8%	0.00 [-0.02, 0.02]
Naud 2016	0	0.01754964	0	52	0.2%	0.00 [-0.03, 0.03]
Joshi 2015	0	0.00326839	0	296	5.7%	0.00 [-0.01, 0.01]
Williams 1993 (3)	0	0.00255314	0	380	9.4%	0.00 [-0.01, 0.01]
Cassidy 1987	0.00108225	0.00150862	1	924	26.9%	0.00 [-0.00, 0.00]
Loobuyck 1993 (4)	0.00343348	0.00190283	4	1165	16.9%	0.00 [-0.00, 0.01]
Allam 2005 (5)	0.01090909	0.00710739	3	275	1.2%	0.01 [-0.00, 0.02]
Goodman 1991 (6)	0.01282051	0.01705193	1	78	0.2%	0.01 [-0.02, 0.05]
Subtotal (95% CI)			**9**	**4218**	**96.1%**	**0.00 [-0.00, 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 4.88, df = 13 (P = 0.98); I² = 0%						
Test for overall effect: Z = 1.34 (P = 0.18)						
2.9.2 Non-physician						
basu zambia	0	0.00620876	0	154	1.6%	0.00 [-0.01, 0.01]
Joshi 2013	0	0.00766574	0	124	1.0%	0.00 [-0.02, 0.02]
Basu unpublished India	0	0.00690912	0	138	1.3%	0.00 [-0.01, 0.01]
Subtotal (95% CI)			**0**	**416**	**3.9%**	**0.00 [-0.01, 0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 2 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)			**9**	**4634**	**100.0%**	**0.00 [-0.00, 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 4.95, df = 16 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.32 (P = 0.19)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%						

Footnotes
(1) bleding reported immediately after treatment: 10/36 - not indicated as major.
(2) reported mean type of bleeding was light to moderate, no major bleeding reported
(3) Farquharson 1987 reported 2% of patients had bleeding requiring hospital atttention (no denominator given)
(4) colposcpically directed biopsy
(5) cytology and histological confirmation
(6) diagnosis: biopsy proven malignant disease

Infection (including fever) by provider, case series



Study or Subgroup	Proportion	SE	No. infection Total	No. treated with TA Total	Weight	Proportion IV, Random, 95% CI
2.8.1 Physician						
Lee 2009 (1)	0	0	0	0		Not estimable
Cremer unpublished	0	0	0	0		Not estimable
Grubisic 2010 (2)	0	0	0	0		Not estimable
Tran 2017 (3)	0	0	0	0		Not estimable
Gordon 1991 (4)	0	0	0	0		Not estimable
Farquharson 1987 (5)	0	0	0	0		Not estimable
Semple 1999 (6)	0	0	0	0		Not estimable
Smart 1987	0	0	0	0		Not estimable
Bambury 2013 (7)	0	0	0	0		Not estimable
Papoutsis 2017 (8)	0	0	0	0		Not estimable
Campbell 2016 (9)	0	0	0	0		Not estimable
Hughes 1992 (10)	0	0	0	0		Not estimable
Duncan 2005 (11)	0	0	0	0		Not estimable
Nessa 2014 (12)	0	0	0	0		Not estimable
Joshi 2015 (13)	0	0	0	0		Not estimable
McCarthy 2016 (14)	0	0	0	0		Not estimable
Rogstad 1992 (15)	0	0	0	0		Not estimable
Hirae 2015 (16)	0	0	0	0		Not estimable
Fergusson 1974	0	0.03519913	0	24	0.0%	0.00 [-0.07, 0.07]
Forestier unpublished (17)	0.02777778	0.03489287	1	36	0.0%	0.03 [-0.04, 0.10]
Viviano 2017	0.09	0.02913055	9	100	0.1%	0.09 [0.03, 0.15]
Singh 1988	0.02173913	0.02793566	1	46	0.1%	0.02 [-0.03, 0.08]
Naud 2016	0.01923077	0.02495019	1	52	0.1%	0.02 [-0.03, 0.07]
Hussein 1985	0	0.01423558	0	65	0.2%	0.00 [-0.03, 0.03]
Staland 1978	0	0.01309432	0	71	0.3%	0.00 [-0.03, 0.03]
Goodman 1991	0	0.01197435	0	78	0.3%	0.00 [-0.02, 0.02]
Williams 1993	0	0.00760624	0	125	0.9%	0.00 [-0.01, 0.01]
Allam 2005	0.01090909	0.00710739	3	275	1.0%	0.01 [-0.00, 0.02]
Javaheri 1981	0	0.00355276	0	272	3.9%	0.00 [-0.01, 0.01]
Zawislak 2003	0.00137931	0.00192038	1	725	13.4%	0.00 [-0.00, 0.01]
Loobuyck 1993	0.00085837	0.00119763	1	1165	34.5%	0.00 [-0.00, 0.00]
Cassidy 1987	0	0.00105622	0	924	44.3%	0.00 [-0.00, 0.00]
Subtotal (95% CI)			**17**	**3958**	**99.2%**	**0.00 [-0.00, 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 13.82, df = 13 (P = 0.39); I² = 6%						
Test for overall effect: Z = 0.95 (P = 0.34)						
2.8.2 Non-physician						
Oga 2016 (18)	0	0	0	0		Not estimable
basu zambia	0	0	0	0		Not estimable
Basu unpublished India (19)	0	0	0	0		Not estimable
Parry-Smith 2015 (20)	0	0	0	0		Not estimable
Joshi 2013	0	0.00766574	0	124	0.8%	0.00 [-0.02, 0.02]
Subtotal (95% CI)			**0**	**124**	**0.8%**	**0.00 [-0.02, 0.02]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)			**17**	**4082**	**100.0%**	**0.00 [-0.00, 0.00]**
Heterogeneity: Tau² = 0.00; Chi² = 13.83, df = 14 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						

Footnotes
(1) not measured
(2) Not measured
(3) not measured
(4) not measured
(5) unclear reporting of treatment of discharge
(6) not measured
(7) not measured
(8) not measured
(9) not reported
(10) not measured
(11) not measured
(12) not measured
(13) not measured
(14) not measured
(15) not measured
(16) not measured
(17) fever
(18) not measured
(19) not measured
(20) not measured

Should women who screen positive after prior treatment with thermal ablation receive a different treatment or repeat treatment with thermal ablation?
(PICO 6 – Recommendation 6)

We did not find studies comparing the effects of different treatments for women who screen positive after prior treatment with thermal ablation. We instead reviewed studies identified in Randall 2018 for repeat thermal ablation.

Data from the WHO guidelines for the use of cryotherapy for cervical intraepithelial neoplasia (2011) were reported as recurrence. Cures were 74% with cryotherapy and 92% with conization. Adverse events were not reported with retreatment.

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

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Cryotherapy	Conization	Relative (95% CI)	Absolute		
Recurrence all CIN												
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 442 more)	⊕◯◯◯	CRITICAL

[1] Follow-up interval 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. [3] Recurrence rate with conization ranged from 0 to 50%.

From the thermal ablation studies of women with CIN 2-3 diagnosis and CIN 2-3 at follow-up, there were 40 women retreated with thermal ablation and 34 were cured = 85%. There were no studies that reported on LLETZ or CKC after prior treatment with thermal ablation (i.e., numbers were not reported or not possible to pull out).

	Follow-up and screened positive	Number retreated with thermal ablation	Number cured after retreatment
Singh 1988	up to 2 years	8	6
Nessa 2017		not reported	
Naud 2016		not reported	
Joshi 2013		not reported	
Javaheri 1981		not reported	
Hussein 1985	at 4 months	6	6
Gordon 1991	approx 18 months	26	22
Rogstad 1992		not reported	
Williams 1993		failures not treated	
Loobuyck 1993		could not calculate	
Hirae 2015		not reported	
Staland 1978		none	

REFERENCES

Systematic reviews

Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, et al. Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. Int J Gynaecol Obstet. 2016;132(3): 259–65.

Randall TC, Sauvaget C, Muwonge R, Trimble EL, Jeronimo J. Worthy of further consideration: An updated meta-analysis to address the feasibility, acceptability, safety and efficacy of thermal ablation in the treatment of cervical cancer precursor lesions. Prev Med. 2019;118:81–91.

Santesso N, Mustafa RA, Wiercioch W, Kehar R, Gandhi S, Chen Y, et al. Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. Int J Gynaecol Obstet. 2016;132(3):266–71.

Santesso N, Mustafa RA, Schünemann HJ, Arbyn M, Blumenthal PD, Cain J, et al. Guideline Support Group. World Health Organization for treatment of cervical intraepithelial neoplasia 2-3 and screen-and-treat strategies to prevent cervical cancer. Int J Gynaecol Obstet. 2016b;132(3):252–8.

Published data (from Randall 2019 review and values and preferences)

Allam M, Paterson A, Thomson A, Ray B, Rajagopalan C, Sarkar G. Large loop excision and cold coagulation for management of cervical intraepithelial neoplasia. Int J Gynaecol Obstet. 2005;88:38–43.

Bambury I, Mullings A, Fletcher H, Johnson N, Tolluch-Reid M. Cervical intraepithelial neoplasia in a cohort of HIV-positive women at the University Hospital of the West Indies: management and outcome. West Indian Med. J. 2013;62 (4)313–317.

Campbell C, Brown H, Walker G, Madetsa B, Deeny M, Kabota B, et al. Use of thermo-coagulation as an alternative treatment modality in a 'screen-and-treat' programme of cervical screening in rural Malawi. Int J Cancer. 2016;139(4):908–915.

Campos NG, Sharma M, Clark A, Kim JJ, Resch SC. Resources required for cervical cancer prevention in low- and middle-income countries. PLoS One. 2016;11(10): e0164000. doi: 10.1371/journal.pone.0164000.

Cassidy L, Mathers A, Kennedy JH. Cold coagulation revisited. Colposc. Gynecol. Laser Surg. 1987;3 (232).

Duncan ID. The Semm cold coagulator in the management of cervical intraepithelial neoplasia. Clin Obstet Gynecol. 1983;26:996–1006.

Duncan ID, McKinley CA, Pinion SB, Wilson SM. A double-blind, randomized, placebo-controlled trial of prilocaine and felypressin (Citanest and Octapressin) for the relief of pain associated with cervical biopsy and treatment with the Semm coagulator. J Low Genit Tract Dis. 2005;9:171–5.

Farquharson DI, West CP, Prescott RC, Smart GE. The patient acceptability of laser and cold coagulation therapy to the cervix for treatment of cervical intra-epithelial neoplasia (CIN) 2-3. Colp Gynecol Laser Surg. 1987;3:49.

Ferguson ICI. 'Cold-coagulator' for use in the outpatient treatment of cervical erosion. J. Obstet. Gynaecol. Br. Commonw. 1974;81, 324–327.

Goodman JD, Sumner D. Patient acceptability of laser and cold coagulation therapy for pre-malignant disease of the uterine cervix. BJOG. 1991;98: 1168–71.

Gordon HK, Duncan ID. Effective destruction of cervical intraepithelial neoplasia (CIN) 3 at 100 degrees C using the Semm cold coagulator: 14 years' experience. BJOG. 1991;98:14–20.

Grubisic G, Vukosavic-Cimic, B, Kraljevic Z, Pirkic A, Grbavac I, Bolanca I. Cytologic follow-up in patients with CIN treated by LLETZ, Cold knife Conization and Semm's cold coagulation. Coll. Antropol. 2010;34 (1)13–17.

Hirae CRR, Gallagher F, Rana K. Three year follow up of cervical intraepithelial neoplasia 2. BJOG. 2015;122, 137.

Hughes RG, Haddad NG, Smart GE, Colquhoun M, McGoogan E, MacIntyre CC, et al. The cytological detection of persistent cervical intraepithelial neoplasia after local ablative treatment: a comparison of sampling devices. BJOG. 1992;99:498–502.

Hussein IY, Galloway RK. Use of cold coagulator in the treatment of cervical intraepithelial neoplasia. J Obstet Gynaecol. 1985;6: 62–4.

Ibrahim N, Hickey K, Bozreiba N. . Outcomes of women under 25 years of age referred for colposcopy clinic at mid-western regional hospital, Limerick. International Journal of Gynecology and Obstetrics. 2012;119(SUPPL. 3): S374.

Javaheri G, Balin M, Meltzer RM. Role of cryosurgery in the treatment of intraepithelial neoplasia of the uterine cervix. Obstet Gynecol. 1981;58:83–7.

Joshi S, Sankaranarayanan R, Muwonge R, Kulkarni V, Somanathan T, Divate U. Screening of cervical neoplasia in HIV-infected women in India. AIDS. 2013;27(4): 607–615.

Joshi S, Kulkarni V, Darak T, Mahajan U, Srivastava Y, Gupta S, et al. Cervical cancer screening and treatment of cervical intraepithelial neoplasia in female sex workers using "screen and treat" approach. Int. J. Womens Health. 2015;7:477–483.

Lee SJ, Kim WY, Lee JW, Kim HS, Choi YL, Ahn GH, et al. Conization using electrosurgical conization and cold coagulation for meta-analysis on the efficacy of cold coagulation international federation of gynecology and obstetrics stage IA1 squamous cell carcinomas of the uterine cervix. Int J Gynecol Cancer. 2009;19:407–11.

Loobuyck HA, Duncan ID. Destruction of CIN 1 and 2 with the Semm cold coagulator: 13 years' experience with a see-and-treat policy. BJOG. 1993;100:465–8.

McCarthy CM, Ramphul M, Madden M, Hickey K. The use and success of cold coagulation for the treatment of high grade squamous cervical intra-epithelial neoplasia: a retrospective review. Eur. J. Obstet. Gynecol. Reprod. Biol. 2016;203:225–228.

WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions - Annexes

Nessa A, Rashid MH, Jahan M, Ferdous NE, Nahar PA, Chowdhury A. Role of the HPV DNA test in follow-up of treated cervical intraepithelial neoplasia in Bangladesh. Asian Pac. J. Cancer Prev. 2014;15(19)8063–8067.

Naud PS, Muwonge R, Passos EP, Magno V, Matos J, Sankaranarayanan R. Efficacy, safety, and acceptability of thermocoagulation for treatment of cervical intraepithelial neoplasia in a hospital setting in Brazil. Int. J. Gynaecol. Obstet. 2016;133(3)351–354.

Paul P, Winkler JL, Bartolini RM, Penny ME, Huong TT, Nga le T, et al. Screen-and-treat approach to cervical cancer prevention using visual inspection with acetic acid and cryotherapy: experiences, perceptions, and beliefs from demonstration projects in Peru, Uganda, and Vietnam. Oncologist. 2013;18 Suppl:6–12.

Papoutsis D, Underwood M, Parry-Smith W, Panikkar J. Comparison of cure rates in women treated with cold-coagulation versus LLETZ cervical treatment for CIN2-3 on pretreatment cervical punch biopsies: a retrospective cohort study. Arch. Gynecol. Obstet. 2017;295(4)979–986.

Parry-Smith W, Underwood M, De Bellis-Ayres S, Bangs L, Redman CW, Panikkar J. Success rate of cold coagulation for the treatment of cervical intraepithelial neoplasia: a retrospective analysis of a series of cases. J. Low. Genit. Tract Dis. 2015;19:(1)17–21.

Rogstad KE, Dixon CA, Ahmed IH. The management of subclinical wart virus infection of the cervix in a genitourinary clinic. Genitourin Med. 1992;68:307–8.

Semple D, Saha A, Maresh M. Colposcopy and treatment of cervical intra-epithelial neoplasia: are national standards achievable? BJOG. 1999;106:351–5.

Singh P, Loke K-L, Hii JHC, Sabaratnam A, Lim-Tan SK, Sen DK, et al. (). Cold coagulation versus cryotherapy for treatment of cervical intraepithelial neoplasia: results of a prospective randomized trial. Colposcopy Gynecol Laser Surg. 1988;4:211–21.

Smart GELJ, Gordon A, Bain SHH, Fletcher J, West C, et al.. Randomised trial to compare laser with cold coagulation therapy in the treatment of CIN II and III. Colposc. Gynecol. Laser Surg. 1987;3:48.

Staland B. Treatment of premalignant lesions of the uterine cervix by means of moderate heat thermosurgery using the Semm coagulator. Ann Chir Gynaecol. 1978;67:112–16.

Tran PL, Kenfack B, Tincho Foguem E, Viviano M, Temogne L, Tebeu PM, et al. Efficacy of thermoablation in treating cervical precancerous lesions in a low-resource setting. Int J Womens Health. 2017;Dec 1; 9: 879–886.

Williams, OE, Bodha M, Alawattegama AB. Outcome of cold coagulation for the treatment of cervical intraepithelial neoplasia in a department of genitourinary medicine. Genitourin. Med. 1993;69 (1):63–65.

Zawislak A, Price JH, McClelland HR, Storey RG, Caughley L. Efficacy of cervical intrarepithelial neoplasia (CIN) treatment by cold coagulation. Ulster Med J. 2003;72:10–15.

Unpublished data

Basu P. Randomized controlled trial of the Liger Thermal Coagulator vs Cryocautery and vs LLETZ to prevent cervical neoplasia in VIA-positive women in Zambia. Results for side effects, acceptability (would recommend procedure), pain, satisfaction. Zambia; 2018.

Basu PThermal ablation and cryotherapy in India. 286 women screened and treated with cryotherapy or thermal ablation (some with CIN confirmed). Results for side effects, adverse events, and satisfaction. India; 2018.

De Vuyst H, Forestier M.. Thermal ablation and cryotherapy in Durban. 46 women. Results for side effects and pain. Durban; 2018.

Cremer M, Maza M.. Current RCT of 65 women comparing CryoPen, CO2 cryotherapy, and thermal ablation (WiSAP) with flat tip for 40s at 120 degrees in Lima Peru; and in El Salvador. Pain and acceptability measured. 2018.

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