


Side effects and acceptability measures for thermal ablation as a treatment for cervical precancer in low-income and middle-income countries: a systematic review and meta-synthesis

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ABSTRACT

Objective Understanding the side effects and acceptability of thermal ablation (TA) is necessary before large-scale application in screen-and-treat programmes can be justified in low-income and middle-income countries (LMICs).

Design Articles were selected for inclusion by two independent reviewers. Risk of bias was assessed using the Downs and Black's criteria. Summary data were extracted, and authors contacted for data when necessary. Proportions of interest and 95% CIs were estimated using a random effects model. Subgroup analysis was performed based on place of treatment and timing of post-treatment follow-up. Heterogeneity was estimated using the I^2 .

Eligibility criteria Studies that reported one or more side effects or patient acceptability measures after treatment of the cervix using TA in women living in LMICs who completed a cervical cancer screening test. Included articles were clinical trials or observational studies available in English and published before 18 December 2020.

Information sources Ovid MEDLINE, EMBASE, CINAHL, CAB Global Health and WHO Global Index Medicus were searched for this systematic review and meta-synthesis.

Results A total of 1590 abstracts were screened, 84 full text papers reviewed and 15 papers selected for inclusion in the qualitative review, 10 for meta-synthesis (N=2039). Significant heterogeneity was found in screening tests used to identify women eligible for TA and in methods to ascertain side effects. The most commonly reported side effect during treatment was pain (70%, 95% CI 52% to 85%; $I^2=98.01%$) (8 studies; n=1454). No women discontinued treatment due to pain. At treatment follow-up, common side effects included vaginal discharge (72%, 95% CI 18% to 100%; $I^2=99.55%$) (5 studies; n=771) and bleeding (38%, 95% CI 15% to 64%; $I^2=98.14%$) (4 studies; n=856). Satisfaction with treatment was high in 99% (95% CI 98% to 100%; $I^2=0.00%$) of women (3 studies; n=679).

Conclusions TA results in a number of common side effects, though acceptability remains high among women treated in LMICs. Standardised side effect and acceptability reporting are needed as TA becomes more readily available.

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INTRODUCTION

Cervical cancer disproportionately affects women in low-income and middle-income countries (LMICs). Of the 311 000 total global cervical cancer deaths in 2018, nearly 90% were reported in LMICs, with this burden of disease expected to increase without meaningful intervention.¹ These disparities are largely due to differing levels of accessibility to effective prevention, screening and treatment strategies. For example, over 80% of high-income countries have an established cervical cancer screening programme while less than 50% of LMICs do, achieving average screening coverages of 63% and 19%, respectively.² What makes these low rates of coverage in LMICs so troubling is that cervical cancer is an almost entirely preventable disease. Practically all cases are caused by human papillomavirus (HPV) types for which an effective vaccine exists.³ Furthermore, the disease's extended natural progression from persistent HPV infection to precancerous cervical lesions, defined as ranging from low to high grade cervical intraepithelial neoplasia (CIN1–3), occurs over the course of years. Where relevant treatment modalities are accessible, early detection and remediation are thus possible within a relatively large window of time prior to the development of invasive cancer.

To address this global health inequity, in November 2020, the WHO announced its goal to eliminate cervical cancer as a public health problem by the end of the century.¹ They have set 90–70–90 targets to be met by every country by 2030. These targets include having 90% of girls vaccinated with the HPV vaccine, 70% of women screened at least twice in their lifetime and 90% of women

receiving treatment when precancerous or cancerous cervical lesions are detected through screening.¹ Given the limited progress of HPV vaccination campaigns in LMICs and current generations already exposed to HPV, effective screening and treatment programmes are essential to reduce global incidence of cervical cancer and related mortality.

To effectively meet the screening and treatment targets, the WHO recommends a screen-and-treat approach for LMICs.⁴ The screen-and-treat approach involves screening women for CIN without histological confirmation followed by rapid treatment when results suggest the presence of precancerous lesions, preferably within the same visit. Screening for high-risk HPV types is the preferred method as resources permit, with visual inspection with acetic acid (VIA) and/or visual inspection with Lugol's iodine (VILI) available as alternative or confirmatory screening methods to HPV testing.⁴ Referrals are given to women who require treatment for invasive cervical cancer.

Following positive screening test results, precancerous lesions can be removed by excision or destroyed by ablation in outpatient clinics. Given the resource requirements of excisional treatment methods, the WHO recommends that ablative techniques be prioritised for eligible patients when available.⁵ The two primary ablative techniques recommended are cryotherapy and TA. Cryotherapy is an ablative technique that destroys tissue by freezing it using nitrous oxide or carbon dioxide gas. These gas-based units have been associated with inefficiencies in LMICs due to the continuous costs, procurement challenges and transportation issues of the gas tanks.⁶ TA, also known as thermocoagulation and cold coagulation, is an ablative technique with comparable efficacy to cryotherapy that destroys tissue by heating it.^{7,8} As with cryotherapy, it can be performed by a variety of medical providers and does not require anaesthesia. TA is relatively portable given its light weight and can be battery powered, enabling greater reliability in low-resource settings. As it does not use disposable parts or gas tanks, this method does not require continuous costs beyond maintenance, making it more feasible across healthcare settings, including community care and rural contexts.⁶

In 2019, TA was endorsed by the WHO guidelines for the treatment of precancerous lesions in LMICs based on early evidence of safety and efficacy, and its simplicity of use in screen-and-treat strategies. Yet, questions remain about the potential harms of overtreatment. Screen-and-treat programmes that use high-risk HPV tests (95% sensitivity and 84% specificity) and/or VIA tests (60% sensitivity and 84% specificity) result in overtreatment when all screened positive women are treated.⁵ Overtreatment is defined as the percentage of women treated despite having no true lesions or lesions graded as CIN1, given that a large proportion of the latter would resolve without treatment. Reported rates of overtreatment from LMICs ranged from 30% to 69%.^{9–12} The high potential for overtreatment highlights the need to consider

treatment side effects and patient acceptability alongside efficacy and logistical concerns when weighing the risks and benefits of different treatment options within screen-and-treat strategies.

This systematic review and meta-synthesis summarises rates of side effects and patient acceptability measures among women in LMICs receiving TA to treat suspected or confirmed precancerous lesions following cervical cancer screening.

METHODS

Protocol and registration

This systematic review was registered on PROSPERO in August 2020 as PROSPERO 2020 CRD42020197605. The full protocol is accessible at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020197605.

Search strategy and selection criteria

A search strategy was developed to identify papers that report on the use of TA for treatment of actual or suspected (HPV+) precancerous lesions on the cervix. A wide range of keywords were used to capture both categories (online supplemental material; p1). To avoid over restricting our search, the search strategy did not include terms related to side effects or LMICs. The search was restricted to papers written in English.

The search strategy was adapted using the Polyglot Search Translator and executed in Ovid MEDLINE (1946–2020), EMBASE (1947–2020), CINAHL and CAB Global Health from database inception to 29 July 2020.¹³ On 18 December 2020, the search strategy was rerun in the original four databases to capture any newly published research. At this time, additional searches were conducted in regional databases to access a greater number of papers from LMICs, specifically: Africa-Wide Information (AIM, 1964–2020) and IMEMR, ISMEAR, LILACS, WPRIM and GHL through the WHO's Global Index Medicus. As a final step, reference lists from relevant literature were reviewed to supplement the search strategy. Papers were uploaded to Covidence for review after duplicates were removed in EndNote (online supplemental figure S1).¹⁴

Research papers were included in this review if they met the following criteria: (1) participants were women living in an LMIC according to the World Bank GNI 2020,¹⁵ (2) participants had completed a cervical cancer screening test to identify them as being at high risk of cervical precancer, with or without additional triage or histopathological diagnosis of cervical neoplasm, (3) the intervention used for treatment of the cervix was a recognised device for TA and (4) the study reported side effects of treatment (such as pain, bleeding, vaginal discharge or other) or quantitative measures of acceptability (such as satisfaction, willingness to recommend treatment to others and patient experience). Papers with any mention of side effects or acceptability measures were included regardless of the use of standard definitions. For the purpose of this review, when referring to women

participants, this includes every person who has a cervix. Papers that presented case studies, lacked original data or were written in a language other than English were excluded. The involvement of patients or the public was not appropriate in the design, conduct, reporting and dissemination of our research.

Study selection

To identify studies for inclusion, articles were assessed through two-stage review processes by BP and EMP. An initial title and abstract review was independently performed by both reviewers to screen papers for use of TA following a positive screening test indicating risk or confirmation of precancerous cervical lesions. For this initial stage, all conflicts regarding decision to include were managed through discussion between the two independent reviewers. Full text articles were then gathered from the original database source, or when full text was not found, corresponding authors were contacted to request manuscript copies. Articles underwent full text review by BP and EMP. Articles were included if they reported any side effects or measures of acceptability following TA and were conducted in LMICs. Any conflict in decision to include at this stage was managed through discussion between the two independent reviewers and with a third reviewer when required (GO).

Data extraction

Data were extracted by one reviewer into a study-specific spreadsheet. Summary data were taken from included studies for all primary outcomes, including side effects, willingness to recommend treatment to others, patient satisfaction and patient experience. Where rates were not provided or only aggregate side effects listed, authors were contacted to request individual participant data. Data extracted from the articles included the authors, year of publication, title, country where screening was conducted, study period, study design, sample characteristics, number of participants who received treatment, screening method, treatment method, treatment setting, treatment provider type, participants' age, time to follow-up, assessment of side effects, side effects/adverse effects reported and reports of acceptability, as well as the study definition of side effects or acceptability measures reported and the way in which these outcomes were measured.

Risk of bias assessment

Full articles were individually evaluated for quality and risk of bias by BP and EMP using the assessment criteria developed by Downs and Black.¹⁶ The final assessment criteria on the risk of bias tool related to sample size and power was modified to a yes/no response to reflect the multiple study types included. This criterion was considered met when a study included justification for the sample size that indicated adequate power was achieved to meet the primary study endpoint. Both authors independently

reviewed all included full text papers, with consensus on final rankings made through discussion.

Statistical analysis

Individual study side effect rates were summarised and 95% CIs calculated for each study using the Wilson score method. Pooled rates of side effects were calculated as proportions using the metaprop package in STATA (<https://archpublichealth.biomedcentral.com/articles/10.1186/2049-3258-72-39>). This method of synthesis estimates pooled proportions using a random effects model with binomial distribution, including the Freeman-Tukey double arcsine transformation to stabilise variances when estimates are close to 0 or 1. Study heterogeneity was estimated by calculating the I^2 . All studies with numerically reported side effects were included in the analysis. Subgroup analysis was planned for place of treatment (facility or community; rural or urban setting), provider type (physician or nurse/midwife) and time to side effect assessment grouped as within 4 weeks of treatment or at >4 weeks after treatment. All analyses were performed using STATA V.15.0.¹⁷

RESULTS

Study selection

A total of 1754 titles were identified through the database search on 29 June 2020. After removing duplicates, 1336 were uploaded to Covidence for abstract and title screening. Two independent reviewers identified 64 papers for full text evaluation of which 12 were found to meet all inclusion criteria for this review.^{9–11 18–26} Of note, 30 papers were identified as abstracts from conference proceedings with no full text available at that time. All authors of these abstracts were contacted to solicit information on final publication. Several authors reported manuscripts were under review and expected before the end of the year. As a result, a repeat of the database search was conducted on 18 December 2020, in addition to the regional databases. This added a further 254 titles for abstract and title screening, and final inclusion of three more full papers.^{12 27 28} Two papers reported on overlapping study populations.^{12 27} The paper reporting on the largest study population was included in the meta-synthesis.¹² A subset of four studies that provided narrative results alone for a composite measure of all side effects were excluded from meta-synthesis due to concerns around reporting bias.^{23–26} Study inclusion and reasons for exclusion at full text review are provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram (online supplemental figure S1).

Study characteristics

There were 2709 participants in the 15 papers included in the narrative portion of this review. The meta-synthesis includes information on side effects or measures of treatment acceptability for 2039 individual women across 10 studies. The studies included were conducted in Africa

Table 1 Study characteristics and screening methods used to select candidates for TA

Author	Year	Study country	Study period	Study design	Study inclusion characteristics for screening	Screening methods used to determine eligibility for TA
Banerjee <i>et al</i> ⁹	2020	India	February 2016–July 2017	Prospective randomised trial	30–60 years old, non-pregnant, previously unscreened women	VIA or HPV
Campbell <i>et al</i> ²³	2016	Malawi	October 2013–March 2015	Quality improvement	16–86 years old, non-pregnant	VIA
Chigbu <i>et al</i> ¹⁸	2020	Nigeria	2014–2018	Prospective analytical/comparative study	Women	VIA and colposcopy
Duan <i>et al</i> ²⁸	2021	China	May 2017–May 2018	Prospective randomised trial	20–49 years old, non-pregnant, negative endocervical curettage and no vaginal lesions, women were excluded if they had a history of invasive cervical treatment or had been previously vaccinated for HPV	Cytology or HPV, and colposcopy, and histology
Eakin <i>et al</i> ²⁴	2018	Cameroon	Single day	Implementation pilot	25+ years old, non-pregnant, no evidence of infection, no previous hysterectomy, university-based population (students, faculty and staff)	VIA or VILI
Fokom Dorgue <i>et al</i> ²⁵	2020	Cameroon	April 2016–ongoing	Implementation	30–65 years old, non-pregnant women	HPV
Joshi <i>et al</i> ¹⁰	2013	India	September 2010–November 2011	Cross-sectional	21–60 years old, HIV-positive women (with serological evidence), no debilitating illness as assessed by the study clinician, intact uterus with no prolapse, no previous history of cervical neoplasia	Colposcopy
Joshi <i>et al</i> ²⁶	2015	India	October 2012–February 2013	Cross-sectional	18–60 years old, female sex workers, non-pregnant, with no history of prolapse, no history of treatment for cervical neoplasia, and having an intact uterus	Colposcopy
Mungo <i>et al</i> ¹⁹	2020	Kenya	August 2019–Feb 2020	Prospective cohort	25–65 years old, HIV-positive, non-pregnant, no history of cervical cancer or precancer treatment	HPV
Naud <i>et al</i> ²²	2016	Brazil	March 2012–October 2019	Retrospective cohort	Not reported	Colposcopy and histology
Pinder <i>et al</i> ¹¹	2020	Zambia	August 2017–January 2019	Prospective, unblinded, randomised control trial, pilot	25+ years old, non-pregnant, no previous treatment to the cervix for any reason, no genital tract cancer	VIA
Sandoval <i>et al</i> ²⁰	2019	Honduras	Over a period of 5 months	–	30–49 years old, non-pregnant, pre-menopausal women	HPV and VIA
Viviano <i>et al</i> ²¹	2017	Cameroon	July 2015–December 2015	Prospective study	30–49 years old, non-pregnant, no previous total hysterectomy	HPV (self-sampling), and VIA for some

Continued

Table 1 Continued

Author	Year	Study country	Study period	Study design	Study inclusion characteristics for screening	Screening methods used to determine eligibility for TA
Zhao <i>et al</i> ¹²	2021	China	April 2017–April 2019	–	20–65 years old, non-pregnant, no history of treatment for cervical lesions	HPV (self-sampling), colposcopy
Zhao <i>et al</i> ²⁷	2020	China	June 2017–unknown	Prospective study	30–65 years old, non-pregnant, intact cervix and ever sexually active, excluded those with debilitating disease or with history of treatment for premalignant or malignant cervical lesions	HPV (self-sampling), colposcopy

HPV, human papillomavirus; TA, thermal ablation; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine.

(seven studies); South-Eastern Asia (three studies); the Americas (two studies); and the Western Pacific region (three studies) (table 1). The number of participants receiving TA in included studies ranged from 5 women to 511 women (table 2). Significant heterogeneity across these studies' inclusion criteria, specifically age range for cervical cancer screening enrolment, is noted in table 1. Included studies also varied in screening method and eligibility protocol used for TA. Screening models used a variety of combinations of methods for eligibility screening, including HPV testing (eight studies), VIA (seven studies), VILI (one studies) and cytology (one study) (table 1). Additional triage was performed using colposcopy or cervical cytology in five studies, and two studies based treatment decision on colposcopy results alone (table 1).

Treatment sample size, method, place, provider and timing also varied between studies (table 2). The most common treatment application was performed using a probe heated to 100°C for 45s with multiple applications as needed to ensure adequate coverage of the transformation zone (TZ) (table 2). In all included papers, women were only eligible for treatment with TA after a positive screening test if the entire lesion was visible on the ectocervix, the squamocolumnar junction was visible, the lesion involved three quadrants or less of the TZ and there was no suspicion of glandular disease or invasive cancer, in accordance with the WHO guidance.⁴

Risk of bias

The risk of bias for included studies was moderate to high with a mean score on the Downs and Black's checklist of 18.2 (± 3.0) out of 27 possible points.¹⁶ This checklist is broken down into sections related to quality of reporting, internal validity, confounding and selection bias, external validity and power. Areas of concern for each study are colour coded and presented in table 3. Quality of reporting was high, but issues of internal validity, confounding and selection bias and power were found in most studies.

Results from individual studies and meta-synthesis

The proportion of women with side effects is reported by 10 of the 15 included studies (online supplemental table S1). Studies included side effects that occurred both during treatment and post treatment, as ascertained during a follow-up study visit. The timing of follow-up visits ranged from 2 weeks to 12 months post treatment with the majority reporting at 1 month (table 2). The proportion of women reporting a composite of any one or more side effect at the time of treatment was 46% (95% CI 35% to 58%; $I^2=92.06\%$) (4 studies; $n=1021$) (figure 1A). No studies reported a composite rate of side effects post treatment.

Pain

Pain during or immediately after treatment was reported by eight studies using a variety of methods, including Visual Analogue Scales, pictorial aides and simple yes/no

Table 2 TA treatment methods and details for included studies

Author	Year	n treated	Age range treated*	Treatment method	Treatment time	Treatment provider	Treatment setting	Follow-up visits
Banerjee <i>et al</i> ⁸	2020	136	36.7±7.3	WISAP Medical Technology GmbH, 100°C, no anaesthetic, multiple overlapping applications as needed	40s	Auxiliary nurse midwifery†	Community clinics	12 months
Campbell <i>et al</i> ²³	2016	381	–	WISAP, 100°C–120°C, no local anaesthetic, multiple overlapping applications as needed	30s	Unspecified health worker	Facility	3 months, 6 months and 12 months
Chigbu <i>et al</i> ¹⁸	2020	511	47.1±12.6	Device not specified, 100°C, multiple overlapping applications as needed	45s	Not reported	Facility	6 months
Duan <i>et al</i> ²⁸	2021	74	31.5±5.2	Liger device, 100°C, no anaesthetic, multiple overlapping applications as needed	45s	Gynaecologist	Facility	4, 8 months
Eakin <i>et al</i> ²⁴	2018	5	–	Device not specified, 100°C, no anaesthetic, multiple overlapping applications as needed	60s	Physician	Facility	N/A
Fokom Domgue <i>et al</i> ²⁵	2020	161	–	WISAP Medical Technology GmbH, 100°C, multiple overlapping applications as needed	45s	Nurse	Primary health clinic	N/A
Joshi <i>et al</i> ¹⁰	2013	124	–	Device not specified, 105°C, no local anaesthetic, multiple overlapping applications as needed	45s	Unspecified health worker	Community clinics	6 months
Joshi <i>et al</i> ²⁶	2015	27	–	WISAP Medical Technology GmbH, 105°C, no local anaesthetic, multiple overlapping applications as needed	45s	Physician or Nurse†	Community clinics	N/A
Mungo <i>et al</i> ¹⁹	2020	293	40.4±8.7	Liger device, 100°C, no local anaesthetic, number of applications not specified	20s	Clinical officer—equivalent to a physician assistant in the USA†	Community clinics	4–6 weeks
Naud <i>et al</i> ²²	2016	52	31 (27–40)	WISAP Medical Technology GmbH, 100°C, no local anaesthetic, multiple overlapping applications as needed	20s	Not reported	Facility	12 months
Pinder <i>et al</i> ¹¹	2020	250	–	Liger device, 100°C, no anaesthetic, multiple overlapping applications as needed	40s	Nurse	Primary health clinic	2 weeks and 6 months
Sandoval <i>et al</i> ²⁰	2019	319	–	Liger device, 100°C, analgesia (NSAIDs) offered post-treatment, multiple overlapping applications as needed	45s	Physicians†	Facility	1 month
Viviano <i>et al</i> ²¹	2017	110	–	WISAP Medical Technology GmbH, 100°C, no anaesthetic, multiple applications as needed	60s	Gynaecologist†	Facility	1 month
Zhao <i>et al</i> ¹²	2021	170	41.0 (35–47)	WISAP Medical Technology GmbH or Liger device, 100°C–110°C, no anaesthetic, multiple applications as needed	45s	Physician	Primary health clinic	1 month, 6 months, 12 months and 18 months
Zhao <i>et al</i> ²⁷	2020	96	–	WISAP Medical Technology GmbH or Liger device, 100°C, no anaesthetic, multiple applications as needed	45s	Unspecified health worker	Primary health clinic	4 weeks

*Average ±SD or median (IQR).

†Based on personal communication with authors (Dr Partha Basu, 2021; Dr Smita Joshi, 2021; Dr Chentai Mungo, 2021; Dr Silvia de Sanjose, 2021; and Dr Manuela Viviano, 2021). NSAIDs, non-steroidal anti-inflammatory drugs; TA, thermal ablation.

Table 3 Risk of bias assessment based on Downs and Black's criteria¹⁶

Author	Year	Reporting	Internal validity	Confounding and selection bias	External validity	Power	Total score
Banerjee <i>et al</i> ⁹	2020	Green	Yellow	Yellow	Green	Red	18
Campbell <i>et al</i> ²³	2016	Yellow	Yellow	Red	Yellow	Red	12
Chigbu <i>et al</i> ¹⁸	2020	Green	Yellow	Yellow	Yellow	Green	17
Duan <i>et al</i> ²⁸	2021	Green	Yellow	Yellow	Green	Green	21
Eakin <i>et al</i> ²⁴	2018	Green	Yellow	Red	Red	Red	17
Fokom Domgoue <i>et al</i> ²⁵	2020	Green	Red	Red	Yellow	Red	14
Joshi <i>et al</i> ²⁶	2015	Green	Yellow	Green	Yellow	Red	20
Joshi <i>et al</i> ¹⁰	2013	Green	Yellow	Yellow	Red	Red	17
Mungo <i>et al</i> ¹⁹	2020	Green	Yellow	Yellow	Green	Red	19
Naud <i>et al</i> ²²	2016	Yellow	Red	Yellow	Red	Red	14
Pinder <i>et al</i> ¹¹	2020	Green	Yellow	Green	Yellow	Green	24
Sandoval <i>et al</i> ²⁰	2019	Green	Yellow	Yellow	Yellow	Green	20
Viviano <i>et al</i> ²¹	2017	Green	Yellow	Yellow	Red	Green	21
Zhao <i>et al</i> ¹²	2021	Green	Yellow	Yellow	Yellow	Red	19
Zhao <i>et al</i> ²⁷	2020	Green	Yellow	Yellow	Red	Red	20

Subsections were scored green if over 80% of indicators met, orange if 40%–79% of indicators met and red if <40% of indicators met.

*Included in the meta-synthesis.

survey questions (online supplemental table S1). In four studies, pain was defined as abdominal pain, cramping and/or discomfort,^{9–11 21} while the remaining defined pain as abdominal pain alone.^{12 19 20 28} No study reported provision of analgesia of any sort prior to treatment. The overall rate of reported pain at or immediately after treatment was 70% (95% CI 52% to 85%; $I^2=98.01\%$) (8 studies; $n=1454$) (figure 1B). Of the eight studies that report pain at treatment, a subset differentiated pain into categories of mild (70%, 95% CI 55% to 83%; $I^2=96.71\%$) (7 studies; $n=1330$), moderate (11%, 95% CI 3% to 22%; $I^2=96.49\%$) (5 studies; $n=1108$) and severe (2%, 95% CI 1% to 4%; $I^2=67.00\%$) (6 studies; $n=1278$) (figure 1C–E). Proportions of women reporting pain did not differ significantly based on study setting overall, but moderate pain and severe pain were more commonly reported when treatment occurred in a facility compared with community clinics (figure 1B,D,E). Two studies reported pain rated on a Visual Analogue Scale with means of 3.0/10.0.^{21 28}

Post-treatment pain at follow-up was less common, being reported by 8% (95% CI 3% to 14%; $I^2=94.06\%$) of women (7 studies, $n=1777$) (figure 2A) with a mean duration ranging from 2 days to 7 days (3 studies) (online supplemental table S1). Less pain was reported in studies with longer follow-up times (figure 2A).

Bleeding

Bleeding during or immediately after treatment was rare and occurred in 2% (95% CI 0% to 5%; $I^2=86.77\%$) of women and did not differ significantly by treatment setting (7 studies; $n=1386$) (figure 1F). Overall, as reported by women at follow-up, ongoing bleeding

after treatment was much more common and occurred in 38% (95% CI 15% to 64%; $I^2=98.14\%$) of women (4 studies; $n=856$) (figure 2B). Reported rates of bleeding were significantly higher after a longer follow-up period, but this comparison is limited to a single small ($n=74$) study reporting after 4 months (figure 2B). Duration of bleeding was reported by 3 studies with one finding a median of 3.3 days (IQR=2–5 days), another reporting a mean of 10.6 days (± 5.8), and the last reporting a mean of 10 days (online supplemental table S1).

Vaginal discharge

Vaginal discharge was ascertained at follow-up visits only and reported by 72% (95% CI 18% to 100%; $I^2=99.55\%$) of women (5 studies; $n=771$) (figure 2C). The duration of vaginal discharge was also reported by three of these studies with a mean ranging from 15 days to 17 days, and by another with a median of 14 days (online supplemental table S1). Vaginal discharge did not differ based on timing of follow-up visit (figure 2C).

Other side effects

There were no reported hospitalisations following TA and no discontinuation of treatment due to side effects. A range of other side effects were reported in single studies or with unclear definitions that prevented meta-synthesis (online supplemental table S1). Seven cases of vasovagal response or faintness were reported overall with unclear timing.^{10 20 22} Clinical suspicion of infection based on foul smelling vaginal discharge was reported by Mungo *et al* in two women,¹⁹ with symptoms resolving following antibiotics. Viviano *et al* describes three women with clinically

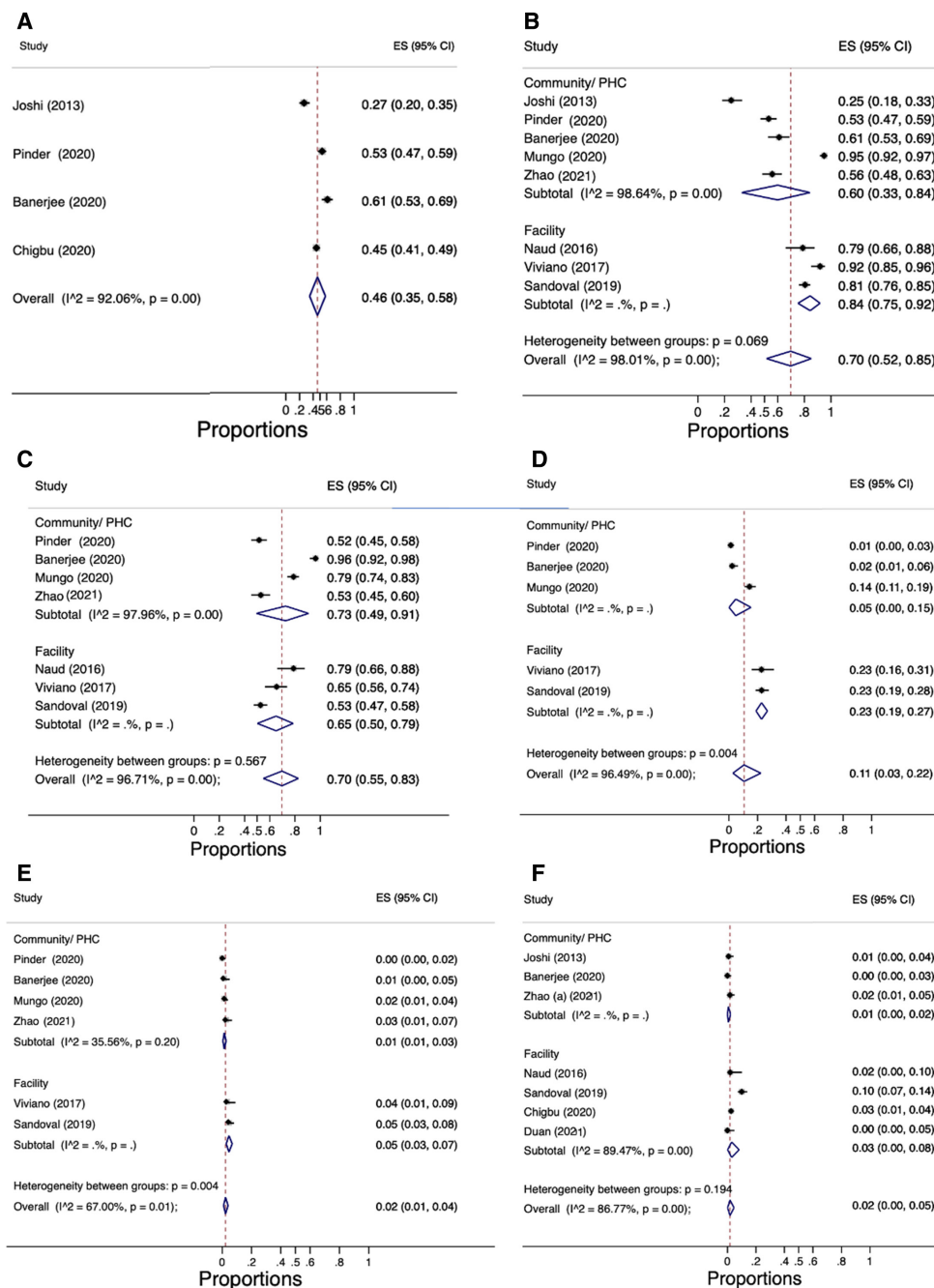


Figure 1 Side effects reported at treatment. (A) One or more side effect at treatment. (B) Pain at treatment, grouped by setting. (C) Mild pain at treatment, grouped by setting. (D) Moderate pain at treatment, grouped by setting. (E) Severe pain at treatment, grouped by setting. (F) Bleeding at treatment, grouped by setting. ES, estimate.

diagnosed infections (specific diagnostic criteria not provided) requiring local antibiotics and an additional 9 women were provided prophylactic antibiotics at the 1-month follow-up visit due to delayed wound healing.²¹ Three studies reported on a sensation of heat during treatment in 88.6%, 25% and 5.9% of women.^{12 19 22} One case of pelvic inflammatory disorder was reported 6 months after treatment (Naud *et al*) and two cases of pain while urinating (Sandoval *et al*).^{20 22}

Patient acceptability

Patient acceptability, reported both at treatment and at follow-up, was most often measured as satisfaction with

treatment or willingness to recommend the treatment to others (online supplemental table S2). Three studies ($n=679$) measured satisfaction with treatment as a binary indicator with 99% (95% CI 98% to 100%; $I^2=0.00\%$) of women indicating they were satisfied (figure 3A). When reported on a 5-point Likert scale by Chigbu *et al* mean satisfaction was 3.9 (± 1.3) at follow-up.¹⁸ Willingness to recommend treatment to others was nearly universal in the 4 studies ($n=998$) reporting this measure (100%, 95% CI 99% to 100%; $I^2=0.00\%$) (figure 3B). Two studies also reported acceptability based on patient experience rated as better or worse than expected immediately

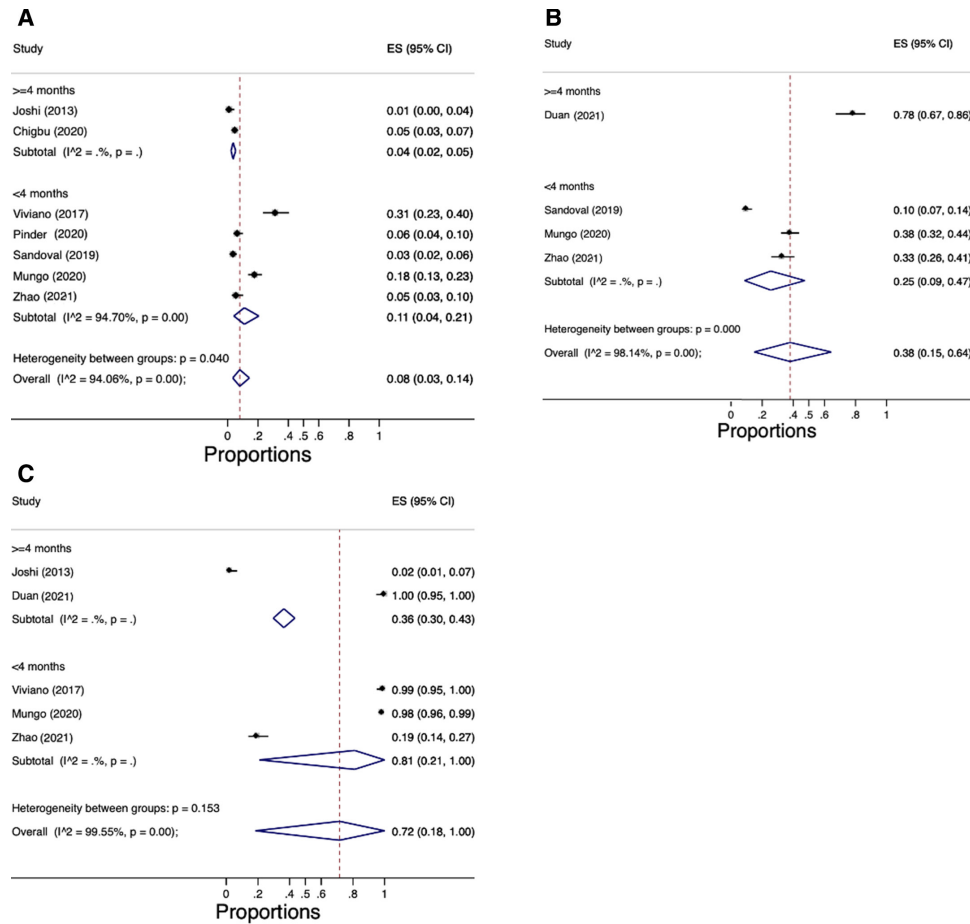


Figure 2 Side effects reported at follow-up. (A) Post-treatment pain at follow-up, grouped by timing of follow-up visit. (B) Post-treatment bleeding at follow-up, grouped by timing of follow-up visit. (C) Post-treatment vaginal discharge at follow-up, grouped by timing of follow-up visit. ES, estimate.

after treatment.^{18 19} Overall, 84% (95% CI 81% to 86%; I²=0.00%) rated the treatment as better than expected while 7% (95% CI 5% to 8%; I²=0.00%) rated the experience as worse than expected (n=804).^{18 19} See online supplemental table S2 for reported acceptability measures in included studies in meta-synthesis.

DISCUSSION

Our systematic review and meta-synthesis provides the first comprehensive picture of the current literature on the side effects and acceptability of TA specific to LMIC settings. Commonly reported side effects of TA are predominantly mild. There is a high level of treatment acceptability overall. The most common side effects were mild pain at treatment (70%, 95% CI 55% to 83%), vaginal discharge following treatment (72%, 95% CI 18% to 100%) and bleeding following treatment (38%, 95% CI 15% to 64%). Infection and vasovagal response to treatment were rare but did occur in a small number of study participants. Importantly, no side effects led to treatment being discontinued and there were no reported hospitalisations. The high rate of acceptability signals that women are willing to tolerate mild symptoms when undergoing treatment for cervical cancer prevention.

The types of side effects reported in this review of TA resemble those of cryotherapy. Literature reviews on cryotherapy report pain rates up to half of that of TA, ranging between 0% and 30% of women.^{5 7 29} However, when restricting analysis to the four available randomised studies, the WHO reports with moderate certainty that slightly fewer women experience pain when treated with TA (60.8%, 95% CI 49.7% to 75.2%) compared with cryotherapy (65.4%).⁵ Due to limited research and inconsistent methodologies, true values remain uncertain. Adverse events following TA such as major bleeding and infections appear to occur at low rates similar to cryotherapy, with higher rates occurring in those treated by excisional methods.^{5 29 30}

Though it is not expected to differ significantly, we were unable to assess rates of side effects and acceptability specific to women living with HIV. As a population at greater risk of developing cervical cancer,³¹ future research should continue to collect data specific to this group. Initial research has shown that women on antiretroviral therapy do not experience an increase in viral shedding following treatment with cryotherapy, suggesting it should not affect the risk of transmission.^{32 33} These findings are likely to carry over to TA,

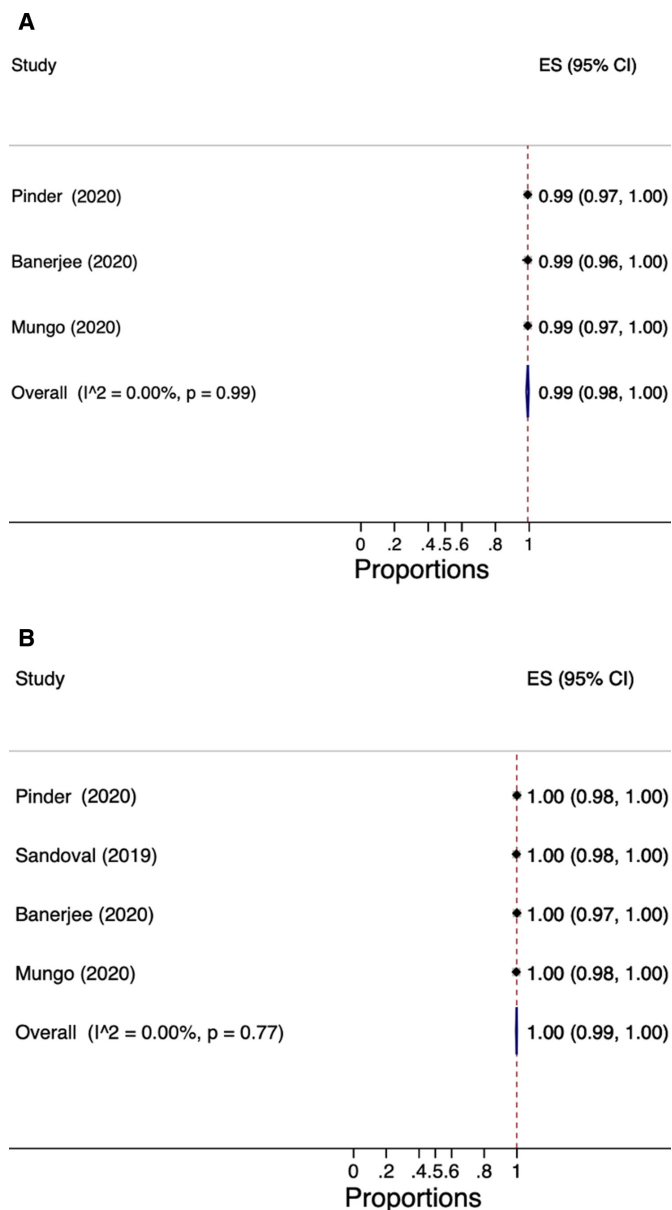


Figure 3 Measures of acceptability. (A) Satisfaction with treatment (yes/no). (B) Willingness to recommend treatment to others. ES estimate.

though additional research is required to demonstrate it.

Applying the search strategy to regional databases allowed for the inclusion of a greater number of relevant publications, though it remained limited to publications in English due to capacity limits in our research team. Additionally, the broad inclusion criteria allowed for a greater number of relevant contexts and diverse study types to be included in the review. However, this also brought limitations such as inconsistent follow-up times, as well as heterogeneity between study populations and treatment methods that likely drove the wide CIs. Use of the random effects model to estimate pooled rates addresses this heterogeneity to some degree. Included studies had considerable heterogeneity in sample size, age, screening and eligibility protocol, data collection and

data reporting. Additionally, clear descriptions of data collection and reporting methods were often lacking, a result of our topics of interests often being secondary outcomes in included studies. Only two (Mungo *et al* and Sandoval *et al*) of the 15 studies included in this review investigated side effects and acceptability as a primary outcome.^{19 20} There is a need for more quality research focused on side effects and measures of acceptability for TA.

A specific limitation in the synthesised pain rate is Sandoval *et al*'s initial failure to consistently distinguish between pain during the TA procedure and pain during the biopsy, leading to an overestimation of pain caused by TA in that study.²⁰ Mungo *et al* also recognise this as a potential limitation in their study despite efforts by the research team to differentiate the two during pain assessments.¹⁹ This represents a limitation to our review as well as a caution to future research to clearly distinguish between pain caused by treatment versus other same-day procedures. A standardised reporting method for side effects and acceptability would benefit intratreatment and intertreatment analyses. The side effects of interest identified in this comprehensive review can be used to support consistent future assessments, both at treatment and at follow-up.

Type of probe, treatment time and temperature also varied across included studies. Though greater consistency across studies may come from the WHO's 2019 guidelines for TA, which suggest a minimum of 100°C for 20–30 s,⁵ more research is needed to concretely establish an optimal treatment protocol to minimise side effects and pain. This may be particularly relevant to pain rates as Banerjee *et al* and Sandoval *et al* identified a positive association between the number of probe applications and reported levels of pain during treatment,^{9 20} though Mungo *et al* found no such association.¹⁹ Within the included studies, 16%–62% of women required 2–4 applications of the probe to cover the entire TZ.^{9 12 19 20 22 28}

Other potential long-term adverse effects of TA, such as its impact on reproductive health outcomes, are key to understanding overall acceptability but were out of scope for this review. Data remain limited, but research non-specific to LMICs report little to no effect of TA on rates of infertility or adverse obstetric outcomes such as premature births.^{5 34}

Focusing on data collected in LMICs makes this review explicitly relevant to contexts where screen-and-treat programmes using TA are most likely to be implemented. Though overtreatment is inevitable with HPV-based and VIA-based screening, the mild side effects and high acceptability of TA suggest overtreatment should not hinder the implementation of accessible screen-and-treat programmes. Expanding access to screen-and-treat strategies by implementing programmes in community clinics is also supported by our findings that such settings resulted in lower rates of moderate and severe pain compared with TA treatment in facilities. This significant variation, however, may be attributed in part to courtesy bias

being more acute in smaller community clinics compared with larger facilities during pain evaluation. Continued assessments of TA across treatment settings is needed to support the development of standard protocols. TA is a relatively low cost, portable and rapid treatment option that can be effectively performed by a variety of health-care providers.⁵ The high levels of acceptability, despite common reports of mild pain, support the standard practice to treat without anaesthesia, further reducing barriers to widespread implementation. Primary care givers should continue to counsel women on the common side effects of TA presented here prior to treatment.

Conclusion

Overall, TA is an acceptable treatment method for cervical precancerous lesions with mostly mild side effects. Compared with alternative treatment methods, TA is feasible and effective within screen-and-treat programmes. These findings support the use of TA as an important tool toward achieving the WHO's 2030 goal of treating 90% of women with detected precancerous lesions in LMICs as part of the 90–70–90 targets. Continued assessments of the side effects and acceptability of TA in low-resource settings are needed to support the optimal implementation of screen-and-treat programmes.

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Contributors EMP was responsible for the literature search, abstract and full text review, data extraction and writing—original draft. BP was responsible for study design and conceptualisation, development of methodology, abstract and full text review, risk of bias assessment, formal data analysis, interpretation of results and writing—reviewing and editing. LWS was responsible for conceptualisation, interpretation of results and writing—review and editing. JT was responsible for development of methodology and writing—review and editing. JO was responsible for interpretation of results and writing—review and editing. GO and CN was responsible for conceptualisation, funding acquisition, supervision, interpretation of results and writing—review and editing.

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