Received: 29 October 2023 | Revised: 21 March 2024 | Accepted: 18 April 2024

DOI: 10.1002/ijc.35036

RESEARCH ARTICLE

Cancer Therapy and Prevention

IJC INTERNATIONAL JOURNAL of CANCER | UICC

Cost-effectiveness analysis of alternative screening strategies for the detection of cervical cancer among women in rural areas of Western Kenya

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Funding information
Bundesministerium für Bildung und Forschung, Grant/Award Number: 01DG13007; Ladenburg Foundation New York; Fogarty International Centre, National Institutes of Health (NIH), United States, Grant/Award Number: 1K43TW011164; Medical Data Scientist Fellowship, Medical Faculty Heidelberg, University of Heidelberg, Germany

Abstract

While the incidence of cervical cancer has dropped in high-income countries due to organized cytology-based screening programs, it remains the leading cause of cancer death among women in Eastern Africa. Therefore, the World Health Organization (WHO) now urges providers to transition from widely prevalent but low-performance visual inspection with acetic acid (VIA) screening to primary human papillomavirus (HPV) DNA testing. Due to high HPV prevalence, effective triage tests are needed to identify those lesions likely to progress and so avoid over-treatment. To identify the optimal cost-effective strategy, we compared the VIA screen-and-treat approach to primary HPV DNA testing with p16/Ki67 dual-stain cytology or VIA as triage. We used a Markov model to calculate the budget impact of each strategy with incremental quality-adjusted life years and incremental cost-effectiveness ratios (ICER) as the main outcome. Deterministic cost-effectiveness analyses show that the screen-and-treat approach is highly cost-effective (ICER 2469 Int$), while screen, triage, and treat with dual staining is the most effective with favorable ICER than triage with VIA (ICER 9943 Int$ compared with 13,177 Int$). One-way sensitivity analyses show that the results are most sensitive to discounting, VIA performance, and test prices. In the probabilistic sensitivity analyses, the triage option using dual stain is the optimal choice above a willingness to pay threshold of 7115 Int$ being cost-effective as per WHO standards. The result of our analysis favors the use of dual staining over VIA as triage in HPV-positive women and portends future opportunities and necessary research to improve the coverage and acceptability of cervical cancer screening programs.

KEYWORDS
cervical cancer screening, cost-effectiveness analyses, dual staining, HPV DNA test, visual inspection with acetic acid

What's new?

In its updated screening recommendations for cervical cancer, the World Health Organization has urged existing programs to use visual inspection with acetic acid (VIA) as a primary screening tool to transition to human papillomavirus (HPV) DNA testing. This study shows that primary HPV testing plus triage with either dual-stain cytology or VIA performs better than VIA screening alone in detecting precancerous lesions in low-resource settings, with dual-stain cytology being the most cost-effective triage option. Furthermore, the results indicate the feasibility of equipping laboratories in low-resource settings with sophisticated technologies and operating them cost-effectively.

1 | INTRODUCTION

Cervical cancer (CC) is one of the leading causes of cancer death among women in Eastern Africa.[1–3] It occurs because of persistent high-risk human papillomavirus (Hr HPV) infections and can be prevented through prophylactic HPV vaccination[4] or the early detection and treatment of the slowly developing precancerous lesions.[5–7] In 2020, the World Health Organization (WHO) launched the global Cervical Cancer Elimination Initiative[8] with clear targets to be achieved by 2030: the vaccination of 90% of girls below the age of 15 years, the screening of 70% of women aged 35 and 45 years with a high-performance test and the treatment of 90% of women identified with CC. Since the required population coverage for vaccination is unlikely to be achieved in the near future due to limited health budgets, screening remains the more feasible option for early detection for most women.

With current screening policies, we are far from achieving these targets. In high-income countries, organized cytological screening programs have drastically reduced the burden of CC[9,10] and are increasingly replaced by more effective primary HPV DNA screen,[11] triage, and treat approaches. In many low- and middle-income countries (LMICs), however, screening guidelines still recommend single-visit visual inspection with acetic acid (VIA) due to cost considerations despite continuing low screening coverage, emerging evidence concerning lower than expected performance[12–15] and scale-up issues.[16,17]

In the 2021 updated screening recommendations, the WHO now urges existing programs using VIA as a primary screening tool to transition rapidly to HPV DNA testing.[18] HPV testing offers high sensitivity and provides strong reassurance against the development of precancerous lesions for up to 10 years.[1] But since HPV infections regress spontaneously,[19] HPV testing is hampered by a low sensitivity when detecting clinically relevant lesions and might lead to substantial overtreatment if used without additional highly specific triage testing.[2] The choice of a triage test, however, is left to the provider, whose choice is determined by assumptions on feasibility, program quality, and available resources.

In multiple studies from LMICs, the cost-effectiveness of HPV-based screening,[20–24] the acceptance of HPV self-sampling and its potential for easier screening access and increased screening coverage[25–28] have been documented. A number of triage tests for LMICs are under investigation, including VIA, genotyping, digitally enhanced VIA, automated visual inspection, and biomarkers.[29–32] The p16/Ki67 dual-stain cytology test[33] detects a transforming HPV infection with a high sensitivity and specificity.[34] Dual-stain cytology has been recommended as a high-performance triage marker in high-income countries[35] and its feasibility to be used as an "enhanced triage test"[28] also for LMICS depends highly on its technical and economic requirements.

There are very few cost-effectiveness studies, especially in low-resource settings,[36–38] and to our knowledge none that compare VIA with dual staining as a triage test after screening with a HPV DNA test. The necessary evidence on the economic implications of testing is largely absent, leaving policy makers in a decision void.

Kenya's nationwide VIA-based CC screening program started in 2015, but annual screening coverage, regardless of HIV status, is low and unevenly distributed.[39] Transitioning to primary HPV-based screening has been recommended since 2018 as a means of increasing screening effectiveness and access. The first implementation trials combining primary screening with VIA as a triage option started in 2020, in spite of the well-known challenges with quality assurance.

This paper addresses this knowledge gap by assessing the cost-effectiveness of three different CC screening strategies: VIA alone, VIA as a triage test after HPV DNA screening, and dual stain as triage after HPV DNA screening compared with the no testing alternative with data derived from a peri-urban population of Kenyan women.

2 | METHODS

2.1 | Setting

Kenya is a lower middle income country in Eastern Africa with a population of 47.5 million,[40] of which 71% live in rural areas.[41] In 2020 there are estimated to be 16.2 million women at risk for CC with an incidence of 19.4/100,000, which is slightly under the regional average of 24.3/100,000.

Primary data were collected in two representative peri-urban health centers (Huruma and Uasin Gishu) in Eldoret, Uasin Gishu County, Kenya. A total of 800 women aged 18–64 were recruited at the respective family planning clinics between September 2016 and November 2017 as part of a diagnostic study aiming to investigate the overall positivity rates for HPV (Hybrid Capture 2™ by Quiagen)

and dual staining (CINtec Plus™ by Roche MTM Laboratories) and compare the results with the performance of VIA.[42] The results showed HPV, VIA, and dual-stain cytology positivity were 33%, 7%, and 2%, respectively. The HPV positivity rate of VIA-positive cases was 32%. For this article, further economic data was gathered at both study sites.

2.2 | Study design and intervention (screening strategies)

Since screening coverage was reported to be very low in the study region,[39] we decided to compare the following screening strategies with a base case where screening is non-existent. We used the screening intervals as they were recommended by the WHO. The compared screening strategies are: (1) Screen and treat approach using VIA every 3 years; (2) screen, triage, and treat strategy using HPV DNA test as a primary screening test, followed by VIA as a triage test every 5 years; (3) screen, triage, and treat strategy using HPV DNA test as a primary screening test, followed by dual staining as a triage test every 5 years.

Screening started at age 30 as per WHO recommendations. If women were considered positive in VIA or both HPV DNA and VIA/dual staining, cryotherapy was performed. Women who tested positive for HPV DNA but negative either in VIA or dual staining were rescreened after 2 years. We assumed an 80% screening coverage for all strategies with loss to follow-up of 15% between diagnosis and treatment. Both assumptions were varied in the sensitivity analysis.

To compare the alternatives, the outcome was measured as incremental cost-effectiveness ratio (ICER) in the international dollar of the year 2021 (Int$) per discounted quality-adjusted life years (QALY). Following WHO recommendations for cost-effectiveness analyses,[43] we defined interventions with an ICER lower than the GDP per capita (5211 Int$) as "very cost-effective" and those with an ICER lower than threefold of the GDP per capita (15,633 Int$) as "cost-effective."

2.3 | Markov model

To address the study question, we constructed a discrete time Markov model using commercially available Software (TreeAge Pro Healthcare 2023) to predict and compare future health-effects and costs of a screen-and-treat approach using VIA and two sequential strategies using either VIA or dual staining as a triage after screening with HPV DNA test to a baseline of no screening.

The Markov model consists of 12 mutual exclusive main health states including Well, Hr HPV infected, CIN 1–3, International Federation of Gynaecology and Obstetrics (FIGO) cancer stages I–IV, death by CC, death from other cause and remission after CC (Figure 1). For the sake of accuracy, several other health states were added, such as the four substates remission after FIGO I–IV, to link different utility values depending on which states of invasive cancer was cured, as well as nine rescreen stages for women who tested negative in triage after screening positive for HPV DNA and had to be rescreened out of the common screening interval.

We attached transition probabilities and utility values extracted from the literature to those states,[44,45] which can be found in the Supporting Information Appendix. Death rates represent the country-specific values by age for Kenya. The age-specific probability of progressing from WELL to Hr HPV was calculated from HPV prevalence observed in the study region and was published elsewhere.[42] The transition probabilities deciding whether a woman remains in a healthy state, progresses to a higher state, or regresses to a lower one were extracted from the literature and applied once per cycle. In the model, we followed a hypothetical cohort of women starting at age

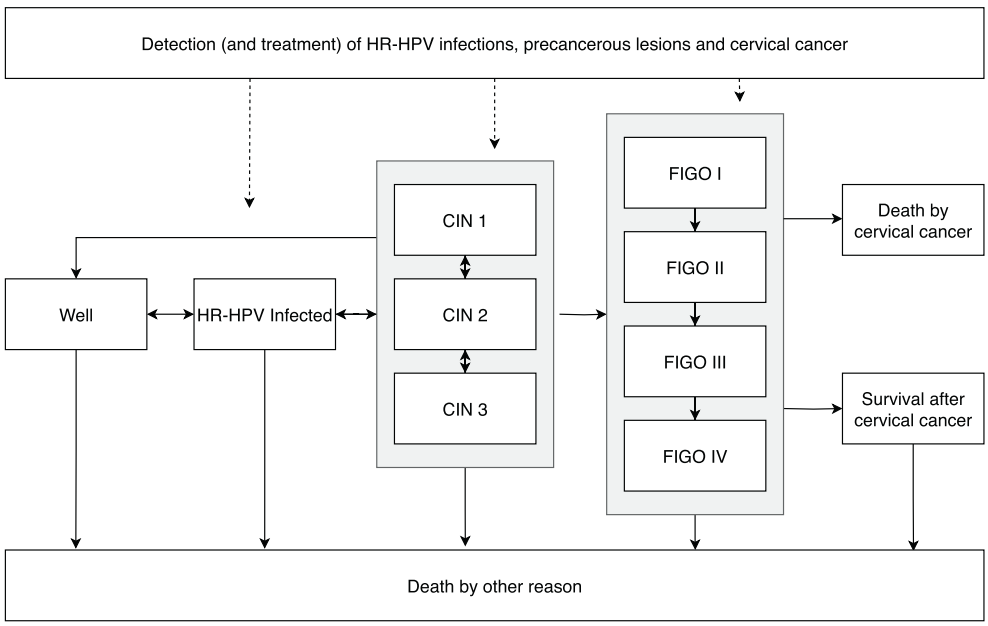


FIGURE 1 Schematic design of the Markov model showing health states, transition ways and intervention points. CIN, cervical intraepithelial neoplasia; FIGO, International Federation of Gynaecology and Obstetrics; Hr HPV, high-risk human papilloma virus.

15 in the health state well through 65 cycles, with each cycle representing a year.

The model was then calibrated to epidemiological data from Kenya, comparing the deaths by CC from the model with those reported in the literature. Afterward, we checked if changes in parameters changed the model according to expectations and so further confirmed its validity.[46]

2.4 | Estimation of costs

Costing was performed from a societal perspective as recommended by the WHO guidelines. Cost data were gathered separately for the two study sites in Huruma and Uasin Gishu nearby Eldoret, Kenya, with a micro-costing approach using budget sheets and administrative data as well as estimates from researchers involved in the trial where cost data was not available.

All costs were collected in 2015 in Euro or Kenyan Shillings, then annualized to 2021 using consumer price indices and later converted to Int$.

Costs include direct medical costs such as equipment, salaries, overheads, supervision, and training, as well as indirect costs such as the women's time and out-of-pocket expenses. Both the latter were obtained by research assistants at both study sites using a questionnaire. Since it was assumed that most women worked in the informal sector, minimum wages were used to calculate their loss-of-productivity due to the time spent for screening. Costs for cryotherapy include the costs of possible complications, which were derived from the literature. The treatment of different FIGO states includes the cost of follow-up as well as the treatment itself (radical hysterectomy or radiochemotherapy). Detailed information on cost data is provided in the Supporting Information Appendix.

2.5 | Estimation of health effects

Since there were no Health State values available for a Kenyan population, the data were extracted from the literature, as it is common practice for similar research questions. The most recent data for LMIC was found in Chauhan et al., where the quality of life values was derived from an Indian population of 223 women between 15 and 70 years of age using a standard EQ-5D-5L tool.[22] Since the authors did not look at the quality of life in women who survived CC, those data had to be taken from Praditsitthikorn et al., who used the Thai version of standard EQ-5D and a visual analog scale in 1035 Thai women between 2007 and 2008.[47] Quality of life in women with Hr HPV infection or asymptomatic CIN was assumed to be 1.

2.6 | Analytical approach

We calculated the ICERs for the three strategies and compared them to the status quo (no screening). In the deterministic analysis, we discounted both costs and health effects at 3% and varied those values between 0% and 6% in the sensitivity analysis.

For the sensitivity analyses we conducted a one-way sensitivity analyses for each parameter and reported the 10 most influential ones in a tornado diagram. In addition, we assessed the joint uncertainty of all relevant model parameters through probabilistic sensitivity analysis (PSA) using Monte Carlo simulation with 5000 iterations. Distribution of model parameters are specified in Table 1.

3 | RESULTS

We first report the cost estimations of the different screening approaches, then proceed to the result of the deterministic cost-effectiveness analyses and lastly present the sensitivity analyses.

3.1 | Costs of different screening strategies

We calculated the cost of VIA to be 20.31 Int$ (16.87–23.75 Int$), the cost of Hr HPV testing 34.10 Int$ (24.13–41.56 Int$) and the costs of dual staining 56.01 Int$ (35.37–59.45 Int$), respectively. Cryotherapy was calculated at 75.49 Int$ (71.93–84.41 Int$). Radical hysterectomy as treatment for FIGO 1 and FIGO 2a including 16 follow-up visits over 5 years[48] was calculated at 2429.24 Int$ (1888.34–2970.14 Int$), treatment of FIGO 3 and 4 including a radical hysterectomy as operative staging, radiochemotherapy and also a 5-year follow-up was calculated to be 6266.53 Int$ (4958.17–7574.89 Int$).

3.2 | Deterministic cost-effectiveness analyses

Compared with the baseline, the screen-and-treat approach using VIA showed an incremental cost of 118.08 Int$ and gained 0.048 QALY, while the screen, triage, and treat approach using VIA after HPV primary test added an incremental cost of 17.08 Int$ with an incremental effectiveness of 0.001 QALY. The screen, triage, and treat approach using dual staining (after the primary HPV screen test) added an incremental cost of 41.54 Int$ and gained 0.004 QALY.

As expected, the screen-and-treat approach using VIA was the least effective but most cost-effective strategy with an ICER of 2468.96 Int$ per QALY, making it very cost-effective by WHO standards. More effectiveness is gained by using HPV/VIA with an ICER of 13,176.96 Int$ per QALY, but this option is dominated by the last one being less expensive but more effective. The greatest effectiveness is gained by primary HPV and dual-stain triage test with an ICER of 9943.40 Int$ per QALY, which was also cost-effective by WHO standards, being lower than the threefold of the GDP per capita (see Figure 2).

As shown by other studies[49] our base case once again confirmes the effectiveness of CC screening programs with a reduction in CC mortality of 83.56% for the VIA screen-and-treat, 84.93% for HPV/VIA, and 86.67% for HPV/dual staining as well as a similar reduction in overall CC cases (see Table 2).

TABLE 1 Model input parameters.

Parameter	Value	Distribution	Reference
Cost			
VIA	20.31 (95% CI 15.43–25.29) Int$	Gamma	Own
Sampling of specimen	21.61 (95% CI 16.32–26.91) Int$	Gamma	Own
HPV test	11.23 (95% CI 08.48–13.99) Int$	Gamma	Own
Dual staining test	25.79 (95% CI 19.47–32.11) Int$	Gamma	Own
Cryotherapy	78.17 (95% CI 59.02–97.32) Int$	Gamma	Own
Treatment FIGO 1	2429 (95% CI 1712–2824) Int$	Gamma	Own
Treatment FIGO 2	4348 (95% CI 3161–5212) Int$	Gamma	Own
Treatment FIGO 3 and 4	6267 (95% CI 4609–7601) Int$	Gamma	Own
Utility			
Utility FIGO 1	0.698 (95% CI 0.614–0.782)	Beta	Chauhan et al. (2020)
Utility FIGO 2	0.632 (95% CI 0.586–0.678)	Beta	Chauhan et al. (2020)
Utility FIGO 3	0.637 (95% CI 0.551–0.723)	Beta	Chauhan et al. (2020)
Utility FIGO 4	0.591 (95% CI 0.409–0.773)	Beta	Chauhan et al. (2020)
Utility FIGO 1, Remission	0.79 (95% CI 0.77–0.81)	Beta	Praditsitthikorn et al. (2011)
Utility FIGO 2, Remission	0.79 (95% CI 0.77–0.81)	Beta	Praditsitthikorn et al. (2011)
Utility FIGO 3, Remission	0.81 (95% CI 0.79–0.83)	Beta	Praditsitthikorn et al. (2011)
Utility FIGO 4, Remission	0.85 (95% CI 0.75–0.95)	Beta	Praditsitthikorn et al. (2011)
Performance			
HPV sensitivity	0.94 (95% CI 0.88–0.97)	Beta	Mustafa et al. (2016)
HPV specificity	0.90 (95% CI 0.86–0.93)	Beta	Mustafa et al. (2016)
VIA triage sensitivity	0.65 (95% CI 0.55–0.75)	Beta	WHO (2021)
VIA triage specificity	0.73 (95% CI 0.65–0.81)	Beta	WHO (2021)
VIA screen sensitivity	0.66 (95% CI 0.61–0.71)		WHO (2021)
VIA screen specificity	0.87 (95% CI 0.84–0.9)		WHO (2021)
Dual staining triage sensitivity	0.91 (95% CI 85.3–93.5)	Beta	Ikenberg et al. (2013)
Dual staining triage specificity	0.953 (95% CI 95.0–95.6)	Beta	Ikenberg et al. (2013)
Screening coverage	0.8 (95% CI 0.604–0.996)	Beta	Assumption
Loss to follow-up	0.15 (95% CI 0.1133–0.1868)	Beta	Assumption
Treatment success cryotherapy CIN2	0.92 (95% CI 0.90–0.94)	Beta	Sauvaget et al. (2013)
Treatment success cryotherapy CIN3	0.85 (95% CI 0.80–0.89)	Beta	Sauvaget et al. (2013)

Abbreviations: CI, confident interval; CIN, cervical intraepithelial neoplasia; FIGO, International Federation of Gynaecology and Obstetrics; HPV, human papilloma virus; VIA, visual inspection with acetic acid.

3.3 | Sensitivity analyses

We report the one-way sensitivity analyses for the most influential parameters of all the screening strategies in Figure 3. We show that the results are most sensitive to discounting, VIA performance and test prices. Especially with a reduction of test prices, the triage strategy using dual stain becomes very cost-effective compared with VIA alone. Similar results have been published by Mezei et al.,[50] who in a 2017 meta-analyses showed, that whether provider-collected HPV testing or VIA was the more efficient alternative mainly depended on the test price and VIA test performance (as loss to follow-up). The cost-effectiveness probabilities for all strategies at different willingness to pay (WTP) levels are shown in Figure 4. Using dual staining for triage after screening with a HPV test is more likely to be the optimal choice above a WTP threshold of 7115 Int$ per QALY and has a 80% chance of being the optimal choice above a WTP threshold of 11,955 Int$ per QALY.

4 | DISCUSSION

Our study makes a unique contribution to the literature by comparing exclusive VIA as a screen and treat approach with a screen, triage, and treat approach using primary HPV testing and either VIA or dual staining as triage in a LMIC population. The base case scenario shows that exclusive screen and treat with VIA remains a very cost-effective

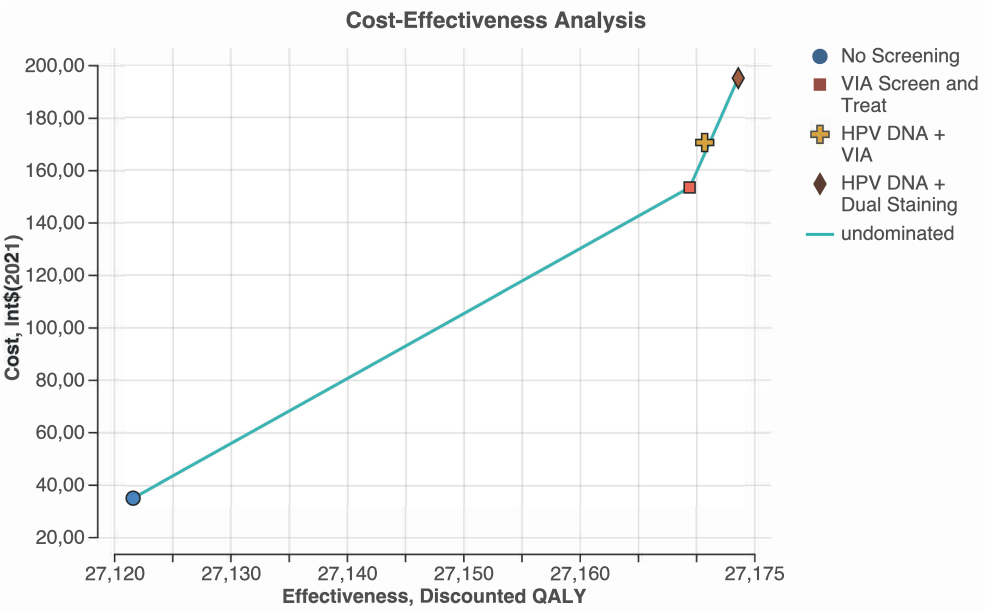


FIGURE 2 Results of the base case scenario. HPV, human papilloma virus; Int$ (2021), international dollar of the year 2021; QALY, quality-adjusted life years; VIA, visual inspection with acetic acid.

TABLE 2 Cost-effectiveness rankings report.

	Mean		Incremental			Reduction of	
Strategy	**Cost (Int$)**	**Effect (QALY)**	**Cost (Int$)**	**Effect (QALY)**	**ICER (Int$/QALY)**	**CC deaths**	**CC cases**
No screening	34.45	27.122					
VIA screen and treat	153.08	27.169	118.08	0.048	2468.96	83.56%	80.95%
Screen with HPV, triage with VIA	170.16	27.171	17.08	0.001	13,176.96	84.93%	82.99%
Screen with HPV, triage with dual stain	194.61	27.1744	41.54	0.004	9943.40	87.67%	84.35%

Abbreviations: CC, cervical cancer; HPV, human papilloma virus; ICER, incremental cost-effectiveness ratio; Int$, International Dollar 2021; QALY, quality-adjusted life years; VIA, visual inspection with acetic acid.

option as per the WHO standards and remains under the country-level cost-effectiveness threshold of 54%, which takes into account the local health system budgetary constraints.[51] While this has been shown in other models as well, there has been increasing evidence of problems with the implementation and scale up[17] of VIA alone leading to doubts about whether VIA is the right method to achieve the WHO CC screening coverage goal of 70%.

We further show that triage with dual staining in LMIC is considered a cost-effective option by WHO standards (and an optimal choice as per the PSA results). In the study we used Hybrid Capture 2™ by Quiagen which was purchased in 2015 for €12 (16.51 Int$ 2021) on the European Market. Since prices have further dropped since then, we have used the average price for WHO-approved HPV tests in the base case (12.48 Int$ 2021)[52] and set a range for the PSAs using our price as the upper and the cheapest from the source above as the lower limit. Similarly, the dual staining kit used in the base case scenario was acquired in 2015 on the German market for €25 (34.39 Int$ 2021). While until today, there are no prices available for LMIC, the prices of similar kits in Germany have dropped by nearly 60%. In Figure 5 we show, that combining a similar price reduction in LMIC with using a less expensive but also WHO-prequalified HPV test[52] and a reduction in sampling costs offers the possibility to make screen-triage-and-treat options not only cost-effective by using the 1x GDP per capita cost-effectiveness threshold but also using the 54% of GDP threshold as suggested by Woods et al.[51]

If one excludes the VIA screen-and-treat due to the reasons mentioned above, PSAs show that dual staining is more likely to be the optimal choice of triage above a WTP threshold of 3850 Int$ per QALY. This fits with other emerging evidence emphasizing the role of dual staining as a triage test in Hr HPV positive women.[38]

While one of the main arguments for screen and treat approaches using VIA is the low price, we show that triage strategies are more effective. For future discussions, it should be considered that HPV testing and dual staining offer the opportunity for self-sampling, which, as literature reviews suggest, might reduce personnel costs as well as cultural, socioeconomic, and gender barriers to screening[18] while also possibly increasing the feasibility of large-scale screening programs. In addition, the preparation of cervical specimens could be further simplified by using liquid based cytology, which has also been shown to improve the diagnostic accuracy of dual staining, especially in resource-scarce settings.[53] This method has seen an even larger drop in the price of over 80% to 2.53 Int$ since 2015, but it was not utilized in this study. Also, VIA is dependent on biennial visits while screening intervals for strategies using HPV tests are significantly

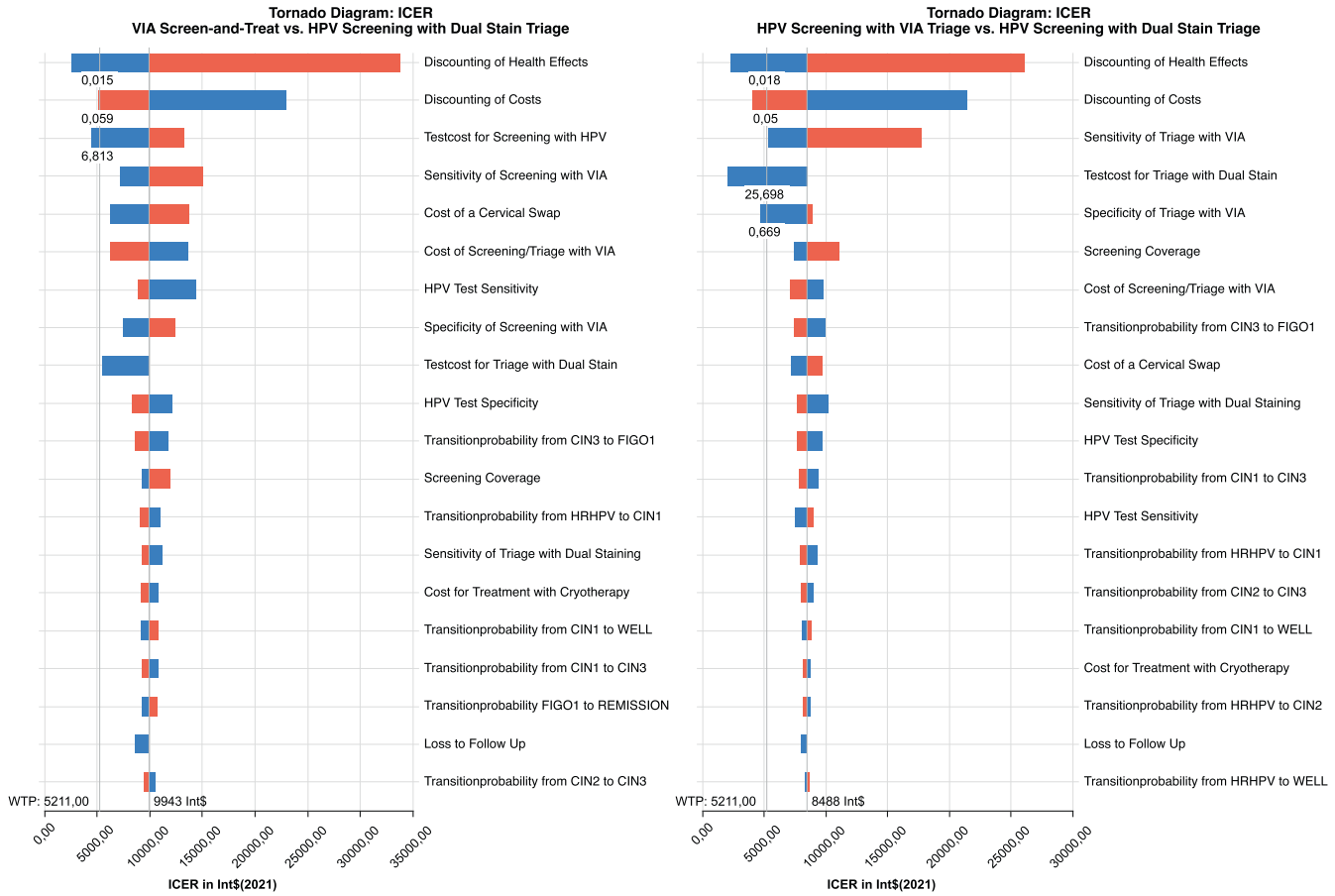
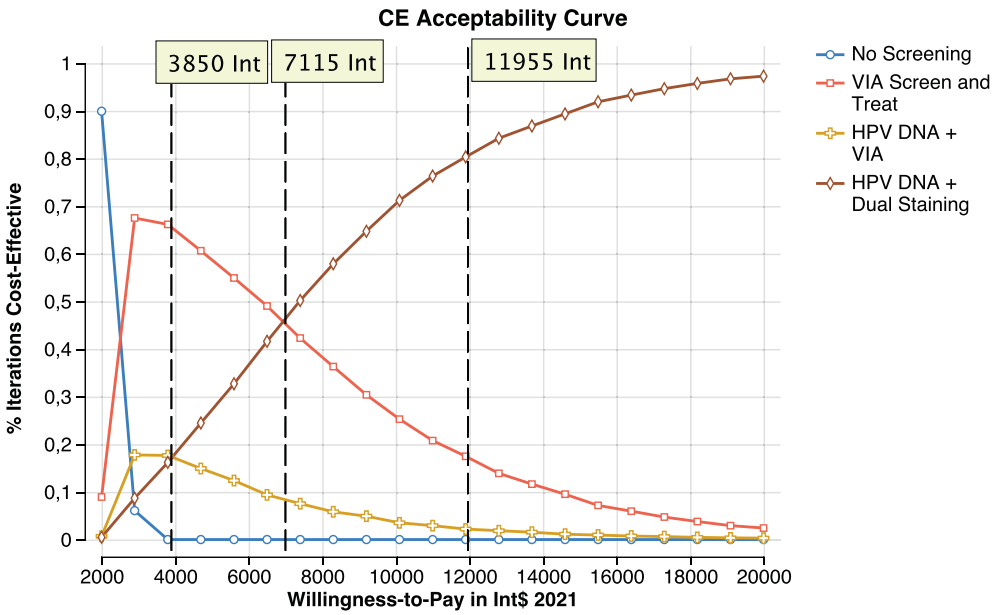


FIGURE 3 One-way sensitivity analyses. EV, expected value; FIGO, International Federation of Gynaecology and Obstetrics; HPV, human papilloma virus; ICER, incremental cost-effectiveness ratio; VIA, visual inspection with acetic acid; WTP willingness to pay.

FIGURE 4 Cost-effectiveness acceptability curve. CE, cost-effectiveness; HPV, human papilloma virus; Int, International Dollar; VIA, visual inspection with acetic acid.



higher (5 years) and might so improve acceptance of screening programs.[54]

Considering these advancements in specimen collection and preparation, as well as the recent reduction of test prices, dual staining costs could be much lower than assumed for this study, and scale-up issues as reported for VIA could be met.

After screening with HPV test, dual staining dominates VIA as a triage in the base case scenario by being more effective and less

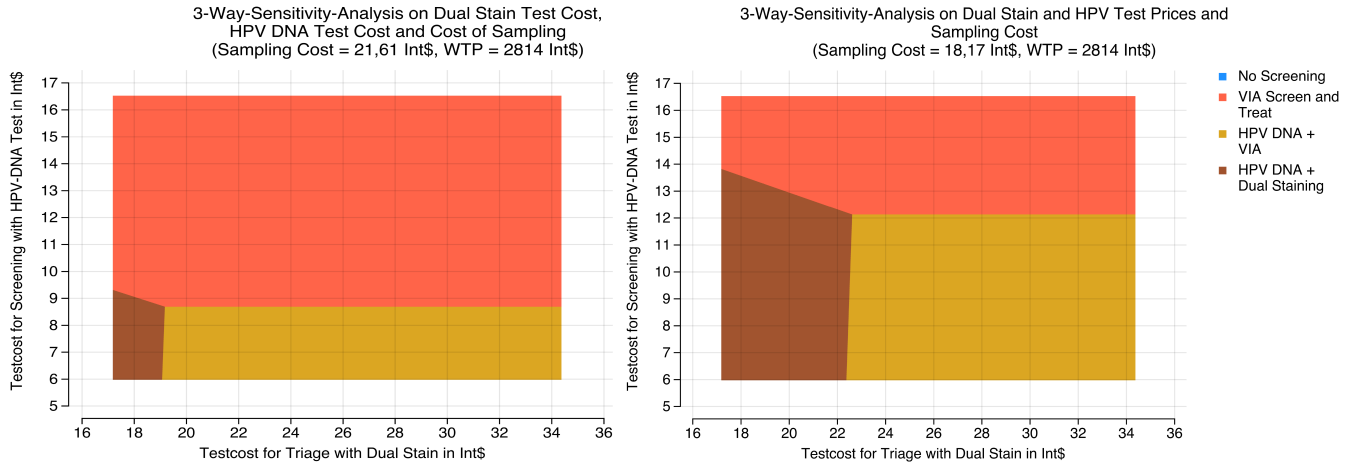


FIGURE 5 Three-way-sensitivity analyses of dual stain and HPV test prices and sampling cost. HPV, human papilloma virus; Int$, international dollar; VIA, visual inspection with acetic acid; WTP, willingness to pay.

expensive. This is most likely due to the lower performance of VIA as a triage test compared with VIA as screening test. Also, by screening with HPV test first, there is a preselection favoring the test with the better performance (dual staining).

4.1 | Limitations of the study

Our Markov model is constructed like the ones used by other researchers and was adapted and calibrated to fit our hypothesis. We need to acknowledge the limitations that arise from deriving transition probabilities from a UK modeling study[44] in the absence of sub-Saharan specific ones. The authors, however, rely mostly on Myers et al.,[55] 2000 using US data. To account for uncertainty, however, we set plausible ranges around these transition probabilities in our sensitivity analysis, with results shown in the Supporting Information Appendix. Estimations, wherever used, are highlighted and varied in the sensitivity analyses. There are, however, some restrictions to this study: costing was hindered by the fact that the original trial was not primarily designed to evaluate cost-effectiveness. We are aware of the potential for bias in estimating indirect costs, reason for which we use out point estimate only as initial reference for the analysis, but then conduct extensive PSA around this value. We note, however, that unlike other studies, we base our initial estimation on real data derived from a real sample of patients incurring the costs and hence being able to report them shortly after having experienced them. As such, we trust for recall bias to play a relatively limited role. Likewise, while we understand that valuing informal sector time using minimum wage may lead us to underestimate the real value of the work foregone, we do not have any better option at our disposal given engagement in the informal economy.

The HPV prevalence as reported in the trial might not be representative for the entire population but could be validated by other trials.[56] Our study addressed HPV-based screening among adult unvaccinated women in Kenya; the protective effect of prophylactic and therapeutic HPV vaccination, however, is not considered in our model.

Because there is a limited comprehensive assessment of CC prevention strategies in Sub-Saharan Africa, the cost-effectiveness results of this study can be used to guide healthcare resource allocation decisions or policy dialog to improve the uptake of HPV-based screening and triage testing for CC prevention.

Our study results have important policy implications as they offer unique insights into the incremental cost components and cost-effectiveness of screen-triage-treat approach using empirical data from a micro-costing study conducted in Kenya. The findings from this study, prompt us to recommend that the capacity to provide primary HPV screening and improve levels of coverage should be considered in the Kenyan healthcare setting. A policy to provide HPV self-test for women aged 30–45 years, followed by dual-staining test should be adopted because this option is superior in terms of value for money (<3x GDP per capita) compared with VIA-only or HPV test followed by VIA triage options, especially with a high level of screening coverage. In terms of research, new screening methods including a "screen-triage-treat" approach, which is increasingly being used in many countries, rely on technology/data systems for broader implementation of triage approaches within complex healthcare delivery systems, and a limited availability of trained health workforce. Innovative health financing or provider incentives may therefore be effective strategies to motivate health workforce participation and to improve population coverage of CC screening.

To conclude, this study shows that strategies of primary HPV testing plus triage testing with either dual-stain cytology or VIA perform better than the exclusive VIA screening strategy in detecting precancerous lesions in low-resource settings with dual-stain cytology being the more cost-effective triage option. The cost of such two-step approaches are highly context related and there are several options to increase their cost-effectiveness, including the reduction of test prices and the utilization of HPV self-sampling strategies. We, however, show that it is possible to equip laboratories in low-resource settings

with sophisticated technologies and operate them cost-effectively. Future research needs to assess the feasibility and cost-effectiveness of such innovative strategies for different low-resource settings.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. *Conceptualization*: Christopher Lobin, Hermann Bussmann, Kavita Singh, Manuela De Allegri, and Magnus von Knebel Doeberitz. *Data curation*: Christopher Lobin, Elkanah Omenge Orang'o, Edwin Were, and Kapten Muthoka. *Formal analysis*: Christopher Lobin and Kavita Singh. *Funding acquisition*: Hermann Bussmann and Magnus von Knebel Doeberitz. *Methodology*: Christopher Lobin, Konrad Obermann, Kavita Singh, Manuela De Allegri, and Kapten Muthoka. *Investigation*: Christopher Lobin and Kapten Muthoka. *Supervision*: Hermann Bussmann and Elkanah Omenge Orang'o. *Software*: Christopher Lobin. *Validation*: Christopher Lobin, Kavita Singh, Elkanah Omenge Orang'o, and Edwin Were. *Visualization*: Christopher Lobin and Kavita Singh. *Writing, original*: Christopher Lobin. *Writing, review and editing*: Christopher Lobin, Hermann Bussmann, Kavita Singh, Manuela De Allegri, Elkanah Omenge Orang'o, Edwin Were, and Konrad Obermann.

ACKNOWLEDGMENTS

We thank the patients, nurses and other personnel at Moi Teaching Referral Hospital and the health centers of Huruma and Uasin Gishu who made this study possible. We also thank Salvador Shabbir for his thoughts, when finalizing this manuscript. This work was supported by a grant from the Federal Ministry of Education and Research Germany (BMBF) under a project titled Novel concepts for cervical cancer screening in two rural African regions (01DG13007). The conduct of the study was supported by the Ladenburg Foundation, New York. Dr. Kavita Singh is supported by the Fogarty International Centre, National Institutes of Health (NIH), United States (1K43TW011164) and by the Medical Data Scientist Fellowship, Medical Faculty Heidelberg, University of Heidelberg, Germany. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Study approval was granted from the local review board at Moi Teaching Referral Hospital and Moi University, Eldoret, Kenya (FAN: IREC 1123) and the Institutional Review Board of the Heidelberg University Hospital, Germany (S-301/2014). Written informed consent was obtained from all participants.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lobin C, Orang'o EO, Were E, et al. Cost-effectiveness analysis of alternative screening strategies for the detection of cervical cancer among women in rural areas of Western Kenya. *Int J Cancer*. 2024;1-11. doi:10.1002/ijc.35036