

OB/GYN Resident Global Health Education Module

Association of
Academic Professionals in
Obstetrics and Gynaecology



Association des
académiciens professionnels
en obstétrique-gynécologie



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Case 5: Gynecologic Cancer



Alice's bleed



World Health
Organization

WHO Guidelines: Screening and treatment of precancerous lesions for cervical cancer prevention, *World Health Organization Geneva* (2013)

Excerpts of the WHO screening guidelines have been provided. The executive summary provides a brief overview of the screen-and-treat recommendations. The recommendations chapter discusses important considerations and evidence supporting various expert-panel recommendations.



The NEW ENGLAND
JOURNAL of MEDICINE

HPV Screening for Cervical Cancer in Rural India, *NEMJ* (2009)

This study assessed and compared the efficacy of a single round of HPV screening, cytologic testing, and VIA on the incidence of cervical cancer and associated death rates in rural India. HPV testing was associated with reduced incidence and deaths from cervical cancer.

IJC

International Journal of Cancer

Health and economic impact of HPV 16/18 vaccination and cervical cancer screening in Eastern Africa, *Int. J. Cancer* (2012)

With Eastern Africa having the highest global cervical cancer incidence and mortality rate, this paper develops HPV vaccination models for five affected countries. The health and economic benefit of HPV vaccination is determined, as well as cost-effective screening programs involving vaccination and follow-up screening tests.

Case 5: Gynecologic Cancer

Alice is a 55 year old mother of three living in Kampala, Uganda. She experienced hot flashes and irregular periods for a number of months before her last menstrual period a few years ago. She continues to use barrier contraception when engaging in intercourse with her husband due to his HIV positive status. Alice has remained HIV negative.

Over the last nine months however, Alice has been experiencing new symptoms. She has been bleeding after vaginal intercourse, and occasionally without any provoking factor. Alice noticed that her clothes seem looser and don't fit her quite as well as they used to. She has also begun to take mid-day naps as she finds she tires easily.

Alice goes to a nearby ("Health Center III") clinic where a history is taken and physical obtained. Alice explains that while she and her husband are very careful to use contraception, she has not received regular screening, as this has not always been readily available. She received one screening test a number of years back. She can't remember the name of the test, but describes what resembles VIA (visual inspection with acetic acid)- a solution of acetic acid (3-5%) was applied to the cervix, after which the cervix was inspected for any dense acetowhite areas or thickened white plaques. Alice recalls receiving some "tissue freezing" the same day as her screening test, which presumably was cryotherapy to the affected area of cervix.

Upon performing a pelvic exam, a small mass (2-3 cm) is observed and palpated on the external cervical os. Under anesthesia, a bimanual rectovaginal examination is performed where a firmness is palpated in the parametrium. The doctor and Alice have a discussion, where she is told she will need to undergo radiation therapy. Unfortunately, the limited resources of this clinic means that Alice will have to go to the radiotherapy department at the National Referral Hospital in Mulago. The doctor senses Alice's apprehension and explains to her that the Mulago radiotherapy clinic sees approximately 2,000 new patients, and is staffed by four doctors, four nurses, and nine technicians. But of most importance, it houses the nation's sole radiotherapy machine...

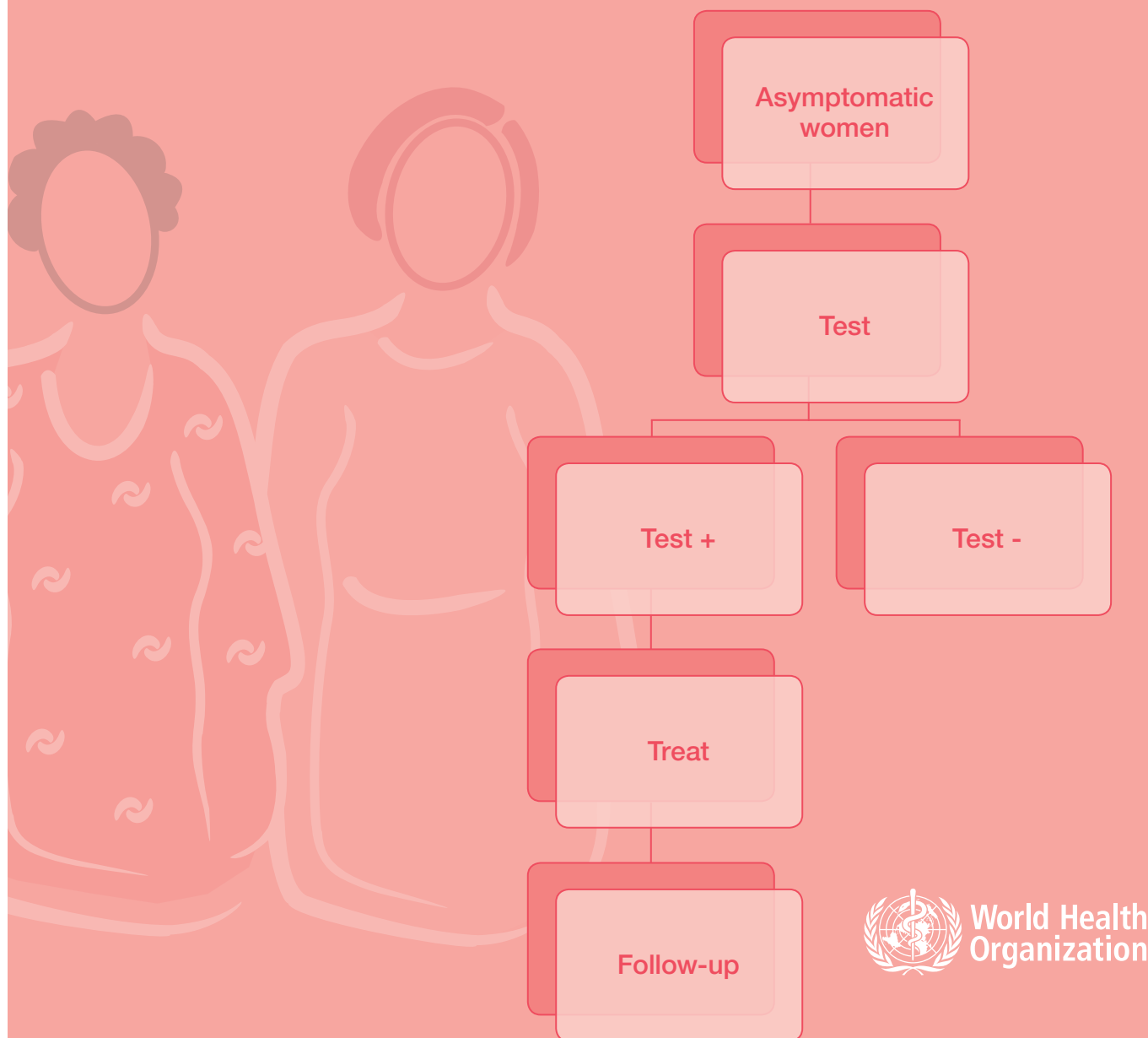
Alice is overwhelmed with questions and worry; she fears that even if she can successfully make it onto the six-month waitlist, she might not be able to afford sufficient treatment.

Questions for Discussion:

1. What are some cervical cancer screening test alternatives to Pap smears?
Understand the nuances of these tests.
 - a. VIA (Visual Inspection with Acetic Acid)
 - b. VILI (Visual Inspection with Lugol's Iodine)
 - c. HPV testing
2. How have these alternatives been implemented in low-resource settings?
3. Is Alice's HIV status important to consider? Why or why not?
 - a. Risk factors of cervical cancer
 - b. Sensitivity and/or specificity of these screening tests
4. What are the challenges with screening follow-ups? Understand the "screen-and-treat" approach.

WHO guidelines

WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention



***NOTE:** Only portions of the WHO Guidelines have been included for educational purposes. Please refer to the full document for more information: http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf

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Supplemental material*: GRADE evidence-to-recommendation tables and evidence profiles for each recommendation

Section A. Negative or unknown HIV status

Section B. HIV-positive status or unknown HIV status in areas with high endemic HIV infection

* Available online: www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/index.html

Executive summary

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion that may exist at any one of three stages: CIN1, CIN2, or CIN3. If left untreated, CIN2 or CIN3 (collectively referred to as CIN2+) can progress to cervical cancer. Instead of screening and diagnosis by the standard sequence of cytology, colposcopy, biopsy, and histological confirmation of CIN, an alternative method is to use a 'screen-and-treat' approach in which the treatment decision is based on a screening test and treatment is provided soon or, ideally, immediately after a positive screening test. Available screening tests include a human papillomavirus (HPV) test, visual inspection with acetic acid (VIA), and cytology (Pap test). Available treatments include cryotherapy, large loop excision of the transformation zone (LEEP/LLETZ), and cold knife conization (CKC).

This guideline provides recommendations for strategies for a screen-and-treat programme. It builds upon the existing *WHO guidelines: Use of cryotherapy for cervical intraepithelial neoplasia* (published in 2011) and on the new *WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and glandular adenocarcinoma in situ* (being published concomitantly with these present guidelines). This guideline 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, at country, regional and district levels.

For countries where a cervical cancer prevention and control programme already exists, these recommendations were developed to assist decision-makers to determine whether to provide a different screening test followed by a different treatment, or to provide a series of tests followed by an adequate treatment. For countries where such a programme does not currently exist, these recommendations can be used to determine which screening test and treatment to provide. In addition to the recommendations, a decision-making flowchart is also proposed in Annex 2 to help programme managers choose the right strategy based on the specific country or regional context. Once the strategy has been chosen, the appropriate screen-and-treat flowchart for that strategy can be followed. The flowcharts for all strategies are provided in Annex 3 (specifically for women of negative or unknown HIV status), and Annex 4 (for women of HIV-positive status or unknown HIV status in areas with high endemic HIV infection).

The methods used to develop these guidelines follow the *WHO handbook for guideline development*, and are described in Chapter 2 of this document. A Guideline Development Group (GDG) was established that included experts, clinicians, researchers in cervical cancer prevention and treatment, health programme directors and methodologists. Conflicts of interest were managed according to World Health Organization (WHO) rules. An independent group of scientists at a WHO collaborating centre conducted systematic reviews on the diagnostic accuracy of the available screening tests and the effects of different treatments for CIN (see Annexes 5–7). This evidence was used to model and compare different screen-and-treat strategies in women of unknown HIV status and women of HIV-positive and HIV-negative status and the results were presented to the GDG in evidence tables following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. The GRADE evidence profiles and evidence-to-recommendation tables for each recommendation are available online (Supplemental material, Sections A and B).

This guideline provides nine recommendations for screen-and-treat strategies to prevent cervical cancer. While a brief summary of the recommendations is included on the next page, the complete recommendations with remarks and a summary of the evidence for each are found in Chapter 3 of this document.

Although the best evidence to assess the effects of a screen-and-treat strategy is from randomized controlled trials, we identified few randomized controlled trials that evaluated these strategies and reported on patient-important outcomes. Areas for future research include screen-and-treat strategies using a sequence of tests (e.g. HPV test followed by VIA); screen-and-treat strategies in women of HIV-positive status; and measurement of important health outcomes following a screen-and-treat strategy.

Screen-and-treat strategy summary recommendations

These recommendations apply to all women regardless of HIV status, but specific recommendations for women living with HIV have been developed.

The expert panel¹ recommends 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 LEEP when the patient is not eligible for cryotherapy.

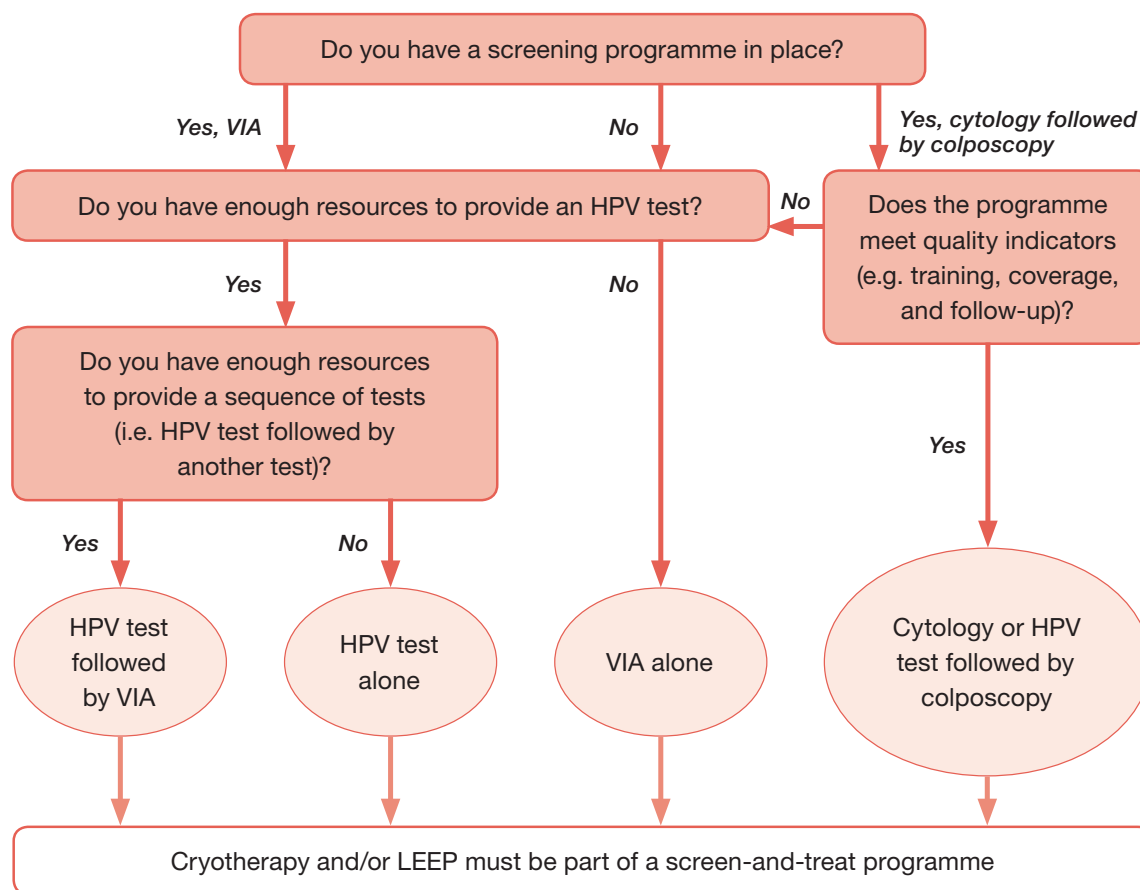
The expert panel suggests:

- ▶ Use a strategy of screen with an HPV test and treat, over a strategy of screen with VIA and treat. In resource-constrained settings, where screening with an HPV test is not feasible, the panel suggests a strategy of screen with VIA and treat.
- ▶ Use a strategy of screen with an HPV test and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat. However, in countries where an appropriate/high-quality screening strategy with cytology followed by colposcopy already exists, either an HPV test or cytology followed by colposcopy could be used.
- ▶ Use a strategy of screen with VIA and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat. The recommendation for VIA over cytology followed by colposcopy can be applied in countries that are currently considering either programme or countries that currently have both programmes available.
- ▶ Use a strategy of screen with an HPV test and treat, over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat.
- ▶ Use either a strategy of screen with an HPV test followed by VIA and treat, or a strategy of screen with an HPV test and treat.
- ▶ Use a strategy of screen with an HPV test followed by VIA and treat, over a strategy of screen with VIA and treat.
- ▶ Use a strategy of screen with an HPV test followed by VIA and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat.
- ▶ Use a strategy of screen with an HPV test followed by VIA and treat, over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat.

¹ The expert panel includes all members of the WHO Steering Group, the Guideline Development Group (GDG), and the External Review Group (ERG).

As shown below, a decision-making flowchart has been developed that will assist programme managers to choose one of the suggested strategies, depending on the context where it will be implemented (also provided in Annex 2). Details about the flow of each different strategy are also presented in the flowcharts in Annex 3 (for women of negative or unknown HIV status) and Annex 4 (for women of HIV-positive status or unknown HIV status in areas with high endemic HIV infection).

Decision-making flowchart for programme managers



Note: each light-pink bubble refers to one strategy in Annex 3 (for women of negative or unknown HIV status) or Annex 4 (for women of HIV-positive status or unknown HIV status in areas with high endemic HIV infection).

3. Recommendations

To aid decision-making by programme managers, a decision-making flowchart or algorithm is provided for choosing the best screen-and-treat strategy for a particular setting at a programme level (see Annex 2). Once the strategy has been chosen, flowcharts for each strategy can be followed; these are provided in Annex 3 (negative or unknown HIV status) and Annex 4 (HIV-positive status or unknown HIV status in areas with high endemic HIV infection). The algorithm and the flowcharts are based on the recommendations detailed in this chapter.

Important considerations that apply to all screen-and-treat recommendations

Population targeted by the recommendations

The recommendations in this guideline apply to women 30 years of age (recommended age to start screening) and older because of their higher risk of cervical cancer. However, the magnitude of the net benefit will differ among age groups and may extend to younger and older women depending on their baseline risk of CIN2+. Priority should be given to screening women aged 30–49 years, rather than maximizing the number of screening tests in a woman's lifetime. Screening even once in a lifetime would be beneficial. Screening intervals may depend on financial, infrastructural, and other resources.

For women of HIV-positive status, or of unknown HIV status in areas with high endemic HIV infection, the following should be noted. Although the evidence about screening and treatment to prevent cervical cancer is of lower quality for women who are HIV-positive than for women who are HIV-negative or of unknown HIV status, cervical cancer screening should be done in sexually active girls and women, as soon as a woman or a girl has tested positive for HIV.

Supplemental material, Section A (negative or unknown HIV status) and Section B

(HIV-positive status or unknown HIV status in areas with high endemic HIV infection) provide the evidence and judgements for each recommendation (this material is available online).

Considerations for screening tests

The recommendations include strategies based on three screening tests: HPV (cut-off level ≥ 1.0 pg/ml), cytology (cut-off level ASCUS+, atypical squamous cells of undetermined significance), and VIA. VIA is appropriate to use in women whose transformation zone is visible (typically in those younger than 50). This is because once menopause occurs, the transformation zone, where most precancerous lesions occur, frequently recedes into the endocervical canal and prevents it from being fully visible.

Considerations for treatments

For all screen-and-treat recommendations, cryotherapy is the first-choice treatment for women who have screened positive and are eligible for cryotherapy. When women have been assessed as not eligible for cryotherapy, LEEP is the alternative treatment. Eligibility for cryotherapy follows the guidance provided in the update of the C4-GEP (10): Screen-positive women are eligible for cryotherapy if the entire lesion is visible, the squamocolumnar junction is visible, and the lesion does not cover more than 75% of the ectocervix. If the lesion extends beyond the cryoprobe being used, or into the endocervical canal, the patient is not eligible for cryotherapy and LEEP is the alternative option.

Before treatment, ALL women who have screened positive with any test (but especially with an HPV test) should be visually inspected with acetic acid to determine eligibility for cryotherapy and to rule out large lesions or suspected cervical cancer. VIA should be performed by a trained provider.

Note that there is a distinction in these recommendations between (a) using VIA

to determine eligibility for treatment (i.e. cryotherapy versus LEEP), and (b) using VIA as a screening test to determine whether or not to treat.

- a. In the 'HPV test' screen-and-treat strategy, women who are HPV-negative are not treated. Women who are HPV-positive will all be treated, and VIA is used to determine eligibility for treatment with cryotherapy or LEEP.
- b. In the 'HPV test followed by VIA' strategy, women who are HPV-negative are not treated. Women who are HPV-positive all undergo VIA, which is used in this case as a second screening test to determine treatment. Women who are HPV-positive and VIA-positive will all be treated, while women who are HPV-positive and VIA-negative will not be treated.

Screening intervals and follow-up

Ideal screening intervals are provided below and for all screen-and-treat strategies in Annexes 3 and 4.

In women who test negative on VIA or cytology (Pap smear), the screening interval for repeat screening should be every three to five years. In women who test negative on an HPV test, rescreening should be done after a minimum interval of five years. Women who have received treatment should receive post-treatment follow-up screening at one year to ensure effectiveness of treatment. Refer to Annex 3 for flowcharts for all strategies for women who are of negative or unknown HIV status.

In women who are of HIV-positive status or of unknown HIV status in areas with high endemic HIV infection, if the screening test is negative, the screening interval for repeat screening should be within three years. Women who have received treatment should receive post-treatment follow-up screening at one year to ensure effectiveness of treatment. Refer

to Annex 4 for flowcharts for all strategies for women who are of HIV-positive status or of unknown HIV status in areas with high endemic HIV infection.

Screen-and-treat recommendations

Recommendation 1. The expert panel recommends against the use of CKC as treatment in a screen-and-treat strategy (strong recommendation, ⊕⊖⊖⊖ evidence)

Remarks: The screen-and-treat strategies considered by the panel with CKC as treatment included an HPV test, VIA, or an HPV test followed by VIA as screening. Although the benefits were similar for CKC compared with cryotherapy or LEEP for all screen-and-treat strategies, the harms were greater with CKC. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B.

Summary of the evidence: Low-quality evidence from pooled observational studies showed that the recurrence of CIN after treatment with CKC may be 3% less than the recurrence after cryotherapy or LEEP. However, this difference did not lead to important differences in cervical cancer incidence or related mortality (risk difference of 0.08%). In contrast, the incidence of major bleeding requiring hospitalization or blood transfusions may be greater (1/1000 treated with CKC versus 1/10 000 with cryotherapy or LEEP for most screen-and-treat strategies) and the risk of premature delivery after treatment with CKC may be greater than with cryotherapy or LEEP (Risk Ratio 3.41 versus 2.00). The increased risks of these complications apply to all treated women, regardless of whether they were correctly or incorrectly classified as having CIN2+ (i.e. including women with false-positive results who are treated unnecessarily). These differences were similar to the benefits and harms found when modelled for women of HIV-positive status.

Recommendation 2. Where resources permit, the expert panel suggests a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

In resource-constrained settings, where screening with an HPV test is not feasible, the expert panel suggests a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible) over a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

Remarks: The benefits of screen-and-treat with an HPV test or VIA, compared to no screening, outweighed the harms, but the reductions in cancer and related mortality were greater with an HPV test when compared to VIA. The availability of HPV testing is resource-dependent and, therefore, the expert panel suggests that an HPV test over VIA be provided where it is available, affordable, implementable, and sustainable over time. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B.

Summary of the evidence: Low-quality to very-low-quality evidence showed that there may be fewer CIN2+ recurrences with the screen-and-treat strategy using an HPV test (3/1000 fewer), as well as fewer cervical cancers (1/10 000 fewer) and fewer deaths (6/100 000 fewer) than with a strategy using VIA for screening. These differences result from fewer missed cases of CIN2+ with the HPV test strategy compared with the VIA strategy (i.e. fewer false negatives). The difference in overtreatment may be relatively small (157 000 cases with an HPV test versus 127 000 cases with VIA out of 1 000 000 women). The number of cancers found at first-time screening may be

slightly greater with VIA (7/10 000 more). There may be little to no difference in complications, such as major bleeding or infections (e.g. 1/100 000 fewer with the VIA strategy). These results are similar to the benefits and harms found when modelled for women of HIV-positive status.

Recommendation 3. The expert panel suggests a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

Remarks: The reductions in cancer and related mortality were slightly greater with an HPV test only compared to cytology followed by colposcopy. Although there may be overtreatment of populations with high HPV prevalence and consequently more harms, as well as fewer cancers seen at first-time screening with an HPV test, there are greater resources required in cytology programmes due to quality control, training, and waiting time. The addition of colposcopy also requires a second visit. However, in countries where an appropriate/high-quality screening strategy with cytology (referring women with ASCUS or greater results) followed by colposcopy already exists, either an HPV test or cytology followed by colposcopy could be used. See Supplemental material, Sections A and B.

Summary of the evidence: As there were few to no studies evaluating the diagnostic accuracy of cytology followed by colposcopy compared to an HPV test, the effects of the sequence of tests were calculated by combining diagnostic data from cytology and colposcopy, resulting in lower-quality evidence. For the strategy of cytology followed by colposcopy (with or without biopsy), we analysed data for two scenarios: (1) Women who screened positive on cytology underwent colposcopy only

(i.e. treatment was based on colposcopic impression); and (2) Women who screened positive on cytology underwent colposcopy, and then women with positive colposcopy results were biopsied (i.e. treatment was based on the biopsy result). Evidence showed that there may be fewer CIN2+ recurrences with the HPV test strategy (3/1000 fewer), as well as fewer cervical cancers (1/10 000 fewer) and fewer deaths (6/100 000 fewer) than with cytology followed by colposcopy. These differences result from fewer missed cases of CIN2+ with the HPV test strategy (i.e. fewer false negatives). Overtreatment, however, may be slightly greater with an HPV test when compared with cytology followed by colposcopy without biopsy (7/100 more women) or with biopsy when indicated (10/100 more women). This may result in slightly more complications with the HPV test strategy. The number of cancers detected at first-time screening may be slightly greater with the cytology followed by colposcopy strategy (1/1000 more).

Recommendation 4. The expert panel recommends a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (strong recommendation, ⊕⊕⊕⊕ evidence)

Remarks: The benefits and harms of the two screen-and-treat strategies are similar, but there are fewer harms with cytology followed by colposcopy with biopsy when indicated. Despite overtreatment with VIA and fewer cancers detected at first-time screening, more resources are required for cytology programmes with colposcopy (with or without biopsy) due to quality control, training, and waiting time, as well as a second visit. The recommendation for VIA over cytology followed by colposcopy can be applied in countries that are currently considering either strategy, or countries that currently have both strategies available. This

recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B.

Summary of the evidence: As there were few to no studies evaluating the diagnostic accuracy of cytology followed by colposcopy compared to VIA, the effects of the sequence of tests were calculated by combining diagnostic data from cytology and colposcopy, resulting in lower-quality evidence. For the strategy of cytology followed by colposcopy (with or without biopsy), we analysed data for two scenarios: (1) Women who screened positive on cytology underwent colposcopy only (i.e. treatment was based on colposcopic impression); and (2) Women who screened positive on cytology underwent colposcopy, and then women with positive colposcopy results were biopsied (i.e. treatment was based on the biopsy result). Evidence showed that there may be little or no difference in CIN2+ recurrence, cervical cancers, and related mortality between the strategies. Overtreatment, however, may be slightly greater with VIA compared to cytology followed by colposcopy without biopsy (11/100 more women) or with biopsy when indicated (18/100 more women). This may result in slightly greater harm with the VIA strategy. The number of cancers detected at first-time screening may be slightly greater with the cytology followed by colposcopy strategy (2/1000 more) compared with the VIA strategy.

Recommendation 5. The expert panel suggests a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊕⊕⊕ evidence)

Remarks: The reductions in cancer and related mortality with either strategy outweigh the harms and costs of no screening, and were

similar between the two strategies. Although overtreatment and, consequently, harms are reduced with the addition of colposcopy (with or without biopsy), there are more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and the potential for more women to be lost to follow-up. The addition of colposcopy to an HPV test would also require a second visit. In countries without an existing screening strategy, an HPV test followed by colposcopy is not recommended. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B.

Summary of the evidence: As there were few to no studies evaluating the diagnostic accuracy of an HPV test followed by colposcopy, the effects of the sequence of tests were calculated by combining diagnostic data from the individual tests, resulting in lower-quality evidence. For the strategy of an HPV test followed by colposcopy (with or without biopsy), we analysed data for two scenarios: (1) Women who screened positive on HPV testing underwent colposcopy only (i.e. treatment was based on colposcopic impression); and (2) Women who screened positive on HPV testing underwent colposcopy, and then women with positive colposcopy results were biopsied (i.e. treatment was based on the biopsy result). Evidence showed that there may be little to no difference in CIN2+ recurrence, cervical cancers, and related mortality between the strategies. Overtreatment, however, may be slightly greater with an HPV test only compared with an HPV test followed by colposcopy without biopsy (5/100 more women) or with biopsy when indicated (12/100 more women). This may result in slightly greater harm with an HPV-test-only strategy. The number of cancers detected at first-time screening may be slightly greater with an HPV test followed by colposcopy strategy (1/1000 more) than with an HPV test only.

Recommendation 6. The expert panel suggests either a strategy of screen with

an HPV test followed by VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) or a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

Remarks: The reductions in cancer and related mortality were greater with an HPV test used as a single screening test than with an HPV test followed by VIA, and this reduction was even greater in women of HIV-positive status. However, there may be overtreatment, and thus potentially greater harms with screen-and-treat when using an HPV test as a single test. There is also some uncertainty about the effects of an HPV test followed by VIA and how VIA performs after a positive HPV test because there was no direct evidence about this strategy. There is also the potential for additional resources that are required to refer women for VIA testing after a positive HPV test, the need for a second visit to perform VIA, and increased training to perform both tests. For these reasons, the recommendation is for either an HPV test followed by VIA or an HPV test only, and it is conditional. It is to be noted that benefits are more pronounced compared to harm in women of HIV-positive status when using an HPV test only. See Supplemental material, Sections A and B.

Summary of the evidence: As there were no studies evaluating the diagnostic accuracy of an HPV test followed by VIA, the effects were calculated by combining diagnostic data from an HPV test only with data for VIA only, resulting in lower-quality evidence. This evidence showed that there may be slightly greater CIN2+ recurrences with an HPV test followed by VIA (4/1000 more), as well as more cervical cancers (1/10 000 more) and more deaths (7/100 000 more) than with an HPV test only. The difference was due to a slightly higher rate of missed cases of CIN 2+ with an HPV test followed by VIA than with an HPV test only (6/1000 more). The number of cancers detected at first-time screening may be slightly greater

with an HPV test followed by VIA (7/10 000 more), and there may be fewer women treated unnecessarily (1/10 fewer) due to the lower false-positive rate with an HPV test followed by VIA. If fewer women are treated unnecessarily, this may result in lower resource use and fewer complications with an HPV test followed by VIA.

However, these results were more pronounced when modelled for women of HIV-positive status. There may be greater differences in benefits and harms. The evidence for women of HIV-positive status showed that there is likely to be an even greater rate of CIN2+ recurrences with an HPV test followed by VIA (22/1000 more), as well as more cervical cancers (17/10 000 more) and more deaths (12/100 000 more) than with HPV only. However, there may be fewer women treated unnecessarily (1/10 fewer) when using the screening strategy of an HPV test followed by VIA, resulting in fewer resources for unnecessary treatment and fewer complications.

Recommendation 7. The expert panel suggests a strategy of screen with an HPV test followed by VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

Remarks: The reductions in cancer and related mortality with an HPV test followed by VIA or with VIA alone outweighed the harms. However, the harms may be greater when using VIA only, which is likely due to overtreatment. Although a slightly larger number of cancers may be detected on initial screen with VIA only. This recommendation is conditional due to the uncertain costs of providing the sequence of two tests (HPV test followed by VIA) over the single VIA test. In countries where an HPV test is not available, we suggest screening with VIA only. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B.

Summary of the evidence: As there were no studies evaluating the diagnostic accuracy of an HPV test followed by VIA, the effects were calculated by combining diagnostic data from an HPV test only with data for VIA only, resulting in lower-quality evidence. This evidence showed little to no difference in CIN2+ recurrence, cervical cancer, and related mortality between a screen-and-treat strategy using an HPV test followed by VIA and a strategy using VIA only. This was likely due to the relatively small differences in the number of missed cases of CIN2+ between the two strategies. Although the number of cancers detected at first-time screening may be slightly greater with VIA only (7/10 000 more), there may be more women treated unnecessarily (1/10 more) due to higher false-positive rates with VIA only (incurring higher resource use for overtreatment). Overtreatment may also result in greater complications with VIA only. These results are similar to the benefits and harms found when modelled for women of HIV-positive status.

Recommendation 8. The expert panel suggests a strategy of screen with an HPV test followed by VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

Remarks: The benefits of the two screen-and-treat strategies are similar. However, there may be higher resources required in cytology programmes due to quality control, training, and waiting time. The addition of colposcopy requires a second visit. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B.

Summary of the evidence: As there were few to no studies evaluating the diagnostic accuracy of cytology followed by colposcopy compared to an HPV test followed by VIA, the effects of the sequence of tests were

calculated by combining diagnostic data, resulting in lower-quality evidence. For the strategy of cytology followed by colposcopy (with or without biopsy), we analysed data for two scenarios: (1) Women who screened positive on cytology underwent colposcopy only (i.e. treatment was based on colposcopic impression); and (2) Women who screened positive on cytology underwent colposcopy, and then women with positive colposcopy results were biopsied (i.e. treatment was based on the biopsy result). Evidence showed that there may be little to no difference in CIN2+ recurrence, cervical cancers, and related mortality between the strategies. There may also be little to no difference in overtreatment between the strategies. The number of cancers detected at first-time screening may be slightly greater with the cytology followed by colposcopy strategy (2/1000 more).

Recommendation 9. The expert panel suggests a strategy of screen with an HPV test followed by VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, ⊕⊖⊖⊖ evidence)

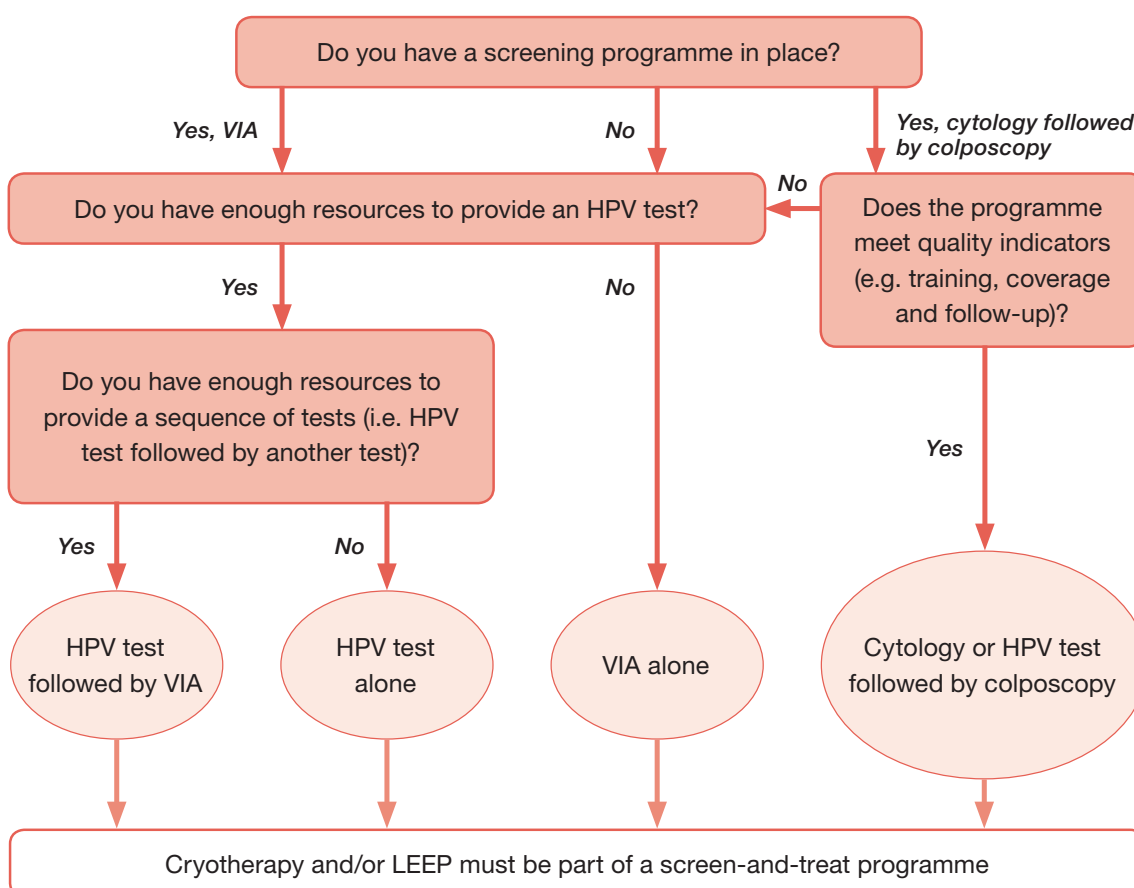
Remarks: The reductions in cancer and related mortality of screen-and-treat with an HPV test followed by colposcopy (with or without biopsy) may be slightly greater compared to an HPV test followed by VIA. The panel agreed that the benefits of either strategy outweigh the harms and costs; however, the difference in costs between the strategies is uncertain. There may be more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and the potential for

more women to be lost to follow-up. It is also unclear whether women would perceive a difference between VIA and colposcopy; however, a biopsy during colposcopy may be less acceptable than VIA. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B.

Summary of the evidence: As there were few to no studies evaluating the diagnostic accuracy of both screening strategies, the effects of the strategies were calculated by combining diagnostic data from the individual tests, resulting in lower-quality evidence. For the strategy of an HPV test followed by colposcopy (with or without biopsy), we analysed data for two scenarios: (1) Women who screened positive on HPV testing underwent colposcopy only (i.e. treatment was based on colposcopic impression); and (2) Women who screened positive on HPV testing underwent colposcopy, and then women with positive colposcopy results were biopsied (i.e. treatment was based on the biopsy result). Evidence showed that there may be fewer CIN2+ recurrences with the HPV test followed by colposcopy without biopsy (3/1000 fewer) and with biopsy (4/1000 fewer), as well as fewer cervical cancers (1/10 000 fewer with or without biopsy) and fewer deaths (6/100 000 fewer, with or without biopsy) than with an HPV test followed by VIA. These differences result from fewer missed cases of CIN2+ with the HPV test followed by colposcopy strategy when compared to an HPV test followed by VIA strategy (i.e. fewer false negatives). Overtreatment, however, may be greater with an HPV test followed by colposcopy without biopsy than with an HPV test followed by VIA (7/100 more women). There may be little to no difference between the strategies in the number of cancers detected at first-time screening.

Annex 2. Decision-making flowchart for screen-and-treat strategies

This decision-making flowchart or algorithm provides a decision tree to use as a quick reference when choosing a screen-and-treat strategy at the programme level. Programme managers and decision-makers can start at the top and answer the questions accordingly to determine which screen-and-treat option is best in the context where it will be implemented. It highlights choices related to resources, which can include costs, staff and training. However, programme managers will also need to consider other factors, such as the number of women who are lost to follow-up with a strategy that involves more than one screening test. Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for more specific guidance about which strategies are recommended, and for information on the specific factors to consider when deciding on a strategy. For details about the flow of each screen-and-treat strategy (e.g. HPV followed by VIA), consult the flowcharts in Annex 3 (for women of negative or unknown HIV status) and Annex 4 (for women of HIV-positive status or unknown HIV status in areas with high endemic HIV infection).



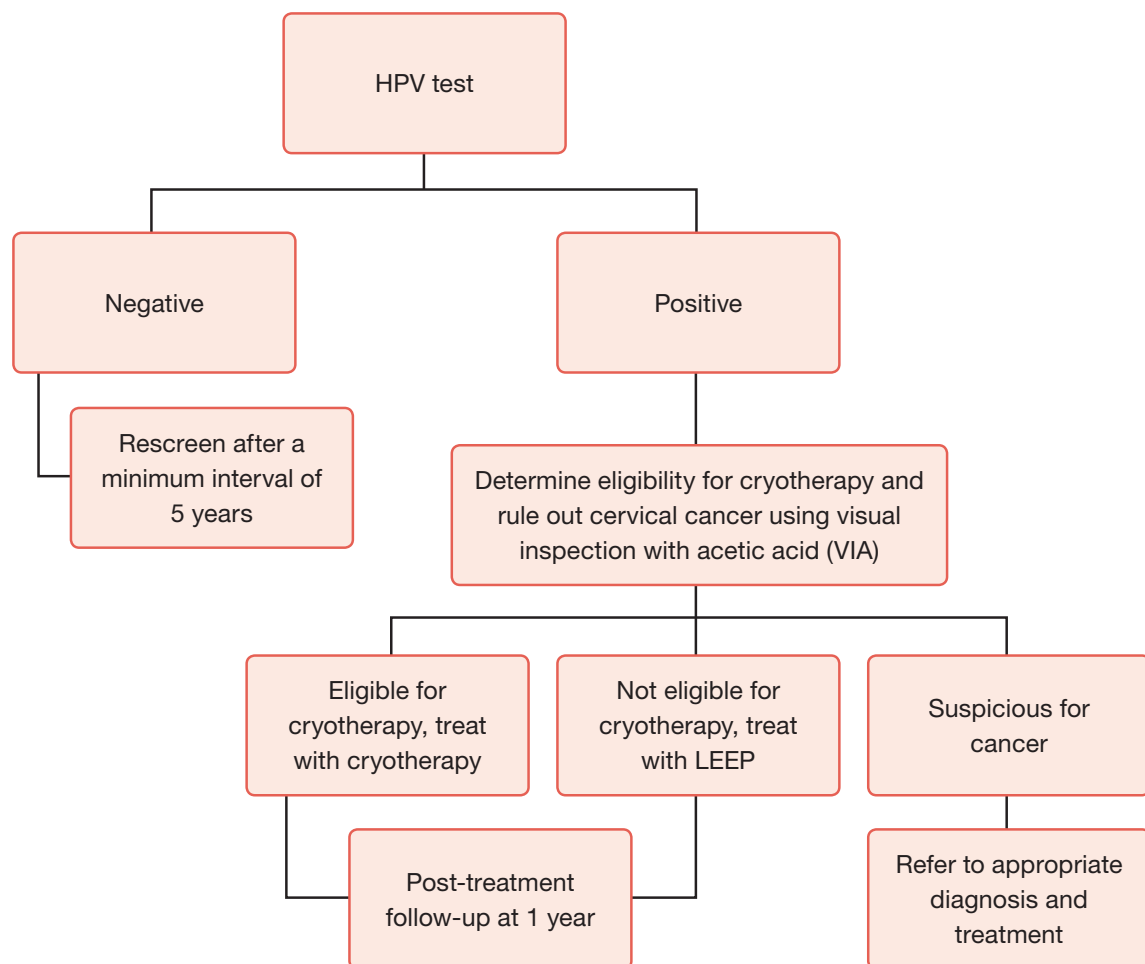
Note: each light-pink bubble refers to one strategy in Annex 3 (for women of negative or unknown HIV status) or Annex 4 (for women of HIV-positive status or unknown HIV status in areas with high endemic HIV infection)

Annex 3. Flowcharts for screen-and-treat strategies (negative or unknown HIV status)

The following flowcharts describe the steps for each of the screen-and-treat strategies that are available. The flowcharts *do not* indicate which strategy is preferred. Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and to the decision-making flowchart in Annex 2. For detailed information about the specific factors the guideline panel considered when making the recommendations, refer to the evidence-to-recommendation tables for each recommendation (Supplemental material, Sections A and B).

Screen with an HPV test and treat with cryotherapy, or LEEP when not eligible for cryotherapy

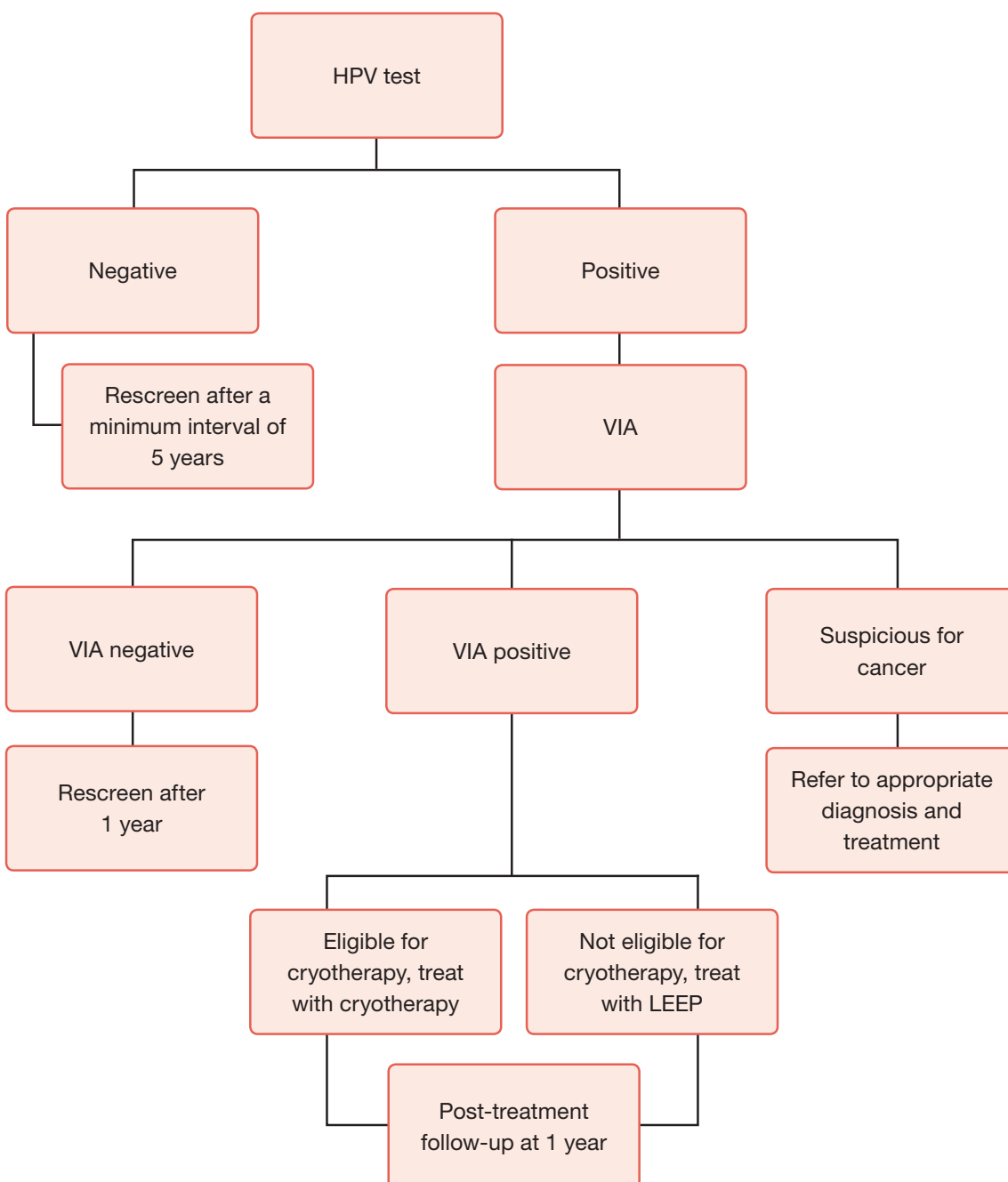
When an HPV test is positive, treatment is provided. With this strategy, visual inspection with acetic acid (VIA) is used to determine **eligibility** for cryotherapy.



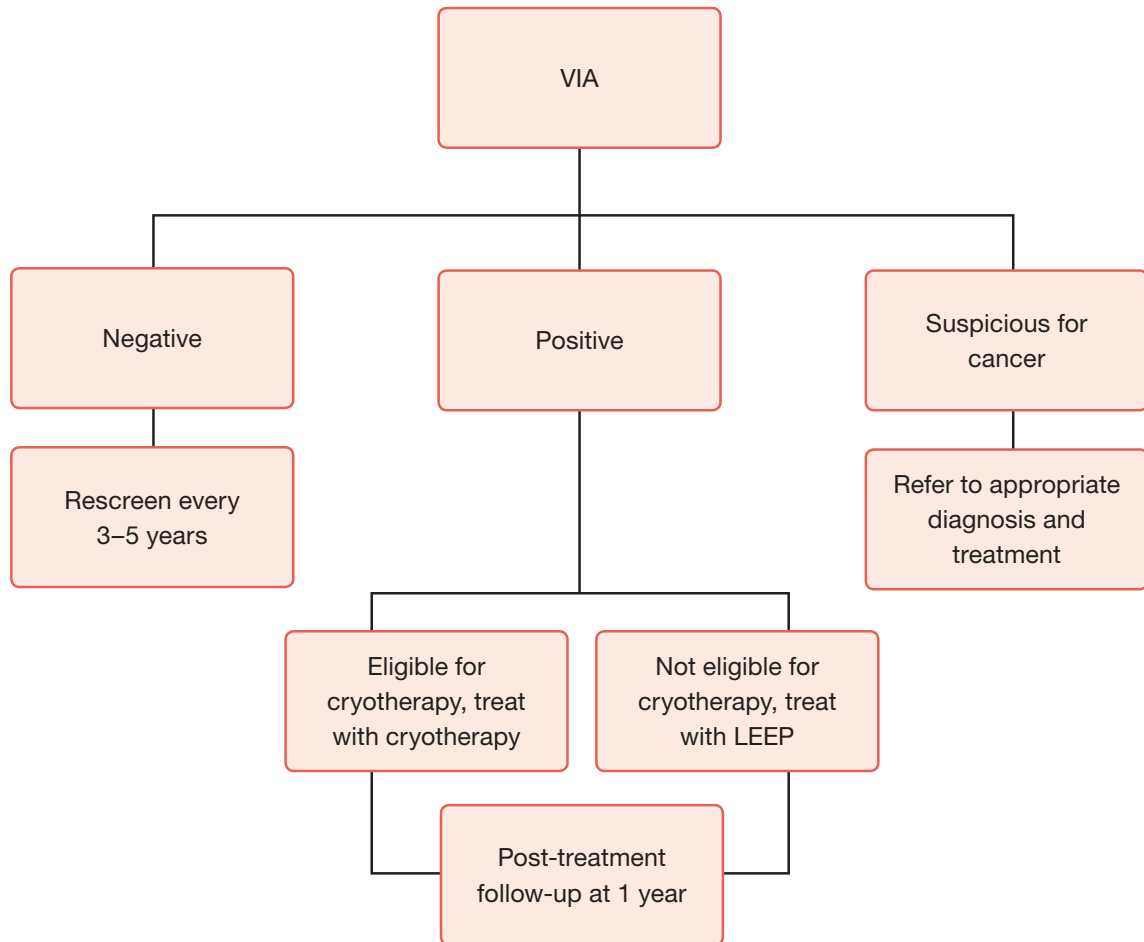
Note: Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and for information on the specific factors to consider when deciding on a strategy.

Screen with an HPV test followed by VIA and treat with cryotherapy, or LEEP when not eligible for cryotherapy

When an HPV test is positive, then VIA is provided as a second screening test to determine whether or not treatment is offered. Treatment is only provided if BOTH the HPV test and VIA are positive.

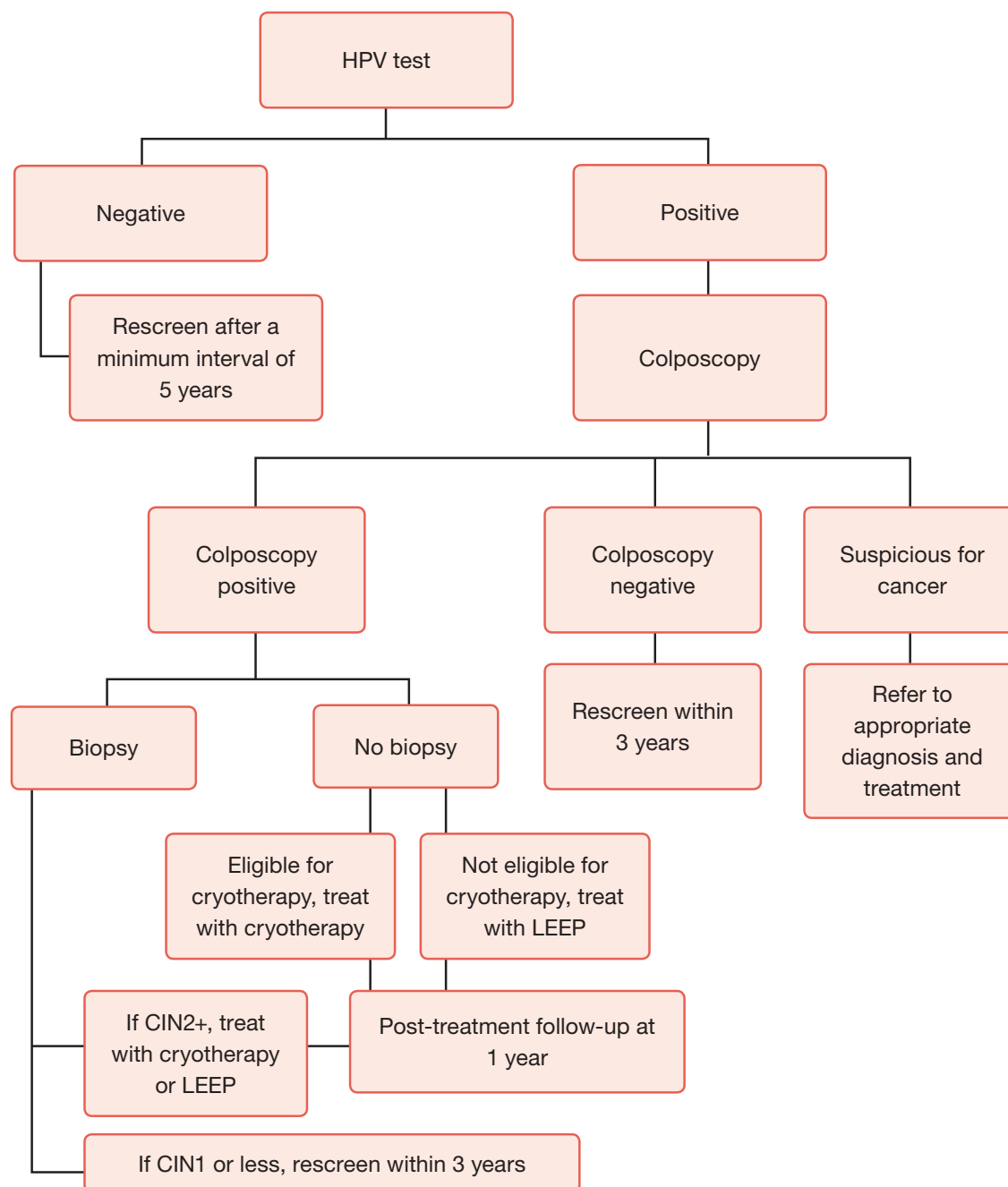


Note: Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and for information on the specific factors to consider when deciding on a strategy.

Screen with VIA and treat with cryotherapy, or LEEP when not eligible for cryotherapy

Note: Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and for information on the specific factors to consider when deciding on a strategy.

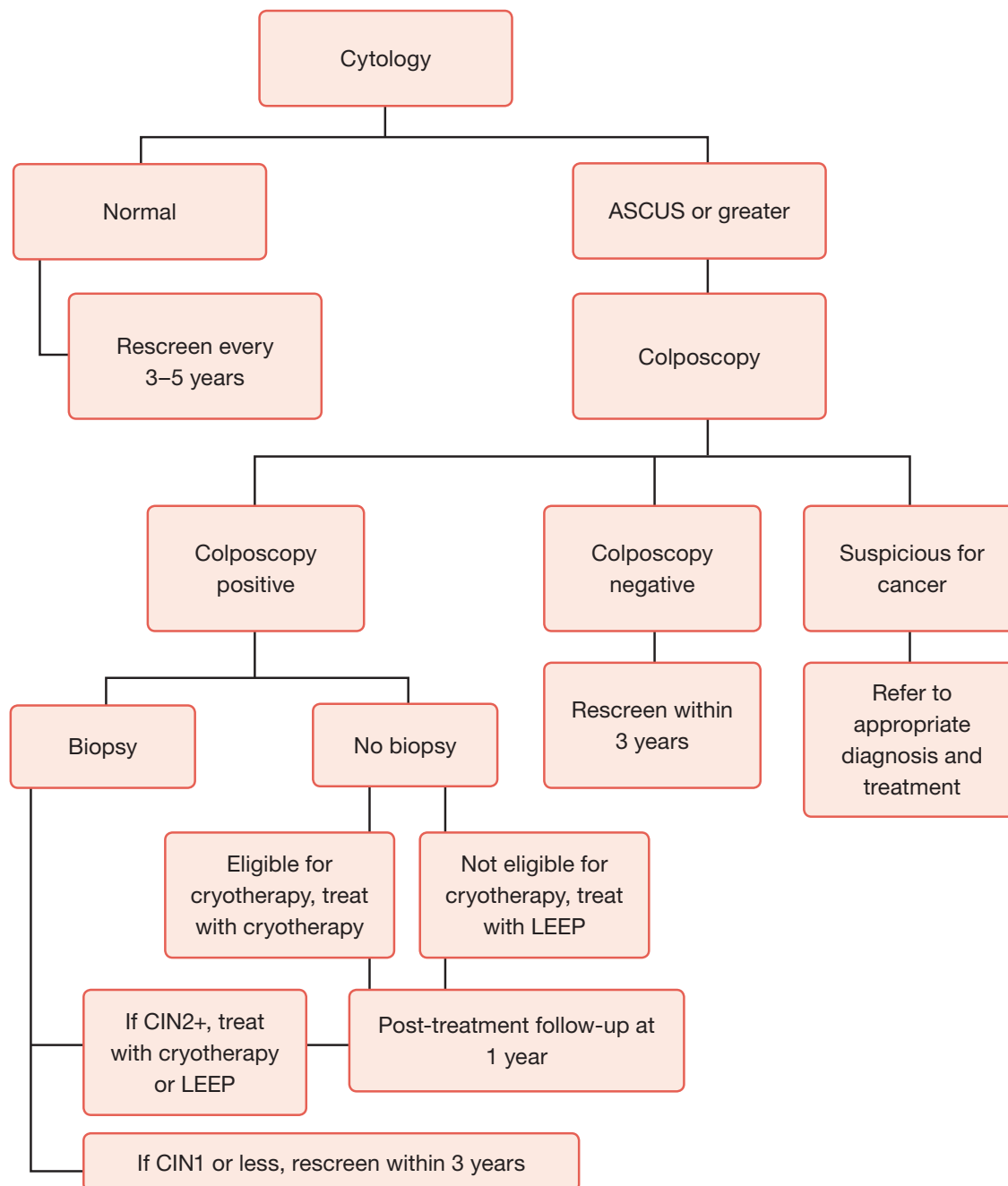
Screen with an HPV test followed by colposcopy (with or without biopsy)¹ and treat with cryotherapy, or LEEP when not eligible for cryotherapy



Note: Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and for information on the specific factors to consider when deciding on a strategy.

¹ Women with positive colposcopic impression can receive biopsy for histological confirmation or be treated immediately.

Screen with cytology followed by colposcopy (with or without biopsy)¹ and treat with cryotherapy, or LEEP when not eligible for cryotherapy



Note: Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and for information on the specific factors to consider when deciding on a strategy.

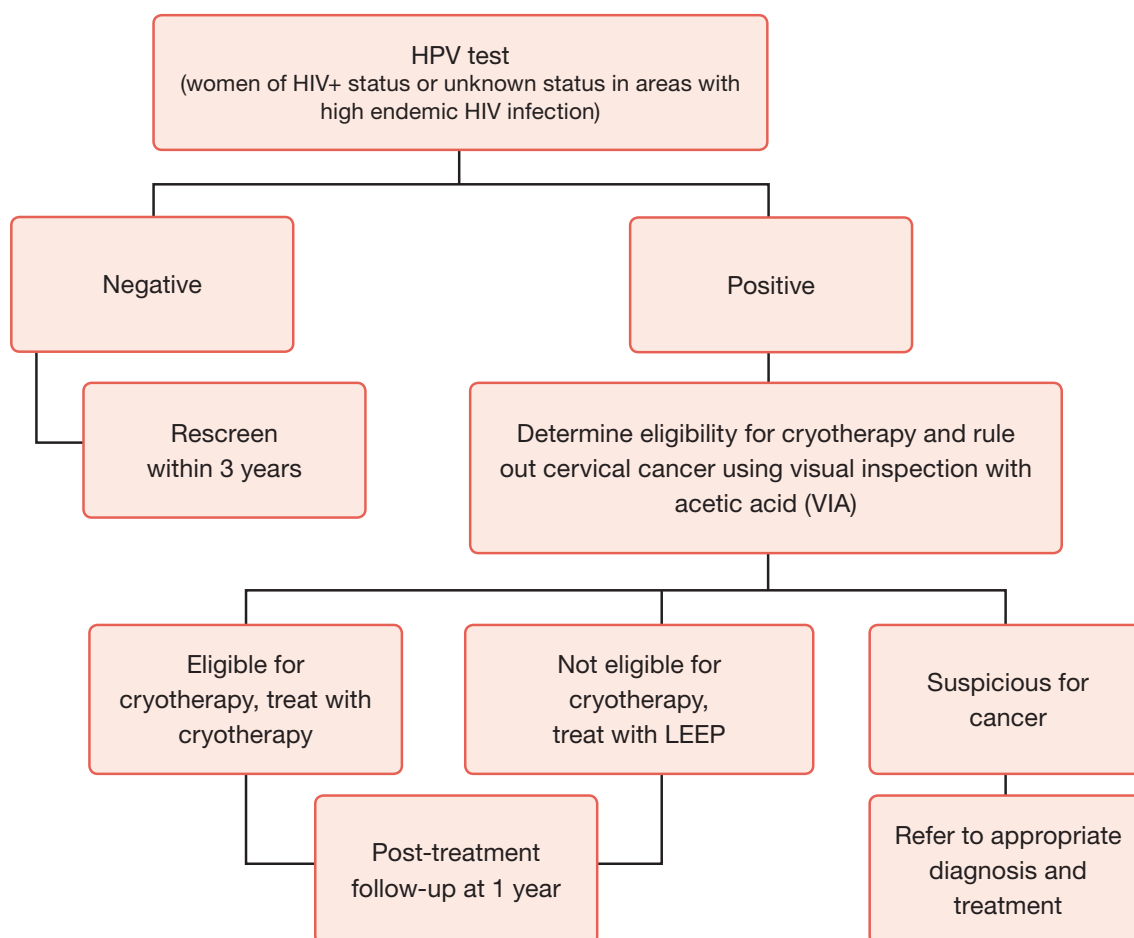
¹ Women with positive colposcopic impression can receive biopsy for histological confirmation or be treated immediately.

Annex 4. Flowcharts for screen-and-treat strategies (HIV-positive status or unknown HIV status in areas with high endemic HIV infection)

The following flowcharts describe the steps for each of the screen-and-treat strategies that are available. The flowcharts *do not* indicate which strategy is preferred. Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and to the decision-making flowchart in Annex 2. For detailed information about the specific factors the guideline panel considered when making the recommendations, refer to the evidence-to-recommendation tables for each recommendation (Supplemental material, Sections A and B).

Screen with an HPV test and treat with cryotherapy, or LEEP when not eligible for cryotherapy

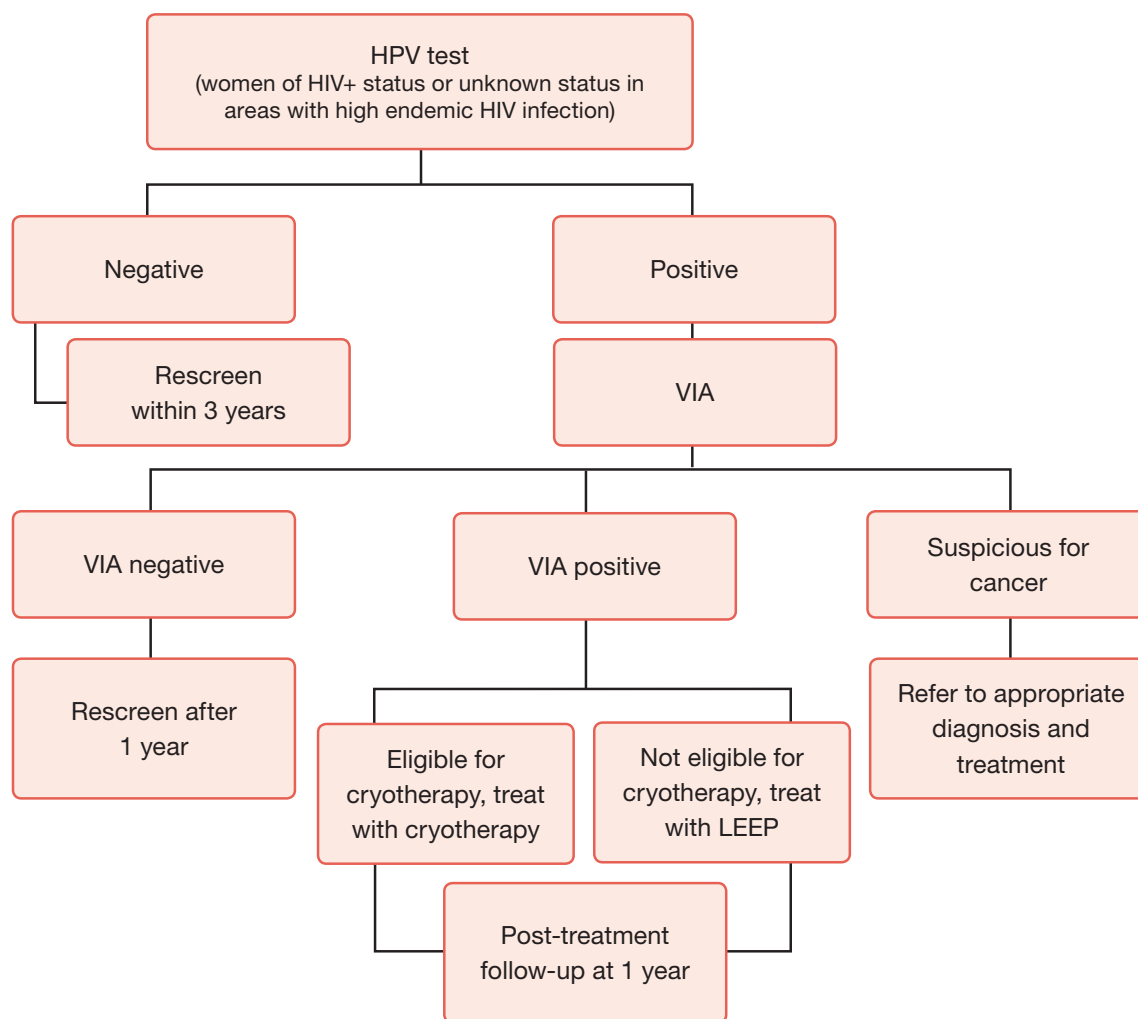
When an HPV test is positive, treatment is provided. With this strategy, visual inspection with acetic acid (VIA) is used to determine **eligibility** for cryotherapy.



Note: Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and for information on the factors to consider when deciding on a strategy.

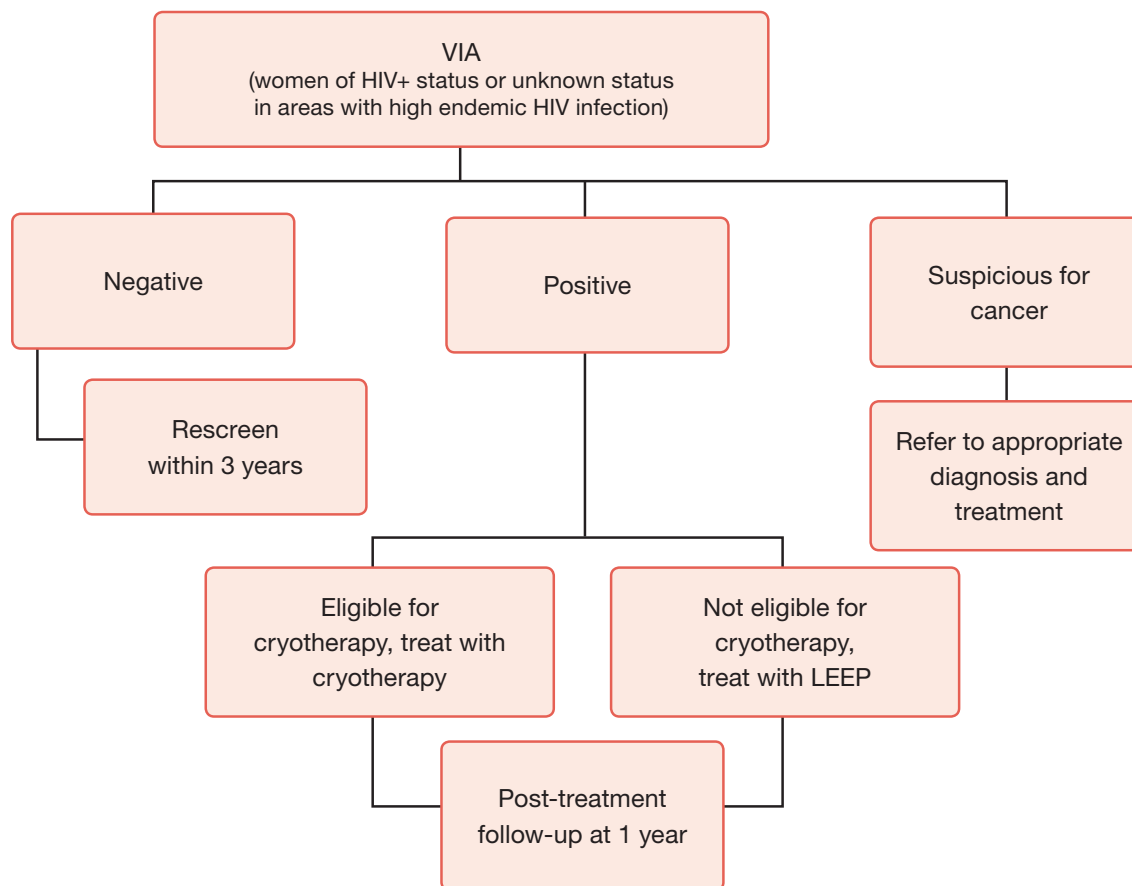
Screen with an HPV test followed by VIA and treat with cryotherapy, or LEEP when not eligible for cryotherapy

When an HPV test is positive, then VIA is provided as a second screening test to determine whether or not treatment is offered. Treatment is only provided if BOTH the HPV test and VIA are positive.



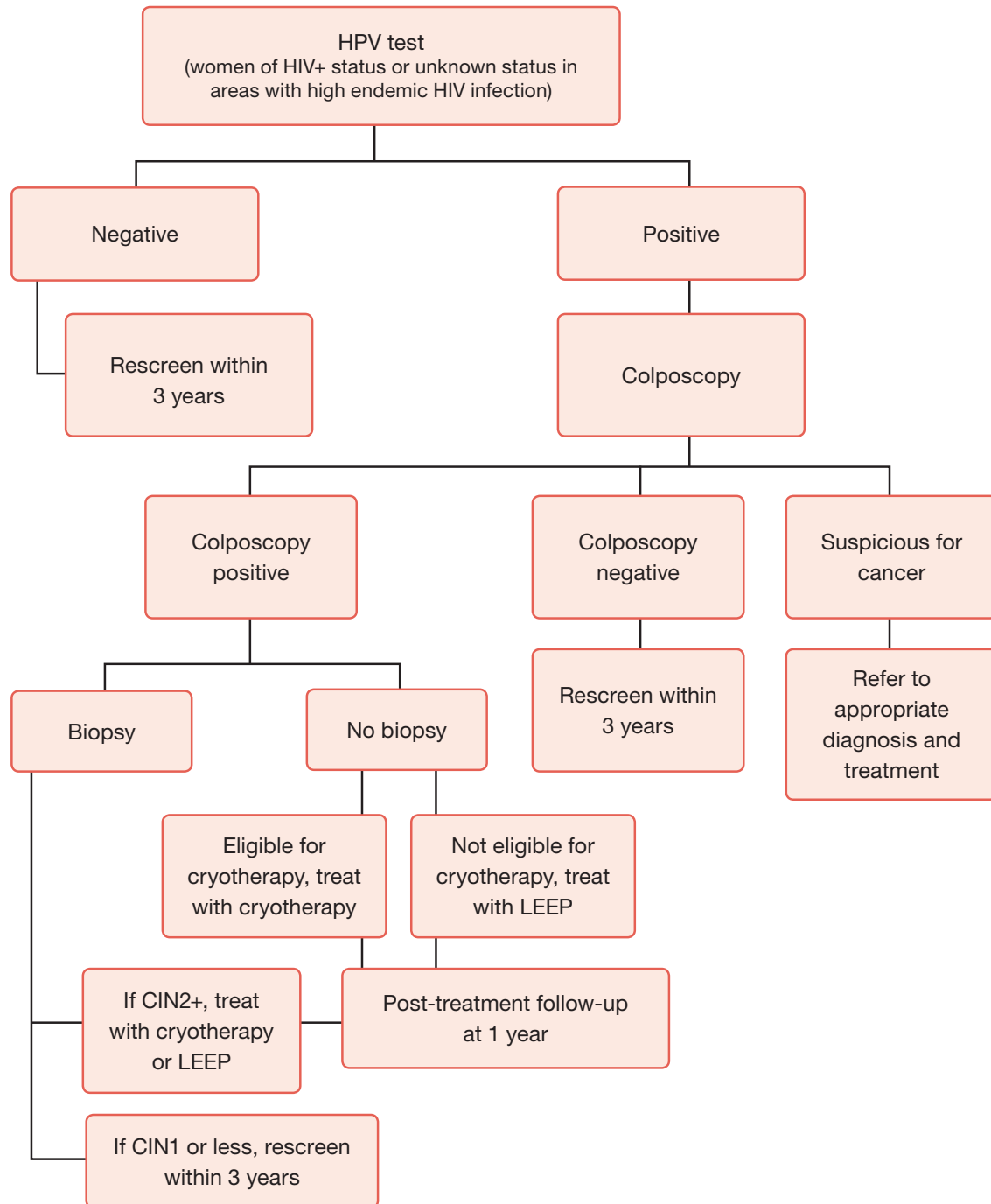
Note: Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and for information on the factors to consider when deciding on a strategy.

Screen with VIA and treat with cryotherapy, or LEEP when not eligible for cryotherapy



Note: Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and for information on the factors to consider when deciding on a strategy.

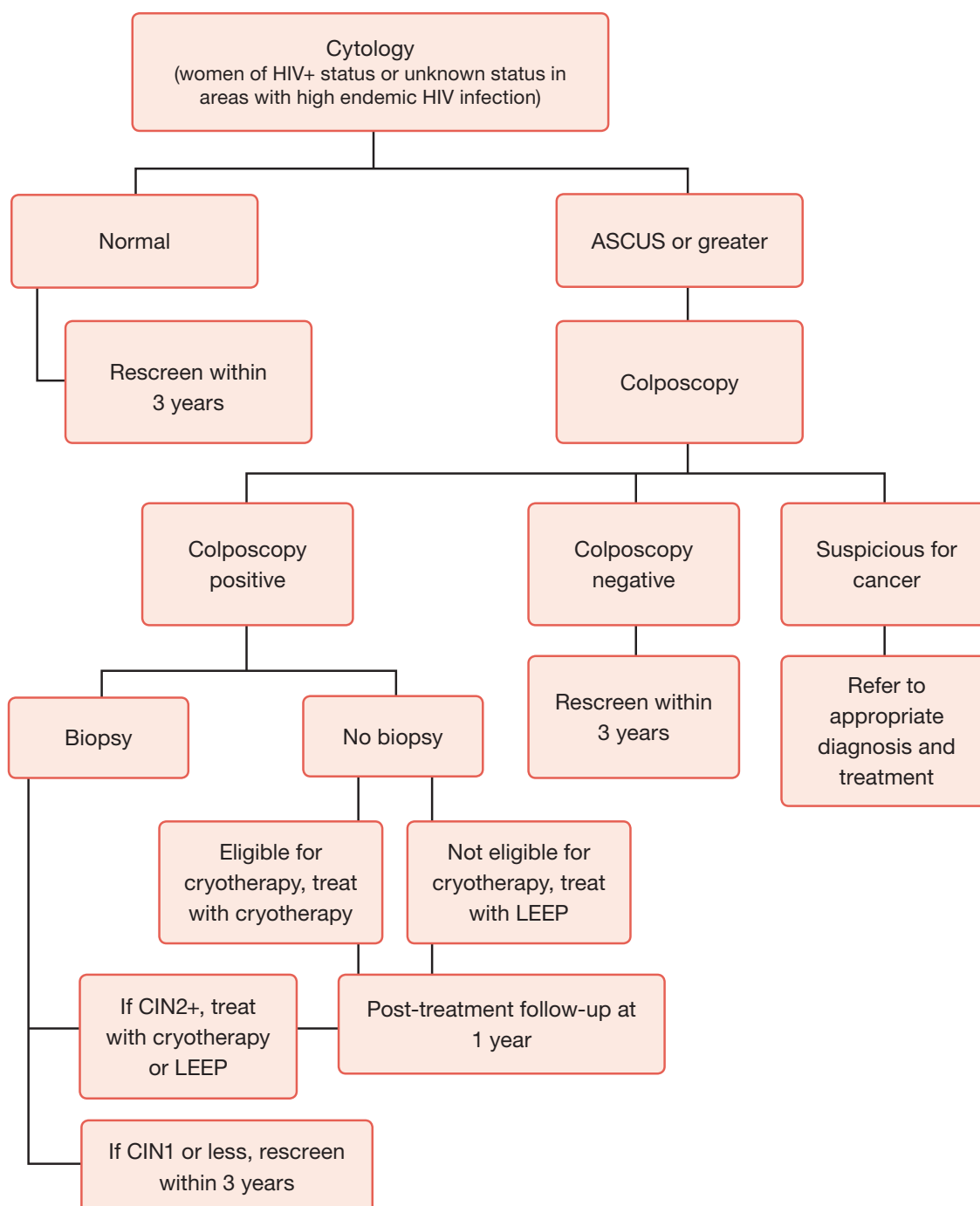
Screen with an HPV test followed by colposcopy (with or without biopsy)¹ and treat with cryotherapy, or LEEP when not eligible for cryotherapy



Note: Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and for information on the factors to consider when deciding on a strategy.

¹ Women with positive colposcopic impression can receive biopsy for histological confirmation or be treated immediately.

Screen with cytology followed by colposcopy (with or without biopsy)¹ and treat with cryotherapy or LEEP (when not eligible for cryotherapy)



Note: Refer to the screen-and-treat recommendations provided in Chapter 3 of the guideline for guidance about which strategies are recommended, and for information on the factors to consider when deciding on a strategy.

¹ Women with positive colposcopic impression can receive biopsy for histological confirmation or be treated immediately.

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HPV Screening for Cervical Cancer in Rural India

Rengaswamy Sankaranarayanan, M.D., Bhagwan M. Nene, M.D., F.R.C.P., Surendra S. Shastri, M.D., Kasturi Jayant, M.Sc., Richard Muwonge, Ph.D., Atul M. Budukh, Ph.D., Sanjay Hingmire, B.Sc., Sylla G. Malvi, M.Sc., Ph.D., Ranjit Thorat, B.Sc., Ashok Kothari, M.D., Roshan Chinoy, M.D., Rohini Kelkar, M.D., Shubhada Kane, M.D., Sangeetha Desai, M.D., Vijay R. Keskar, M.S., Raghevendra Rajeshwarkar, M.D., Nandkumar Panse, B.Com., and Ketayun A. Dinshaw, M.D., F.R.C.R.

ABSTRACT

BACKGROUND

In October 1999, we began to measure the effect of a single round of screening by testing for human papillomavirus (HPV), cytologic testing, or visual inspection of the cervix with acetic acid (VIA) on the incidence of cervical cancer and the associated rates of death in the Osmanabad district in India.

METHODS

In this cluster-randomized trial, 52 clusters of villages, with a total of 131,746 healthy women between the ages of 30 and 59 years, were randomly assigned to four groups of 13 clusters each. The groups were randomly assigned to undergo screening by HPV testing (34,126 women), cytologic testing (32,058), or VIA (34,074) or to receive standard care (31,488, control group). Women who had positive results on screening underwent colposcopy and directed biopsies, and those with cervical precancerous lesions or cancer received appropriate treatment.

RESULTS

In the HPV-testing group, cervical cancer was diagnosed in 127 subjects (of whom 39 had stage II or higher), as compared with 118 subjects (of whom 82 had advanced disease) in the control group (hazard ratio for the detection of advanced cancer in the HPV-testing group, 0.47; 95% confidence interval [CI], 0.32 to 0.69). There were 34 deaths from cancer in the HPV-testing group, as compared with 64 in the control group (hazard ratio, 0.52; 95% CI, 0.33 to 0.83). No significant reductions in the numbers of advanced cancers or deaths were observed in the cytologic-testing group or in the VIA group, as compared with the control group. Mild adverse events were reported in 0.1% of screened women.

CONCLUSIONS

In a low-resource setting, a single round of HPV testing was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer.

From the International Agency for Research on Cancer, Lyon, France (R.S., R.M.); and the Nargis Dutt Memorial Cancer Hospital, Tata Memorial Centre Rural Cancer Project, Barshi (B.M.N., K.J., A.M.B., S.H., S.G.M., R.T., A.K., V.R.K., R.R., N.P.), and the Tata Memorial Centre, Mumbai (S.S.S., R.C., R.K., S.K., S.D., K.A.D.) — both in India. Address reprint requests to Dr. Sankaranarayanan at the International Agency for Research on Cancer, 150 cours Albert Thomas, Lyon 69008, France, or at sankar@iarc.fr.

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IN DEVELOPING COUNTRIES, THERE IS A lack of effective screening programs for cervical cancer. In these countries, no clinically significant reduction in the incidence of cervical cancer has occurred during the past three decades.¹⁻⁴ In developed countries, by contrast, there has been a major decline in cervical-cancer mortality after the introduction of large-scale cytologic testing. The limited success of such screening in developing countries has stimulated evaluation of testing for human papillomavirus (HPV) and visual inspection of the cervix with acetic acid (VIA).

In October 1999, we initiated a cluster-randomized, controlled trial to evaluate the effectiveness of a single round of HPV testing, cytologic testing, or VIA in reducing the incidence of cervical cancer, as compared with a control group that received usual care in a previously unscreened, high-risk population in the Osmanabad district in the state of Maharashtra, India.⁵ We report the cervical-cancer incidence and mortality in the four groups after 8 years of follow-up.

METHODS

STUDY DESIGN

The study design and methods have been described in detail previously.⁵ The scientific and ethical review committees of the International Agency for Research on Cancer (IARC) and the Tata Memorial Centre (TMC) and the Nargis Dutt Memorial Cancer Hospital (NDMCH) reviewed and approved the protocol. Clusters of villages consisting of a total of 497 villages in the Osmanabad district that had a primary health care center constituted the randomization unit. A statistician at the IARC who was not involved in the project randomly assigned 52 such clusters to four groups consisting of 13 clusters each. The groups were randomly assigned to receive screening by HPV testing, cytologic testing, or VIA or to receive standard care (control group). Although both practitioners and subjects were aware of study-group assignments, the blinded outcome assessment was performed by cancer-registry personnel in the Osmanabad district. The study was initiated in January 2000, and the results reported here are based on follow-up through December 31, 2007. The study was supported by the Bill and Melinda Gates Foundation through the Alliance for Cervical Cancer Prevention.

SUBJECTS

Eligible women were between the ages of 30 and 59 years, were healthy, were currently or had been married, and were not pregnant. All the women had an intact uterus with no prolapse, had no history of cervical cancer, and were living in the study clusters. The women were identified with the use of household surveys. After explaining the study and obtaining written informed consent, female health workers interviewed the women in each of the four study groups with respect to sociodemographic and reproductive characteristics, using a structured questionnaire. They also instructed all the women about the causes of cervical cancer, signs and symptoms, prevention, early detection, and treatment.

Women in the 13 control clusters were not offered screening but were advised on how to seek screening at local hospitals. Women in the clusters who were assigned to screening were given a card indicating the date, time, and place of screening.

TRAINING

Screening was performed by nine auxiliary nurse-midwives who were trained in a 3-week course with the use of IARC manuals in the collection of cervical cells for HPV testing and cytologic testing and in performing VIA and cryotherapy.^{6,7} Nine doctors were trained to supervise the auxiliary nurse-midwives and to perform colposcopy, cryotherapy, and the loop electrosurgical excision procedure (LEEP).^{5,7} Two pathologists reviewed the reporting of cervical neoplasms at the TMC. The technicians who were responsible for processing and reading Papanicolaou smears, processing biopsy specimens, and testing for HPV using the Hybrid Capture II test (Qiagen) were trained for 3 months at the TMC.

SCREENING, DIAGNOSIS, AND TREATMENT

Women were screened in village clinics that were organized in local primary health centers, municipal offices, or schools. The screening process, investigations, and treatments were explained to the women.

In the HPV-testing group, cervical samples, collected in a special transport medium, were processed with the use of the Hybrid Capture II assay for 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) on the basis of the

manufacturer's instructions. A positive result was recorded for specimens with a ratio of the relative light unit to a positive control (RLU/PC) of 1 or more, corresponding to 5000 or more viral copies. In the cytologic-testing group, cervical cells were collected with the use of Cervex brushes, and the smears were processed at NDMCH and reported according to the 1991 Bethesda system.⁸ Results for women with atypical squamous cells of uncertain significance or higher-grade lesions were defined as positive. In the VIA group, women with well-defined, dense aceto-white lesions in the cervix, close to the squamocolumnar junction or the os, or aceto-whitening of a cervical growth 1 minute after the application of 4% acetic acid were categorized as VIA-positive.^{5,6} Subjects in this group underwent immediate colposcopy and directed biopsies from abnormal areas by a physician in the field clinic and were given appointments for treatment at the NDMCH. Results of HPV testing or cytologic testing were delivered to the subjects within 2 weeks after testing, and those with positive tests were given appointments for colposcopy, biopsy, and treatment.

Women with a positive screening test were evaluated by means of colposcopy, and doctors reported the results as normal findings, inflammation, probable low-grade or high-grade precancerous lesions, or invasive cancer.⁷ The colposcopic findings were explained to the women, and punch-biopsy specimens were obtained from abnormal areas. Biopsy specimens were processed at the NDMCH and reported according to typical terminology regarding cervical intraepithelial neoplasia (CIN) grade.⁹ Women with colposcopic findings of low-grade or high-grade lesions were offered immediate cryotherapy after the directed biopsy, if all the following criteria were met: the lesion could be covered by the cryoprobe and involved three quadrants or less of the cervix with no extension into the endocervix or vaginal walls, the squamocolumnar junction was fully visible, and there was no suspicion of invasive cancer. LEEP or conization was offered to women with CIN lesions that were unsuitable for cryotherapy. Women with CIN grade 2 or 3 lesions were brought back for cryotherapy or LEEP. Women with suspected invasive cancer were referred to the NDMCH or to the hospital of their choice for investigations and treatment with surgery, radiotherapy, or both.

QUALITY ASSURANCE

Provider competency was maintained by medical supervision in the field and by periodic refresher courses to monitor their performance, along with rates of positive results on screening, correlation between colposcopy and histologic findings, and positive predictive values for CIN.⁵ Internal and external quality-control measures were in place for colposcopy and pathological analysis.⁵

OUTCOME MEASURES

The primary outcomes were the incidence of cervical cancer and associated rates of death. Secondary outcomes included stage distribution according to the International Federation of Gynecology and Obstetrics (FIGO) staging system¹⁰ and survival and case fatality rates. Cancer-registry staff members who were unaware of study-group assignments collected data on the date of diagnosis, stage, treatment, and follow-up details for subjects with cervical cancer, using active case-finding methods.¹¹ Information on all deaths among the subjects was collected from the district death-registration offices, hospital records, and annual house visits. The cause of death for each subject with cervical cancer in the district was assessed by the cancer-registry staff after evaluation of data from hospital records, death certificates, house visits, and interviews of relatives or friends. The screening-project staff then matched the subjects who had incident cervical cancer and those who died with the study database.

STATISTICAL ANALYSIS

The study was designed to have a power of 80% to detect a 50% reduction in the cumulative rate of death from cervical cancer within 15 years after enrollment in one of the intervention groups, as compared with the control group. The death rate from cervical cancer in women between the ages of 30 and 59 years was assumed to be around 20 per 100,000. We assumed that clusters consisting of an average of 2500 women would provide about 25,600 person-years of observation after 15 years (assuming a yearly dropout rate of 2.5%). Taking into account the effect of the intraclass correlation, we assumed a coefficient variation of 0.3 — in other words, the true rates of death from cervical cancer in the control group would vary between 8 and 32 per 100,000. Since this assump-

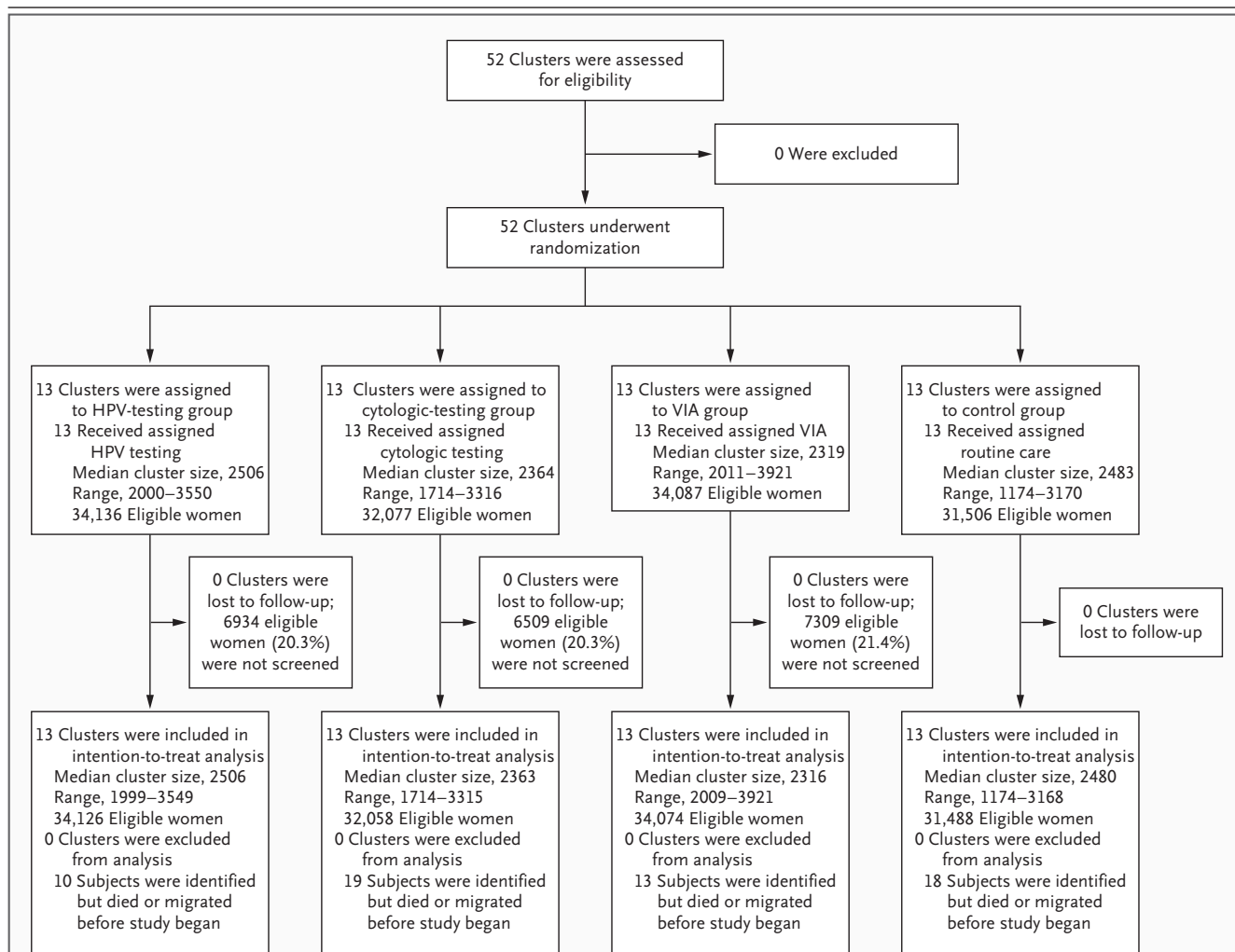


Figure 1. Enrollment and Outcomes.

HPV denotes human papillomavirus, and VIA visual inspection of the cervix with acetic acid.

tion led to a design effect of 1.38, we needed to randomize at least 13 clusters in each study group.¹² The sample-size requirement was satisfied, since each group involved 13 clusters of an average of 2744 women. A P value of less than 0.05 was considered to indicate statistical significance.

Data were entered in an ACCESS database and analyzed with the use of a Stata software package, version 10.0. Analysis was performed according to the intention-to-treat principle: all eligible women in the randomized clusters were included, regardless of their participation in interviews or screening visits. Since the trial used a cluster design, analyses of household and individual characteristics were performed with the use of the cluster as the unit of analysis. Comparisons of cluster proportions or means of household and individual characteristics within the four study

groups were performed with the use of the Kruskal–Wallis rank test. Multivariate analysis of the primary outcomes of cervical-cancer incidence and associated mortality was performed with the use of Cox proportional-hazards regression, taking into account the cluster design and with adjustment for age.

The subjects' participation in screening and treatment, rates of positivity on screening, positive predictive values, CIN grades, and cancer-detection rates and stage distribution were calculated as proportions. For the calculation of the incidence of cervical cancer, the numbers of person-years in the intervention groups and the control group were estimated from the date of the study initiation (January 1, 2000) to the date of diagnosis, death, migration, or last follow-up visit, whichever occurred first; for rates of death, the

Table 1. Baseline Characteristics of the Subjects.*

| Variable | HPV Testing | Cytologic Testing | VIA | Control | P Value† |
|---|-------------|-------------------|------------|-------------|----------|
| Subjects — no. | | | | | |
| All | 34,126 | 32,058 | 34,074 | 31,488 | |
| Range | 1999–3549 | 1714–3315 | 2009–3921 | 1174–3168 | |
| Living in traditional home with thatched roof | | | | | |
| Subjects — no. | 8089 | 10,291 | 10,082 | 8453 | 0.77 |
| Average proportion in clusters — % (range) | 26 (4–72) | 33 (3–87) | 28 (1–83) | 28 (<1–61) | |
| Age — yr | | | | | |
| Mean | 39±0.6 | 39±0.6 | 39±0.4 | 40±0.7 | 0.008 |
| Range | 38–40 | 39–40 | 39–40 | 39–41 | |
| Hindu religion | | | | | |
| Subjects — no. | 30,750 | 28,650 | 30,197 | 27,660 | 0.29 |
| Average proportion in clusters — % (range) | 93 (86–98) | 93 (79–99) | 92 (86–98) | 94 (77–100) | |
| No formal education | | | | | |
| Subjects — no. | 22,955 | 22,259 | 22,772 | 18,129 | 0.30 |
| Average proportion in clusters — % (range) | 70 (62–75) | 73 (67–78) | 70 (61–75) | 71 (68–76) | |
| Working exclusively in the home | | | | | |
| Subjects — no. | 20,552 | 19,470 | 20,051 | 14,515 | 0.74 |
| Average proportion in clusters — % (range) | 62 (48–80) | 64 (44–79) | 62 (54–71) | 58 (35–78) | |
| Currently married | | | | | |
| Subjects — no. | 29,601 | 27,615 | 29,674 | 23,095 | 0.84 |
| Average proportion in clusters — % (range) | 90 (88–93) | 91 (87–92) | 91 (88–93) | 91 (88–94) | |
| No. of pregnancies | | | | | |
| Mean | 4.0±0.1 | 4.0±0.3 | 4.0±0.2 | 4.0±0.2 | 0.87 |
| Range | 4–5 | 4–5 | 4–5 | 4–5 | |

* Plus-minus values are means ±SD. Proportions of subjects are averages of percentages in each 13-unit cluster for each study group. HPV denotes human papillomavirus, and VIA visual inspection of the cervix with acetic acid.

† P values are for all comparisons among the four study groups.

number of person-years was calculated from the time of study initiation to the date of death, migration, or last follow-up visit, whichever occurred first. Data were censored on December 31, 2007.

RESULTS

SUBJECTS

Of the 131,806 eligible women, 60 died or migrated before the study began; thus, complete data were available for 131,746 eligible women (Fig. 1). The study groups were equally distributed in terms of household type, religion, education, occupation, marital status, and number of pregnancies (Table 1). Only eight of the eligible women had undergone previous cervical screening.

SCREENING AND DETECTION RATES OF CIN

Screening was initiated in January 2000 and was completed by April 2003. Table 2 lists the number of invited and screened women, the number and proportion of positive screen results, and the number of women detected with CIN and cervical cancer according to age. Of the 34,126 women in the HPV-testing group, 27,192 (79.7%) were screened and 2812 (10.3%) had positive results; of the 32,058 women in the cytologic-testing group, 25,549 (79.7%) were screened and 1787 (7.0%) had positive results; and of the 34,074 women in the VIA group, 26,765 (78.5%) were screened and 3733 (13.9%) had positive results. More than 88% of subjects with positive results underwent colposcopy. The detection rate of CIN grade 1 was

Table 2. Rates of Screening, Colposcopy, and Detection of Cervical Intraepithelial Neoplasia (CIN) and Cancer, According to Age Group.*

| Variable and Age Group | HPV Testing | Cytologic Testing <i>no./total no. (%)</i> | VIA |
|---|----------------------|---|----------------------|
| Subjects who underwent screening/those who were invited | | | |
| 30–39 yr | 15,340/18,751 (81.8) | 14,750/17,823 (82.8) | 15,057/18,563 (81.1) |
| 40–49 yr | 7628/9503 (80.3) | 6981/8796 (79.4) | 7547/9578 (78.8) |
| 50–59 yr | 4224/5872 (71.9) | 3818/5439 (70.2) | 4161/5933 (70.1) |
| All ages | 27,192/34,126 (79.7) | 25,549/32,058 (79.7) | 26,765/34,074 (78.5) |
| Subjects with positive results on screening | | | |
| 30–39 yr | 1500/15,340 (9.8) | 1028/14,750 (7.0) | 2681/15,057 (17.8) |
| 40–49 yr | 796/7628 (10.4) | 493/6981 (7.1) | 786/7547 (10.4) |
| 50–59 yr | 516/4224 (12.2) | 266/3818 (7.0) | 266/4161 (6.4) |
| All ages | 2812/27,192 (10.3) | 1787/25,549 (7.0) | 3733/26,765 (13.9) |
| Subjects with positive results who underwent colposcopy | | | |
| 30–39 yr | 1358/1500 (90.5) | 914/1028 (88.9) | 2661/2681 (99.3) |
| 40–49 yr | 704/796 (88.4) | 420/493 (85.2) | 763/786 (97.1) |
| 50–59 yr | 443/516 (85.9) | 236/266 (88.7) | 260/266 (97.7) |
| All ages | 2505/2812 (89.1) | 1570/1787 (87.9) | 3684/3733 (98.7) |
| Subjects with CIN grade 1 | | | |
| 30–39 yr | 380/15,340 (2.5) | 315/14,750 (2.1) | 1088/15,057 (7.2) |
| 40–49 yr | 164/7628 (2.1) | 110/6981 (1.6) | 267/7547 (3.5) |
| 50–59 yr | 59/4224 (1.4) | 51/3818 (1.3) | 74/4161 (1.8) |
| All ages | 603/27,192 (2.2) | 476/25,549 (1.9) | 1429/26,765 (5.3) |
| Subjects with CIN grade 2 or 3 | | | |
| 30–39 yr | 121/15,340 (0.8) | 146/14,750 (1.0) | 119/15,057 (0.8) |
| 40–49 yr | 82/7628 (1.1) | 70/6981 (1.0) | 50/7547 (0.7) |
| 50–59 yr | 42/4224 (1.0) | 46/3818 (1.2) | 26/4161 (0.6) |
| All ages | 245/27,192 (0.9) | 262/25,549 (1.0) | 195/26,765 (0.7) |
| Subjects with cancer diagnosis | | | |
| 30–39 yr | 16/15,340 (0.1) | 26/14,750 (0.2) | 29/15,057 (0.2) |
| 40–49 yr | 30/7628 (0.4) | 34/6981 (0.5) | 27/7547 (0.4) |
| 50–59 yr | 27/4224 (0.6) | 23/3818 (0.6) | 26/4161 (0.6) |
| All ages | 73/27,192 (0.3) | 83/25,549 (0.3) | 82/26,765 (0.3) |

* HPV denotes human papillomavirus, and VIA visual inspection of the cervix with acetic acid.

higher in the VIA group than in either the HPV-testing group or the cytologic-testing group ($P<0.001$ for both comparisons). The detection rates of CIN grade 2 or 3 lesions and invasive cancer were similar in the three intervention groups ($P=0.06$ for CIN grade 2 and $P=0.16$ for CIN grade 3 for all comparisons). CIN grade 2 or 3 lesions were detected in 245 women in the HPV-testing group, 262 women in the cytologic-testing group, and 195 women in the VIA group. The positive predictive value for detecting CIN grade

2 or 3 lesions was 11.3% in the HPV-testing group, 19.3% in the cytologic-testing group, and 7.4% in the VIA group. The numbers of subjects with CIN grade 1 lesions who underwent treatment were 197 of 603 (32.7%) in the HPV-testing group, 214 of 476 (45.0%) in the cytologic-testing group, and 555 of 1429 (38.8%) in the VIA group; the corresponding numbers for subjects with CIN grade 2 or 3 lesions were 216 of 245 (88.2%), 234 of 262 (89.3%), and 176 of 195 (90.3%).

Of the 31,488 eligible women in the control

Table 3. Distribution of Clinical Stages and Rates of Death, According to Study Group (2000–2007).*

| Stage at Diagnosis and Death from Cervical Cancer | HPV Testing | Cytologic Testing | VIA | Control |
|---|--------------------------|-------------------|---------------|---------------|
| | <i>no./total no. (%)</i> | | | |
| Subjects with positive screening results | | | | NA |
| Stage at diagnosis | | | | |
| IA | 45/87 (51.7) | 58/88 (65.9) | 34/91 (37.4) | |
| IB | 25/87 (28.7) | 20/88 (22.7) | 19/91 (20.9) | |
| ≥II | 14/87 (16.1) | 10/88 (11.4) | 35/91 (38.5) | |
| Unknown | 3/87 (3.4) | 0 | 3/91 (3.3) | |
| Death from cervical cancer | 12/87 (13.8) | 18/88 (20.5) | 27/91 (29.7) | |
| Subjects with negative screening results | | | | NA |
| Stage at diagnosis | | | | |
| IA | 0 | 2/22 (9.1) | 1/25 (4.0) | |
| IB | 2/8 (25.0) | 4/22 (18.2) | 4/25 (16.0) | |
| ≥II | 5/8 (62.5) | 15/22 (68.2) | 19/25 (76.0) | |
| Unknown | 1/8 (12.5) | 1/22 (4.5) | 1/25 (4.0) | |
| Death from cervical cancer | 0 | 9/22 (40.9) | 8/25 (32.0) | |
| Subjects not screened | | | | NA |
| Stage at diagnosis | | | | |
| IA | 2/32 (6.2) | 0 | 0 | |
| IB | 6/32 (18.8) | 5/42 (11.9) | 8/41 (19.5) | |
| ≥II | 20/32 (62.5) | 33/42 (78.6) | 32/41 (78.0) | |
| Unknown | 4/32 (12.5) | 4/42 (9.5) | 1/41 (2.4) | |
| Death from cervical cancer | 22/32 (68.8) | 27/42 (64.3) | 21/41 (51.2) | |
| All subjects assigned to undergo screening | | | | NA |
| Stage at diagnosis | | | | |
| IA | 47/127 (37.0) | 60/152 (39.5) | 35/157 (22.3) | |
| IB | 33/127 (26.0) | 29/152 (19.1) | 31/157 (19.7) | |
| ≥II | 39/127 (30.7) | 58/152 (38.2) | 86/157 (54.8) | |
| Unknown | 8/127 (6.3) | 5/152 (3.3) | 5/157 (3.2) | |
| Death from cervical cancer | 34/127 (26.8) | 54/152 (35.5) | 56/157 (35.7) | |
| Subjects with symptoms at diagnosis | NA | NA | NA | |
| Stage at diagnosis | | | | |
| IA | | | | 7/118 (5.9) |
| IB | | | | 26/118 (22.0) |
| ≥II | | | | 82/118 (69.5) |
| Unknown | | | | 3/118 (2.5) |
| Death from cervical cancer | | | | 64/118 (54.2) |

* HPV denotes human papillomavirus, NA not applicable, and VIA visual inspection of the cervix with acetic acid.

group, 1946 (6.2%) requested screening and were tested with cytologic testing; of these subjects, 15 CIN grade 2 or 3 lesions were detected, and 41 subjects had invasive cancer (18% in stage I and 58% in stage III).

CERVICAL CANCER INCIDENCE AND MORTALITY

The numbers of cervical cancers that were detected on screening (i.e., those that were diagnosed within 3 months after positive results) were 73 in the HPV-testing group, 83 in the cytologic-testing

Table 4. Incidence of Cervical Cancer and Rates of Death.*

| Variable | HPV Testing | Cytologic Testing | VIA | Control |
|---|------------------|-------------------|------------------|---------|
| Incidence of all cervical cancer — no. | 127 | 152 | 157 | 118 |
| Person-yr of follow-up — no. | 268,185 | 250,523 | 267,326 | 247,895 |
| Rate per 100,000 person-yr | 47.4 | 60.7 | 58.7 | 47.6 |
| Hazard ratio (95% CI) | 1.05 (0.77–1.43) | 1.34 (0.99–1.82) | 1.30 (0.95–1.78) | 1.00 |
| Incidence of stage II or higher cervical cancer — no. | 39 | 58 | 86 | 82 |
| Person-yr of follow-up — no. | 268,185 | 250,523 | 267,326 | 247,895 |
| Rate per 100,000 person-yr | 14.5 | 23.2 | 32.2 | 33.1 |
| Hazard ratio (95% CI) | 0.47 (0.32–0.69) | 0.75 (0.51–1.10) | 1.04 (0.72–1.49) | 1.00 |
| Death — no. | 34 | 54 | 56 | 64 |
| Person-yr of follow-up — no. | 268,674 | 251,144 | 267,917 | 248,175 |
| Rate per 100,000 person-yr | 12.7 | 21.5 | 20.9 | 25.8 |
| Hazard ratio (95% CI) | 0.52 (0.33–0.83) | 0.89 (0.62–1.27) | 0.86 (0.60–1.25) | 1.00 |

* Rates and hazard ratios have been adjusted for age. Hazard ratios are for the comparison between each intervention group and the control group. CI denotes confidence interval, HPV human papillomavirus, and VIA visual inspection of the cervix with acetic acid.

group, and 82 in the VIA group. The numbers of subsequent incident cancers (i.e., those that were diagnosed 3 months after positive results on screening or among women who had received negative results) were 22 in the HPV-testing group, 27 in the cytologic-testing group, and 34 in the VIA group. The proportions of cancers that were detected in stage I were about 60% in the HPV-testing and cytologic-testing groups, 42% in the VIA group, and 28% in the control group (Table 3).

There were 34 deaths from cervical cancer in the HPV-testing group, 54 in the cytologic-testing group, 56 in the VIA group, and 64 in the control group (Table 3). The incidence rate of cervical cancer of stage II or higher and death rates from cervical cancer were significantly higher in the cytologic-testing group and the VIA group than in the HPV-testing group. In the HPV-testing group, the hazard ratio for the detection of advanced cancer was 0.47 (95% confidence interval [CI], 0.32 to 0.69) and the hazard ratio for death was 0.52 (95% CI, 0.33 to 0.83), as compared with the control group (Table 4). During the 8-year follow-up period, invasive cervical cancer developed in 8 of 24,380 HPV-negative women, in 22 of 23,762 women who had negative results on cytologic testing, and in 25 of 23,032 women who had negative results on VIA, with age-standardized rates of 3.7, 15.5, and 16.0 cases of invasive

cervical cancer per 100,000 person-years, respectively.

Figure 2 shows the cumulative incidence of cervical cancer, rates of stage II or higher disease, and cumulative mortality. The cumulative incidence of advanced cervical cancer and the cumulative rate of death were lower in the HPV-testing group than in the control group, and the gap widened throughout the follow-up period. There was no significant reduction in the rate of death from any cause in the intervention groups, as compared with the control group (data not shown).

Among the women who were screened and treated, mild adverse events were reported in 123 women, and a severe adverse event of uncontrolled bleeding after LEEP that resulted in hysterectomy was reported in 1 woman.

DISCUSSION

In our cluster-randomized, controlled trial, a screening program for the detection of cervical cancer was accomplished in a low-resource setting. Since there is little screening for cervical cancer in India, women who did not undergo screening (control group) were considered to receive the standard of care. The inclusion of this control group was approved by the IARC and Indian institutional ethics committees.

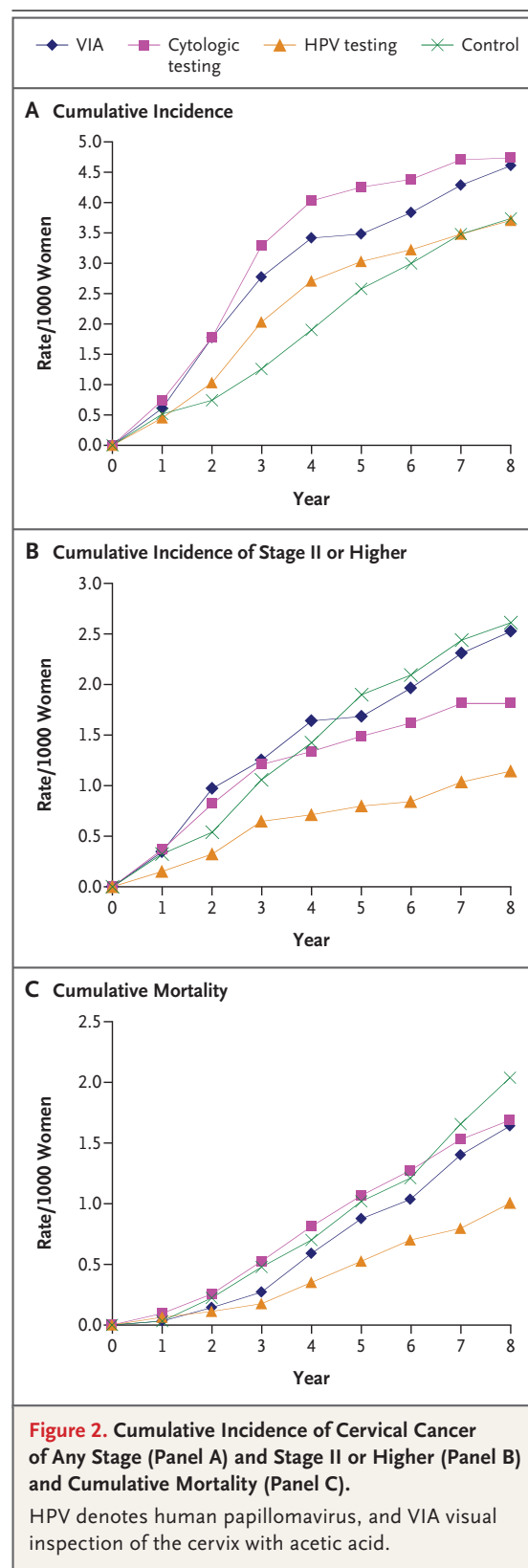
The difference in the number of eligible women that were reported previously⁵ and the number reported here was due to the erroneous inclusion of ineligible women in the original report and updates of data. The randomization of groups of women in clusters minimized the possibility that those assigned to one study group would receive the intervention provided to another study group.

Our study found that a single round of HPV testing was associated with a significant decline in the rate of advanced cervical cancers and associated deaths, as compared with the unscreened control group. By contrast, there was no significant reduction in the rate of death in either the cytologic-testing group or the VIA group, as compared with the control group. The age-standardized rate of invasive cancer among women who had negative results on cytologic testing or VIA was more than four times the rate among HPV-negative women, indicating a high negative predictive value associated with a negative HPV test. The reduction in the incidence of advanced cancers and deaths associated with HPV testing probably reflects the higher sensitivity of HPV testing to detect lesions with a high potential for malignant transformation than that of cytologic testing or VIA.

No reduction in the rate of cervical cancer was observed in the VIA group in our study, whereas the procedure was associated with a 25% reduction in cervical-cancer incidence and a 35% reduction in mortality in a randomized trial in South India.¹³ The reason for these differences in outcomes between the two studies is unknown but may be due to the higher rate of treatment in the South Indian trial.

We found that HPV testing was the most objective and reproducible of all cervical screening tests and was less demanding in terms of training and quality assurance. In low-resource settings with no capacity for colposcopy and histopathological analysis (e.g., many countries in sub-Saharan Africa), HPV-positive women without clinical evidence of invasive cancer could receive immediate treatment, such as cryotherapy.¹⁴ However, since most HPV infections in young women regress rapidly without causing clinically significant disease, such an approach raises a legitimate concern. Hence, HPV testing should not be used for primary screening of women under 30 years of age.

A drawback to HPV testing is that it is more expensive (\$20 to \$30 per test, in U.S. dollars) and



time-consuming than other screening tests, and it requires a sophisticated laboratory infrastructure. A simple, affordable, and accurate HPV test

(careHPV test, Qiagen) that provides results within 3 hours was evaluated in China, and its accuracy was similar to that of the Hybrid Capture II test that we used in our study. The careHPV test had higher sensitivity than VIA (90.2% vs. 41.4%) but a lower specificity (84.2% vs. 94.5%).¹⁵ The careHPV test is expected to be commercially available in developing countries in the near future. Our results, combined with those of the Chinese study of the new HPV test, indicate that HPV testing is appropriate as a primary screening approach in low-resource settings for women who are at least 30 years of age.¹⁵

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Health and economic impact of HPV 16/18 vaccination and cervical cancer screening in Eastern Africa

Nicole G. Campos^{1,2}, Jane J. Kim¹, Philip E. Castle³, Jesse D. Ortendahl¹, Meredith O'Shea¹, Mireia Diaz^{1,4} and Sue J. Goldie^{1,5}

¹Center for Health Decision Science, Department of Health Policy and Management, Harvard School of Public Health, Boston, MA

²Center of Excellence for Health Disparities Research: El Centro, School of Nursing and Health Studies, University of Miami, Coral Gables, FL

³American Society for Clinical Pathology Institute, Washington, DC

⁴Unit of Infections and Cancer (UNIC), Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO), IDIBELL, Barcelona, Spain

⁵Harvard Global Health Institute, Harvard University, Cambridge, MA

Eastern Africa has the world's highest cervical cancer incidence and mortality rates. We used epidemiologic data from Kenya, Mozambique, Tanzania, Uganda, and Zimbabwe to develop models of HPV-related infection and disease. For each country, we assessed HPV vaccination of girls before age 12 followed by screening with HPV DNA testing once, twice, or three times per lifetime (at ages 35, 40, 45). For women over age 30, we assessed only screening (with HPV DNA testing up to three times per lifetime or VIA at age 35). Assuming no waning immunity, mean reduction in lifetime cancer risk associated with vaccination ranged from 36 to 45%, and vaccination followed by screening once per lifetime at age 35 with HPV DNA testing ranged from 43 to 51%. For both younger and older women, the most effective screening strategy was HPV DNA testing three times per lifetime. Provided the cost per vaccinated girl was less than \$10 (\$2 per dose), vaccination had an incremental cost-effectiveness ratio [\$(international dollars)/year of life saved (YLS)] less than the country-specific per capita GDP, a commonly cited heuristic for "very cost-effective" interventions. If the cost per vaccinated girl was between \$10 (\$2 per dose) and \$25 (\$5 per dose), vaccination followed by HPV DNA testing would save the most lives and would be considered good value for public health dollars. These results should be used to catalyze design and evaluation of HPV vaccine delivery and screening programs, and contribute to a dialogue on financing HPV vaccination in poor countries.

Cervical cancer, caused by infection with carcinogenic "high-risk" types of human papillomavirus (HPV), is a leading cause of cancer deaths among women in Africa.¹ In Eastern Africa, which has the world's highest reported rates of cervical cancer incidence and mortality,¹ HPV types 16 and 18 are associated with ~75% of cases.²

In countries with organized cervical cancer screening programs, incidence and mortality have decreased substantially.³

Key words: human papillomavirus, cervical cancer, vaccination, screening, economic evaluation, Eastern Africa

Abbreviations: CIN: cervical intraepithelial neoplasia; HIV: human immunodeficiency virus; HPV: human papillomavirus; \$: international dollars; VIA: visual inspection with acetic acid; YLS: year of life saved.

Additional Supporting Information may be found in the online version of this article.

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Correspondence to: Nicole G. Campos, P.O. Box 248153, Coral Gables, FL 33124-3850, E-mail: gastin@post.harvard.edu

To date, screening in East African countries has been limited to demonstration projects or low levels of opportunistic screening in young women.^{4*} Barriers to secondary prevention in poor countries include lack of health delivery infrastructure, trained personnel, and equipment required for screening, diagnosis, and treatment; limited health budgets; and competing healthcare priorities.⁵ Despite the difficulties of implementing and scaling up secondary prevention programs, economic evaluations and studies assessing test performance suggest that one- and two-visit screen-and-treat approaches could be feasible, beneficial, and cost-effective in resource-poor settings.⁶ A large randomized trial in India demonstrated that a single round of screening using HPV DNA testing in women over age 30 reduced advanced cervical cancer incidence and mortality in a developing country setting by 50%.⁷ A recently developed, lower-cost and less time-consuming HPV DNA test that is being piloted in several demonstration projects facilitates same-day testing and treatment, and may reduce costs and loss to follow-up in low-income countries.^{8,9}

The potential for primary prevention has been realized with the availability of two HPV vaccines, both with high

*In April 2011, the Rwandan government announced the launch of a comprehensive cervical cancer prevention program including screening with HPV DNA testing and HPV vaccination.

efficacy against infection with HPV 16/18, and recently pre-qualified by the World Health Organization.^{10–12} Challenges to vaccination of preadolescent girls include the high cost of the vaccines, the need for three doses at an age not routinely targeted for vaccination, and limited data on optimal delivery strategies for preadolescents.¹³

Acknowledging that country-specific data are limited, this analysis aims to synthesize available data to (1) inform policy makers and high-level decision makers of the potential value of alternative cervical cancer prevention strategies; and (2) explore the comparative performance of, and potential synergies between primary and secondary prevention strategies. We estimate the reduction in lifetime risk of cervical cancer associated with HPV vaccination of preadolescent girls and screening of older women in five East African countries: Kenya, Mozambique, Tanzania, Uganda, and Zimbabwe. For selected countries, we assess the cost-effectiveness of prevention strategies, estimate the financial costs of preadolescent HPV vaccination, and explore alternative assumptions about vaccine efficacy, coverage, and duration of protection, as well as the impact of screening coverage, test performance, and loss to follow-up.

Material and Methods

Analytic overview

Using epidemiologic data for five East African countries, we adapted a previously described computer-based simulation model of cervical carcinogenesis^{14,15} to Kenya, Mozambique, Tanzania, Uganda, and Zimbabwe. Adopting a decision analytic approach, we estimated the health impact (e.g., reduction in lifetime cervical cancer risk) of: (1) HPV 16/18 vaccination of preadolescent girls; (2) screening of adult women over age 30 using HPV DNA testing or visual inspection with acetic acid (VIA); and (3) preadolescent vaccination followed by screening at older ages. Following standard guidelines for cost-effectiveness analysis^{16–18} for four countries,[†] we estimated incremental cost-effectiveness ratios, defined as the additional cost of a particular strategy (per woman, in 2005 international dollars, I\$) divided by its additional benefit (per woman life expectancy gain), compared with the next most costly strategy after eliminating strategies that are dominated (defined as more costly and less effective, or having higher incremental cost-effectiveness ratios than more effective options). We performed sensitivity analysis to evaluate the impact of uncertain parameters and assumptions.

Model

The model is described in previous publications.^{14,15,19} Briefly, the natural history of cervical carcinogenesis in an

individual woman is represented as a sequence of monthly transitions between mutually exclusive health states, including HPV infection status, grade of cervical intraepithelial neoplasia (CIN), and stage of cancer. Individual girls representative of a single birth cohort enter the model at age 9, prior to sexual debut, and are followed over their lifetimes. Transitions between health states depend upon HPV type, age, and history of prior type-specific infection (naturally acquired immunity). HPV types are categorized hierarchically, with a woman classified according to her dominant type of infection: (1) HPV 16; (2) HPV 18; (3) other high-risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and possibly high-risk types (26, 53, 66, 73, 82, and 82v); and (4) low-risk types.²⁰ Strategies in the model can include age-specific vaccination, screening, or both, and the model differentiates the number of doses (in the case of vaccination) and test choice, frequency, and diagnostic protocol (in the case of screening). Women with cervical cancer can be detected *via* symptoms or screening, and are subject to stage-specific mortality rates in addition to all-cause age-specific mortality rates.

Epidemiologic data and calibration

Our model parameterization process has been described previously and is detailed in the Supporting Information Appendix.^{14,15,19}

Briefly, we leveraged epidemiologic data (country-specific when possible) on age-specific prevalence of high-risk HPV in women with normal cytology, age-specific cervical cancer incidence, and prevalence of HPV 16/18 in cervical cancer. Data sources and summary statistics are listed in Table 1 and described further in the Supporting Information Appendix.

Based on data from the published literature, a plausible range was established for each natural history parameter, and uniform distributions were sampled jointly. Each round of sampling generated a different set of candidate values to input into the model. For each of the greater than 2 million input parameter sets, outcomes generated by model simulations were compared with the country-specific epidemiologic data. A composite goodness-of-fit score for each parameter set was computed based on the sum of the log-likelihoods of each model outcome. We selected the top 50 sets for each country to use as model inputs for our analysis. Graphs depicting model fit to each country's epidemiologic data may be found in the Supporting Information Appendix. To incorporate the effects of parameter uncertainty, we report results as a mean and range of outcomes. Incremental cost-effectiveness ratios are reported as the ratio of the mean costs divided by the mean effects of one strategy versus another across the top 50 parameter sets.²¹

Strategies

To compare the potential benefits of any cervical cancer intervention with other public health interventions evaluated under optimistic delivery assumptions,²² our baseline “comparative” analysis assumed 70% of the target population

[†]Because the Zimbabwe dollar was discontinued in 2009 due to severe hyperinflation, we do not report cost-effectiveness results for Zimbabwe. The reliability of international dollars to convey the purchasing power of local currency units within a country's borders is limited when the value of local currency changes dramatically within a short period.

Table 1. Selected model variables from the baseline comparative analysis, and summary calibration data and sources¹

| Model variable | Baseline value | | | |
|---|-----------------------------------|------------------------------------|------------------------------------|-------------------------------------|
| Characteristics of screening tests ² | | | | |
| HPV DNA testing | | | | |
| Sensitivity | | | | 90% |
| Specificity | | | | 77% |
| Visual inspection with acetic acid | | | | |
| Sensitivity | | | | 41% |
| Specificity | | | | 82% |
| Characteristics of screening program ³ | | | | |
| Population coverage | | | | 70% |
| Loss to follow-up (per visit) | | | | 15% |
| Characteristics of vaccination program | | | | |
| Population coverage of pre-adolescent girls with at least one dose | | | | 70% |
| Attrition rate (per dose) ⁴ | | | | 15% |
| Efficacy against HPV 16/18 (1 dose, 2 doses, 3 doses) | | | | 30%, 90%, 100% |
| Duration of vaccine protection | | | | Lifelong |
| Costs (2005 US) | | | | |
| Visual inspection with acetic acid ⁵ | Kenya | Mozambique | Tanzania | Uganda |
| | | | | Zimbabwe |
| | | | | |
| Woman's time and transport (1-visit strategy; 2-visit strategy) ⁶ | 1.78 | 1.55 | 1.70 | 1.63 |
| | 7.67; 15.20 | 6.59; 13.04 | 7.50; 14.92 | 7.19; 14.23 |
| HPV DNA test ⁵ | 10.68 | 9.99 | 10.43 | 10.22 |
| | 9.36; 15.20 | 8.27; 13.04 | 8.44; 14.92 | 8.99; 14.23 |
| Woman's time and transport (1-visit strategy; 2-visit strategy) ⁶ | | | | |
| | 23.78 | 20.44 | 22.56 | 21.53 |
| Cryosurgery ⁵ | | | | |
| Summary of data used for model calibration | | | | |
| Prevalence of high-risk HPV among women with normal cytology, % (95% CI) ⁷ | 25 (21–30) (N = 369) | 23 (17–29) (N = 195) | 23 (19–28) (N = 381) | ⁸ [23 (17–29)] (N = 195) |
| Data source: | De Vuyst, 2003 | Castellsague, 2001 | Mayaud, 2001 | [Castellsague, 2001] |
| Prevalence of HPV 16 in cervical cancer, % (95% CI) | 43 (37–51) ⁹ (N = 204) | 50 (42–58) ¹⁰ (N = 302) | 41 (32–51) ¹⁰ (N = 102) | 50 (43–58) ¹⁰ (N = 157) |
| Prevalence of HPV 18 in cervical cancer, % (95% CI) ¹¹ | 17 (12–23) ⁹ (N = 204) | 25 (20–30) ¹⁰ (N = 302) | 31 (23–41) ¹⁰ (N = 102) | 26 (20–34) ¹⁰ (N = 43) |
| | | | | 61 (51–71) (N = 98) |
| | | | | 14 (8–23) (N = 98) |

Table 1. Selected model variables from the baseline comparative analysis, and summary calibration data and sources¹ (Continued)

| Model variable | Baseline value | | | |
|--|---|------------------------------------|--|------------------------------------|
| Data source: | De Vuyst, 2008 | Castellsague, 2008; Nauciler, 2004 | Bosch, 1995; ter Meulen, 1992 | Bosch, 1995; Odida, 2008 |
| Cancer incidence (crude rate per 100,000 women) ⁷ | 10.18 | 32.1 | 40.6 | 16.22 |
| Data source (registry): | Eldoret, 1998–2000 (<i>Cancer in Africa</i>) | Globocan, 2008 | Globocan, 2002; Dar es Salaam, 1990–1991; Kilimanjaro, 1998–2000 | Kyadondo County, 1998–2002 (CI5C) |
| | | | | Harare (African), 1998–2002 (CI5C) |

¹HPV, human papillomavirus; \$, international dollars; CI, confidence interval; CI5C, Cancer incidence in five continents; NA, not available. ²Sensitivity is defined as the probability of a positive test given the presence of cervical intraepithelial neoplasia grade 2 or higher. Specificity is defined as the probability of a negative test given the presence of no lesion. Because the prevalence of high-risk HPV (and thus the probability of testing positive on HPV DNA testing) varies slightly by country, HPV DNA test sensitivity and specificity vary slightly by country; we present HPV DNA test performance from Kenya here. ³For screening strategies that relied on a single visit, we assumed that women who were screen positive and eligible for cryosurgery were treated in the same day; for those not eligible for cryosurgery (e.g., those with lesions covering more than 75% of the cervix or extending to the vaginal wall), we assumed referral to a secondary facility for further diagnostic testing and treatment. For two-visit screening strategies, we assumed women were screened during the first visit and returned for a second visit to obtain results (in the case of HPV DNA testing) and, if they screened positive and were eligible, receive cryosurgery. Loss to follow-up between visits, as well as additional time and transport costs for the second visit, distinguishes the two-visit strategies from the one-visit strategies. ⁴Of the 70% who received at least one dose, 15% received one dose, 12.75% received two doses, and 72.25% received all three doses. ⁵Cost estimate includes direct medical costs (disposable supplies, staff time, equipment, laboratory transport, staff, and facilities). For cryotherapy, cost estimate includes direct medical costs for follow-up care and complications. ⁶Cost estimate includes woman's time and transportation (roundtrip time and transportation to a primary health clinic, waiting time at the clinic, and screening procedure time). ⁷The model was calibrated to age-specific high-risk HPV prevalence and age-specific cancer incidence, but we report overall prevalence and crude incidence rates per 100,000 women here to summarize the data. Age-specific data and descriptions of calibration data sources are presented in the Supporting Information Appendix. ⁸Country-specific data unavailable. Data from Mozambique (Castellsague, 2001) were used as a proxy. ⁹Data were drawn from a frequency-matched study of HIV-positive and HIV-negative women. Here we weighted the prevalence statistics for HPV 16 and 18 in each group by the prevalence of HIV in the study population prior to matching. Further details are available in the Supporting Information Appendix. ¹⁰Prevalence and confidence intervals were derived using fixed or random effects model to pool data from more than one available in-country study (see Supporting Information Appendix for details). ¹¹Because our model categorized women hierarchically according to the dominant type of infection, we counted study subjects with both HPV 16 and 18 infections as having cancer attributable to HPV 16 only. Thus the prevalence of HPV 18 in cervical cancer presented here represents women without accompanying HPV 16 infections.

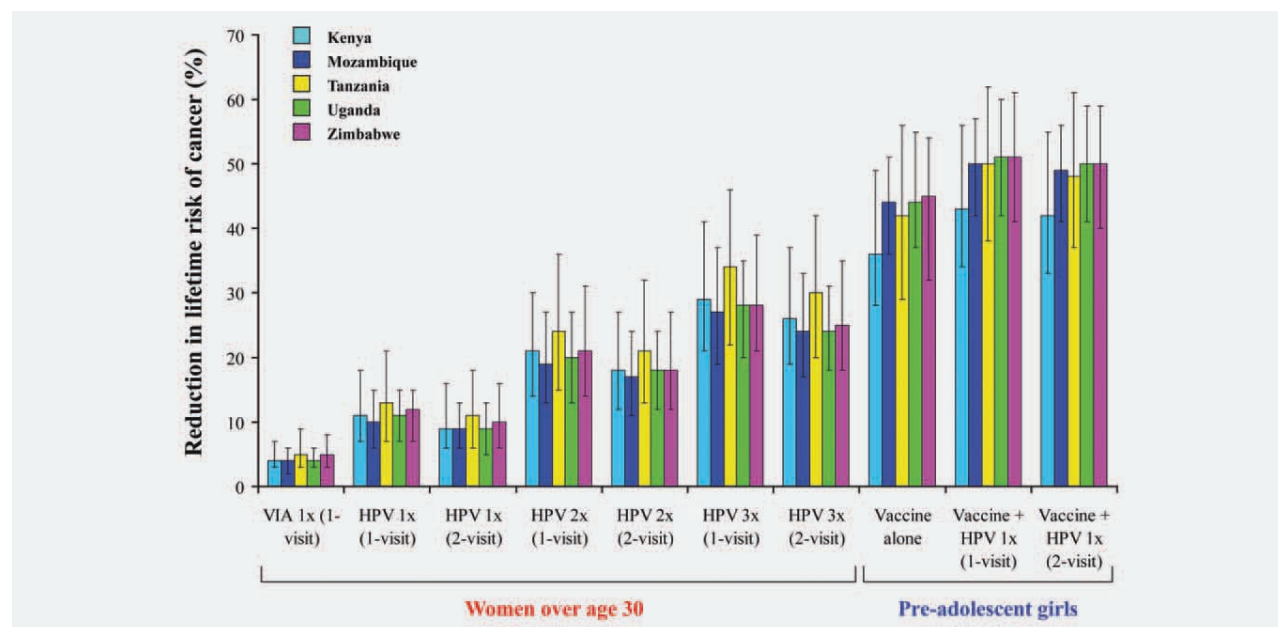


Figure 1. Reduction in lifetime risk of cervical cancer attributable to selected vaccination and screening strategies. Colored vertical bars represent the mean reduction in lifetime risk of cancer (on the y-axis) for selected strategies (on the x-axis) in each country (light blue: Kenya; dark blue: Mozambique; yellow: Tanzania; green: Uganda; pink: Zimbabwe). Error bars represent the range of uncertainty in cancer reduction based on the 50 top-fitting parameter sets in each country. VIA, visual inspection with acetic acid; HPV, HPV DNA testing; 1x, screening once per lifetime at age 35; 2x, screening twice per lifetime at ages 35 and 40; 3x, screening three times per lifetime at ages 35, 40, and 45.

received the first step of the intervention (first dose of vaccination or screening), with an attrition rate of 15% for each subsequent intervention step (Table 1).

We assumed vaccination occurred before age 12 (prior to sexual debut for most women). For girls receiving all three doses, we assumed the vaccine provided full lifelong protection against HPV 16/18, while two doses conferred 90%, and one dose conferred 30% lifelong protection (Table 1). Because of uncertainty in achievable coverage and real-world clinical effectiveness of the vaccine, we varied coverage and per-dose attrition rates, overall effectiveness (a function of per-dose efficacy and the per-dose attrition rate), and duration of immunity in additional analyses.

Screening strategies primarily used HPV DNA testing, and we varied screening frequency (once, twice, or three times in a lifetime, at ages 35, 40, and 45, respectively) and the number of required clinical visits for screening and treatment. Only one VIA strategy was considered—a single test at age 35—due to concerns about low sensitivity for incident lesions and declining test performance in older women.^{23–25} For screening strategies that relied on a single visit, we assumed that women who were screen positive and eligible for cryosurgery were treated the same day; for those not eligible for cryosurgery, we assumed referral to a secondary facility for further diagnostic testing and treatment. For two-visit screening strategies, we assumed women were screened during the first visit and returned for a second visit to obtain results (in the case of HPV DNA testing) and, if they screened positive and were eligible, received cryosurgery

(Table 1; Supporting Information Appendix). We assessed the impact of varying screening coverage rates and loss to follow-up after each clinic visit. To allow decision makers to contextualize results based on likelihood of uptake and coverage in a specific population, we also varied coverage for vaccination and screening differentially.

Cost data

Selected costs are presented in Table 1, and complete documentation of cost assumptions is provided in the Supporting Information Appendix. Costs are presented in 2005 international dollars (\$), a currency that provides a means of translating and comparing costs among countries, taking into account differences in purchasing power. When country-specific data were unavailable, we adapted cost data from other countries using previously published methods.^{6,14,19,26} Because the price of the HPV vaccine[†] and programmatic costs of delivering an adolescent vaccine in Eastern Africa are not known, we express vaccine costs as an approximate composite value referred to as the “cost per vaccinated girl,” which we varied from \$5 to \$200; this was categorized into vaccine costs, wastage, freight and supplies, administration, immunization support, and programmatic costs. For example, a cost of \$10 per vaccinated girl approximated three doses of vaccine at \$2.00 each, with the remainder allocated to the other component costs. For screening strategies, direct medical costs

[†]In June 2011, Merck announced that it will offer its HPV vaccine to the GAVI Alliance at US\$5 per dose. (http://www.gavialliance.org/media_centre/press_releases/vaccine_prices.php).

(e.g., staff, supplies, equipment, specimen transport) and women's time and transportation costs were included.

Results

Population-level health benefits

First we present results for our baseline analysis, in order to compare the potential value of HPV vaccination and cervical cancer screening, analyzed under optimistic assumptions (e.g., 70% coverage, lifelong immunity), to other public health interventions.²² Results are then presented for more conservative scenarios.

For preadolescent girls eligible for vaccination, the mean reduction in the lifetime risk of cancer with vaccination ranged from 36% (Kenya, range: 28–49%) to 45% (Zimbabwe, range: 32–54%) (Fig. 1). The most effective strategy was a combined approach of adolescent vaccination followed by screening once per lifetime at age 35 using one-visit HPV DNA testing; this strategy was associated with a mean cancer reduction ranging from 43% in Kenya (range: 34–56%) to 51% in Uganda (range: 42–60%) and Zimbabwe (range: 41–61%). Results for additional strategies may be found in the Supporting Information Appendix.

For women older than age 30, the most effective strategy was one-visit HPV DNA testing and the least effective once per lifetime screening strategy was VIA. Screening three times per lifetime with one-visit HPV DNA testing reduced cancer risk from 27% (Mozambique, range: 19–37%) to 34% (Tanzania, range: 22–46%).

Cost-effectiveness analysis

For preadolescent girls eligible for vaccination, results of analyses in which we vary the cost per vaccinated girl from I\$5 (I\$0.55 per dose) to I\$200 (I\$54.25 per dose) are shown in Table 2. Two independent analyses are shown—one assuming screening with one-visit HPV DNA testing, and one assuming screening with two-visit HPV DNA testing.

Provided the cost per vaccinated girl was equal to, or below I\$10 (I\$2 per dose), vaccination was less than I\$500 per year of life saved (YLS), and was more effective and had lower (more attractive) cost-effectiveness ratios than screening alone. For vaccine costs at or below I\$25 per vaccinated girl (I\$5 per dose), preadolescent vaccination followed by screening with one-visit HPV DNA testing at age 35 was associated with a cost per YLS ranging from I\$740 (Tanzania) to I\$2090 (Kenya). As the cost per vaccinated girl approached I\$50 (I\$12.25 per dose), vaccination alone was more costly and less cost-effective than screening alone, with the exception of two-visit HPV DNA testing in Uganda (I\$1240 per YLS). At I\$200 per vaccinated girl (I\$54.25 per dose), adolescent vaccination followed by screening with one-visit HPV DNA testing at age 35 was associated with a cost per YLS ranging from I\$5610 (Tanzania, Uganda) to I\$15,000 (Kenya).

For women older than age 30, analyses shown in Table 3 assumed either one-visit VIA or HPV testing or two-visit

VIA or HPV testing. We assumed countries would choose screening modality, frequency, and number of visits based on a number of factors—including existing pilot programs, available infrastructure and human resources, operational feasibility, and patient and cultural preferences—and thus, we present scenarios based on alternative choices a country might make for reasons other than cost-effectiveness. Additional scenarios are presented in the Supporting Information Appendix.

Provided that HPV DNA testing is available, HPV DNA testing strategies were more effective with lower cost-effectiveness ratios than VIA, ranging from I\$450 (one-visit HPV testing once per lifetime, Tanzania) to I\$1860 (two-visit HPV testing once per lifetime, Kenya) per YLS. When we assumed VIA was the only available option, screening once per lifetime yielded cost-effectiveness ratios ranging from I\$700 (Tanzania) to I\$2010 (Kenya) per YLS, reflecting both the low cost and low effectiveness of VIA.

In each of the four countries considered, screening three times per lifetime with one-visit HPV DNA testing was less than I\$1400 per YLS, and with two-visit HPV DNA testing less than I\$1800 per YLS. Additional results, including other screening ages and frequencies, are presented in the Supporting Information Appendix.

Additional analyses

Results from sensitivity analyses are shown below and in the Supporting Information Appendix using examples from Kenya and Uganda. The performance of vaccination depended upon vaccine efficacy, level of population coverage with at least one dose, attrition rate per dose, and duration of protection. As shown previously, the comparative performance of screening strategies depends on test performance, population coverage, and loss to follow-up.^{6,14,19}

Varying efficacy, population coverage, and attrition rate per dose of the vaccine in Kenya. Figure 2 shows the reduction in the lifetime risk of cancer in Kenya as per-dose efficacy and coverage were varied. Overall effectiveness of the vaccine is a function of per-dose efficacy—for which we considered a scenario with the same protection as in the baseline analysis (one dose: 30%; two doses: 90%; three doses: 100% lifelong protection), as well as a more conservative scenario (one dose: 0%; two doses: 50%; three doses 100% lifelong protection) and a more optimistic scenario (any doses: 100% lifelong protection)—and the attrition rate following administration of each vaccine dose, which we varied from 0 to 40%. When 75% of girls received at least one dose of vaccine, the mean reduction in the lifetime risk of cancer was 22%, even with the more conservative vaccine protection scenario and an attrition rate of 40% for each subsequent dose. When 75% of girls received a vaccine conferring 100% protection with just one dose, cancer risk was reduced by 45%.

Assuming an initial coverage rate with the first dose of vaccine of 75%, as overall vaccine effectiveness was varied

Table 2. Cost-effectiveness results for preadolescent girls¹

| | Kenya ² I\$/YLS | Mozambique ² I\$/YLS | Tanzania ² I\$/YLS | Uganda ² I\$/YLS |
|---|-------------------------------|------------------------------------|----------------------------------|--------------------------------|
| Adolescent vaccination followed by a single lifetime HPV DNA testing at age 35 (1-visit)³ | | | | |
| <i>Cost per vaccinated girl: I\$5 (I\$0.55 per dose)</i> | | | | |
| Vaccine | 160 | 80 | CS | 20 |
| Screening with HPV, age 35 | – ⁴ | – ⁴ | – ⁴ | – ⁴ |
| Vaccine + screening with HPV, age 35 | 2,090 | 1,260 | 740 | 1,000 |
| <i>Cost per vaccinated girl: I\$10 (I\$2.00 per dose)</i> | | | | |
| Vaccine | 470 | 250 | 90 | 130 |
| Screening with HPV, age 35 | – ⁴ | – ⁴ | – ⁴ | – ⁴ |
| Vaccine + screening with HPV, age 35 | 2,090 | 1,260 | 740 | 1,000 |
| <i>Cost per vaccinated girl: I\$25 (I\$5.00 per dose)</i> | | | | |
| Screening with HPV, age 35 | 1,400 | – ⁴ | – ⁴ | – ⁴ |
| Vaccine | 1,440 | 750 | 440 | 490 |
| Vaccine + screening with HPV, age 35 | 2,090 | 1,260 | 740 | 1,000 |
| <i>Cost per vaccinated girl: I\$50 (I\$12.25 per dose)</i> | | | | |
| Screening with HPV, age 35 | 1,400 | 770 | 450 | 570 |
| Vaccine | – ⁴ | – ⁴ | – ⁴ | – ⁴ |
| Vaccine + screening with HPV, age 35 | 3,580 | 1,870 | 1,260 | 1,300 |
| <i>Cost per vaccinated girl: I\$200 (I\$54.25 per dose)</i> | | | | |
| Screening with HPV, age 35 | 1,400 | 770 | 450 | 570 |
| Vaccine | – ⁴ | – ⁴ | – ⁴ | – ⁴ |
| Vaccine + screening with HPV, age 35 | 15,000 | 7,850 | 5,610 | 5,610 |
| Adolescent vaccination followed by a single lifetime HPV DNA testing at age 35 (2-visit)³ | | | | |
| <i>Cost per vaccinated girl: I\$5 (I\$0.55 per dose)</i> | | | | |
| Vaccine | 160 | 80 | CS | 20 |
| Screening with HPV, age 35 | – ⁴ | – ⁴ | – ⁴ | – ⁴ |
| Vaccine + screening with HPV, age 35 | 2,810 | 1,690 | 1,060 | 1,370 |
| <i>Cost per vaccinated girl: I\$10 (I\$2.00 per dose)</i> | | | | |
| Vaccine | 470 | 250 | 90 | 130 |
| Screening with HPV, age 35 | – ⁴ | – ⁴ | – ⁴ | – ⁴ |
| Vaccine + screening with HPV, age 35 | 2,810 | 1,690 | 1,060 | 1,370 |
| <i>Cost per vaccinated girl: I\$25 (I\$5.00 per dose)</i> | | | | |
| Screening with HPV, age 35 | – ⁴ | – ⁴ | – ⁴ | – ⁴ |
| Vaccine | 1,420 | 750 | 440 | 490 |
| Vaccine + screening with HPV, age 35 | 2,810 | 1,690 | 1,060 | 1,370 |
| <i>Cost per vaccinated girl: I\$50 (I\$12.25 per dose)</i> | | | | |
| Screening with HPV, age 35 | 1,860 | 1,010 | 630 | 770 |
| Vaccine | – ⁴ | – ⁴ | – ⁴ | 1,240 |
| Vaccine + screening with HPV, age 35 | 3,480 | 1,830 | 1,220 | 1,370 |
| <i>Cost per vaccinated girl: I\$200 (I\$54.25 per dose)</i> | | | | |
| Screening with HPV, age 35 | 1,860 | 1,010 | 630 | 770 |
| Vaccine | – ⁴ | – ⁴ | – ⁴ | – ⁴ |
| Vaccine + screening with HPV, age 35 | 14,570 | 7,650 | 5,420 | 5,450 |

¹YLS, years of life saved; HPV, human papillomavirus DNA testing; CS, cost-saving. All currencies are reported in 2005 international dollars (I\$).

²Gross domestic product (GDP) per capita, 2005 I\$ for each country is as follows: Kenya (I\$1470); Mozambique (I\$791); Tanzania (I\$1167); Uganda (I\$1077).²⁷ ³Analyses assume either 1-visit HPV testing or 2-visit HPV testing. The results should be interpreted assuming that a country has already decided to utilize a 1-visit or 2-visit strategy. Analyses that rely on alternative assumptions are provided in the Supporting Information Appendix. ⁴These strategies are either more costly and less effective, or have higher incremental cost-effectiveness ratios than more effective options, and are thus considered dominated.

Table 3. Cost-effectiveness results for screening in women over age 30¹

| | Kenya ² I\$/YLS | Mozambique ² I\$/YLS | Tanzania ² I\$/YLS | Uganda ² I\$/YLS |
|--|-------------------------------|------------------------------------|----------------------------------|--------------------------------|
| Screening with one-visit VIA once per lifetime³ | | | | |
| VIA at age 35 | 2,010 | 1,080 | 700 | 840 |
| Screening with either one-visit VIA or HPV DNA testing once per lifetime³ | | | | |
| VIA at age 35 | — ⁴ | — ⁴ | — ⁴ | — ⁴ |
| HPV at age 35 | 1,400 | 770 | 450 | 570 |
| Screening with either two-visit VIA or HPV DNA testing once per lifetime³ | | | | |
| VIA at age 35 | — ⁴ | — ⁴ | — ⁴ | — ⁴ |
| HPV at age 35 | 1,860 | 1,010 | 630 | 770 |
| Screening with one-visit HPV DNA testing once or three times per lifetime^{3,5} | | | | |
| HPV at age 35 | — ⁴ | — ⁴ | — ⁴ | 570 |
| HPV at ages 35, 40, 45 | 1,370 | 720 | 450 | 720 |
| Screening with two-visit HPV DNA testing once or three times per lifetime^{3,5} | | | | |
| HPV at age 35 | — ⁴ | — ⁴ | — ⁴ | 770 |
| HPV at ages 35, 40, 45 | 1,770 | 920 | 610 | 930 |

¹YLS, years of life saved; VIA, visual inspection with acetic acid; HPV, human papillomavirus DNA testing. ²Gross domestic product (GDP) per capita, 2005 I\$ for each country is as follows: Kenya (I\$1470); Mozambique (I\$791); Tanzania (I\$1167); Uganda (I\$1077).²⁷ ³Analyses assume either 1-visit VIA or HPV testing or 2-visit VIA or HPV testing. The results should be interpreted assuming that a country has already decided to utilize the strategy shown if a single strategy is presented; when two strategies are shown as options, this assumption is not made. ⁴These strategies are either more costly and less effective, or have higher incremental cost-effectiveness ratios than more effective options, and are thus considered dominated. ⁵HPV DNA testing three times per lifetime is compared with HPV DNA testing twice per lifetime, unless the strategy was dominated, in which case HPV DNA testing was compared to testing once per lifetime. Results for screening twice per lifetime are presented in the Supporting Information Appendix.

from 60 to 100%, the corresponding cost-effectiveness ratios associated with vaccination were reduced by ~60% (Supporting Information Appendix).

Varying vaccination and screening coverage in Uganda. Figure 3 shows the reduction in the lifetime risk of cancer as screening and vaccination coverage were varied as part of a strategy that followed preadolescent vaccination with a single-lifetime screen with one-visit HPV DNA testing at age 35.

Each level of vaccination coverage displayed represents a potential scenario in Uganda, depending on which proxy indicators for achievable HPV vaccination coverage prove to be most realistic. For example, a modeled vaccination coverage level of 25% resembles the coverage achieved with the hepatitis B vaccine in its first year of roll-out in Uganda (29%).²⁸ Under this assumption, combined HPV vaccination

and screening reduced cancer risk by 19 to 26%, depending on screening coverage, and cost less than I\$700 per YLS. If girls' likelihood of continuation to school grade 5 is a better indicator of achievable HPV vaccination coverage, coverage could be closer to 50%.²⁷ Under this assumption, the strategy reduced cancer risk by 35 to 40% and cost less than I\$850 per YLS. If HPV vaccination coverage were to exceed current childhood vaccination coverage with three doses each of DTP, Hepatitis B, and Hib vaccines (64–68%), a reasonable proxy for projections might be a modeled coverage level of 75%. Under this assumption, the strategy reduced cancer risk by 50 to 54% and cost less than I\$1100 per YLS.

Varying the performance and cost of HPV DNA testing in women over age 30 in Kenya. As we varied HPV DNA test sensitivity to detect cervical intraepithelial neoplasia grade 2 or higher (CIN2+) from ~90% to 63%, the expected reduction in lifetime risk of cancer associated with a single lifetime screening (one-visit) fell from 11% to 8% and the cost-effectiveness ratio increased from I\$1400 to I\$1840 per YLS.

If the cost of HPV DNA testing was reduced from the baseline assumption of I\$10.68 to I\$5.34, the cost-effectiveness ratio for a single lifetime screening (one-visit) decreased from I\$1400 to I\$1120 per YLS. If instead the HPV DNA testing cost was doubled to I\$21.36, the cost-effectiveness ratio for a single lifetime screening increased to I\$1940 per YLS (Supporting Information Appendix).

We describe the dramatic impact on the population-level benefits and the cost-effectiveness of two-visit HPV DNA testing, as loss to follow-up associated with each clinical visit was varied, in the Supporting Information Appendix.

Discussion

The vaccine-preventable burden of cervical cancer in Eastern Africa is a function of cervical cancer incidence, the proportion of disease attributable to HPV 16/18, long-term vaccine efficacy, and the ability to achieve widespread coverage in girls prior to sexual debut. In our analysis—intended to provide estimates of the potential value of vaccination and screening if implemented under optimistic assumptions—we found that HPV 16/18 vaccination at 70% coverage of girls between ages 9 and 12 is expected to reduce the lifetime risk of cancer by ~40%, even when considering attrition rates of 15% between doses. For girls vaccinated as preadolescents, subsequent screening with HPV DNA testing at least once per lifetime between ages 35 and 40 is expected to cut the lifetime risk of cancer nearly in half. For women over age 30 today, screening three times per lifetime with one-visit HPV DNA testing reduced cancer risk from 27% in Mozambique to 34% in Tanzania.

We may have over- or underestimated vaccine performance. Clinical benefits associated with the vaccine may be greater than predicted if there are herd immunity benefits to nonvaccinated individuals, or if the vaccine provides long-term cross-protection against high-risk HPV types other than

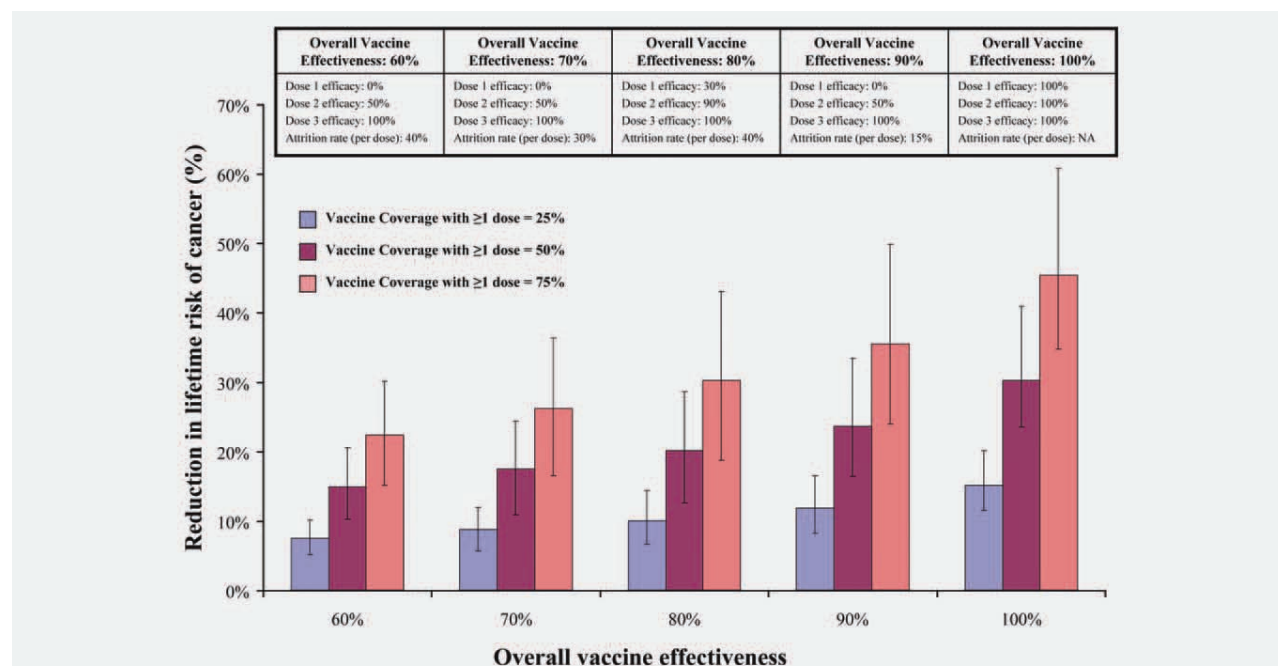


Figure 2. Impact of vaccine effectiveness and coverage level on reduction in lifetime risk of cervical cancer in Kenya. Colored vertical bars represent the mean reduction in cancer risk (on the y-axis) at different levels of overall vaccine effectiveness (60–100%, on the x-axis) for varying levels of vaccination coverage (*i.e.*, proportion of the target population that receives at least one dose of vaccine) (blue, 25%; purple, 50%; pink, 75%). Error bars represent the range of uncertainty in cancer reduction based on the 50 top-fitting parameter sets. Overall vaccine effectiveness is a function of per-dose efficacy and the attrition rate following each dose (*e.g.*, for an attrition rate of 40%: of the girls who received at least one dose, 40% received only the first dose, 24% received two doses, and 36% received three doses). For example, an overall vaccine effectiveness of ~60% would be realized with a vaccine conferring 100% efficacy with administration of 3 doses, 50% for 2 doses, and no benefit for 1 dose, and an attrition rate of 40% between each dose. The table at the top of the graph describes scenarios that yield costs, benefits, and reduction in cancer risk similar to each corresponding level of overall vaccine effectiveness shown.

HPV 16/18. Analysis of clinical trial data suggests that the quadrivalent HPV vaccine may provide some degree of cross-protection against HPV 31 and HPV 59,²⁹ while the bivalent vaccine appears to provide cross-protection against persistent infection at 6 months with HPV 31, 45, and 52.³⁰ While HPV types 31, 45, 52, and 59 are detected in 2.5%, 6.3%, 1.2%, and 0.4%, respectively, of cancers in Eastern Africa,² nearly 17% of cancers in the region are associated with multiple HPV types, and thus any improved efficacy due to cross-protection may not be fully additive.

The effectiveness of the vaccine may be lower than our baseline analysis suggests if vaccine-induced immunity is low due to malnutrition, severe anemia, or comorbidities such as HIV. Effectiveness of vaccination programs may also be less than predicted if the attrition rate between doses is high and administration of less than three doses confers little protection against HPV16/18. At this time, published data on the efficacy of one- and two-dose regimens are limited. A bivalent vaccine trial in Costa Rica found comparable efficacy for one, two, or three doses against persistent HPV infection over a 3-year period.³¹ Vaccination may be less effective if the vaccine wanes while women are still at high risk of new HPV infections. Because clinical studies of vaccine efficacy

only extend to 5–7 years of follow-up,^{10,11} the actual duration of protection is uncertain.

There is no universal criterion that defines a threshold cost-effectiveness ratio, below which an intervention would be considered cost-effective. One heuristic has evolved from the Commission on Macroeconomics and Health, suggesting interventions with a cost-effectiveness ratio less than the Gross Domestic Product (GDP) per capita would be “very cost-effective” and less than three times the GDP per capita, “cost-effective.”³² Provided the cost per vaccinated girl was less than \$10 (\$2 per dose), vaccination had an incremental cost-effectiveness ratio less than the country-specific per capita GDP. If the cost per vaccinated girl was between \$10 (\$2 per dose) and \$25 (\$5 per dose), vaccination followed by screening at age 35 with one-visit HPV DNA testing would also be considered good value for public health dollars. These results are similar to those reported previously in a different analysis.³³

The single most influential factor on the cost-effectiveness of vaccination is the cost of vaccinating adolescents with a three-dose vaccine. There is uncertainty both in the price of the vaccine for countries of different income levels and in the programmatic costs associated with an adolescent vaccine. By

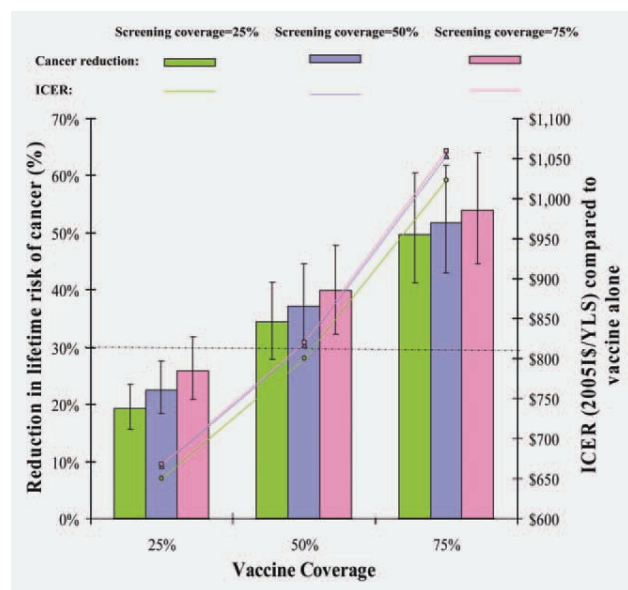


Figure 3. Impact of vaccination coverage and screening coverage on reduction in the lifetime risk of cervical cancer and the incremental cost-effectiveness ratio of vaccination followed by one screening per lifetime with one-visit HPV DNA testing (comparator: vaccine alone; cost per vaccinated girl: I\$10), Uganda. Colored vertical bars represent mean reduction in lifetime risk of cancer (on the primary y-axis) at different levels of vaccination coverage (25–75%, on the x-axis) and screening coverage (green, 25%; blue, 50%; pink, 75%). Error bars represent the range of uncertainty in cancer reduction based on the 50 top-fitting parameter sets. Lines with colors corresponding to level of screening coverage represent the incremental cost-effectiveness ratio (on the secondary y-axis) at different levels of vaccination coverage. The dashed black line represents a threshold of 30% cancer reduction. ICER, incremental cost-effectiveness ratio; YLS, years of life saved.

expressing a composite cost per vaccinated girl, we capture the potential cost-effectiveness of vaccination under a wide range of vaccine price and program cost scenarios. Should future studies indicate that one- or two-dose regimens are noninferior, the cost per vaccinated girl may be closer to the lower range we consider. The HPV vaccine will be competing for the same resources as other new vaccines, such as the *Haemophilus influenzae* type B (Hib) and hepatitis B vaccines, which have been introduced in 80% and 96% (respectively) of African countries, and vaccines against rotavirus and pneumococcal diseases, which are eligible for GAVI Alliance support (roll-out of pneumococcal vaccination has begun in Kenya).³⁴ The estimated cost per disability-adjusted life year (DALY) averted for the Hib vaccine in Kenya was \$38, and for the hepatitis B vaccine in The Gambia was \$28.^{35,36} Estimated cost-effectiveness of rotavirus vaccination in Kenya and Malawi ranges from \$75 to \$227 per DALY averted when the vaccine course (including two doses and programmatic costs) cost \$9.26 to \$11.70.^{37,38} Given these

comparative cost-effectiveness estimates, it will be difficult for the HPV vaccine to compete for dollars earmarked for existing programs or dollars considered for new programs if the cost per vaccinated girl exceeds I\$10 (I\$2 per dose). That being said, provided the price and cost of programmatic delivery can be lowered, the benefits are comparable to those of other new vaccines.³³

While cost-effectiveness analysis provides information on value for money, this is not equivalent to affordability, or the financial impact of a cervical cancer prevention program on a payer's budget. The estimated financial costs of vaccine roll-out scenarios in four countries at an estimated cost of I\$10 per vaccinated girl³³ are displayed in the Supporting Information Appendix. Both the cost-effectiveness profile and financial costs of rolling out a vaccine program will need to be favorable to implement a sustainable vaccination program.

The effectiveness of a screening program depends upon population coverage, test performance, and the ability to screen and treat in as few visits as possible. The impact of multiple screenings may be less than our analysis indicates if attendance at one screening correlates with attendance at subsequent sessions. Based on the most recently available data, VIA was less effective and cost-effective than the strategy appeared in older analyses.⁶ While data on the performance of both VIA and lower-cost HPV DNA testing, used in a single-visit screening strategy, are limited in Eastern Africa, a recent trial in South Africa found that conventional HPV DNA testing reduced CIN2+ over three years by 70–80%; reductions in the VIA arm were less evident.³⁹ We used recent data from a Chinese study comparing VIA with conventional [Hybrid Capture 2 (HC2); Qiagen, Gaithersburg, MD, USA] and lower-cost HPV DNA (careHPV; Qiagen) testing to inform test performance⁸; HC2 and careHPV were found to have comparable sensitivity. In China, careHPV had a sensitivity of 81% on self-collected vaginal specimens (95% confidence interval: 72–91%), and we examined the impact of an HPV test with approximately 63% sensitivity to capture the effectiveness of this strategy if patient preferences and operational constraints necessitate self-sampling.

The cost of the careHPV test has not been established, and may be different than the values assumed in our baseline comparative analysis. Like vaccination, HPV testing costs strongly influence the cost-effectiveness of screening with the rapid test. If self-sampling is accepted and facilitates greater screening coverage at lower costs, the cost-effectiveness of HPV testing will become even more attractive. Some have advocated VIA as an alternative for very low-resource settings until HPV DNA testing becomes more economical,^{13,40} arguing that training health workers to visualize the transformation zone of the cervix will be an essential component of screen-and-treat strategies involving HPV DNA testing in the future.

We have previously discussed inherent limitations in any model-based decision analytic approach,^{14,19} but we reiterate key points here. In addition to model structure and parameter uncertainty, there are uncertainties with respect to the natural history of HPV (particularly in older women), the

nature of type-specific immunity following natural infection, and the relationship between HIV and the course of HPV infection. We summarize limitations related to the availability and quality of country-specific data used for model calibration in the Supporting Information Appendix.

In the countries considered here, where adult HIV prevalence ranges from 5.4% (Uganda) to 15.3% (Zimbabwe), we are mindful of how current data limitations regarding the interaction between HPV and HIV may affect results. While several studies from developed countries report increased incidence of invasive cervical cancer among those infected with HIV,^{41,42} cancer registries in African countries have not generally reflected increased incidence rates corresponding to time trends in the HIV epidemic.⁴³ Our assumption of steady time trends for cervical cancer incidence over the lifetime of a cohort of preadolescent girls may over- or underestimate health benefits, depending on changes in HIV prevalence in women, the future availability of antiretroviral therapy, and the extent to which antiretroviral therapy leads to increased (due to greater life expectancy) or decreased (due to immune reconstitution) cervical cancer incidence. (We note, however, that for women with HIV whose lives are prolonged by antiretroviral therapy, cervical cancer is a preventable cause of mortality.) Adding to the uncertain dynamic between the two viruses, early data suggest a potential beneficial impact of HPV vaccination on acquisition of HIV.^{44–46} If these findings are valid and substantial, the benefits of the HPV vaccine in Eastern Africa will be greater.

We did not consider the impact of vaccination on other HPV-related diseases that are attributable to HPV 16/18—including anal cancer, vulvar and vaginal cancer, and oropharyngeal and oral cancer—and thus may have underestimated potential benefits of the vaccine. We assumed there was no correlation between the probability a woman received the vaccine as a preadolescent girl and the probability she subsequently received screening as an adult. The validity of this assumption in a resource-poor setting is unclear. Additionally, country-specific cost data are lacking and many of our estimates were derived using indirect estimation techniques as summarized in the Supporting Information Appendix.

Given the above limitations, our estimates of the benefits and cost-effectiveness of cervical cancer prevention strategies should be interpreted in the context of our analytic purpose—namely, to provide initial insight to policy makers in Africa, financing alliances (e.g., GAVI), and other potential payers by leveraging the best available data. Country implementation will require a second series of decisions and corresponding new analyses that consider the likelihood of uptake and acceptability with country-contextualized strategies. Forthcoming evidence from vaccine demonstration projects in Uganda and Tanzania^{47,48} and implementation in Rwanda⁴⁹ will provide valuable information regarding the effectiveness and costs of delivery strategies, as well as the role of specific communication and educational efforts.

Following implementation, decisions regarding whether and how to monitor vaccine impact through investment in monitoring systems and cancer registries in target areas will also be necessary. Vaccination and screening are applied to different age groups, rely on different components of existing infrastructure, and require the mobilization of financial resources that are likely to come from different payers. Programs are synergistic in that vaccination prevents infection with HPV 16/18, while screening allows for treatment of precancerous lesions caused by any high-risk HPV type before progression to invasive cancer. Screening adult women once has been shown to decrease cancer incidence and mortality in a resource-poor setting in less than 10 years.^{7,24} We will not see cancer reduction from a vaccination program for many years to come. Screening programs will reduce cancer risk among those who do not receive the vaccine, those who are infected with nonvaccine targeted HPV types, and those who may experience reduced vaccine efficacy (as a result of immunosuppression or missed doses), and will provide insurance at the population level, given the uncertainties surrounding the long-term vaccine performance. Furthermore, screening with HPV DNA tests may eventually enable surveillance of HPV infection (with HPV typing in a subset who are HPV positive), and thus assessment of vaccine impact, within a population.⁵⁰ Finally, screening remains the only cervical cancer prevention for the millions of women in Eastern Africa over age 20, who are beyond the targeted age for vaccination.

In 2008, an estimated 53,000 women on the African continent died of cervical cancer. By 2030, this number will be nearly double.¹ Most of these women will not have access to curative treatment and will die from this preventable disease at an age when they are vital to social and economic stability. In societies already ravaged by HIV, the loss of these women will be felt acutely. Preadolescent vaccines to prevent infection with HPV 16/18 and a lower-cost HPV DNA test offer opportunity to prevent these deaths. Provided vaccine and screening test costs are low, these interventions are of great promise. Yet even those strategies we have identified as cost-effective will likely be unaffordable without assistance from the global community. We hope this analysis will catalyze the current dialogue about how to (1) expediently secure these necessary resources, (2) develop delivery programs and evaluate alternative implementation strategies for primary and secondary prevention, and (3) begin the discourse at the country level over preferences for prevention modality, prioritization relative to other health problems, timing of introduction, and mechanisms for evaluation.

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