Community-based self-collected HPV testing vs. visual inspection with acetic acid in Uganda: a cost-effectiveness analysis of the ASPIRE trial
TECHNICAL APPENDIX

Supplementary methods: cost data

Exchange rates

Results for this study are presented in 2014 USD. Table 1 presents the exchange rates and GDP deflators used to convert currencies to 2014 USD. Cost data for CHW salary, midwife salary, colposcopy direct medical costs (DMCs), biopsy DMCs, phones, laboratory transport, program assistant salary and community mobilization was collected in 2014 CAD and converted to 2014 USD using the 2014 exchange rate. Cost data for HPV test DMCs and cryotherapy DMCs was collected in 2011 Ugandan shillings (UGX), while cost data on women's wages average wages was collected in 2002 UGX. For these variables, we multiplied the costs by one plus the percent increase in the GDP deflator (Table 1) to convert the costs to the year 2014, and then applied 2014 exchange rates to convert the costs to USD. Cancer treatment costs were collected in 2000 Kenyan Shillings (KES), which we then multiplied by one plus the percent increase in the GDP deflator, and then converted to 2014 USD using the 2014 exchange rate.

Table 1. Exchange rates and GDP deflators

Exchange rate	
USD/CAD (2014)	0.9042
USD/UGX (2014)	0.0004
USD/KES (2014)	0.0114

GDP deflator[a]	
Kenya (2000-2014)	1.9576
Uganda (2011-2014)	0.2879
Uganda (2002-2014)	1.9490

Source: World Bank, WDI. Accessed on Dec 16, 2016

[a]GDP deflators are presented as the percent increase over the specified years

Women's time costs

As shown in Table 2, we derived women's time costs by stratifying the ASPIRE cohort based on education level and using average monthly income data from the 2006 Labour Market Information Status Report for Uganda by the Ugandan Ministry of Gender, Labour and Social Development to come up with a weighted average income of $0.46. Monthly average income was converted to an average hourly wage by assuming there are four weeks in a month and then dividing by 44.9 hours, the length of the average work week in Uganda (Ministry of Gender, Labour and Social Development 2006). Local currency data were converted to US$ using GDP deflators and exchange rates from the World Bank (World Bank WDI).

Table 2. Weighted average of women's wages

	ASPIRE cohort[a]	Avg monthly income (2002 UGX)[b]	Avg hourly income (2002 UGX)	Avg hourly income (2014 UGX)	Avg hourly income (2014 USD)
No schooling	119	UGX 25,000.00	UGX 139.20	UGX 410.50	$0.16
Primary	306	UGX 74,000.00	UGX 412.03	UGX 1,215.07	$0.47
Secondary	51	UGX 99,000.00	UGX 551.22	UGX 1,625.57	$0.63
Post-secondary	24	UGX 237,000.00	UGX 1,319.60	UGX 3,891.51	$1.50
Weighted average hourly income	500				**$0.46**

[a]Education level of the women enrolled in the ASPIRE trial is derived from a demographic survey conducted concurrently with the trial.
[b]Average monthly income data, stratified by education level, is derived from 2006 Labour Market Information Status Report for Uganda by the Ugandan Ministry of Gender, Labour and Social Development

Women's time estimates

Women's time estimates for different aspects of screening are shown in Table 3. When available, patient time variables were informed by demographic surveys collected during the trial. For instance, travel time to and from the clinic was estimated by asking women "how far is the walk to the nearest health clinic?". For all women, this was the Kisenyi Health Center where the trial was conducted. When demographic survey data was not available, time estimates were made by consulting researchers and clinicians who took part in the ASPIRE trial. We excluded time estimates for NGCT screening and follow up for positive NGCT results.

Table 3. Time estimates

	Time (minutes)	Source
Instruction on HPV self-collection	15	Estimate
HPV self-collection	10	Estimate
Round trip transport to Kisenyi	40	Demographic survey
Wait time for VIA or cryotherapy at Kisenyi	120	Estimate
VIA procedure time	20	Estimate
Cryotherapy procedure time	30	Estimate
Round trip transport to Mulago National Referral Hospital	90	Estimate
Waiting time for colposcopy at Mulago	240	Estimate
Colposcopy/biopsy procedure	30	Estimate

Transport cost estimates

For any visits to Kisenyi clinic, we assumed all transport was on foot because all women worked and/or lived in Kisenyi and usually walked, thus accruing no transportation cost. For visits to Mulago National Referral Hospital for colposcopy and treatments, we also assumed no transport cost, as the hospital is only 5 kilometers from Kisenyi.

Provider costs

Midwives

In the ASPIRE trial, midwives were the providers of VIA and cryotherapy. Table 4 demonstrates the per procedure provider cost. Data on total payments to midwives for training and performing VIAs/Cryotherapy was extracted from ASPIRE grant reconciliation sheets. The payments to midwives did not specify whether the payment was for a VIA or a cryotherapy. Therefore, we estimated the amount of time each procedure takes and then multiplied our estimates by the number of VIAs and cryotherapies that were performed to come up with a proportion of time allocated to VIA vs. cryotherapy. This proportion was used to derive the total payment to midwives for each procedure, which was then divided by the number of each procedure performed to come up with a per woman cost.

We assumed midwives spent no extra time on NGCT screening. Midwives performed a total of 111NGCT swabs, all of which occurred at the same time as the VIA. The extra time for the swab was estimated to be 2 minutes by research assistants, compared to 20 minutes for a VIA and 30 minutes for cryotherapy. In ASPIRE, a total of 154 VIAs and 11 cryotherapies were performed, for a total of 3410 midwife minutes. Adding the extra time for an NGCT swab (222 minutes) to the total time spent by midwives on VIA and cryotherapy (3410 minutes), and then dividing by 222, yields a total proportion of midwife time spent on NGCT of 6.5%. This difference was felt to be negligible and falls within the range of sensitivity analyses on direct medical costs that had no effect on the rank ordering of strategies and only minimally affected ICERs.

Community health workers (CHWs)

Table 4 states the CHW time cost for each woman enrolled in the trial. In the ASPIRE trial, CHW time costs included the following: visiting women at their homes or places of work to enroll them in the trial, instructing women on self-collection, transporting HPV samples, and calling women to deliver results and remind women to attend VIA. Data on total payments to CHWs were extracted from ASPIRE grant reconciliation sheets. As a demographic survey was conducted for research purposes, 10% of CHW time costs were excluded to account for survey administration time. The payments to CHWs did not specify which arm of the trial the payment represented. Research assistants who were involved with the trial estimated that CHWs spent 60% of their time on the VIA arm of the trial compared to 40% for the HPV-VIA arm, due to the time required to encourage compliance with VIA at the clinic. We used this proportion to estimate total payments to CHWs for each arm of the trial, which then was divided by the number of women enrolled in each arm of the trial to come up with a per woman cost.

We assumed that no extra time was spent by the CHWs on NGCT screening. Research assistants involved in the trial estimated that the self-collection of an HPV and NGCT sample took an average of 5 minutes total, or 2.5 minutes per sample. CHWs would enrol an average of 5 women per day during an 8 hour work day, half of which were randomized to VIA. This means that CHWs spent an extra 6.25 minutes out of an 8 hour day waiting for NGCT samples, or 1.3% of their time. This time difference was felt to be negligible and falls within the range of sensitivity analyses on direct medical costs that had no effect on the rank ordering of strategies and only minimally affected ICERs.

Colposcopy providers

Colposcopy occurred at Mulago National Referral Hospital and was paid for privately. The fee paid was $22.60 (2014 USD) per colposcopy.

Phone costs

Phones were used by community health workers to provide HPV results, schedule VIA follow-up and remind women about upcoming VIA appointments. Table 4 presents the average phone cost, per woman, for each arm of the trial. Data on total phone and airtime purchases were extracted from ASPIRE grant reconciliation sheets. Research assistants estimated that airtime was evenly split between each arm of the trial, so total phone costs were equally divided into each arm of the trial. This was divided by the number of women who CHWs tried to contact by phone in each arm of the trial, yielding a phone cost per women screened. As only 10/500 women needed to be called about NGCT results, many of whom were being contacted for HPV results anyway, the phone costs associated with NGCT screening were assumed to be zero.

Laboratory costs

HPV test costs

Lab testing was conducted at MBN Laboratories in Kampala, Uganda. MBN uses the Ecoli s.r.o real-time PCR test (Bratislava, Slovak Republic) to identify HPV high risk genotypes (16, 18, 31, 33, 35, 39, 45, 52, 56, 58, 59 and 66). However, the ASPIRE trial was not originally designed with cost-effectiveness analysis in mind and consequently the amount paid for lab testing was substantially higher than what would reasonably be expected in a pragmatic cervical cancer screening program. To account for this, we assumed the use of careHPV and used data from the PATH START-UP Uganda demonstration project to inform costs of test kits, lab supplies, lab equipment and staff costs.

Biopsy laboratory costs

The fee paid per biopsy to MBN laboratories is listed in table 4. We assumed one biopsy per colposcopy.

Sample transport costs

In the ASPIRE trial, HPV and *N. gonorrhea/C. trachomatis* samples were transported by car to MBN laboratories for testing. ASPIRE grant reconciliation sheets detailed the number of trips taken to transport samples and the cost per trip. We multiplied these figures to come up with total transport costs for the trial, and then divided by the number of HPV and NGCT samples to come up with a transport cost per sample, as shown in table 4.

Supply costs

Supply costs for each test are shown on table 4. HPV supply costs were derived from the PATH START-UP demonstration project.[1,2] VIA and cryotherapy supply costs were derived from receipts and ASPIRE grant reconciliation sheets. As the supply costs for VIA and cryotherapy were presented total costs, we divided through by the number of procedures to come up with a supply cost per procedure. We excluded the costs of extra swabs for NGCT testing from supply cost calculations.

Programmatic costs

Programmatic costs are shown on table 4. Programmatic costs included the Program Assistant's salary and expenses for the three months of the trial and one month beforehand (total of 4 months). They also include costs for community preparedness, which was an education campaign to educate women about cervical cancer that occurred in the month before the trial. Programmatic costs were divided by the number of women enrolled in the trial (500) to come up with a per woman programmatic cost. We assumed there were no additional programmatic costs associated with NGCT screening.

Equipment costs

As several pieces of equipment that were purchased for the three-month trial have a lifespan that is much longer, we amortized the costs to reflect the cost of use for three months using a discount rate of 3% per year. The total cost, amortized cost, and cost per procedure for each item is listed in Table 5. There were no importation costs as all equipment was purchased in Uganda. ASPIRE was never billed for installation, so it was assumed that this was included with in the amount paid for equipment. There were no costs for maintenance of equipment in the 3 months of the APSIRE trial. In the base case analysis, START-UP costs were used to inform cryotherapy costs, so the cryotherapy equipment costs in Table 5 were only used to inform sensitivity analyses. As this equipment would be required with or without NGCT screening, no adjustment in the costs was made.

Table 4. Costing data.

	Aggregate cost	Cost per women enrolled	Cost per women screened	Cost per procedure
CHW time cost[a]	$3,453.59	-	-	-
HPV test	$1,243.29	-	$4.97	-
VIA	$1,864.94	-	$7.46	-
NGCT[b]	$345.36	-	-	-
Midwife cost	$874.48	-	-	-
Training	$206.77	-	$1.34	-
Per VIA	$789.85	-	-	$5.13
Per cryotherapy[c]	$84.63	-	-	$7.69
DMC per colposcopy[d]	-	-	-	$22.60
Lab cost per biopsy	-	-	-	$29.65
Telephone airtime	$326.07	-	$0.65	-
Clinic equipment and supplies		-	-	
Per HPV test		-	-	$6.06
Per VIA		-	-	$0.71
Laboratory costs[e]				
Per HPV test		-	-	$0.62
Per biopsy	-	-	-	$29.65
Laboratory transport cost	$666.94	-	-	
Per sample		-	-	$1.08
Programmatic costs	$3,289.46	-	-	-
Program assistant cost	$2,531.65	$5.06	-	-
Community mobilization cost	$757.81	$1.52	-	-

Note: all costs are in 2014 USD. DMC: direct medical cost.
[a]CHW costs were higher for VIA than HPV testing because more time was spent by CHWs confirming VIA appointments
[b]NGCT costs were excluded in this analysis due to model limitations
[c]Midwife costs per cryotherapy were only used in sensitivity analysis. In the base case, cryotherapy costs were estimated using PATH START-UP data[1,2]
[d]Colposcopies were paid for privately, and thus include all direct medical costs.
[e]Laboratory costs include supplies, equipment and staffing costs specific to the indicated test.

Table 5. Amortization of ASPIRE equipment costs.

	Unit	Quantity	Total cost	Amortized cost[1]	Cost per woman
VIA equipment					
Examination table	2014 USD		$161.55	$8.70	$0.06
Examination light	2014 USD		$84.62	$4.56	$0.03
# women who received VIA	persons	154			
Cryo equipment					
Frigotronics cryo-plus surgical package	2014 USD		$6,042.80	$325.42	$29.58

Liquid nitrogen cylinder - 70L	2014 USD		$12,539.48	$675.28	$61.39
Ring forceps	2014 USD		$9.62	$0.52	$0.05
# women who received cryo	persons	11			

[1]The amortized cost represents the cost of the use of the equipment for the length of the ASPIRE trial.

Cryotherapy costs

For our base case we used PATH START-UP demonstration project data on direct medical costs of cryotherapy that we believe better reflect costs in a real-world setting.[1,2] For the ASPIRE trial, equipment and supplies for cryotherapy (such as liquid nitrogen) were purchased so that they could be used after the trial ended. Moreover, only eleven women received cryotherapy treatments at Kisenyi Health Centre. Breaking these costs down into a cost per cryotherapy required us to assumptions on the number of lifetime uses that we were not very confident about. Nevertheless, while we used the PATH START-UP data in the base case, we still used the ASPIRE cost in a sensitivity analysis.

Cancer treatment costs

Treatment of invasive cancer was done through the Ugandan health care system and was not paid for by ASPIRE. To estimate treatment costs for Uganda, we updated the direct medical costs and transport costs for treatment used in Goldie et al. and Campos et al. to 2014 USD using exchange rates and Kenyan GDP deflators listed in Table 1.[3,4] For women's time costs, we assumed the same amount of time as Goldie et al. and Campos et al., however, we adjusted the costs to include the hourly wage that we have been using for all other calculations in this paper.

Table 6. Cancer treatment costs

	Unit	Qty	Cost per woman treated
Local Cancer	2014 USD		**$627**
Direct medical costs	2014 USD		$438
Time	hours	169.85	
Women's time cost	2014 USD		$78
Transport cost	2014 USD		$111
Regional Cancer	2014 USD		**$797**
Direct medical costs	2014 USD		$433
Time	hours	169.85	
Women's time cost	2014 USD		$78
Transport cost	2014 USD		$285
Distant Cancer	2014 USD		**$797**
Direct medical costs	2014 USD		$433
Time	hours	169.85	
Women's time cost	2014 USD		$78
Transport cost	2014 USD		$285

Supplementary methods: sensitivity analysis

VIA test performance (primary screening)

The test performance characteristics of VIA are heavily dependent on the health care provider. As such, there is concern about the potential for variability in VIA test performance between settings. Our base case analysis assumed a test sensitivity/specificity of 73.6%/66.6% for CIN2+. These values were derived from the Uganda results in a multi-country evaluation of cervical cancer screening technology test performance.[5] Looking at the VIA test performance from other sites included in this study, as well as other studies on VIA,[6] there was substantial

variability in VIA sensitivity (range 21.9%-73.6%) and specificity (range 66.6%-94.6%) for CIN2+. The Uganda test performance characteristics used in the base case have the highest sensitivity of any of the sites or other studies. To evaluate a lower bound on VIA sensitivity, we evaluated how changing test sensitivity/specificity to 41.4%/94.5% affected our outcomes.[6]

VIA test performance (triage test only)

It is plausible that VIA test characteristics would change when it is used as a triage test for women that are already known to be HPV-positive. We examined the literature to find upper and lower bounds of VIA triage test sensitivity. Muwonge et al. evaluated the performance of VIA in HPV+ women and found a sensitivity of 81.9% for CIN2+.[7] No specificity was reported, so we used our base case specificity of 66.6%. Tebeu et al. found a sensitivity of 36.4% and a specificity of 90.4% for CIN2+.[8] We explored both of these extreme scenarios in a sensitivity analysis.

Cryotherapy eligibility

37/147 (25.2%) women in the ASPIRE trial that received VIA as either a primary screen or triage test were deemed ineligible for immediate cryotherapy due to inability to visualize the squamocolumnar junction (28/147) or lesions suspicious of invasive cervical cancer (9/147).[9] While we did not use any ASPIRE trial data to inform treatment characteristics and eligibility variables in the base case analysis, it highlights the uncertainty surrounding the proportion of women that would be cryotherapy eligble vs. ineligible in VIA, HPV-VIA and HPV-ST strategies. To explore this uncertainty, we evaluated cryotherapy eligibility based off of the ASPIRE eligibility data, as well as the three following studies:

Gage et al.:[10] In this article, Gage et al. propose a new application of VIA called "visual triage", in which the goal is to determine the treatability of lesions, not identify pre-cancer. There were at total of 552 HPV+ women in this study. Midwives judged 69.2% to be treatable with cryotherapy. Almost a third of women were untreatable for reasons such as inability to visualize the SCJ, lesions extending into the endocervical canal, large lesions and suspected cancer. Stratifying based on cytology results at enrolment, 72.2% with normal changes, 66% with ASCUS, 70.7% with LSIL and 58.1% with HSIL were judged treatable by midwives. We explored this eligibility data in sensitivity analysis using values of 72.2% for no lesion, 58.1% for CIN2 and CIN3, and 10% with cancer.

Gage et al.:[11] Two expert gynecologists reviewed the 559 HPV-positive women to determine whether cryotherapy at the time of HPV screening could treat HPV-positive women. 74.2% of these women were deemed treatable by experts. Stratifying based on cytology results at enrolment, 79.6% with normal changes, 73.9% with ASCUS, 42.2% with LSIL and 42.2% with HSIL+ were judged to be treatable by cryotherapy. We explored this eligibility data in sensitivity analysis using values of 79.6% for no lesion, 42.2% of CIN2 and CIN3 and 10% with cancer.

WHO demonstration project:[12] This demonstration project occurred at seven sites in six African countries (19,579 patients) and evaluated VIA screen and treat strategies. 1737/1980 (87.7%) of VIA+ cases were eligible for cryotherapy. There was no stratification of eligibility based on histology or cytology. To convert this to model inputs, we assumed 87.7% eligibility was for CIN2. We assumed that eligibility would increase by 5% for no lesion, decrease by 5% for CIN3, and that only 10% of cancerous lesions would be eligible. It is of note that the eligibility results from this demonstration project nearly mirror those of Nelson et al. 2015, who found that 83% of VIA+ lesions were eligible for immediate cryotherapy.

HPV test costs

In the base case, we used data from the PATH START-UP demonstration project to estimate a total direct medical cost for an HPV test of $12.74.[2] In ASPIRE, HPV test costs were much higher and are unlikely to reflect what actual programmatic costs would be as HPV genotyping was performed. The specific HPV test used was the E. Coli s.r.o. real time PCR test.[13] Nevertheless, we explored a scenario of setting HPV test cost to the amount paid in the ASPIRE trial of $28.03.

Cryotherapy costs

Cryotherapy costs are another area where we did not apply ASPIRE data to the base case analysis because the amount paid for supplies and equipment was unrealistic outside of a research setting and amortization of costs was challenging due to inability to find data on the number of lifetime uses of cryotherapy equipment. The START-UP data estimated a direct medical cost of cryotherapy of $5.85.[1,2] Nevertheless, to explore uncertainty around the

costs of cryotherapy, we performed a sensitivity analysis where we used the ASPIRE cryotherapy costs. We amortized the equipment costs under the assumption that the equipment would have a ten year life span and would be used five days per week, five times per day. For supply costs, ASPIRE paid to fill a full 70L liquid nitrogen cylinder. In consultation with local providers, we assumed the amount of liquid nitrogen paid for could be used for 219 cryotherapies, and then allocated only the proportion of the cost based on use to cryotherapies for ASPIRE. Under these assumptions, we estimated a cryotherapy cost of $27.37 and input this cost in a sensitivity analysis.

Cancer treatment costs

As our cancer treatment cost estimates in the base case were derived from what was originally Kenyan data, we performed a literature search to find studies that used cancer treatment costs from other Sub-Saharan African countries. Nelson et al. used cancer treatment cost estimates from Tanzania in 2002-2011.[14] We converted these costs from TZS to UGX, applied Ugandan GDP deflators, converted the costs to 2014 USD, added women's time costs. Per women treatment costs were more than three times as high as our base case, so we explored how these higher costs would affect our results.

Direct medical costs

In the base case, the direct medical cost of an HPV test was $12.73, compared to $14.64 for a VIA. We evaluated three scenarios in which we adjusted the direct medical costs for the two screening tests (Table 7):

i. Scenario A: In the base case, research assistants involved in the trial estimated that CHWs spent 60% of their time on women in the VIA arm of the trial, compared to 40% on the HPV-VIA arm. As described above, we used these estimates to come up with our CHW cost per women. Given that this estimation method is quite subjective, we performed a sensitivity analysis in which we assumed that community health worker's evenly split their time between the two trial arms. This led to direct medical costs of $13.98 for an HPV test compared to $13.40 for a VIA.
ii. Scenario B: In the base case, mid wife costs were estimated by dividing the total payments to midwives by the number of procedures performed, as described above. This costing technique led us to estimate midwife time cost of $5.13 per women screened. We feel that this may be an overestimation of midwife costs compared to a real world setting. For instance, in Table 2 we present data that shows the average hourly wage, in 2014 USD, for women with post-secondary education in Uganda is $1.50 per hour. Midwives in ASPIRE were paid $5.13 per VIA, and as we estimated that a VIA takes 20 minutes, this would lead to an hourly wage of $15.39, approximately ten times the average age of women with post-secondary education in Uganda. Therefore, we ran a sensitivity analysis where we set midwives' wages equal to the women's time cost we estimated in Table 2, or $0.15 per VIA. In this scenario, direct medical costs were $12.73 for HPV testing and $9.66 for a VIA.
iii. Scenario C: We evaluated a scenario where we assumed a 50/50 time split for CHWs (as in scenario A) and that midwives were paid $0.15 per VIA (as in scenario B). This led to direct medical costs of $13.98 for an HPV test and $8.42 for a VIA.

Table 7. Direct medical costs, base case and sensitivity analyses

	Base case	Scenario A	Scenario B	Scenario C
HPV test	**$12.73**	**$13.98**	**$12.73**	**$13.98**
CHW costs (per HPV test)	$4.97	$6.22	$4.97	$6.22
Lab transport cost (per HPV test)	$1.08	$1.08	$1.08	$1.08
Self-collection supplies/equipment (per HPV test)	$6.06	$6.06	$6.06	$6.06
Lab supplies/equipment/staff costs (per HPV test)	$0.62	$0.62	$0.62	$0.62
VIA	**$14.64**	**$13.40**	**$9.66**	**$8.42**
CHW costs (per VIA)	$7.46	$6.22	$7.46	$6.22
Midwife cost (per VIA)	$5.13	$5.13	$0.15	$0.15
Midwife VIA training costs (per VIA)	$1.34	$1.34	$1.34	$1.34

Supply costs (per VIA)	$0.62	$0.62	$0.62	$0.62
Equipment costs (per VIA)	$0.09	$0.09	$0.09	$0.09

Cryotherapy efficacy

Our base case analysis assumed a treatment efficacy of 81% (Olatunbosun et al. 1992).[15] A meta-analysis on the effectiveness of cryotherapy in the treatment of CIN demonstrated a pooled cure rate of 92% for CIN2.[16] While this meta-analysis included studies from HICs and LMICs, we explored the effect of this higher effectiveness in a sensitivity analysis. As there were very few studies from Africa included in the meta-analysis, we also explored a scenario of setting cryotherapy effectiveness at 70% to reflect the possibility that cure rates may be lower in LMICs

Telephone compliance

During the ASPIRE trial, 34/73 (46.6%) HPV+ women were successfully contacted over the phone with their results.[9] However, there were a number of issues with adherence to protocol, and after the correcting the adherence issues the proportion of women successfully contacted rose to 34/54 (63.0%). At a one year follow up, community health workers attempted to contact all women in the trial over the phone again, and had a success rate of 315/500 (63.0%). To explore this uncertainty, we have evaluated three scenarios in sensitivity analysis. First, we set telephone compliance equal to 46.6% to evaluate the scenario of improper adherence to protocol. Second, we set telephone compliance equal to 75%, as it is plausible that immediate follow up could be even higher than the 63% one year follow up rate with proper adherence to protocol. Third, we set telephone compliance equal to 90% to evaluate the health and economic benefits of a strategy that is able to retain more women over the phone.

Loss to follow up

For all visits that did not have follow up compliance dictated by ASPIRE trial data, we assumed a loss to follow up of 15% in the base case. We explored scenarios of 0% loss to follow up and 40% loss to follow up in sensitivity analysis.

Screening coverage

In the base case, we assumed a screening coverage of 70%. We evaluated screening coverage rates of 100%, 85%, 55% and 40% in sensitivity analyses.

HPV test performance

In the base case, we assumed an HPV test sensitivity/specificity of 77/82% to detect CIN2+.[5] To evaluate a scenario of perfect test performance, we set sensitivity/specificity to 100% to detect a high risk HPV infection.

Cryotherapy compliance

In our base case, we assumed that no women that refused immediate cryotherapy returned for cryotherapy at a later date, in keeping with results from ASPIRE. However, in ASPIRE only three women refused cryotherapy, and a larger study found that over 50% of women return for cryotherapy.[14] We test Nelson et al.'s finding that 52% of women returned for cryotherapy in a sensitivity analysis in the HPV-VIA strategy and VIA-ST strategies. We were unable to test the HPV-ST as the model programming did not allow for women to return for cryotherapy.

Colposcopy transport costs

For reasons discussed previously, colposcopy transport costs were not included in the base case analysis. To explore a scenario in which there was a transport cost accrued, we assumed a cost of $0.50 for round trip transport from Kisenyi to Mulago.

Discount rates

In the base case, we assumed a discount rate of 3% for future health and economic benefits/costs. To explore differences in preferences regarding the time value of money and health, we explored scenarios of discounting at 5% and no discounting.

Supplementary methods: scenario analyses

Cryotherapy vs. LEEP

In the base case analysis, we assumed that all treatment after colposcopy was cryotherapy. We ran a scenario analysis in which only LEEPs were performed after colposcopy instead of cryotherapy under the following assumptions: the effectiveness of LEEP after colposcopy is 96.4%,[6] and the direct medical cost of a LEEP is $86.70.[1,2]

CHW door to door follow up to increase follow up

In ASPIRE, 129/250 (51.6%) women were lost to follow up in the VIA arm after the first home visit by the CHW and 34/54 (63.0%) of HPV+ women in the HPV-VIA arm were lost to follow up after CHWs could not contact them over the phone. Retaining women throughout the screening pathways, especially if they are HPV+, could increase the cost-effectiveness of screening strategies. One strategy to reduce loss to follow up is to have CHWs go door to door to remind women of their appointments. Goldhaber-Fiebert et al. showed that using up to two CHW visits to remind women of their appointments reduced loss to follow up from 25% to 10% at a cost of $2.68 per women (adjusted for exchange rate and Ugandan GDP deflator).[17] We evaluated these findings in the VIA, HPV-VIA and HPV-ST strategies by increasing CHW costs per women by $2.68, reducing loss to follow up by the same proportion after the first visit in the VIA strategy and reducing loss to follow up for HPV+ women due to inability to reach them over the phone in the HPV-VIA and HPV-ST strategies.

Supplementary methods: model parameterization

Tables 8-16 show the range of values for the top 50 parameter sets that was sampled from during the calibration process.

Table 8. Monthly HPV incidence, stratified by HPV type and age group

HPV Type and Age Group, years	Range of Values for Top 50 Parameter Sets	
	Min	Max
HPV 16		
<21	0.00000	0.01483
21-24	0.00037	0.00943
25-29	0.00032	0.00652
30-49	0.00092	0.00623
>=50	0.00010	0.00530
HPV 18		
<21	0.00000	0.01155
21-24	0.00034	0.01060
25-29	0.00018	0.00889
30-49	0.00016	0.00571
>=50	0.00004	0.00294
HPV 31		
<21	0.00000	0.01063
21-24	0.00033	0.00746
25-29	0.00020	0.00523
30-49	0.00017	0.00426
>=50	0.00004	0.00236
HPV 33		
<21	0.00028	0.00461
21-24	0.00021	0.00361
25-29	0.00012	0.00206
30-49	0.00012	0.00128
>=50	0.00005	0.00076

HPV 45		
<21	0.00000	0.00799
21-24	0.00013	0.00581
25-29	0.00010	0.00272
30-49	0.00005	0.00242
>=50	0.00004	0.00120
HPV 52		
<21	0.00000	0.00695
21-24	0.00008	0.00410
25-29	0.00006	0.00125
30-49	0.00005	0.00102
>=50	0.00002	0.00177
HPV 58		
<21	0.00000	0.00945
21-24	0.00018	0.00753
25-29	0.00014	0.00342
30-49	0.00016	0.00351
>=50	0.00002	0.00190
Other Oncogenic HPV		
<21	0.00000	0.01477
21-24	0.00057	0.01259
25-29	0.00038	0.00766
30-49	0.00022	0.00654
>=50	0.00013	0.00350
Nononcogenic HPV		
<21	0.00000	0.03828
21-24	0.00132	0.03450
25-29	0.00071	0.03204
30-49	0.00030	0.02764
>=50	0.00007	0.01196

Table 9. Monthly progression of HPV Infection to CIN2

HPV Type and Age Group, months	Values for Top 50 Parameter Sets
HPV 16	
1-15	0.00171
16-27	0.00242
28-39	0.00258
40-51	0.00552
52+	0.01500
HPV 18	
1-15	0.00004
16-27	0.00019
28-39	0.00019
40-51	0.00773
52+	0.00773
HPV 31	
1-15	0.00026
16-27	0.00278
28-39	0.00309
40-51	0.00693
52+	0.00693
HPV 33	
1-15	0.00072
16-27	0.00072
28-39	0.00494
40-51	0.00494
52+	0.00494
HPV 45	
1-15	0.00000
16-27	0.00000
28-39	0.00226
40-51	0.00533
52+	0.00533
HPV 52	
1-15	0.00088
16-27	0.00168
28-39	0.00168
40-51	0.00198
52+	0.00568

HPV 58	
1-15	0.00059
16-27	0.00247
28-39	0.00247
40-51	0.00462
52+	0.01025
High Risk HPV	
1-15	0.00013
16-27	0.00037
28-39	0.00196
40-51	0.00196
52+	0.00196
Low Risk HPV	
1-15	0.00021
16-27	0.00029
28-39	0.00031
40-51	0.00066
52+	0.00066

Table 10. Monthly progression of HPV Infection to CIN3

HPV Type and Age Group, months	Values for Top 50 Parameter Sets
HPV 16	
1-15	0.00057
16-27	0.00081
28-39	0.00086
40-51	0.00184
52+	0.00502
HPV 18	
1-15	0.00001
16-27	0.00005
28-39	0.00005
40-51	0.00194
52+	0.00194
HPV 31	
1-15	0.00007
16-27	0.00070
28-39	0.00077
40-51	0.00174
52+	0.00174
HPV 33	
1-15	0.00018
16-27	0.00018
28-39	0.00124
40-51	0.00124
52+	0.00124
HPV 45	
1-15	0.00000
16-27	0.00000
28-39	0.00056
40-51	0.00134
52+	0.00134
HPV 52	
1-15	0.00022
16-27	0.00042
28-39	0.00042
40-51	0.00049

52+	0.00142
HPV 58	
1-15	0.00015
16-27	0.00062
28-39	0.00062
40-51	0.00116
52+	0.00257
High Risk HPV	
1-15	0.00003
16-27	0.00009
28-39	0.00049
40-51	0.00049
52+	0.00049
Low Risk HPV	
1-15	0.00002
16-27	0.00003
28-39	0.00003
40-51	0.00007
52+	0.00007

Table 11. Monthly progression of CIN2 to Cancer

HPV Type and Age Group, years	Range of Values for Top 50 Parameter Sets	
	Min	Max
HPV16		
1-5	0.00003	0.00005
6-10	0.00004	0.00005
11-20	0.00087	0.00128
21-29	0.00255	0.00374
30-34	0.00511	0.00748
35-39	0.00553	0.00811
40-44	0.01191	0.01746
45-49	0.01277	0.01871
50+	0.34040	0.49880
HPV 18		
1-5	0.00003	0.00005
6-10	0.00004	0.00005
11-20	0.00087	0.00128
21-29	0.00255	0.00374
30-34	0.00511	0.00748
35-39	0.00553	0.00811
40-44	0.01191	0.01746
45-49	0.01277	0.01871
50+	0.34040	0.49880
HPV 31		
1-5	0.00002	0.00003
6-10	0.00002	0.00004
11-20	0.00058	0.00085
21-29	0.00170	0.00249
30-34	0.00340	0.00499
35-39	0.00369	0.00540
40-44	0.00794	0.01164
45-49	0.00851	0.01247
50+	0.22693	0.33254
HPV 33		
1-5	0.00003	0.00005
6-10	0.00004	0.00005
11-20	0.00087	0.00128
21-29	0.00255	0.00374
30-34	0.00511	0.00748
35-39	0.00553	0.00811

40-44	0.01191	0.01746
45-49	0.01277	0.01871
50+	0.34040	0.49880
HPV 45		
1-5	0.00002	0.00003
6-10	0.00002	0.00004
11-20	0.00058	0.00085
21-29	0.00170	0.00249
30-34	0.00340	0.00499
35-39	0.00369	0.00540
40-44	0.00794	0.01164
45-49	0.00851	0.01247
50+	0.22693	0.33254
HPV 52		
1-5	0.00002	0.00003
6-10	0.00002	0.00004
11-20	0.00058	0.00085
21-29	0.00170	0.00249
30-34	0.00340	0.00499
35-39	0.00369	0.00540
40-44	0.00794	0.01164
45-49	0.00851	0.01247
50+	0.22693	0.33254
HPV 58		
1-5	0.00002	0.00003
6-10	0.00002	0.00004
11-20	0.00057	0.00085
21-29	0.00167	0.00249
30-34	0.00335	0.00498
35-39	0.00363	0.00540
40-44	0.00781	0.01163
45-49	0.00837	0.01246
50+	0.22312	0.33229
High Risk HPV		
1-5	0.00003	0.00005
6-10	0.00004	0.00005
11-20	0.00087	0.00128
21-29	0.00255	0.00374
30-34	0.00511	0.00748

35-39	0.00553	0.00811
40-44	0.01191	0.01746
45-49	0.01277	0.01871
50+	0.34040	0.49880

Table 12. Monthly progression of CIN3 to Cancer

HPV Type and Age Group, years	Range of Values for Top 50 Parameter Sets	
	Min	Max
HPV16		
1-5	0.00016	0.00025
6-10	0.00018	0.00027
11-20	0.00429	0.00639
21-29	0.01255	0.01869
30-34	0.02510	0.03738
35-39	0.02719	0.04050
40-44	0.05857	0.08723
45-49	0.06275	0.09346
50+	0.33468	0.49844
HPV 18		
1-5	0.00016	0.00025
6-10	0.00018	0.00027
11-20	0.00429	0.00639
21-29	0.01255	0.01869
30-34	0.02510	0.03738
35-39	0.02719	0.04050
40-44	0.05857	0.08723
45-49	0.06275	0.09346
50+	0.33468	0.49844
HPV 31		
1-5	0.00011	0.00016
6-10	0.00012	0.00018
11-20	0.00286	0.00426
21-29	0.00837	0.01246
30-34	0.01673	0.02492
35-39	0.01813	0.02700
40-44	0.03905	0.05815
45-49	0.04184	0.06230
50+	0.22312	0.33229
HPV 33		
1-5	0.00016	0.00025
6-10	0.00018	0.00027
11-20	0.00429	0.00639
21-29	0.01255	0.01869
30-34	0.02510	0.03738
35-39	0.02719	0.04050

40-44	0.05857	0.08723
45-49	0.06275	0.09346
50+	0.33468	0.49844
HPV 45		
1-5	0.00011	0.00016
6-10	0.00012	0.00018
11-20	0.00286	0.00426
21-29	0.00837	0.01246
30-34	0.01673	0.02492
35-39	0.01813	0.02700
40-44	0.03905	0.05815
45-49	0.04184	0.06230
50+	0.22312	0.33229
HPV 52		
1-5	0.00011	0.00016
6-10	0.00012	0.00018
11-20	0.00286	0.00426
21-29	0.00837	0.01246
30-34	0.01673	0.02492
35-39	0.01813	0.02700
40-44	0.03905	0.05815
45-49	0.04184	0.06230
50+	0.22312	0.33229
HPV 58		
1-5	0.00011	0.00016
6-10	0.00012	0.00018
11-20	0.00286	0.00426
21-29	0.00837	0.01246
30-34	0.01673	0.02492
35-39	0.01813	0.02700
40-44	0.03905	0.05815
45-49	0.04184	0.06230
50+	0.22312	0.33229
High Risk HPV		
1-5	0.00011	0.00016
6-10	0.00012	0.00018
11-20	0.00286	0.00426
21-29	0.00837	0.01246
30-34	0.01673	0.02492

35-39	0.01813	0.02700
40-44	0.03905	0.05815
45-49	0.04184	0.06230
50+	0.22312	0.33229

Cancer transitions

Table 13. Monthly progression of invasive cancer stages

	Values for Top 50 Parameter Sets
Local to regional	0.02
Regional to distant	0.025
Invasive cancer mortality	
Undetected Cancers	
Local	0.005876
Regional	0.0151371
Distant	0.0655189
Detected Cancers	
Local	
Year 1	0.005876
Years 2-3	0.0052
Years 4-20	0.0052
Years 20+	0.0052
Regional	
Year 1	0.0151371
Years 2-3	0.01251
Years 4-20	0.01251
Years 20+	0.01251
Distant	
Year 1	0.0655189
Years 2-3	0.04339
Years 4-20	0.04339
Years 20+	0.04339
Monthly probability of symptom detection	
Local	0.0039
Regional	0.1333
Distant	0.1746

Table 14. Monthly regression of HPV Infected to Normal Cervix

HPV Type and Age Group, months	Values for Top 50 Parameter Sets
HPV 16	
1-15	0.041886
16-27	0.040754
28-39	0.033905
40-51	0.031888
52+	0.019846
HPV 18	
1-15	0.073342
16-27	0.063235
28-39	0.053605
40-51	0.020616
52+	0.020616
HPV 31	
1-15	0.063447
16-27	0.033826
28-39	0.033826
40-51	0.033826
52+	0.033826
HPV 33	
1-15	0.083452
16-27	0.044955
28-39	0.036156
40-51	0.036156
52+	0.036156
HPV 45	
1-15	0.078517
16-27	0.042579
28-39	0.041675
40-51	0.030133
52+	0.030133
HPV 52	
1-15	0.062999
16-27	0.044401
28-39	0.044401
40-51	0.039325
52+	0.039325

HPV 58	
1-15	0.065572
16-27	0.05443
28-39	0.053968
40-51	0.033319
52+	0.033319
High Risk HPV	
1-15	0.080766
16-27	0.066633
28-39	0.053972
40-51	0.049229
52+	0.005094
Low Risk HPV	
1-15	0.051888
16-27	0.050005
28-39	0.034649
40-51	0.034649
52-63	0.034649
64+	0.028608

Table 15. Monthly regression of CIN2

HPV Type and Age Group, years	Range of Values for Top 50 Parameter Sets	
	Min	Max
HPV 16		
1-5	0.02503	0.03547
6-10	0.01752	0.02483
11-20	0.00651	0.00922
21-29	0.00025	0.00035
30-39	0.00005	0.00007
40+	0.00003	0.00004
All Other HPV Types		
1-5	0.02618	0.19759
6-10	0.01833	0.13832
11-20	0.00681	0.05137
21-29	0.00026	0.00198
30-39	0.00005	0.0004
40+	0.00003	0.0002

Table 16. Monthly regression of CIN3

HPV Type and Age Group, years	Range of Values for Top 50 Parameter Sets	
	Min	Max
HPV 16		
1-5	0.01251	0.03302
6-10	0.00876	0.02312
11-20	0.00325	0.00859
21-29	0.00013	0.00033
30-39	0.00003	0.00007
40+	0.00001	0.00003
All Other HPV Types		
1-5	0.01598	0.09814
6-10	0.01119	0.0687
11-20	0.00415	0.02552
21-29	0.00016	0.00098
30-39	0.00003	0.0002
40+	0.00002	0.0001

Supplementary results

Table 17. Base case results including discounted lifetime costs and discounted life expectancy

	Discounted lifetime cost per woman	Discounted life expectancy	ICER ($/YLS)	Relative cancer risk reduction[a]	Absolute lifetime cancer risk
NoScreen	$9.19 (8.14-10.45)	26.2445 (26.2134-26.2737)	-	-	4.2% (3.8-4.7)
HPV-ST 1x	$13.37 (12.30-14.43)	26.2755 (26.2485-26.3025)	$130 (110-150)	15.0% (13.3-16.6)	3.5% (3.2-4.0)
VIA 1x	$13.88 (12.84-15.06)	26.2602 (26.2315-26.2883)	DOM	7.2% (6.3-8.2)	3.9% (3.5-4.3)
HPV-VIA 1x	$13.99 (12.90-15.12)	26.2618 (26.2334-26.2898)	DOM	7.6% (6.7-8.7)	3.9% (3.5-4.3)
HPV-ST 3x	$22.61 (21.59-23.60)	26.3139 (26.2932-26.3363)	$240 (210-280)	33.0% (30.6-35.5)	2.8% (2.4-3.1)
VIA 3x	$23.77 (22.77-24.83)	26.2827 (26.2575-26.3086)	DOM	16.9% (15.4-18.8)	3.5% (3.1-3.9)
HPV-VIA 3x	$23.94 (22.84-25.10)	26.2860 (26.2612-26.3117)	DOM	18.4% (16.7-20.5)	3.4% (3.0-3.8)
HPV-ST 5x	$32.24 (31.23-33.05)	26.3345 (26.3164-26.3540)	$470 (410-550)	42.8% (39.8-45.6)	2.4% (2.1-2.7)
VIA 5x	$33.52 (32.58-34.49)	26.2993 (26.2763-26.3235)	DOM	24.2% (22.0-26.4)	3.2% (2.8-3.5)
HPV-VIA 5x	$33.85 (32.72-34.85)	26.3033 (26.2812-26.3272)	DOM	26.1% (23.9-28.5)	3.1% (2.7-3.4)

Note: 1x: screening at age 39; 3x = screening at ages 30, 40 and 50; 5x = screening at ages 30, 35, 40, 45 and 50; DOM: dominated strategy (i.e. more costly and less effective or having a higher ICER than equally or more effective strategies); ICER: incremental cost effectiveness ratio (expressed in 2014 USD per year of life saved).

*Values indicate the mean results across the top 50 best fitting parameter sets. The minimum and maximum values across these 50 parameter sets are shown in parentheses.

[a]Relative reduction in lifetime risk of cancer is compared to no screening

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