IJC
International Journal of Cancer

Cervical cancer screening in low-resource settings: A cost-effectiveness framework for valuing tradeoffs between test performance and program coverage

Nicole G. Campos[1*], Philip E. Castle[2,3], Thomas C. Wright Jr[4] and Jane J. Kim[1]

[1] Department of Health Policy and Management, Harvard T.H. Chan School of Public Health, Center for Health Decision Science, Boston, MA
[2] Global Coalition against Cervical Cancer, Arlington, VA
[3] Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY
[4] Department of Pathology and Cell Biology, Columbia University Medical Center, NY

As cervical cancer screening programs are implemented in low-resource settings, protocols are needed to maximize health benefits under operational constraints. Our objective was to develop a framework for examining health and economic tradeoffs between screening test sensitivity, population coverage and follow-up of screen-positive women, to help decision makers identify where program investments yield the greatest value. As an illustrative example, we used an individual-based Monte Carlo simulation model of the natural history of human papillomavirus (HPV) and cervical cancer calibrated to epidemiologic data from Uganda. We assumed once in a lifetime screening at age 35 with two-visit HPV DNA testing or one-visit visual inspection with acetic acid (VIA). We assessed the health and economic tradeoffs that arise between (*i*) test sensitivity and screening coverage; (*ii*) test sensitivity and loss to follow-up (LTFU) of screen-positive women; and (*iii*) test sensitivity, screening coverage and LTFU simultaneously. The decline in health benefits associated with sacrificing HPV DNA test sensitivity by 20% (*e.g.*, shifting from provider- to self-collection of specimens) could be offset by gains in coverage if coverage increased by at least 20%. When LTFU was 10%, two-visit HPV DNA testing with 80–90% sensitivity was more effective and more cost-effective than one-visit VIA with 40% sensitivity and yielded greater health benefits than VIA even as VIA sensitivity increased to 60% and HPV test sensitivity declined to 70%. As LTFU increased, two-visit HPV DNA testing became more costly and less effective than one-visit VIA. Setting-specific data on achievable test sensitivity, coverage, follow-up rates and programmatic costs are needed to guide decision making for cervical cancer screening.

Epidemiology

Cervical cancer is a leading cause of cancer death among women worldwide,[1] despite the fact that the disease is preventable through screening programs that detect and treat precancerous lesions. While routine screening with Pap smear testing has reduced cervical cancer incidence in the United States and other high-income countries,[2] the implementation of Pap-based screening programs has largely been unsuccessful in most low-resource settings due to a lack of healthcare delivery infrastructure, competing health priorities and limited health budgets. Consequently, nearly 90% of cervical cancer deaths worldwide occur in the developing world.[1] Although opportunities for primary prevention now exist with the availability of two prophylactic vaccines efficacious against HPV types 16 and 18, which cause ~70% of cervical cancers[3,4] and a recently approved 9-valent vaccine against five additional HPV types,[5] screening remains the only form of prevention for 2 to 3 generations of women beyond the adolescent target age for vaccination. Despite the difficulties of implementing and scaling up cervical cancer screening programs, one- and two-visit screen-and-treat approaches using visual inspection with acetic acid (VIA) or human papillomavirus (HPV) DNA testing have been demonstrated to be effective and potentially cost-effective in resource-poor settings.[6–9] Moreover, the World Health Organization has recently recommended the use of HPV testing or VIA for cervical cancer screening in those regions and countries that have not already established an effective, high-coverage Pap-based program.[10]

Inherent in any screening strategy are tradeoffs between test-performance characteristics (*i.e.,* sensitivity to maximize early detection of precancers that can be treated; specificity

Key words: cancer screening, human papillomavirus, HPV DNA tests, uterine cervical neoplasms, decision analysis

Abbreviations: CIN: cervical intraepithelial neoplasia; GDP: gross domestic product; HPV: human papillomavirus; I$: international dollars; ICER: incremental cost-effectiveness ratio; LTFU: loss to follow-up; VIA: visual inspection with acetic acid; YLS: year of life saved

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

Grant sponsor: U.S. National Cancer Institute; **Grant number:** R01CA160744; **Grant sponsor:** Bill & Melinda Gates Foundation
DOI: 10.1002/ijc.29594
History: Received 6 Aug 2014; Accepted 21 Apr 2015; Online 5 May 2015

***Correspondence to**: Nicole G. Campos, 718 Huntington Avenue, 2nd Floor, Boston, MA 02115, USA, Tel.: [617-432-2019], Fax: +[617-432-0190], E-mail: ncampos@hsph.harvard.edu

What's new?

Cervical cancer is a leading cause of cancer death among women worldwide, despite the fact that the disease is preventable through screening programs. While routine screening with Pap smear testing has reduced incidence in high-income countries, implementation has largely been unsuccessful in low-resource settings due to insufficient budgets, lack of healthcare delivery infrastructure and competing health priorities. Tailored protocols that maximize health benefits under operational constraints are needed. This study presents a framework for examining health and economic tradeoffs between screening test sensitivity, population coverage and follow-up of screen-positive women, to help decision-makers identify where program investments yield the greatest value.

Table 1. Characterization of screening approaches[1]

Modality	Number of clinic visits	Test sensitivity	Quality control constraints	Test cost
VIA	1	Low/Moderate	High	Low
HPV DNA testing (Provider-collection)[2]	2	High	Low/moderate	High
HPV DNA testing (Self-collection)[2]	1-2	Moderate	Low/moderate	Moderate/high

[1]VIA: visual inspection with acetic acid; HPV: human papillomavirus.
[2]Provider-collection refers to collection of HPV DNA specimens by a health care provider. Self-collection refers to collection of HPV DNA specimens by the woman herself.

to minimize the number of healthy women treated unnecessarily) and programmatic attributes (*i.e.,* achievable population coverage of both the initial screening test and necessary diagnostic and treatment procedures; costs; sociocultural preferences; ease of quality control measures; Table 1). For instance, HPV DNA testing is associated with higher sensitivity than VIA to detect precancer[11–13] and a large randomized trial in India demonstrated that a single round of HPV DNA testing in women over age 30 reduced advanced cervical cancer incidence and mortality by 50% whereas VIA did not.[6] The impact of VIA is less robust, with randomized trials finding modest or no associated reductions in cancer incidence[6,8,14] and possible cancer mortality reductions of around 30% that are not evident across all studies.[6,8,14] Yet VIA is associated with programmatic advantages, including lower costs and the ability to screen and treat within a single visit. Even within the screening modality of HPV DNA testing, there are tradeoffs between logistical considerations, such as patient ("self")- *versus* provider-collection of specimens. While self-collection of a vaginal specimen requires fewer clinical resources, is less dependent on health care infrastructure and may be more acceptable to women in some settings than clinic-based screening—thus enabling greater participation rates[15–17]—this approach tends to have lower sensitivity for detecting precancerous lesions than when a provider collects the specimen, depending on what test is used.[18,19]

As cervical cancer screening programs are developed and scaled up in low-resource settings, decision makers will need to develop evidence-based, setting-specific protocols to maximize health benefits under operational constraints. Acknowledging that country-specific data are limited, we developed a framework for examining the health and economic tradeoffs between screening test sensitivity and the programmatic attributes of population coverage and follow-up of screen-positive women. This framework aims to (*i*) help decision makers identify where program investments yield the greatest value, given a program's current operating parameters; and (*ii*) determine circumstances under which a decision maker might preferentially invest in one strategy *versus* another. We illustrate the utility of this framework by presenting a stylized example of a single lifetime screening in Uganda.

Material and Methods

Model overview

We used a previously developed, individual-based Monte Carlo simulation model of the natural history of HPV and cervical cancer (Fig. 1) to estimate lifetime health and economic outcomes as test characteristics and programmatic attributes associated with screening were varied.[20–24] 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, histologic grade of precancer [*i.e.,* cervical intraepithelial neoplasia (CIN) grade 2 or 3] and stage of cancer. States are further stratified by oncogenic HPV types 16, 18, 31, 33, 45, 52 and 58, other oncogenic types and nononcogenic types. Transitions between health states can vary by factors such as age, HPV type, duration of infection or lesion status, a woman's history of prior HPV infection and patterns of vaccination and/or screening. The model tracks disease progression and regression, clinical events and economic outcomes over the lifetime for each individual woman, which are then aggregated for analysis to estimate the population impact. 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.

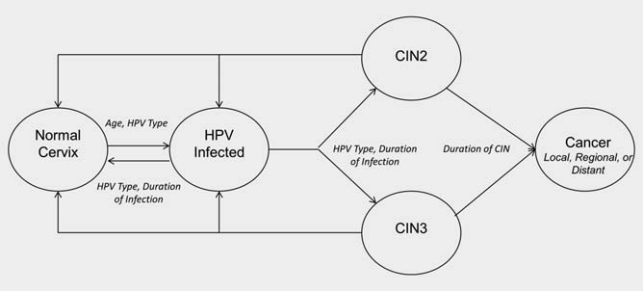

Figure 1. Cervical cancer natural history model. HPV infections and precancer are stratified by genotype (16, 18, 31, 33, 45, 52, 58, other oncogenic types and nononcogenic types). Precancerous health states were considered as heterogeneous entities with differential probabilities of regression and progression to cancer. Progression to cancer required infection with an oncogenic type. Cancer could be symptom-detected or screen-detected at either the local, regional or distant stage. HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia (grade 2 or 3). This diagram is reproduced with permission from: Campos NG, Maza M, Alfaro K, Gage JC, Castle PE, Felix JC, Cremer ML and Kim JJ. The comparative and cost-effectiveness of HPV-based cervical cancer screening algorithms in El Salvador. International Journal of Cancer 2015. Published by Wiley; © 2015 UICC.

A previous version of the model had been calibrated to epidemiologic data from Uganda using a likelihood-based approach and was used for analyses regarding HPV vaccination.[9,23] For this analysis, we used similar calibration methods to fit an updated version of the model (described above)[24] to age-specific prevalence of carcinogenic HPV,[13] age-specific cervical cancer incidence[25] and type distribution of HPV16 and HPV18 in cancer.[26] We used the parameter set that achieved the best simultaneous fit to all calibration target data for analysis. Screening costs included direct medical and patient time/transportation costs based on an analysis of screening in Kenya.[7,9] Further details are presented in the Supporting Information Appendix.

Analytic approach

In our stylized example, we assumed screening occurs once in a woman's lifetime at age 35, when prevalence of precancer and early, treatable invasive cervical cancer in the absence of screening is high. For VIA, we assumed that women who were screen-positive and eligible for cryosurgery were treated in a single clinical visit; for those not eligible for cryosurgery, we assumed referral to a secondary facility for further diagnostic testing and treatment. For HPV DNA testing, we assumed women were screened during the first visit and returned for a second visit to obtain results and, if they screened positive and were eligible, received cryosurgery. We selected one-visit VIA and two-visit HPV testing to focus attention on the main parameters of interest in this analysis: test sensitivity, loss to follow-up (LTFU) between visits and screening coverage.

We conducted three distinct analyses to assess the relative impacts and tradeoffs of: (*i*) test sensitivity and screening coverage; (*ii*) test sensitivity and LTFU of screen-positive women; and (*iii*) test sensitivity, screening coverage and LTFU simultaneously. To assess the tradeoff between test sensitivity and population coverage, we explored the impact of varying HPV DNA test sensitivity (defined as the probability of testing positive among women with precancer CIN grade 2 and more severe [CIN2+]) and population coverage from 30 to 100%, holding other parameters constant. For this baseline analysis, we held test specificity at ~80% and LTFU between visits at 10%. In a scenario analysis, we examined the impact of a potential shift from provider-collection of HPV DNA samples, with 90% sensitivity and population coverage ranging from 30 to 70%, to self-collection, with lower (70%) sensitivity but gains in population coverage ranging from 10 to 40%.

We assessed the tradeoff between test sensitivity and LTFU by comparing two different screening modalities: two-visit HPV DNA testing and one-visit VIA. We assumed test sensitivity for VIA ranged from 40 to 60% and for HPV DNA testing ranged from 70 to 90%, in accordance with recent meta-analyses of test performance studies.[11,19] We varied LTFU (defined as the proportion of women who do not return for each subsequent clinical encounter, relative to the previous visit) from 10 to 60% and held other parameters constant; we held specificity and population coverage at ~80%.

To assess the simultaneous impact of test performance, screening coverage and LTFU, analyses were conducted first assuming only HPV DNA testing was available and then assuming both HPV testing and VIA were available. We assumed HPV test sensitivity was 70% (representing self-collection) or 90% (representing provider-collection) and VIA sensitivity was 50%. We varied population coverage from 30 to 100% (assuming that coverage was equivalent for the clinic-based strategies of provider-collection and VIA) and LTFU from 10 to 60%.

Model outcomes included reductions in the lifetime risk of cervical cancer, total lifetime costs (in 2005 international dollars [I$]) and life expectancy. Cost-effectiveness results were expressed using incremental cost-effectiveness ratios (ICERs), defined as the additional cost of a particular strategy divided by its additional health benefit, compared with the next most costly strategy after eliminating strategies that are dominated (defined as more costly and less effective, or having higher ICERs than more effective options). Consistent with guidelines for cost-effectiveness analysis,[27,28] future costs and life-years were discounted at a rate of 3% per year to reflect time preferences.

Results

Test sensitivity and population coverage: HPV DNA testing

As HPV DNA test sensitivity and population coverage varied from 30 to 100%, we found that improvements in test sensitivity yielded similar reductions in cancer incidence as comparable gains in population coverage. One-time screening at age 35 yielded cancer incidence reductions of 15.8% to 48.9% as test sensitivity varied from 30 to 100% and other

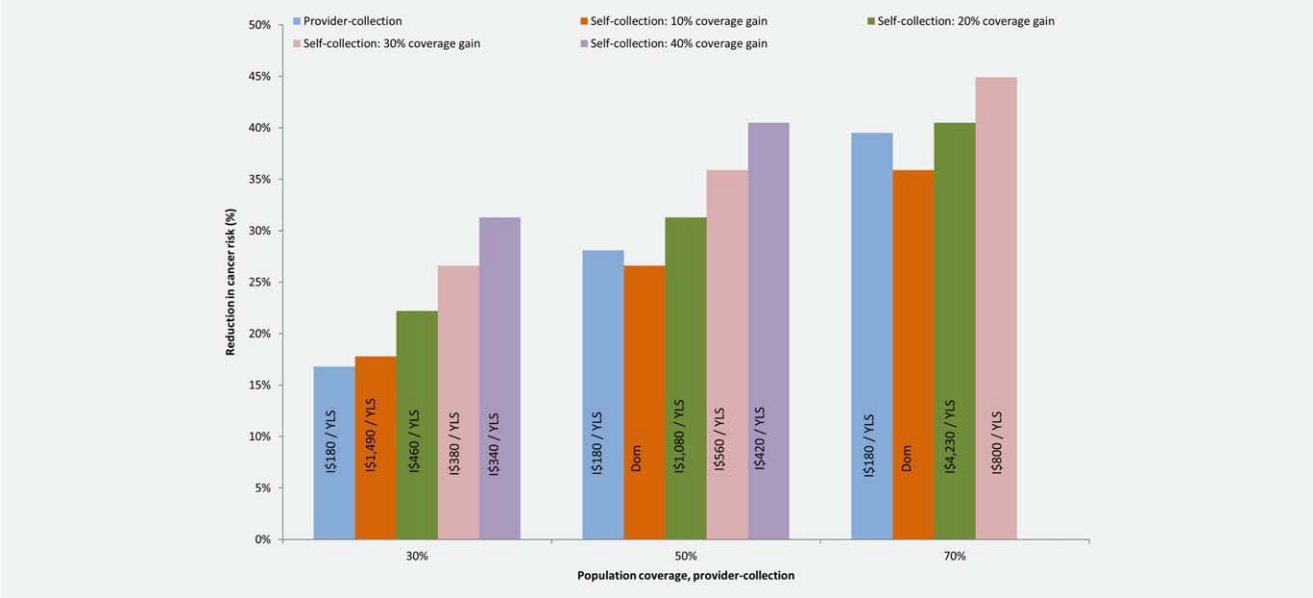

Figure 2. HPV self- *versus* provider-collection: Impact of population coverage level on lifetime risk of cancer and incremental cost-effectiveness ratios. Colored bars represent the reduction in lifetime risk of cancer (relative to no screening, on the y-axis) of provider- and self-collected HPV DNA specimens at various population coverage levels of provider-coverage (on the x-axis). Blue bars represent provider-collection at the specified level; orange, green, pink and purple bars represent self-collection yielding absolute coverage gains of 10, 20, 30 and 40%, respectively, compared with provider-collection. Incremental cost-effectiveness ratios are displayed within the bars, with provider-collection compared with no screening and self-collection compared with provider-collection. Sensitivity values were assumed to be 90 and 70% for provider- and self-collection, respectively. Dom: dominated strategy; I$: international dollars (2005); YLS: year of life saved. Uganda per capita GDP: I$1,165.[29] [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

parameters were held constant. When population coverage was varied over the same range, cancer incidence reductions ranged from 15.1% to 50.6%, all else being equal. Across the range we examined, test sensitivity had little impact on total lifetime costs per woman ($17.06–$19.07), as rising costs due to increased lesion detection were mostly offset by savings from cancer prevention. Population coverage, however, increased costs from $13.26 to $18.96 as more women received screening and follow-up.

In a scenario analysis comparing provider-collection of HPV samples with self-collection, we explored the tradeoff between test sensitivity and population coverage. We assumed self-collected sampling for HPV testing achieved higher coverage than provider-collected sampling but had lower sensitivity (70 *versus* 90%). When coverage with provider-collection was low (*i.e.,* 30%), self-collection that achieved minimally greater coverage (*i.e.,* 40%) yielded slightly greater reductions in cancer incidence (Fig. 2). As coverage with provider-collection increased to 40%, a 10% absolute gain in coverage associated with self-collection was no longer sufficient to offset the reduced sensitivity of the sampling method. Provider-collection was associated with greater reductions in cancer incidence unless self-collection could increase coverage by >10%. Once coverage gains attributable to self-collection increased by 20% or more, the decrement in sensitivity associated with self-collection was more than offset by gains in coverage, yielding greater health benefits than provider-collection at a lower coverage level.

Under these scenarios, the programmatic cost of self-collection was always higher than provider-collection due to the greater cost of covering more women, yet the ICERs relative to provider-collection decreased as coverage gains increased. For example, at 50% coverage with provider-collection, a 10% gain in coverage attributable to self-collection was dominated, but a 40% gain in coverage yielded an ICER of I$420 per YLS. At higher levels of baseline coverage with provider-collection, the marginal benefit of increased coverage attributable to self-collection diminished and ICERs rose. While a 30% gain in coverage attributable to self-collection yielded an ICER of I$380 per YLS when baseline coverage with provider-collection was 30%, a 30% gain when baseline coverage was 70% yielded an ICER of I$800 per YLS.

Test sensitivity and LTFU: one-visit *via versus* two-visit HPV DNA testing

We examined the tradeoff between test sensitivity and LTFU by comparing one-visit VIA with two-visit HPV DNA testing across a reasonable range of uncertainty in test sensitivity for both tests (40–60% for VIA; 70–90% for HPV DNA testing); coverage was held constant at 80%. When LTFU was low (*e.g.,* 10%), HPV DNA testing was consistently more effective than VIA, reducing cancer incidence by 35.9 to 45.3% (Table 2). By comparison, VIA reduced cancer incidence by 19.4 to 28.1%. ICERs varied depending on the relative sensitivity of each test. When sensitivity of both tests was low (40% for VIA; 70% for HPV DNA testing), VIA cost I$220 per YLS and HPV

Table 2. Incremental cost-effectiveness ratios, one-visit VIA *versus* two-visit HPV DNA testing strategies[1]

Screening modality	Test sensitivity[2]	Reduction in cancer incidence[3]	ICER (I$/YLS)
LTFU:[4] 10%			
VIA	40	19.4%	220
HPV	70	35.9%	300
VIA	40	19.4%	Dom
HPV	80	40.5%	210
VIA	40	19.4%	Dom
HPV	90	45.3%	180
VIA	60	28.1%	140
HPV	70	35.9%	850
VIA	60	28.1%	140
HPV	80	40.5%	410
VIA	60	28.1%	140
HPV	90	45.3%	260
LTFU:[4] 40%			
VIA	40	17.7%	240
HPV	70	21.9%	1,360
VIA	40	17.7%	240
HPV	80	24.6%	620
VIA	40	17.7%	240
HPV	90	27.5%	380
VIA	60	25.6%	140
HPV	70	21.9%	Dom
VIA	60	25.6%	140
HPV	80	24.6%	Dom
VIA	60	25.6%	140
HPV	90	27.5%	13,750
LTFU:[4] 60%			
VIA	40	17.0%	240
HPV	70	14.2%	Dom
VIA	40	17.0%	240
HPV	80	16.0%	Dom
VIA	40	17.0%	240
HPV	90	17.8%	Dom
VIA	60	24.6%	140
HPV	70	14.2%	Dom
VIA	60	24.6%	140
HPV	80	16.0%	Dom
VIA	60	24.6%	140
HPV	90	17.8%	Dom

[1]VIA: visual inspection with acetic acid; HPV: human papillomavirus; ICER: incremental cost-effectiveness ratio; I$: 2005 international dollars; LTFU: loss to follow-up; YLS: year of life saved; Dom: dominated (*i.e.,* either more costly and less effective, or having a higher incremental cost-effectiveness ratio than a more effective strategy). Assumes 80% population coverage. ICERs are calculated for each pair of VIA and HPV test sensitivity levels, given the level of LTFU. Uganda per capita GDP: I$1,165.[29]
[2]Test sensitivity is defined as the proportion of women with CIN grade 2 or higher (CIN2+) who test positive.
[3]Percent reduction in cancer incidence relative to no screening.
[4]LTFU is defined as the proportion of women who do not return for each subsequent clinical encounter, relative to the previous visit (which may include the results/cryotherapy visit for two-visit HPV DNA testing or diagnostic confirmation and treatment visits for one-visit VIA or two-visit HPV DNA testing).

DNA testing cost I$300 per YLS. These ICERs decreased as the sensitivity of both tests rose and HPV DNA testing with 90% sensitivity cost I$260 per YLS when compared to VIA with 60% sensitivity (I$140 per YLS). When the discrepancy in test sensitivity between modalities was greatest (*i.e.,* when sensitivity of HPV DNA testing was 80–90% and VIA was 40%), HPV DNA testing was the dominant screening strategy.

As LTFU reached 40%, the reductions in cancer incidence with one-visit VIA changed only marginally and ranged from 17.7 to 25.6% relative to no screening; this slight decline in effectiveness was due to a small proportion of women who were ineligible for cryotherapy being lost prior to further diagnostic testing and treatment. Two-visit HPV DNA testing became dramatically less effective as fewer women returned for screening results and treatment, with cancer reductions ranging from 21.9 to 27.5% as sensitivity was varied from 70 to 90%. While ICERs associated with VIA increased only slightly, HPV DNA testing was either dominated or prohibitively expensive (I$13,750 per YLS) when the sensitivity of VIA was 60%. When the sensitivity of VIA was 40%, HPV DNA testing cost I$380 to I$1,360 per YLS as HPV test sensitivity varied from 70 to 90%, reflecting the declining effectiveness of two-visit HPV testing relative to VIA when LTFU is high.

As LTFU reached 60% per visit, two-visit HPV DNA testing was consistently more costly and less effective than VIA.

We present results that include a 1-visit HPV DNA testing strategy in the Supporting Information Appendix.

Test sensitivity, population coverage and LTFU

When we simultaneously varied test sensitivity, population coverage and LTFU, results depended upon our assumptions about which screening modalities were available. Figure 3 displays a grid of cost-effectiveness results when we assumed only HPV DNA testing was available, with either provider-collection (90% sensitivity) or self-collection (70% sensitivity). The rank ordering of strategies changed as relative coverage

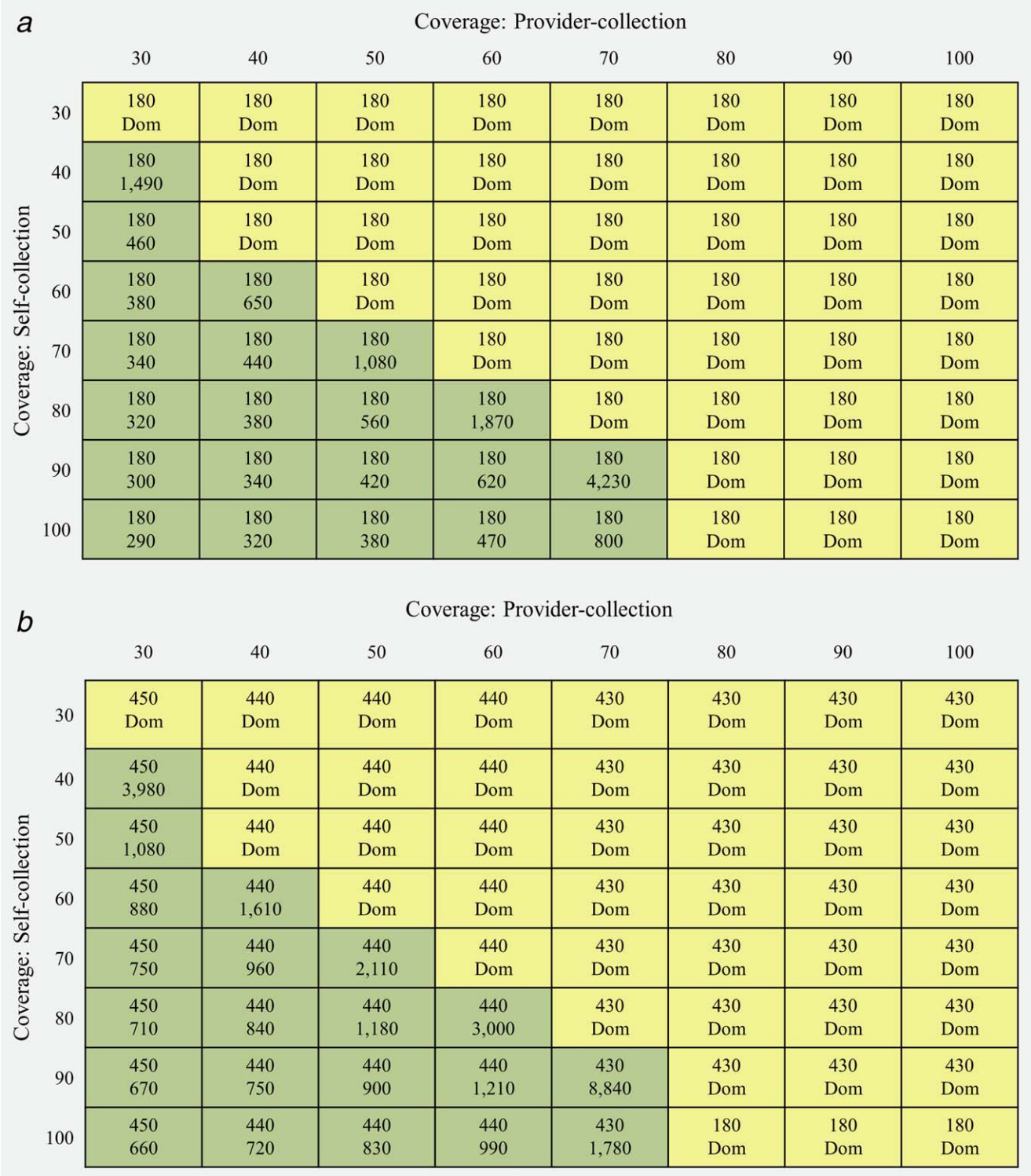

Figure 3. Incremental cost-effectiveness ratios for two-visit HPV self- and provider-collection, by level of population coverage and LTFU. The grid displays incremental cost-effectiveness ratios (ICERs) associated with level of population coverage (varied from 30 to 100%) of HPV provider-collection (columns) *versus* self-collection (rows), assuming levels of 90 and 70% test sensitivity, respectively. Yellow squares indicate that self-collection is dominated at specified levels of coverage, while green squares indicate ICERs for provider- (top) and self- (bottom) collection. LTFU is varied from 10% (panel a) to 60% (panel b). Dom: dominated strategy; LTFU: loss to follow-up. Uganda per capita GDP: I$1,165.[29] [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

varied, but did not change as LTFU simultaneously varied from 10% to 60%. Provider-collection dominated self-collection when coverage gains associated with self-collection were less than or equal to 10%, except when coverage level was low (30%). When self-collection yielded coverage gains of 20% or more, it was consistently more effective than and no longer dominated by provider-collection (except when provider-collection coverage level was 80%), although the ICERs for self-collection remained higher than those for provider-collection due to greater population coverage. ICERs for self-collection were lower (*i.e.,* more attractive) when baseline levels of provider-coverage were low and coverage gains associated with self-collection were high. The relationship between coverage and test sensitivity of provider- *versus* self-collection did not change as LTFU varied from 10% (Figure 3, panel a) to 60% (Figure 3, panel b). However, ICERs associated with both provider- and self-collection rose substantially as fewer women received screening results and necessary treatment. For instance, provider-collection at 50% coverage cost I$440 per YLS when LTFU was 60% (relative to I$180 per YLS in the comparable scenario when LTFU was 10%), while self-collection associated with coverage gains of 20% cost I$2,110 per YLS when LTFU was 60% (up from I$1,080 per YLS when LTFU was 10%).

Figure 4 displays a grid of cost-effectiveness results when we assumed both one-visit VIA (with 50% sensitivity) and two-visit HPV DNA testing (either provider- or self-collection) were available. In this scenario, the rank ordering of strategies depended upon both population coverage and LTFU. When LTFU was low (*i.e.,* 10%; Figure 4, panel a) and HPV self-collection yielded coverage gains of 10% or less, VIA and HPV provider-collection were the only attractive strategies. VIA cost I$170-I$180 per YLS, depending on coverage level, while HPV provider-collection cost I$190 per YLS; these ICERs remained stable due to the proportional incremental increases in costs and health benefits associated with expanded coverage when other variables were held constant. The one exception occurred when coverage associated with HPV provider-collection and VIA was 30% and HPV self-collection coverage was 40%, in which case self-collection was the most effective but also most costly strategy at I$1,490 per YLS. As coverage gains attributable to self-collection increased, self-collection became more attractive with ICERs ranging from I$290 to I$4,230 per YLS, depending on baseline level of coverage with VIA and provider-collection.

When LTFU reached 60% (Figure 4, panel b), VIA dominated both HPV provider- and self-collection unless coverage associated with VIA was very low (*i.e.,* 30%) and HPV self-collection yielded coverage gains of 20 to 30% or more. Even when HPV self-collection was not dominated by VIA, ICERs were higher than those for VIA (I$910 to I$7,090 per YLS for HPV self-collection *vs*. I$180-I$190 per YLS for VIA).

Discussion

Our primary objective was to develop a framework to help decision makers identify where program investments toward cervical cancer screening yield the greatest value, given a program's current operating parameters. We present this framework in the context of examining health and economic tradeoffs between screening test sensitivity and programmatic attributes, including population screening coverage and LTFU rates between clinical visits. Using a stylized example of one-time screening at age 35 in Uganda, our modeling analysis demonstrates that commensurate improvements in HPV DNA test sensitivity and population coverage led to comparable health gains. All other variables being equal, expanding coverage was more costly. Findings from our scenario analysis comparing provider- *versus* self-collection of HPV samples suggest that under certain circumstances, self-collection may yield greater health benefits than provider-collection despite lower test sensitivity. By examining the relative effectiveness and cost-effectiveness of strategies that embody the tradeoff between population coverage and test sensitivity, we demonstrate that a shift to self-collection may be desirable if anticipated coverage gains exceed 10–20%, particularly if achievable coverage with provider-collection is low. The presentation of a range of results allows decision makers to estimate the relative health and economic impacts of a shift in strategies, based on a current program's parameters and anticipated improvements. The impact of parameter uncertainty can also be considered and may help determine if further data collection is needed prior to a decision.

In a comparison of one-visit VIA and two-visit HPV DNA testing, we quantified the tradeoff between the higher retention and lower costs that are considered strengths of VIA and the enhanced test sensitivity associated with HPV DNA testing. The rank ordering of strategies depended heavily upon values for test sensitivity and LTFU. When LTFU was 10%, HPV DNA testing was more effective than VIA for the range of test sensitivity values we examined; HPV testing dominated VIA when the discrepancy between test sensitivity values was high. As LTFU increased to 40%, HPV testing remained slightly more effective (and more costly) than VIA unless the HPV test performed at the lower bounds of sensitivity (*i.e.,* 70 to 80%) while VIA operated at the upper bounds (*i.e.,* 60%), in which case HPV testing was dominated. When LTFU reached 60%, VIA dominated HPV DNA testing. If an existing VIA-based screening program suffers from low sensitivity, decision makers can use the framework and results presented to estimate the reduction in cancer risk and ICERs associated with either increased VIA training efforts to improve performance or a shift to HPV testing. If an existing two-visit HPV testing program suffers from high attrition rates after the initial screening visit, decision makers have information on the potential impact of a shift to VIA in remote areas or increased efforts at reducing LTFU.

When test sensitivity, population coverage and LTFU were varied simultaneously, the rank ordering of VIA and HPV DNA testing changed dramatically across the range we examined. While the assumptions underlying results presented in Figure 4—for instance, that HPV provider-collection and VIA achieve similar coverage levels and that relative test sensitivity

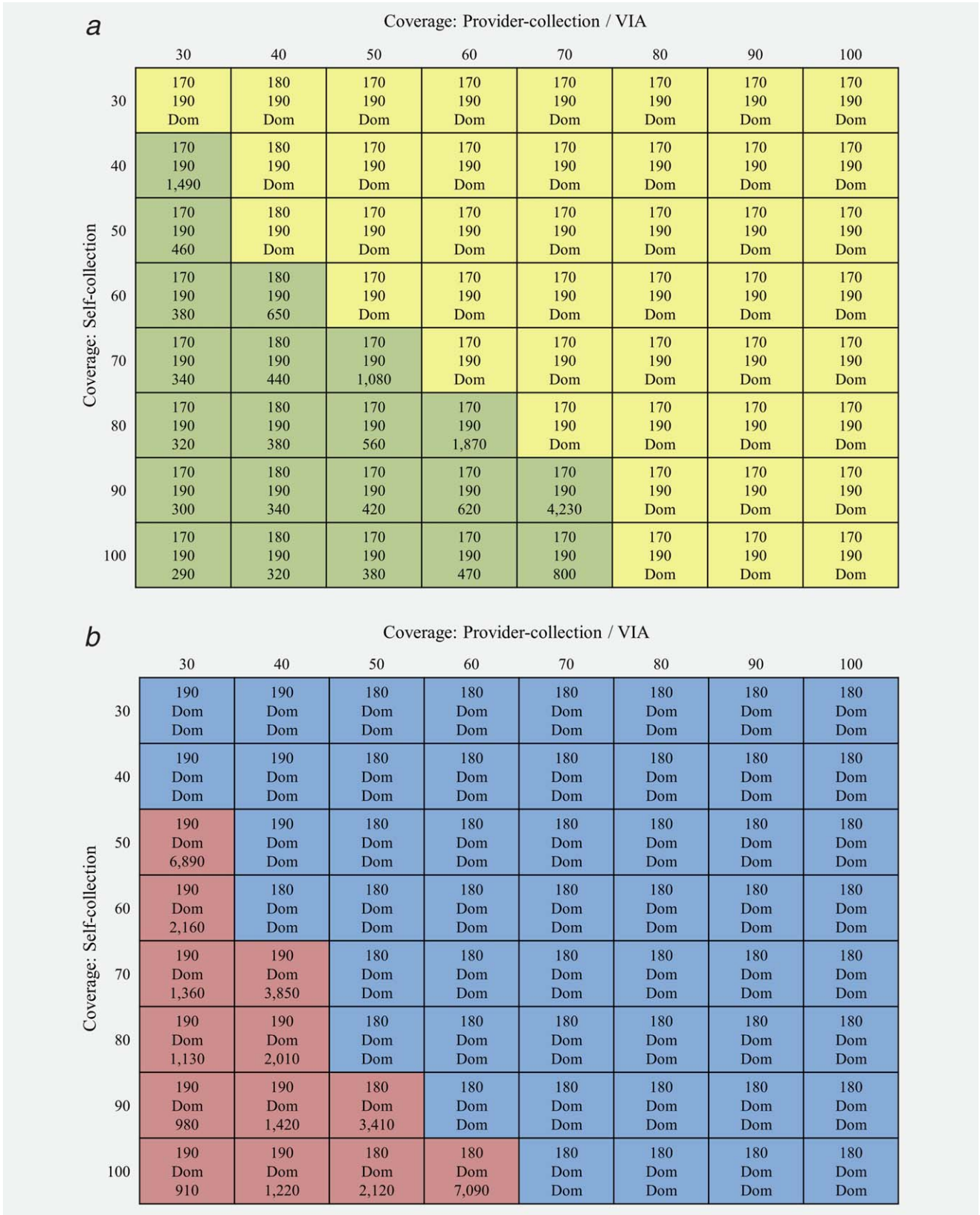

Figure 4. Incremental cost-effectiveness ratios for one-visit VIA, two-visit HPV self-collection and two-visit HPV provider-collection, by level of population coverage and LTFU. The grid displays incremental cost-effectiveness ratios (ICERs) associated with level of population coverage of VIA and HPV provider-collection (columns) *versus* HPV self-collection (rows), assuming 50% (VIA), 70% (HPV self-collection) and 90% (HPV provider-collection) test sensitivity. Coverage levels for VIA and HPV provider-collection were assumed to be equivalent due to the traditionally clinic-based nature of these strategies. Yellow squares indicate that self-collection is dominated, green squares indicate ICERs for all strategies (VIA: top; HPV provider-collection: middle; HPV self-collection: bottom), blue squares indicate that HPV self- and provider-collection are dominated, and orange squares indicate that HPV provider-collection is dominated. LTFU is varied from 10% (panel a) to 60% (panel b). Dom: dominated strategy; LTFU: loss to follow-up. Uganda per capita GDP: I$1,165.[29] [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

levels apply in a given setting—may need to be modified as setting-specific data become available, such grids provide a "roadmap" for decision makers to identify what tradeoffs might be worthwhile between test sensitivity, coverage and LTFU based on a program's current operating stance and estimated improvements that might be achieved and at what cost.

There is no universal criterion that defines a threshold cost-effectiveness ratio below which an intervention is considered good value for money. One common benchmark suggests that 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."[30] By this heuristic and given Uganda's per capita GDP of I$1,165,[29] HPV self-collection could be a very cost-effective alternative to provider-collection despite the higher programmatic cost of covering more women, so long as coverage gains reach 20 to 30% and baseline coverage with provider-collection is <70%. Provided that LTFU is 40% or less and VIA sensitivity is low, HPV testing would be considered good value for public health dollars; these findings are robust even as the direct medical costs associated with HPV testing are varied (see Supporting Information Appendix). If LTFU reaches 60%, two-visit HPV testing is unlikely to be an attractive alternative to VIA regardless of VIA test performance unless HPV DNA testing is associated with significant gains in screening coverage. Of note, the attractiveness of HPV DNA testing relative to VIA could increase dramatically if screening and treatment could be provided in a single visit (*i.e.,* point-of-care testing), which may be an option with newly available "rapid" HPV tests, some of which can be completed in one hour.[31] However, these next-generation HPV tests will need to be validated against currently available tests in low-resource settings and offered at affordable prices, if they are to further improve the relative attractiveness of HPV testing.

We present our framework with a stylized example because data on programmatic costs are limited. For example, we assumed the costs of HPV self- and provider-collection strategies were similar, aside from differences due to test sensitivity and the proportion of women covered. This assumption was based on a scenario where self-collection occurs at the clinic and requires one visit for screening and a second for receiving results and treatment (see Supporting Information Appendix for analysis of a 1-visit self-collection strategy taking place at the clinic); however, different options for self-collection may lead to differential costs. While the two-visit clinic-based approach we assumed is one possible delivery mechanism, other possibilities include mobile clinics and home visits by community health workers, which might increase direct medical costs while reducing women's time and transportation costs, as well as LTFU. An exploratory analysis, in which we assumed a 20% increase in direct medical costs and a 75% decrease in patient time and transportation costs associated with the screening visit, yielded a similar rank ordering of provider- and self-collection, but ICERs associated with self-collection were reduced due to the relatively high burden of screening costs attributable to women's time and transportation in Uganda (see Supporting Information Appendix).

Furthermore, we did not include the programmatic costs of scaling up coverage or reducing LTFU for either VIA or HPV testing. There are likely to be economies of scale as screening coverage increases to a certain threshold, after which the marginal cost of covering additional women will likely increase. The impact of these costs and the threshold at which the cost per woman screened increases or decreases is unclear. The costs of improving patient compliance with follow-up visits may alter the relative cost-effectiveness of one-visit and two-visit strategies; one study found that a community health worker intervention substantially improved follow-up, but was costly to implement.[32] Without data on programmatic costs, the true tradeoff between screening strategies cannot be captured. As further cost data become available from demonstration projects, it will be critical to update the assumptions underlying our framework to determine circumstances under which a decision maker might preferentially invest in one strategy *versus* another.

There are important limitations to this analysis. The values we selected for model inputs of interest, while based on thorough reviews of the literature, may not reflect the range of parameter uncertainty in the setting of Uganda. With regards to test performance values, the test sensitivity of VIA varies widely across settings. Several studies suggest that VIA sensitivity is often overestimated due to imperfect verification and the correlation between colposcopically directed biopsies and VIA findings (given the visual nature of both the screening and confirmatory test).[33] We assumed VIA sensitivity ranged from 40 to 60%, approximately corresponding with the 95% confidence interval suggested by a recent meta-analysis that included a substantial number of studies that relied upon disease confirmation with four-quadrant biopsies rather than colposcopically directed biopsies alone.[11] A recent clinical trial in India that evaluated the impact of four rounds of VIA screening relative to the standard of care in over 75,000 women reduced cervical cancer mortality by 31% but did not reduce cervical cancer incidence.[14] Another recent trial found that VIA was not associated with reductions in advanced cancers or deaths.[6] These findings may indicate that the sensitivity of VIA for cervical precancerous lesions may be <40% in a real-world setting, where the screening test may be delivered by many providers without rigorous quality control.

While clinical studies demonstrate less variability in HPV DNA test performance, there are few studies that have assessed the sensitivity of self-collection and HPV testing. We conservatively assumed HPV self-collection was 70% sensitive for detection of CIN2+, but self-collection will be associated with greater health gains and lower ICERs if sensitivity is closer to 80%, as suggested by a recent meta-analysis,[19] or even higher as suggested by a recent study from China.[34]

We held values of specificity at approximately 80% for all screening modalities. Varying specificity within the range of uncertainty (70–90%) has a negligible impact on health benefits and for a test with 80% sensitivity only changes the ICER for 2-visit HPV testing from I$210 to I$240 per YLS. In women with HIV, specificity of HPV testing may be somewhat lower due to increased prevalence of HPV,[35] leading to increased referrals and possible overtreatment of women; the impact of this potentially unnecessary care on the cost-effectiveness of population-based screening is unclear and we have not considered the possible harms of overtreatment in this analysis. However, there may be potential health benefits associated with treating HPV infections prior to progression to precancerous lesions, as evidence suggests that a one-time positive HPV test is associated with CIN3+ up to 18 years later.[36] A recent randomized trial in South Africa found that a screen-and-treat approach with HPV DNA testing led to reduced incidence rates of CIN2+ in HIV-positive and HIV-negative women.[37] Moreover, speculatively, the ablation of the squamocolumnar junction may reduce future risk of acquiring a new HPV infection that could progress to cancer.[38] We focused the present analysis on varying test sensitivity, which is a more influential parameter in determining health outcomes and cost-effectiveness when screening opportunities are limited.

Although self-collection of HPV samples may potentially improve coverage of under-screened women by eliminating the needs for a clinic visit (*e.g.,* with home kits) and invasive pelvic exam, few studies in low-resource populations have evaluated the relative increase in screening uptake associated with self-collection of HPV. A recent trial in Argentina found a four-fold increase in screening uptake with home self-collection.[39] A meta-analysis that examined trials and one comparative study in Europe and North America found that women were twice as likely to participate in screening if they were offered a self-sampling home kit compared to women who were invited to the clinic for Pap testing.[17] Relative compliance was similar for the two North American studies among populations with limited access to health services.[16,40] The response rate for self-collection among under-screened women varied widely, ranging from 6% to 98%. Absolute coverage gains associated with self-sampling will likely depend upon baseline coverage rate and existing health infrastructure. Thus we considered a range of baseline coverage rates (30% to 70%) for provider-collection and potential coverage gains associated with self-collection (10% to 40%) to capture the uncertainty and variability in relative uptake in a low-resource setting.

There are few studies of LTFU in cervical cancer screening programs, but one study from South Africa found that only approximately 60% of scheduled follow-up visits were attended prior to additional outreach attempts by community health workers, suggesting LTFU rates of around 40% in this peri-urban African setting.[32] A recent demonstration project in six African countries, including Uganda, found that of women who screened positive with VIA, 35% were LTFU and did not receive cryotherapy, suggesting a potentially high rate of loss even among high-risk women with a screen-and-treat approach.[41] We varied LTFU over a wide range (10–60%) due to the uncertainty in this parameter. We may have overestimated compliance with treatment for the one-visit VIA strategy by assuming perfect compliance for cryotherapy-eligible women, as screen-and-treat approaches may not always be feasible in resource-limited settings due to equipment malfunction, wait times and women's preferences.[41] Furthermore, we assumed that LTFU rates were similar for each clinical visit, in the absence of data to the contrary. While LTFU rates may increase as women are referred to higher level facilities, it is also possible that women referred to further diagnostic testing and treatment may be more likely to attend visits due to their elevated risk. Whichever of these possibilities holds true, the most influential LTFU rate when comparing one- and two-visit screen-and-treat strategies is associated with the second visit in the two-visit strategy, when cryotherapy occurs.

In addition to uncertainty in test performance and LTFU parameters, there are limited published data on screening costs in Uganda at present. We derived screening costs using indirect estimation techniques as summarized in the Supporting Information Appendix and elsewhere.[9,23]

A further limitation of this analysis is that we focused exclusively on economic constraints, rather than constraints on human resources or infrastructure that afflict many resource-poor settings. We also do not consider how investment in cervical cancer screening programs might bolster or diminish health system responsiveness to other diseases. A country's decision to implement a particular screening strategy will depend upon multiple factors—including sociocultural preferences, which may have varying degrees of malleability by setting—that are beyond the scope of this analysis and are not presently included in the framework we describe here. Rather, our goal is to introduce an objective framework for quantitatively integrating parameters with known relevance to screening program impact across settings and to demonstrate how the framework can be applied in Uganda to inform decision-making and investments. Many cervical cancer screening programs in low-resource countries are in the planning and early implementation phases, still determining which screening strategies are effective and cost-effective in a given setting. There are key variables—test performance, screening coverage and LTFU—that are uncertain. Our analysis demonstrates that, within the current ranges of uncertainty suggested by empirical data, the optimal screening strategy can change. While we have restricted this stylized analysis to one country and selected screening strategies that showcase parameters of interest, the methods and framework we present may be easily adapted to other settings and honed as setting-specific empirical data on achievable coverage, LTFU and costs become available through planning and demonstration projects. While results in other settings may bear qualitative similarities to our findings from Uganda, the framework we present here is not a substitute for country-specific analyses, as results will be driven by setting-

specific information, including data on costs, existing infrastructure and available strategies. However, the overarching framework we present can inform planning, early data collection and value-of-information analyses to enhance implementation of nascent screening programs in countries within and outside of Sub-Saharan Africa.

We present this framework to highlight the potential tradeoffs and relative importance of variables that influence the effectiveness and cost-effectiveness of cervical cancer screening programs in resource-poor settings. By explicitly considering these tradeoffs in the planning and early program evaluation stages through data collection efforts, decision makers can improve the health and economic outcomes associated with screening programs.

Acknowledgements

The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. PEC has received commercial HPV tests for research at a reduced or no cost from Roche, Qiagen, Norchip, Arbor Vita Corporation, BD and mtm; has been compensated financially as a member of a Merck Data and Safety Monitoring Board for HPV vaccines; has been a paid consultant for BD, Gen-Probe/Hologic, Roche, Cepheid, ClearPath, Guided Therapeutics, Teva Pharmaceutics, Genticel, Inovio and GE Healthcare; and has received speaker honoraria from Roche and Cepheid. TCW is a consultant and paid speaker for Roche, BD Diagnostics and Cepheid.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer, 2013.
2. Kitchener HC, Castle PE, Cox JT. Chapter 7: achievements and limitations of cervical cytology screening. *Vaccine* 2006;24Suppl3:S3/63–70.
3. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009;374:301–14.
4. Villa LL, Costa RL, Petta CA, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 l1 virus-like particle vaccine through 5 years of follow-up. *Br J Cancer* 2006;95:1459–66.
5. United States Food and Drug Administration. "FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV." December 10, 2014. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426485. Accessed on March 20, 2015.
6. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. *N Engl J Med* 2009;360:1385–94.
7. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, et al. Cost-effectiveness of cervical-cancer screening in five developing countries. *N Engl J Med* 2005;353:2158–68.
8. Sankaranarayanan R, Esmy PO, Rajkumar R, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet* 2007;370:398–406.
9. Campos NG, Kim JJ, Castle PE, et al. Health and economic impact of HPV 16/18 vaccination and cervical cancer screening in eastern Africa. *Int J Cancer* 2012;130:2672–84.
10. World Health Organization. WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention. Geneva: World Health Organization, 2013.
11. Zhao FH, Lin MJ, Chen F, et al. Performance of high-risk human papillomavirus DNA testing as a primary screen for cervical cancer: a pooled analysis of individual patient data from 17 population-based studies from china. *Lancet Oncol* 2010;11:1160–71.
12. Qiao YL, Sellors JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural china. *Lancet Oncol* 2008;9:929–36.
13. Jeronimo J, Bansil P, Lim J, et al. A multicountry evaluation of careHPV testing, visual inspection with acetic acid, and papanicolaou testing for the detection of cervical cancer. *Int J Gynecol Cancer* 2014;24:576–85.
14. Shastri SS, Mittra I, Mishra GA, et al. Effect of via screening by primary health workers: randomized controlled study in Mumbai, India. *J Natl Cancer Inst* 2014;106:dju009
15. Gravitt PE, Rositch AF. HPV self-testing and cervical cancer screening coverage. *Lancet Oncol* 2014;15:128–9.
16. Castle PE, Rausa A, Walls T, et al. Comparative community outreach to increase cervical cancer screening in the Mississippi delta. *Prev Med* 2011;52:452–5.
17. Racey CS, Withrow DR, Gesink D. Self-collected HPV testing improves participation in cervical cancer screening: a systematic review and meta-analysis. *Can J Public Health* 2013;104:e159–66.
18. Belinson JL, Du H, Yang B, et al. Improved sensitivity of vaginal self-collection and high-risk human papillomavirus testing. *Int J Cancer* 2012;130:1855–60.
19. Arbyn M, Verdoodt F, Snijders PJ, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* 2014;15:172–83.
20. Goldie SJ, Kim JJ, Kobus K, et al. Cost-effectiveness of HPV 16, 18 vaccination in Brazil. *Vaccine* 2007;25:6257–70.
21. Kim JJ, Kuntz KM, Stout NK, et al. Multiparameter calibration of a natural history model of cervical cancer. *Am J Epidemiol* 2007;166:137–50.
22. Kim JJ, Kobus KE, Diaz M, et al. Exploring the cost-effectiveness of HPV vaccination in vietnam: insights for evidence-based cervical cancer prevention policy. *Vaccine* 2008;26:4015–24.
23. Kim JJ, Campos NG, O'Shea M, Diaz M, Mutyaba I. Model-based impact and cost-effectiveness of cervical cancer prevention in Sub-Saharan Africa. *Vaccine* 2013;31S:F60–72.
24. Campos NG, Burger EA, Sy S, et al. An updated natural history model of cervical cancer: derivation of model parameters. *Am J Epidemiol* 2014;180:545–55.
25. Parkin DM, Whelen SL, Ferlay J, et al. Cancer Incidence in Five Continents Vol. I-VIII. Lyon, France: International Association of Cancer Registries CancerBase No. 7, 2005.
26. Odida M, de Sanjose S, Quint W, et al. Human papillomavirus type distribution in invasive cervical cancer in Uganda. *BMC Infect Dis* 2008;8:85
27. Gold MR. Cost-effectiveness in health and medicine. New York: Oxford University Press, 1996.
28. Tan-Torres Edejer T, Baltussen R, Adam T, et al., eds. Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis. Geneva, Switzerland: World Health Organization, 2003.
29. World Bank. World Development Indicators. Available at: http://data.worldbank.org/data-catalog/world-development-indicators Accessed on January 6, 2014.
30. World Health Organization. Macroeconomics and Health: Investing in Health for Economic Development: Report of the Commission on Macroeconomics and Health. Geneva: World Health Organization, 2001.
31. Einstein MH, Smith KM, Davis TE, et al. Clinical evaluation of the Cartridge-based GeneXpert human papillomavirus assay in women referred for colposcopy. *J Clin Microbiol* 2014;52:2089–95.
32. Goldhaber-Fiebert JD, Denny LA, De Souza M, et al. Program spending to increase adherence: South African cervical cancer screening. *PLoS One* 2009;4:e5691
33. Pretorius RG, Bao YP, Belinson JL, et al. Inappropriate gold standard bias in cervical cancer screening studies. *Int J Cancer* 2007;121:2218–24.
34. Zhao FH, Lewkowitz AK, Chen F, et al. Pooled analysis of a self-sampling HPV DNA test as a cervical cancer primary screening method. *J Natl Cancer Inst* 2012;104:178–88.
35. Dartell MA, Rasch V, Iftner T, et al. Performance of visual inspection with acetic acid and human papillomavirus testing for detection of high-grade cervical lesions in HIV positive and HIV negative tanzanian women. *Int J Cancer* 2014;135:896–904.
36. Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four european randomised controlled trials. *Lancet* 2014;383:524–32.
37. Kuhn L, Wang C, Tsai WY, et al. Efficacy of human papillomavirus-based screen-and-treat for cervical cancer prevention among HIV-infected women. *AIDS* 2010;24:2553–61.

38. Herfs M, Yamamoto Y, Laury A, et al. A discrete population of squamocolumnar junction cells implicated in the pathogenesis of cervical cancer. *Proc Natl Acad Sci U S A* 2012;109:10516–21.
39. Arrossi S, Thouyaret L, Herrero R, et al. Effect of self-collection of HPV DNA offered by community health workers at home visits on uptake of screening for cervical cancer (the EMA study): a population-based cluster-randomised trial. *Lancet Glob Health* 2015;3:e85–94.
40. Lazcano-Ponce E, Lorincz AT, Cruz-Valdez A, et al. Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): a community-based randomised controlled trial. *Lancet* 2011;378: 1868–73.
41. World Health Organization. Prevention of cervical cancer through screening using visual inspection with acetic acid (VIA) and treatment with cryotherapy: a demonstration project in six African countries: Malawi, Madagascar, Nigeria, Uganda, the United Republic of Tanzania, and Zambia. Geneva: World Health Organization, 2012.