Papillomavirus Research 1 (2015) 38–58

Contents lists available at ScienceDirect

Papillomavirus Research

journal homepage: www.elsevier.com/locate/pvr

When and how often to screen for cervical cancer in three low- and middle-income countries: A cost-effectiveness analysis

Nicole G. Campos [a,*], Vivien Tsu [b], Jose Jeronimo [b], Mercy Mvundura [c], Kyueun Lee [a], Jane J. Kim [a]

[a] Center for Health Decision Science, Harvard T.H. Chan School of Public Health, 718 Huntington Avenue, Boston, MA, USA
[b] PATH, Reproductive Health Global Program, PO Box 900922, Seattle, WA, USA
[c] PATH, Devices and Tools Program, PO Box 900922, Seattle, WA, USA

ARTICLE INFO

Article history:
Received 28 April 2015
Received in revised form
26 May 2015
Accepted 27 May 2015
Available online 15 June 2015

Keywords:
Cancer screening
Human papillomavirus (HPV)
Cervical cancer
Cost-effectiveness analysis
Visual inspection with acetic acid

ABSTRACT

World Health Organization guidelines recommend that cervical cancer screening programs should prioritize screening coverage in women aged 30 to 49 years. Decisions about target ages and screening frequency depend upon local burden of disease, costs, and capacity. We used cost and test performance data from the START-UP demonstration projects in India, Nicaragua, and Uganda to evaluate the cost-effectiveness of screening at various start ages, intervals, and frequencies. We calibrated a mathematical simulation model of cervical carcinogenesis to each country and compared screening with *care*HPV (cervical and vaginal sampling), visual inspection with acetic acid (VIA), and cytology between the ages of 25 and 50 years, at frequencies of once to three times in a lifetime, at 5- and 10-year intervals. Screening with *care*HPV (cervical sampling) was the most effective and cost-effective strategy in all settings; *care*HPV (vaginal sampling) was only slightly less effective. The most critical ages for screening are between ages 30 and 45 years. Within this age range, screening at certain ages may be relatively more cost-effective, but cancer risk reductions are similar for a given screening test and interval. Screening three times between 30 and 45 years was very cost-effective and reduced cancer risk by ~50%.

1. Introduction

Cervical cancer is the fourth most common cancer in women, resulting in an estimated 528,000 incident cases and 266,000 deaths worldwide in 2012 [1]. Approximately 85% of cases and deaths occur in the developing world, where the implementation of cytology-based screening programs to detect and treat precancerous lesions do not exist, or they have not been effective due to lack of health delivery infrastructure and limited financial resources [2]. Despite the difficulties of implementing organized screening programs, several clinical and economic studies have suggested that one- and two-visit screen-and-treat approaches using visual inspection with acetic acid (VIA) or human papillomavirus (HPV) DNA testing can be feasible, beneficial, and cost-effective in low-resource settings [3–6]. HPV DNA testing is associated with higher sensitivity than VIA to detect precancer [7–9], yet VIA is associated with programmatic advantages, including lower costs and the ability to screen and treat within a single visit. A public–private collaboration has led to the development of *care*HPV (QIAGEN, Gaithersburg, MD), a lower-cost DNA test that can be used in clinics that lack reliable clean water or electricity; the performance of *care*HPV has been validated in demonstration projects and it has been shown to be cost-effective when part of a screen-and-treat algorithm in El Salvador [10].

The World Health Organization (WHO) recommends that screening begin at 30 years of age, with priority given to maximizing population screening coverage of women aged 30 to 49 years rather than maximizing the number of screening tests in an individual woman's lifetime [11,12]. Recommended screening tests include HPV testing and VIA, with suggested rescreening intervals of 3 to 5 years following a negative VIA screening result, and no less than 5 years following a negative HPV test [11,12]. Where high quality cytology (i.e., Pap) programs are already in place, cytology may be used as a screening test [11]. For HIV-infected women or women with unknown HIV status in high endemic areas, rescreening following a negative screening test is recommended within 3 years [11,12]. The WHO guidelines state that screening even once in a lifetime is beneficial, and intervals may depend on available

Abbreviations: CIN, cervical intraepithelial neoplasia; GDP, gross domestic product; HPV, human papillomavirus; I$, international dollar; ICER, incremental cost-effectiveness ratio; VIA, visual inspection with acetic acid; WHO, World Health Organization; YLS, year of life saved

* Corresponding author at: 718 Huntington Avenue, Boston, MA 02115, USA. Tel.: +1 617 432 2019; fax: +1 617 432 0190.
E-mail address: ncampos@hsph.harvard.edu (N.G. Campos).

http://dx.doi.org/10.1016/j.pvr.2015.05.003

resources and infrastructure; decisions about the target ages and frequency of screening depend upon local burden of disease, costs, and infrastructure, and are left to country-level decision makers [12].

In settings where screening may only take place once, twice, or three times in a woman's lifetime, decision makers need information on the optimal screening ages and intervals to maximize the health benefits and value associated with limited screening opportunities. Using cost and test performance data from the Screening Technologies to Advance Rapid Testing–Utility and Program Planning (START–UP) demonstration projects in India, Nicaragua, and Uganda, our objective was to evaluate the cost-effectiveness of screening at various start ages, intervals, and frequencies in resource-limited settings with different epidemiologic profiles.

2. Material and methods

2.1. Analytic overview

We used an existing individual-based Monte Carlo simulation model of the natural history of HPV and cervical cancer to estimate lifetime health and economic outcomes associated with screening with HPV DNA testing, VIA, and cytology at selected ages and intervals [10,14–17]. The model was calibrated to epidemiologic data from India, Nicaragua, and Uganda. Test performance and cost data were drawn from the START–UP multi-site demonstration project conducted in India (Hyderabad), Nicaragua (Masaya Province), and Uganda (Kampala) [7,18]; a fourth site in India was not included in this evaluation. Model outcomes included lifetime risk of cervical cancer, total lifetime costs (in 2011 international dollars [I$]), and life expectancy. Cost-effectiveness ratios 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). While there is no universal criterion that defines a threshold cost-effectiveness ratio, we considered the heuristic that an intervention with an ICER less than the country's per capita gross domestic product (GDP) would be "very cost-effective" and less than three times per capita GDP would be "cost-effective"[19]. In addition to value for money, we estimated the financial costs of screening to determine a country's budget impact over a 1-year period. Consistent with guidelines for cost-effectiveness analysis [20–22], we adopted a societal perspective, including costs irrespective of the payer, and discounted future costs and life-years at a rate of 3% per year to account for time preferences.

2.2. Mathematical simulation model

The natural history model of cervical carcinogenesis in an individual woman is represented as a sequence of monthly transitions between mutually exclusive health states, including type-specific HPV infection status, grade of precancer (i.e., cervical intraepithelial neoplasia [CIN] grade 2 or 3), and stage of invasive cancer [10,14]. Transition probabilities may vary by age, HPV type, duration of infection or precancerous lesion status, and prior HPV infection. Cancer detection can occur through symptoms or via screening. Each month, death can occur from non-cervical causes or from cervical cancer after its onset. 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.

Details of the model parameterization process, including calibration, have been previously published [10,14,15] and are described in the Appendix. Briefly, we estimated baseline "prior" input parameter values for natural history transitions using longitudinal data [23–27]. To reflect heterogeneity in age- and type-specific HPV incidence between settings, as well as natural immunity following initial infection and uncertainty in progression and regression of precancer, we set plausible ranges around these input parameter values. Repeated model simulations in the absence of any intervention selected a single random value from the plausible range for each uncertain parameter, creating a unique natural history input parameter set. We then computed a goodness-of-fit score by summing the log-likelihood of model-projected outcomes for each unique parameter set to represent the quality of fit to country-specific epidemiologic data (i.e., calibration targets). For each country, we selected the top 50 input parameter sets that produced good fit to the epidemiologic data to use in analyses as a form of probabilistic sensitivity analysis [14,15,28]. Model fit to empirical data on age-specific high-risk HPV prevalence data from the START–UP projects and age-specific cancer incidence is displayed in the Appendix. We report results as the mean and range of outcomes across these top 50 parameter sets; incremental cost-effectiveness ratios are reported as the ratio of the mean costs divided by the mean effects of one strategy versus another across sets [29].

2.3. Strategies

We assumed available screening tests included *care*HPV (provider-collected [cervical] and self-collected [vaginal] sampling), VIA, and conventional cytology, with site-specific test performance parameters informed by the START–UP demonstration projects. Self-collection of vaginal HPV samples does not require pelvic evaluation, and thus was evaluated as an alternative to provider-collection. Test performance and treatment parameters are presented in Table 1 [7,30–36]. For VIA, we assumed that women who were screen-positive and eligible for cryosurgery were generally treated at the same clinical visit but that a proportion refused immediate treatment and either returned for a subsequent visit or was lost to follow-up; for those not eligible for cryosurgery, we assumed referral to a secondary facility for further diagnostic testing and treatment. For *care*HPV testing, we assumed women were screened during the first visit and returned for a second visit to obtain results; if they screened positive and were eligible, most received same-day cryosurgery. Cytology included an initial visit for screening, a second visit to receive results, a third visit to receive diagnostic colposcopy and biopsy for screen-positive women, and if necessary, a fourth visit for treatment. Treatment protocols for women who were not eligible for immediate cryosurgery, and management following treatment, were based on current practice in each country and are documented in the Appendix.

To focus on the ages recommended by the WHO as well as ages when opportunistic screening may occur, we evaluated each screening test at the following frequencies, ages, and intervals: (1) once in a lifetime at ages 25, 30, 35, 40, 45, or 50 years; (2) twice in a lifetime at ages 25 and 35 years; 30 and 40 years; or 35 and 45 years; and (3) three times in a lifetime at ages 25, 35, and 45 years; 30, 35, and 40 years; 35, 40, and 45 years; or 30, 40, and 50 years. At each target age in a given screening strategy, the model randomly selected 70% of women for screening. Thus, for screening at later ages in strategies involving two or three screenings in a lifetime, women did not have to have been screened previously in order to be selected for screening at a later target age.

2.4. Cost data

Cost data (in 2011 I$) are presented in Table 1. Direct medical costs of screening, diagnosis, and treatment of precancerous lesions were drawn from the START–UP study sites, and included staff time, clinical supplies, drugs, clinical equipment, laboratory staff time, laboratory

Table 1
Baseline values for model variables [a].

Variable [Reference]	India	Nicaragua	Uganda
Population coverage of screening program	70%	70%	70%
Loss to follow-up per visit[b]	15%	15%	15%
Proportion of eligible women receiving immediate cryosurgery following VIA[c] [30]	70%	70%	70%
Proportion of eligible women receiving immediate cryosurgery following *care*HPV results[c]	80%	80%	80%
Proportion of eligible women lost to follow-up prior to delayed cryosurgery [30]	10%	10%	10%
Test sensitivity/specificity for CIN2+			
*care*HPV (cervical specimen)[7]	90%/95%	78%/89%	89%/82%
*care*HPV (vaginal specimen)[7]	76%/95%	67%/86%	77%/82%
VIA (30–49 years)[7]	55%/92%	64%/78%	74%/67%
VIA (≥ 50 years)[7,31–33]	26% /94%	17%/94%	35%/80%
Cytology[7]	74%/98%	41%/94%	69%/49%
Test sensitivity/specificity for CIN1+, colposcopy[d]	50%/96%	95%/68%	95%/51%
Eligibility for cryotherapy [10]			
No lesion or CIN1	100%	100%	100%
CIN2	85%	85%	85%
CIN3	75%	75%	75%
Cancer	10%	10%	10%
Effectiveness of cryotherapy [10,34–36]	92%	92%	92%
Effectiveness of cryotherapy/LEEP following colposcopy [10,35]	96%	96%	96%
Direct medical costs [7,18][e]			
*care*HPV (cervical specimen)[f]	9.24	15.61	8.78
*care*HPV (vaginal specimen)[f]	8.90	13.48	8.48
VIA	3.55	9.61	2.90
Cytology	15.15	13.71	12.25
Colposcopy[g]	9.86	15.25	7.08
Colposcopy and biopsy[g]	30.06	39.48	32.90
Cryotherapy	38.13	33.04	13.49
LEEP	NA	133.64	139.54
Direct non-medical costs[e]			
Transportation (round-trip, clinic) [5,10,16]	0.08	0.69	4.46
Transportation (round-trip, secondary facility) [5,10,16]	15.29	2.75	10.87
Women's time (per hour) [37]	1.14	1.41	0.68
Treatment of local cancer (FIGO stages 1a–2a) [5,10,16][e,h]	1821	3322	888
Treatment of regional/distant cancer (FIGO stages ≥ 2b) [5,10,16][e,h]	2652	4268	1176

[a] CIN: cervical intraepithelial neoplasia; FIGO: International Federation of Gynecology and Obstetrics; LEEP: loop electrosurgical excision procedure; VIA: visual inspection with acetic acid. Further details on unit cost assumptions are available in the Appendix.

[b] Loss to follow-up is defined as the proportion of women who do not return for each subsequent clinical encounter, relative to the previous visit (loss to follow-up applies to the results visit for *care*HPV testing, or diagnostic confirmation and treatment visits for cytology or women who are ineligible for cryosurgery in a screen-and-treat approach [i.e., VIA or *care*HPV testing]).

[c] We assumed that a slightly higher proportion of screen-positive women (80%) would receive cryotherapy at the HPV results visit than at the screening visit with VIA (70%). Compliance with same-day cryotherapy after VIA was drawn from the published literature [30], and we assumed that women might be more likely to delay cryotherapy after VIA than with 2-visit HPV testing, when they would have already received counseling in the screening visit.

[d] Test performance characteristics of colposcopy in START–UP were derived from the worst diagnosis of the local pathologist relative to the worst diagnosis by a quality control pathologist (gold standard); we applied the treatment threshold of CIN1+, although this was not the treatment threshold in START–UP. To derive test performance of colposcopy, we excluded histological classifications that were inadequate or with a histological classification other than negative, CIN1, CIN2, CIN3, or cancer. Because CIN1 is not a true underlying health state in the model, performance of colposcopy in the model is based on the underlying health states of no lesion, HPV infection, CIN2, or CIN3. For a treatment threshold of CIN1, we weighted sensitivity of colposcopy for women with HPV based on the country-specific prevalence of CIN1 among women with HPV infections in the START–UP studies.

[e] All costs are in 2011 international dollars (I$).

[f] This includes the cost of the careHPV test, which was assumed to be I$5.

[g] The proportion of colposcopies that were accompanied by a biopsy was drawn from START-UP data as follows: 93.1% (India); 95.6% (Uganda); and 99.5% (Nicaragua).

[h] All cancer costs presented include the value of women's time spent pursuing care and transportation to health facilities.

supplies, and laboratory equipment. In the START–UP sites, because women self-collected a vaginal sample for *care*HPV testing in the clinics rather than in a community setting, most costs are similar to those for provider-collected cervical samples. As documented in the Appendix, we converted local currency units to 2011 I$, a hypothetical currency that provides a means of translating and comparing costs among countries, taking into account differences in purchasing power; we assumed the *care*HPV test kit was a tradable good valued at US$5.

Women's time spent traveling, waiting, and receiving care and transportation costs were dependent upon the facility level and were derived from START–UP data and the published literature, as described in the Appendix [5,7,10,16,18,37]. Costs associated with cancer care by stage include direct medical costs, women's time costs, and transportation costs, and were derived from published studies (see Appendix).

To assess the budget impact of screening at the country level, we used the individual-based simulation model to estimate the expected direct medical cost per woman screened, including the costs of screening and any relevant diagnostic testing and treatment of pre-cancer, for cost-effective strategies. We multiplied the expected cost per woman screened at each age by the number of women at each of the target ages in 2015, assuming 70% screening coverage. We report the 1-year financial costs of screening in 2013 US$ instead of I$ to provide a meaningful estimate to the international and donor communities. This budget impact analysis did not consider cost offsets from future cancer cases prevented and patient time and transportation costs.

3. Results

3.1. Reduction in cancer risk

The health impact of once in a lifetime screening associated with each screening test and age is presented in Fig. 1. Across countries and

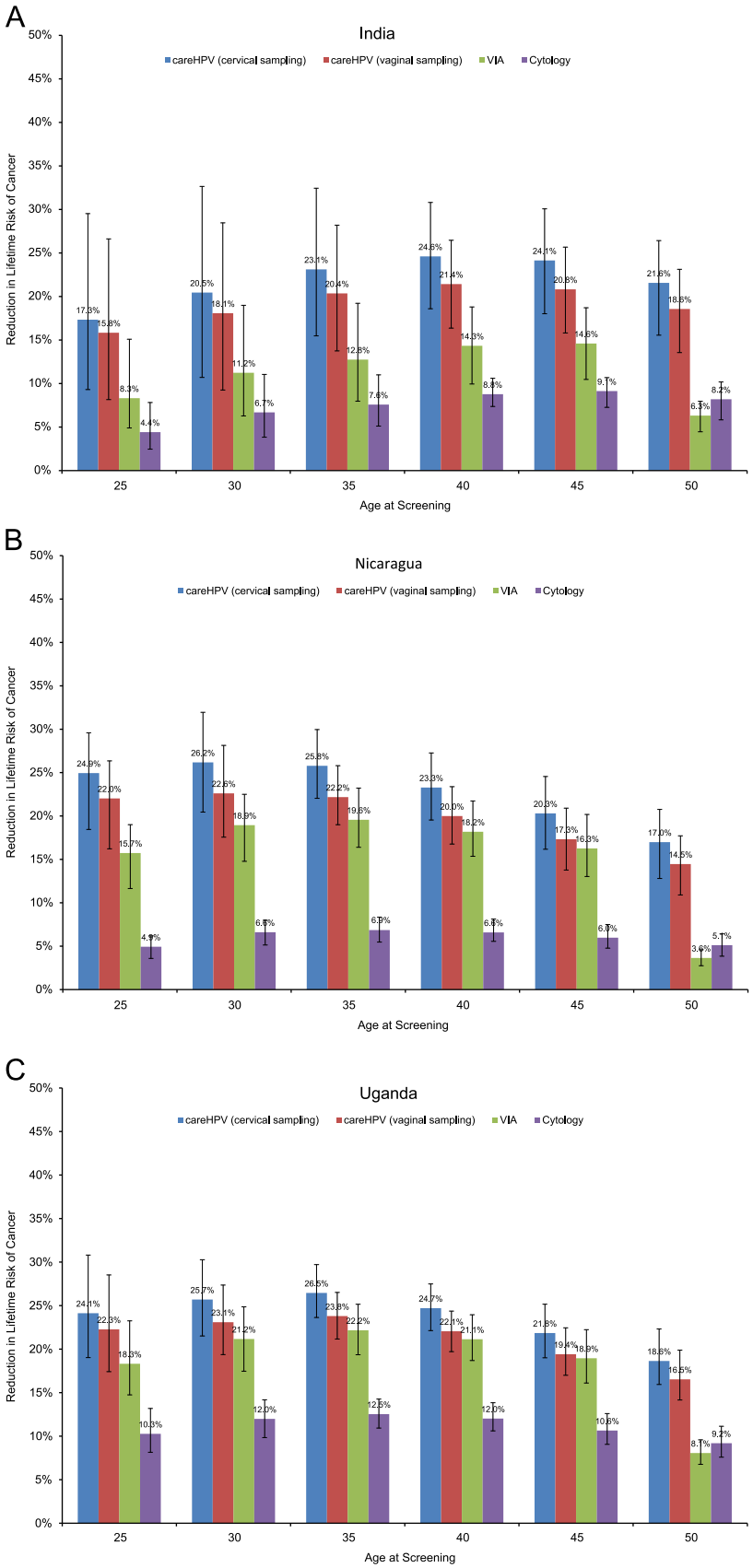

Fig. 1. Reduction in lifetime risk of cancer, once in a lifetime screening. Reduction in lifetime risk of cancer (*y*-axis) is displayed for each age at which once in a lifetime screening was considered (*x*-axis) for (A) India; (B) Nicaragua; and (C) Uganda. Cancer reduction associated with *care*HPV (cervical sampling) is displayed by the blue bars; *care*HPV (vaginal sampling) by the red bars; VIA by the green bars; and cytology by the purple bars. Error bars display the range in cancer reduction across the 50 good-fitting input parameter sets. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ages considered, screening with *care*HPV (cervical sampling) yielded the greatest mean reductions in lifetime risk of cancer relative to other screening tests. Self-collected vaginal sampling with *care*HPV testing was slightly less effective due to lower test sensitivity in all sites. VIA was associated with lower reductions in cancer risk than *care*HPV testing, particularly in India, where VIA test sensitivity (CIN2+ threshold) was approximately 20% lower than *care*HPV with vaginal sampling. Reductions in cancer risk with cytology were low even in India, where its sensitivity for CIN2+ (74%) was similar to *care*HPV testing (vaginal sampling), due to the number of required visits between screening and necessary treatment resulting in higher loss to follow-up.

Screening once in a lifetime with *care*HPV (cervical sampling), the most effective screening test, achieved the lowest mean reductions in cancer risk when screening occurred at age 25 years (17.3%) and highest when screening occurred at age 40 years (24.6%) in India; lowest at age 50 years (17.0%) and highest at age 30 years (26.2%) in Nicaragua; and lowest at age 50 years (18.6%) and highest at age 35 years (26.5%) in Uganda (Fig. 1). In every country and at every age, *care*HPV (vaginal sampling) was the second most effective, with mean reductions in cancer risk just a few percentage points below *care*HPV (cervical sampling). Screening twice in a lifetime with *care*HPV (cervical sampling) was associated with mean reductions in cancer risk that were lowest when screening occurred at ages 25 and 35 years (34.7%) and highest when screening occurred at ages 35 and 45 years (40.6%) in India; lowest at ages 35 and 45 years (39.4%) and highest at ages 25 and 35 years (42.5%) in Nicaragua; and lowest at ages 35 and 45 years (41.5%) and highest at ages 30 and 40 years (43%) in Uganda (Appendix). Screening three times in a lifetime with *care*HPV (cervical sampling) was associated with mean reductions in cancer risk that were lowest at ages 30, 35, and 40 years (48.7%) and highest at ages 30, 40, and 50 years (51.3%) in India; lowest at ages 35, 40, and 45 years (48.9%) and highest at ages 25, 35, and 45 years (53.5%) in Nicaragua; and lowest at ages 35, 40, and 45 years (50.9%) and highest at ages 25, 35, and 45 years (55.4%) in Uganda (Appendix).

3.2. Cost-effectiveness analysis

The cost-effectiveness of screening for each test, age, frequency, and interval in India is displayed in Fig. 2A. HPV testing with

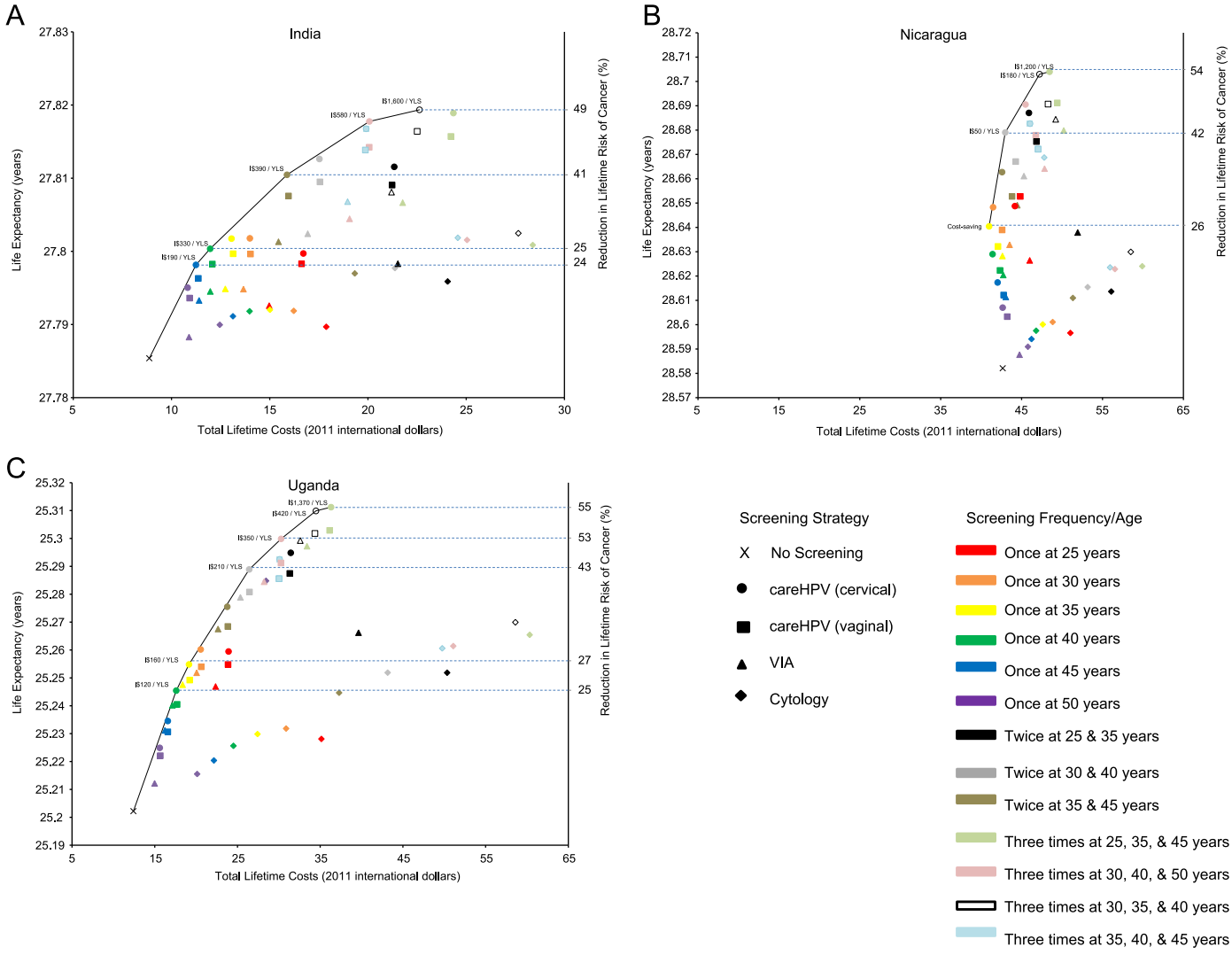

Fig. 2. Cost-effectiveness of screening for cervical cancer. The discounted lifetime costs (in 2011 international dollars) and life expectancy associated with each screening test, age, interval, and frequency are shown for (A) India; (B) Nicaragua; and (C) Uganda. The cost-effectiveness associated with a change from one strategy to a more costly alternative is represented by the difference in cost divided by the difference in life expectancy associated with the two strategies. Strategies that lie on the efficiency curve dominate those to the right of the curve because they are more effective and either cost less or have a more attractive cost-effectiveness ratio than less effective options. An incremental cost-effectiveness ratio is shown for each non-dominated strategy and is the reciprocal of the slope of the line connecting the two screening strategies under comparison. This slope is steeper when the incremental gain in life expectancy per international dollar is greater. I$: 2011 international dollars; VIA: visual inspection with acetic acid; YLS: year of life saved.

*care*HPV (cervical sampling) dominated other screening tests, which either were more costly and less effective (i.e., cytology, VIA) or had higher ICERs and were less effective (i.e., VIA). The strategy with the lowest ICER was *care*HPV (cervical sampling) at age 45 years (I$190 per YLS). Screening once in a lifetime at age 40 years yielded greater life expectancy gains and had a slightly higher ICER (I$330 per YLS). While screening twice in a lifetime at ages 35 and 45 years was a ranking strategy (I$390 per YLS), screening twice in a lifetime at either 30 and 40 years or 25 and 35 years with *care*HPV (cervical sampling) was dominated by screening three times in a lifetime with *care*HPV (cervical sampling) at ages 30, 40, and 50 years (I$580 per YLS). Screening three times in a lifetime at ages 30, 35, and 40 years (I$1600 per YLS) was the strategy that achieved the greatest life expectancy gains, with an ICER well below India's per capita GDP of I$5240 per YLS.

The cost-effectiveness of screening by test, age, frequency, and interval in Nicaragua is presented in Fig. 2B. As in India, *care*HPV (cervical sampling) dominated other screening tests. In Nicaragua, screening with *care*HPV (cervical sampling) at age 35 years was cost-saving due to the high costs of treating cervical cancer relative to the costs of screening and treatment, high reductions in cancer risk attributable to screening, and the high gain in life expectancy from averting early cancers (estimated cancer incidence in Nicaragua peaks around age 45). Screening twice in a lifetime with *care*HPV (cervical sampling) at ages 30 and 40 years was associated with an ICER of I$50 per YLS. Screening three times in a lifetime with *care*HPV (cervical sampling) at ages 30, 35, and 40 years (I$180 per YLS) or 25, 35, and 45 years (I$1200 per YLS) would be considered very cost-effective, with ICERs falling well below Nicaragua's per capita GDP of I$4220.

Cost-effectiveness results for Uganda are displayed in Fig. 2C. As in India and Nicaragua, *care*HPV (cervical sampling) dominated other screening tests. In Uganda, the ICER was lowest when screening occurred once in a lifetime at age 40 years (I$120 per YLS); screening once in a lifetime at age 35 years was more effective and associated with an ICER of I$160 per YLS. Screening twice per lifetime at ages 30 and 40 years was associated with an ICER of I$210 per YLS. Screening three times in a lifetime at ages 25, 35, and 45 was the most effective strategy. Screening three times in a lifetime was very cost-effective at ages 30, 40, and 50 years (I$350 per YLS); ages 30, 35, and 40 years (I$420 per YLS); and 25, 35, and 45 years (I$1370).

Cost-effectiveness results tables, assuming each country has decided *a priori* to screen either once, twice, or three times in a lifetime, are presented in the Appendix along with additional sensitivity analyses.

3.3. Budget impact

The estimated financial costs of screening in 2015, assuming 70% coverage of the target population, are reported in Table 2. If India were to opt for the strategy with the lowest ICER (i.e., *care*HPV with cervical sampling at age 45 years), the direct medical costs associated with screening alone would be an estimated US$34.2 million in 2015. The most effective strategy in India with an ICER below the country's per capita GDP (i.e., *care*HPV with cervical sampling at ages 30, 35, and 40 years) would cost an estimated US$126.5 million in 2015. In Nicaragua, where once in a lifetime screening with *care*HPV at 35 years is cost-saving, the estimated financial costs of screening 70% of this target population in 2015 would be US$0.4 million; the most effective strategy with an ICER below per capita GDP, screening with *care*HPV at ages 25, 35, and 45 years, would cost an estimated US$1.1 million in 2015. Once in a lifetime screening with *care*HPV at age 40 years in Uganda, the strategy with the lowest ICER, would cost US$0.6 million in 2015, while screening at ages 25, 35, and 45 would cost an estimated US$3.1 million.

Table 2
Financial costs of screening, by strategy, in 2015.

Age group in 2015, by country[a]	Number of women in target age group in 2015[b] [47]	Cost of screening 70% of the target population with *care*HPV (US$)[c]
India		
45 years	7,657,000	34,167,000
40 years	8,446,000	38,768,000
35 & 45 years	16,696,000	76,749,000
30, 40, & 50 years	24,510,000	111,920,000
30, 35, & 40 years	27,077,000	126,547,000
Nicaragua		
35 years	45,000	358,000
30 & 40 years	89,000	707,000
30, 35, & 40 years	135,000	1,065,000
25, 35, & 45 years	138,000	1,122,000
Uganda		
40 years	135,000	625,000
35 years	179,000	892,000
30 & 40 years	375,000	1,858,000
30, 40, & 50 years	460,000	2,190,000
30, 35, & 40 years	554,000	2,750,000
25, 35, & 45 years	607,000	3,116,000

[a] We considered non-dominated strategies from Fig. 2.
[b] The number of women in the target age group includes only those at target age(s) in 2015.
[c] US$: 2013 US$. As described in the Methods, the expected cost per woman screened (including direct medical costs associated with *care*HPV [cervical sampling], relevant diagnostic testing, and treatment of precancer) were derived from the mathematical simulation model. Patient time and transportation costs are not included in this budget impact analysis.

4. Discussion

We incorporated test performance and cost data from the START–UP demonstration projects in India, Nicaragua, and Uganda into a mathematical simulation model to determine the optimal ages, frequencies, and intervals in terms of long-term health and cost outcomes for limited cervical cancer screening opportunities in countries with different epidemiologic profiles.

We found that, when all screening tests were evaluated, *care*HPV (cervical sampling) was the dominant (i.e., most effective and most cost-effective) strategy in all sites due to superior test sensitivity and the use of a screen-and-treat approach requiring as few as two visits. The screening ages associated with the greatest reductions in lifetime risk of cancer were between 30 and 45 years of age; screening before age 30 or after age 45 was associated with lower reductions in cancer risk. These results support WHO guidelines that advocate for screening to take place between ages 30 and 49 years. However, when identifying a particular age at which to screen, we observed differences by country. For once in a lifetime screening, older ages (e.g., 40 or 45 years) were associated with the greatest reductions in cancer risk in India, while screening at younger ages (e.g., 30 or 35 years) yielded the greatest cancer risk reductions in Nicaragua and Uganda due to the relatively early peaks in cancer incidence in these two countries. While screening once in a lifetime at age 25 would not be considered very cost-effective in any country relative to one-time screening between ages 30 and 45, screening at age 25 may provide health benefits and be cost-effective if coupled with two additional screenings between the critical ages of 30 and 45 years. The WHO guidelines are ambiguous on screening at younger ages, stating both that cervical cancer screening should not start prior to 30 years of age, and that screening may be extended to younger ages if there is evidence of a high risk of precancer [12]. Our

findings suggest that the health and economic impact of extending screening to women under 30 years depends upon cancer incidence in younger women and the likelihood of access to subsequent screenings later in life. While screening once in a lifetime at age 50 would not be considered cost-effective in any of these countries, screening at 50 with HPV testing may be very cost-effective and provide health benefits if coupled with earlier screenings between 30 and 45 years in India and Uganda, due to sustained high cancer incidence at later ages.

In all 3 countries evaluated, when all screening tests, frequencies and age combinations were compared, screening three times in a lifetime with *care*HPV at adequate intervals and at critical ages provided good value for money. The addition of a third screening reduced cancer risk by an additional 10% relative to screening twice in a lifetime. When three screenings in a woman's lifetime are feasible, screening at either 5- or 10-year intervals may be very cost-effective. This is consistent with WHO guidelines, which recommend a minimum interval of 5 years following a negative HPV test [11,38]. In India, screening three times in a lifetime at 30, 35, and 40 years was associated with the greatest life expectancy gains compared to other strategies considered, and was very cost-effective. In Nicaragua and Uganda, screening three times at 30, 35, and 40 years was also very cost-effective, and only slightly less effective than screening three times at 25, 35, and 45 years.

While screening up to three times in a lifetime would be considered very cost-effective using per capita GDP as a benchmark for cost-effectiveness, it is important to consider the consequences of varying this threshold and to note the limitations of selecting it. In each country considered, at least one strategy for screening three times per lifetime is associated with an ICER that is approximately 25% to 30% of per capita GDP, and would thus be considered very cost-effective even if the threshold were lowered substantially. Although this benchmark is promoted by the WHO-CHOICE program [39], the categorization of an intervention as cost-effective based on the relation of its ICER to per capita GDP may not lead to the best allocation of scarce resources if there are other necessary and feasible interventions with greater value for public health dollars that remain unfunded [40]. Furthermore, information on the value for money is not equivalent to affordability, or the financial impact of a program on a payer's budget [40]. To provide information on affordability, we present estimates of the 1-year financial cost of a screening program that would cover 70% of the target population in each country in 2015 for each of the strategies that would be considered very cost-effective. While both the cost-effectiveness profile and recurrent financial costs must be favorable to implement a sustainable screening program, decision makers responsible for priority setting will also need information on the programmatic investments that will be necessary to scale up infrastructure, train personnel, and conduct social marketing campaigns, as well as how the relative costs and benefits of cervical cancer screening compare to other health interventions under consideration. Ultimately, the affordability of screening programs in these settings will likely depend upon the extent of financial assistance from donors.

Our objective was to evaluate the cost-effectiveness of screening at various start ages, intervals, and frequencies in women who are past the primary target age for HPV vaccination [41]. For these two to three generations of women in low-resource settings, screening remains the only recommended option for cervical cancer prevention. As HPV vaccination programs are introduced and scaled up, it will be important to consider the impact of young adolescent HPV vaccination on screening protocols. Although screening in the context of HPV vaccination will be associated with higher ICERs as the relative benefits of screening decrease, particularly following next-generation vaccines with fewer required doses and protection against more HPV types [42], it will be critical to evaluate the optimal screening start age, frequency, and interval in vaccinated cohorts and in the general population, dependent upon vaccination coverage. Additional questions about the impact of vaccinating older women on optimal screening age and frequency will also need to be addressed, as recent data from bivalent and quadrivalent HPV vaccine trials suggest that the vaccines are somewhat protective against persistent HPV16/18 infections in older women [43,44].

There are several limitations to this analysis. We did not model all screening strategies covered by the WHO guidelines, such as HPV testing followed by VIA triage and, in settings with high coverage cytology programs, HPV testing followed by colposcopy [11]. Instead, we restricted our analysis to screening tests that were evaluated in the START–UP study in order to use country-specific data on costs and test performance. We also did not evaluate every possible screening interval starting with the WHO-recommended minimum interval, as it does not seem realistic for health care systems in low-resource settings to have the capabilities to recall women at precise intervals. Rather, we attempted to provide insight about general interval ranges (i.e., 5 to 10 years). We assumed that screening coverage at each target age in a given strategy was random and not conditioned upon a woman receiving screening at the previous ages. Thus, for screening three times in a lifetime, each woman in the model had an opportunity to receive screening at each of the specified ages, resulting in slightly greater health benefits than if we had assumed the same women are consistently being screened (or not) at each age. While the WHO guidelines recommend follow-up within 3 years following a negative screening test in populations with a high burden of HIV [11], we did not consider shorter intervals than 5 years in Uganda. Many of the countries with a high prevalence of HIV are in Sub-Saharan Africa, where currently available resources limit access to more frequent screening. We did not consider the possible harms of overtreatment. Costing estimates for screening and treatment of precancer were based upon the START–UP study, and thus do not reflect programmatic costs associated with scale-up, nor do they reflect potential economies of scale associated with screening at the country level. For all 3 countries, the cost of *care*HPV with vaginal sampling was based on collection of samples at the clinic. Thus, we did not capture potentially lower costs and greater population coverage associated with home collection of HPV samples [45,46], which might make vaginal sampling as or more attractive than cervical sampling at the clinic even if accompanied by reduced test sensitivity.

There are also limitations surrounding our model calibration approach. While we used HPV prevalence data from the START–UP study populations, in Nicaragua and India data were only available for women aged 30 to 49 years (in Uganda, data were available for women aged 25 to 60 years). Furthermore, model-predicted cancer incidence at younger ages in Uganda may contribute to the attractiveness of screening in women under 30 years; there remains uncertainty surrounding the impact of screening at 25 years in all 3 sites. Additional limitations pertaining to costing and modeling assumptions are described in the Appendix.

From a program planning perspective, it will be difficult to target precise ages and intervals (in the case of more than one screening) for cervical cancer screening in settings where access to health care is limited. These findings provide reassurance that the most critical screenings occur in a wide age range (30 to 45 years), for countries with varying epidemiologic profiles. Within this age range, screening at certain ages may be relatively more cost-effective, but reductions in cancer risk are similar for a given screening test and interval. When screening is only available once in a woman's lifetime, it is not possible to set a precise target age at which screening should occur in all settings. Among once in a lifetime screening strategies, screening at age 30 years was the

most effective strategy that was also very cost-effective in Nicaragua and Uganda (Appendix). However, screening only once at this early age was cost-prohibitive in India. These findings highlight the need for cancer registration in low-resource settings, as narrowing the optimal window for once in a lifetime screening may be informed by age-specific cervical cancer incidence.

In 2012, there were nearly 1 billion women aged 30 to 49 years; most of these women have not been screened for cervical cancer [38]. Using cost and test performance data from screening demonstration projects in 3 countries with different epidemiologic profiles, we found that screening with HPV testing three times in a lifetime between 30 and 45 years is very cost-effective and can reduce cancer risk by approximately 50%. It is reassuring to note that precise targeting of age within this critical range is not needed to reap this benefit and that even screening with HPV testing twice in a lifetime can achieve high reductions in cancer risk. Despite evidence of value for money, considerations of affordability and sustainability of such strategies will be critical to assess in low-resource settings.

Funding source

The research leading to these results has received funding from the Bill & Melinda Gates Foundation. The funders had no role in study design; data collection, analysis, and interpretation; preparation of the manuscript; or decision to submit the article for publication.

Conflicts of interest

NGC has no conflict to declare. VT has no conflict to declare. JJ was the director of the START–UP demonstration projects and received all tests used in the study as a donation from QIAGEN. MM has no conflict to declare. KL has no conflict to declare. JJK has no conflict to declare.

Acknowledgements

The authors thank all investigators and field workers that participated in the START–UP demonstration projects, and the cervical cancer modeling team at the Center for Health Decision Science, Harvard T.H. Chan School of Public Health, for their research contributions. Screening tests used in the START–UP demonstration projects were donated by QIAGEN.

Appendix. When and how often to screen for cervical cancer in three low- and middle-income countries: A cost-effectiveness analysis

This Appendix provides additional details on methods, assumptions, and results presented in the main manuscript.

Model calibration

Overview of the calibration process

Details of the model development process, including initial parameterization and calibration, have been previously published [48]. Derivation of model parameter values requires an iterative process involving comprehensive literature reviews, data synthesis and analysis, consultations with experts, and explorations of the influence of uncertain parameters and assumptions in the model. Baseline HPV incidence rates, as a function of genotype and age, were derived from published data from a prospective cohort of sexually active women aged 15–85 years in Bogota, Colombia [49]. Because HPV incidence is known to vary by population as a function of sexual behaviors, age-specific HPV incidence and natural immunity following initial infection were considered important candidates for calibration. Transitions occurring from the HPV state (i.e., time-dependent rates of HPV clearance and progression by genotype) were informed by longitudinal data from the control arm of the Costa Rica Vaccine Trial [50]. Type-specific data on CIN2 and CIN3 regression and progression are limited [51–56], so these parameters were also candidates for calibration. Because of the computational intensity of microsimulation models, we selected parameters for calibration based on the availability of (1) a range of plausible values and (2) good empirical data to inform calibration targets (i.e., high-risk HPV prevalence to calibrate HPV incidence rates; cancer incidence to calibrate CIN2 and CIN3 regression and progression rates).

To calibrate the model, we set plausible search ranges around baseline input values for age- and type-specific HPV incidence, as well as natural immunity following initial infection and progression and regression of CIN, and performed repeated model simulations in the absence of any preventive intervention. For each simulation, we randomly selected a single value for each of the uncertain parameters from the identified plausible range, creating a unique vector of parameter values (i.e., parameter "set"). Following over 1,475,000 repeated samplings, we identified the parameter sets with the highest correspondence to the empirical calibration target data by calculating and aggregating the log-likelihood of model-projected outcomes. We used the 50 parameter sets with the highest likelihood scores (i.e., best overall fit to the empirical data) from each country for analysis to capture uncertainty in the model parameters as a form of probabilistic sensitivity analysis. We report results as a mean and a range of outcomes across these top 50 parameter sets; incremental cost-effectiveness ratios are reported as the ratio of the mean costs divided by the mean effects of one strategy versus another across sets.

Calibration targets

We assessed model fit by observing projected model outcomes of age-specific prevalence of high-risk HPV and age-specific cancer incidence relative to empirical data. The scoring algorithms for India and Nicaragua included age-specific prevalence of high-risk HPV and age-specific cervical cancer incidence. For Uganda, only age-specific cancer incidence was included in the scoring algorithm, as we observed a better fit to cancer incidence data when we did not include HPV prevalence in the scoring algorithm; however, we still considered visual fit to HPV prevalence to arrive at the final scoring algorithm.

Age-specific prevalence of high-risk HPV was drawn from START–UP data on *care*HPV positivity using a cut-off ratio cut-point of 0.5 relative light units (Tables A1–A3). For each age group, we derived a 95% binomial confidence interval around the point prevalence, which comprised the calibration target. The likelihood function for each age group was assumed to follow a binomial distribution.

Table A1
Age-specific prevalence of high-risk HPV, India [7][a].

Age group	Number of women	Number of women with high-risk HPV	Prevalence (95% CI)
30–34 years	1949	214	0.11 (0.10, 0.13)
35–39 years	1158	99	0.09 (0.07, 0.10)
40–44 years	708	76	0.11 (0.09, 0.13)
45–49 years	687	85	0.12 (0.10, 0.15)

[a] HPV positivity was based on a cut-off of 0.5 relative light units.

Table A2
Age-specific prevalence of high-risk HPV, Nicaragua [7][a].

Age group	Number of women	Number of women with high-risk HPV	Prevalence (95% CI)
30–34 years	1693	310	0.18 (0.17, 0.20)
35–39 years	1141	184	0.16 (0.14, 0.18)
40–44 years	933	125	0.13 (0.11, 0.16)
45–49 years	878	121	0.14 (0.12, 0.16)

[a] HPV positivity was based on a cut-off of 0.5 relative light units.

Table A3
Age-specific prevalence of high-risk HPV, Uganda [7][a].

Age group	Number of women	Number of women with high-risk HPV	Prevalence (95% CI)
25–34 years	1367	426	0.31 (0.28, 0.34)
35–44 years	1131	284	0.25 (0.23, 0.28)
45–54 years	558	127	0.22 (0.19, 0.26)
55–60 years	90	28	0.31 (0.22, 0.42)

[a] HPV positivity was based on a cut-off of 0.5 relative light units. We did not include HPV prevalence in our scoring algorithm for Uganda, although we did consider visual fit to HPV prevalence.

Table A4
Age-specific cervical cancer incidence, India (Nagpur registry, 1998–2002) [57][a].

Age group	Cases	Rate per 100,000 women (95% CI)
20–24 years	9	1.8 (0.6, 2.9)
25–29 years	11	2.3 (0.9, 3.6)
30–34 years	43	10.6 (7.4, 13.7)
35–39 years	62	16.9 (12.7, 21.1)
40–44 years	90	32.4 (25.7, 39.1)
45–49 years	107	46.2 (37.5, 55.0)
50–54 years	105	58.9 (47.6, 70.1)
55–59 years	70	52.4 (40.1, 64.7)
60–64 years	104	75.0 (60.6, 89.4)
65–69 years	71	62.5 (47.9, 77.0)
70–74 years	44	57.6 (40.6, 74.6)
≥75 years	9	26.8 (9.3, 44.2)

[a] Although our scoring algorithm included cancer incidence in women aged 30 to 49 years, we considered visual fit to all age groups.

Table A5
Age-specific cervical cancer incidence, Nicaragua (GLOBOCAN 2012) [58].

Age group	Cases	Rate per 100,000 women (95% CI)
40–44 years	123	78.7 (64.8, 92.6)
45–49 years	112	85.4 (69.6, 101.2)
50–54 years	102	88.4 (71.2, 105.6)
55–59 years	85	88.1 (69.4, 106.8)
60–64 years	51	84.0 (61.0, 107.1)
65–69 years	37	80.8 (54.8, 106.8)
70–74 years	30	74.6 (47.9, 101.3)
≥75 years	45	70.3 (49.8, 90.8)

Age-specific cancer incidence was drawn from registries in *Cancer in Five Continents* [57] for India and Uganda, and from Globocan for Nicaragua due to the lack of a cancer registry [58] (Tables A4–A6). The likelihood function for each age group was assumed to follow a normal distribution.

Table A6
Age-specific cervical cancer incidence, Uganda (Kyadondo registry, 2003–2007) [57][a].

Age group	Cases	Rate per 100,000 women (95% CI)
25–29 years	42	7.6 (5.3, 9.9)
30–34 years	84	26.5 (20.8, 32.2)
35–39 years	111	53.7 (43.7, 63.7)
40–44 years	138	99.7 (83.1, 116.3)
45–49 years	105	121.7 (98.4, 145.0)
50–54 years	108	181.3 (147.1, 215.5)
55–59 years	59	163.2 (121.6, 204.8)
60–64 years	68	199.7 (152.2, 247.2)
65–69 years	33	145.8 (96.1, 195.6)
70–74 years	35	175.0 (117.0, 233.0)

[a] Although our scoring algorithm included cancer incidence in aged 40 years and above, we considered visual fit to all age groups.

Composite goodness-of-fit scores for each input parameter set were generated by summing the log likelihood of each model outcome (i.e., age-specific HPV prevalence, age-specific cancer incidence). The 50 input parameter sets with the highest goodness-of-fit scores thus yielded the model outputs that were simultaneously closest to all calibration targets, and were selected for analysis. Figs. A1–A6 display model fit to epidemiologic data on age-specific prevalence of high-risk HPV and age-specific cancer incidence in each country.

Cost data

Direct medical costs: Screening, diagnosis, and treatment of precancerous lesions

The direct medical costs of screening, diagnosis, and treatment of precancerous lesions were drawn from the Screening Technologies to Advance Rapid Testing for Cervical Cancer Prevention–Utility and Program Planning (START–UP) demonstration studies in India (Hyderabad), Nicaragua (Masaya Province), and Uganda (Kampala). Direct medical costs included clinical staff time, clinical supplies, drugs, clinical equipment, laboratory staff time, laboratory supplies, and laboratory equipment.

We report costs in 2011 international dollars (I$) to facilitate comparisons across regions. The relevant GDP deflators were applied to local currency units to inflate to year 2011 levels, and local currency units were then converted to international dollars by means of purchasing power parity (PPP) exchange rates [59]. The exceptions were for equipment, which was generally procured in the United States, and the cost of the *care*HPV test kit, which was assumed to be US$5. For these tradable goods, one international dollar is equivalent to one U.S. dollar. Costs are reported in Table 1 of the main manuscript.

Cost of cancer care by stage

Costs associated with cancer care by stage (Local vs. Regional or Distant), including direct medical costs, women's time costs for time spent receiving care, women's transportation costs to health facilities, and cancer staging costs were derived from previous analyses and converted to 2011 I$ as described above. Cancer care costs in India were based on primary data [60], while costs from Uganda were based on primary data from Kenya, as we have previously described [60,61]. Cancer care costs from Nicaragua were based on primary data from the cost of treating cancer in El Salvador (excluding staging costs) [62]. To adjust cancer costs from El Salvador to the setting of Nicaragua, we assumed direct medical costs were reduced by the ratio of WHO-CHOICE inpatient bed-day

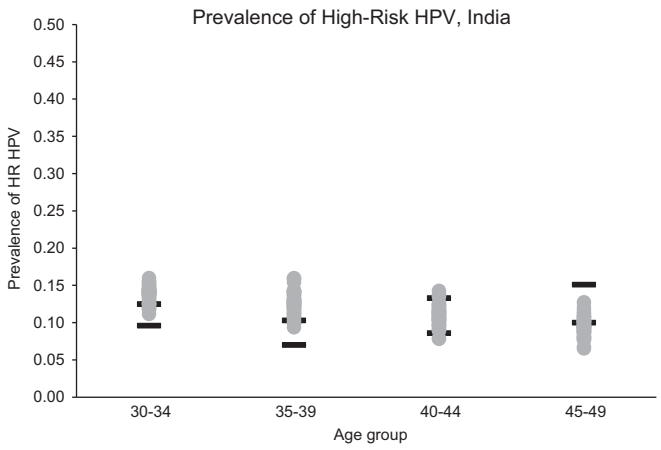

Fig. A1. Selected model output from the top 50 input parameter sets compared with empirical data (i.e., calibration targets) on age-specific prevalence of high-risk HPV in India (Hyderabad), based on a relative light unit cut-off value of 0.5 in the START–UP studies [7]. Bold lines represent the 95% confidence intervals around the empirical data, and gray circles represent model output from each of the top 50 input parameter sets.

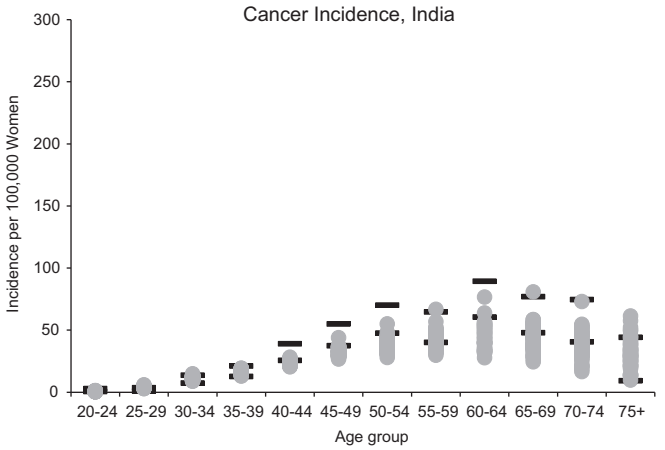

Fig. A4. Selected model output from the top 50 input parameter sets compared with empirical data (i.e., calibration targets) on age-specific cancer incidence in India (Nagpur registry, 1998–2002) [57]. Bold lines represent the 95% confidence intervals around the empirical data, and gray circles represent model output from each of the top 50 input parameter sets.

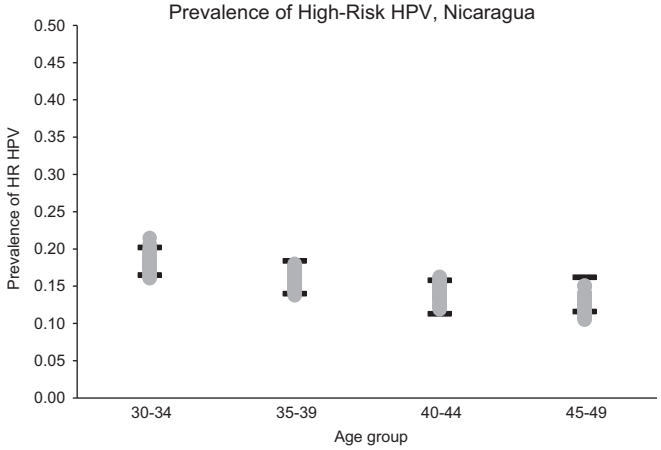

Fig. A2. Selected model output from the top 50 input parameter sets compared with empirical data (i.e., calibration targets) on age-specific prevalence of high-risk HPV in Nicaragua, based on a relative light unit cut-off value of 0.5 in the START–UP studies [7]. Bold lines represent the 95% confidence intervals around the empirical data, and gray circles represent model output from each of the top 50 input parameter sets.

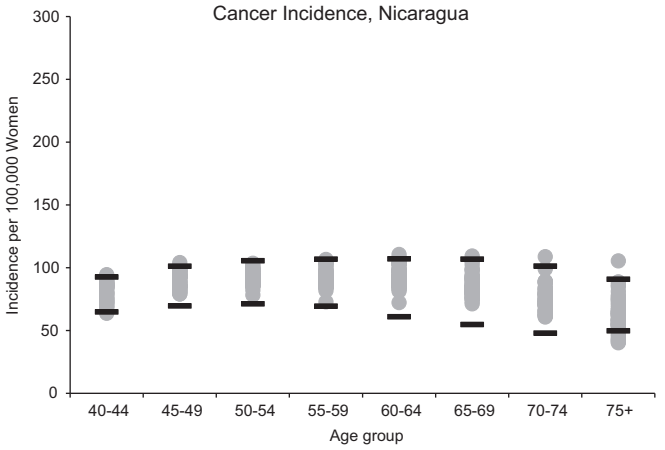

Fig. A5. Selected model output from the top 50 input parameter sets compared with empirical data (i.e., calibration targets) on age-specific cancer incidence in Nicaragua (GLOBOCAN 2012) [58]. Bold lines represent the 95% confidence intervals around the empirical data, and gray circles represent model output from each of the top 50 input parameter sets.

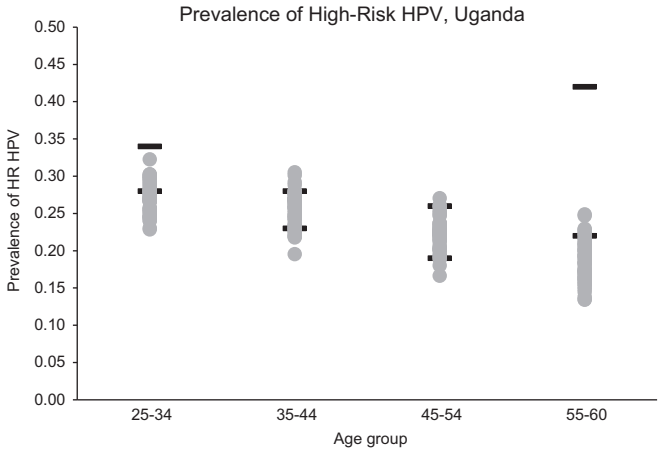

Fig. A3. Selected model output from the top 50 input parameter sets compared with empirical data (i.e., calibration targets) on age-specific prevalence of high-risk HPV in Uganda, based on a relative light unit cut-off value of 0.5 in the START–UP studies [7]. Bold lines represent the 95% confidence intervals around the empirical data, and gray circles represent model output from each of the top 50 input parameter sets.

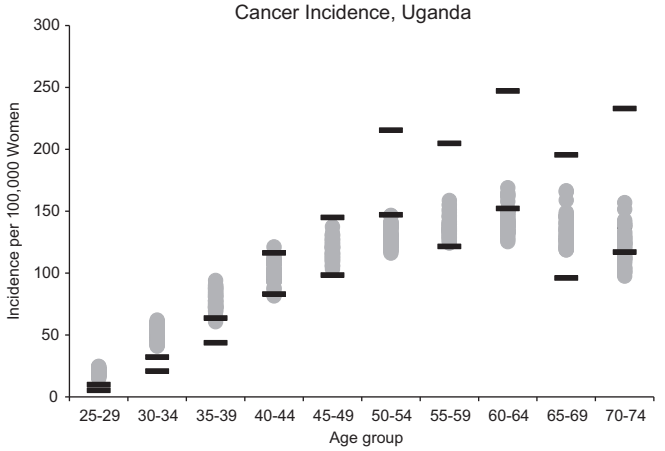

Fig. A6. Selected model output from the top 50 input parameter sets compared with empirical data (i.e., calibration targets) on age-specific cancer incidence in Uganda (Kyadondo registry, 2003–2007) [57]. Bold lines represent the 95% confidence intervals around the empirical data, and gray circles represent model output from each of the top 50 input parameter sets.

costs at a teaching hospital (for cancer center procedures) or WHO-CHOICE outpatient procedures at a secondary-level hospital (for regular follow-up care after cancer treatment) in Nicaragua relative to El Salvador; women's time costs were reduced by the ratio of wages (in 2011 I$) in Nicaragua relative to El Salvador, and transportation and incidental costs were reduced by the ratio of GNI per capita (in 2011 I$). Costs are reported in Table 1 of the main manuscript.

Women's time and transportation costs

We derived women's time costs from the United Nations Development Programme Human Development Indicator, "Estimated GNI per capita, female", which was derived from the ratio of female to male wage, female and male shares of economically active population, and gross national income (GNI) and reported in constant 2011 I$ [37]. We assumed this represented annual income for working 40 h per week, 50 weeks per year to estimate an average hourly wage (Table 1).

Estimates for time spent traveling, waiting, and receiving care was dependent upon the facility level where care was assumed to take place (Table A7). Women's time estimates for round-trip transportation and waiting were obtained from prior studies in El Salvador (for Nicaragua) [62], India, and Kenya (for Uganda) (Table A8) [60,61]. Estimates of women's time spent receiving a procedure were based on site-specific data from the START–UP demonstration projects, with staff time spent on the procedure (excluding preparation and registration time, which we assumed were built into patient waiting time) used as a proxy for women's procedure time. Round-trip transportation costs to each health facility level were obtained from previous analyses [60,61,62] and converted to 2011 I$; these are reported in Table 1 of the main manuscript.

Protocols for treatment of precancer

We assumed that VIA was primarily a one-visit strategy, with women receiving screening and, if eligible, treatment with cryotherapy in the same visit at a primary facility. To account for delayed cryotherapy due to menses, equipment malfunction, or a woman's desire to discuss treatment with her family, we assumed 70% of women would receive same-day cryotherapy, while the remaining women would delay treatment. We assumed HPV DNA testing was primarily a two-visit strategy, where screening occurred during the first visit and women returned to the clinic to receive results (and treatment with cryotherapy, if screen-positive and eligible) in a second visit. To account for the fact that women in a two-visit strategy have had the opportunity to consider the possibility of treatment prior to receiving results, we assumed 80% would receive same-day cryotherapy, with the remaining women delaying treatment. Women who delayed treatment accrued the time and transportation costs of an additional clinic visit unless they were lost to follow-up.

Women who screened positive with either VIA or HPV DNA testing who were ineligible for cryotherapy were assumed to be referred to a secondary facility for colposcopy and subsequent treatment. Treatment protocols were based on information from in-country clinicians familiar with standard of care and availability of and preferences for treatment options. In Hyderabad, we assumed that, upon a histologic diagnosis of CIN1, CIN2, or CIN3, women received cryotherapy at a secondary facility. In Nicaragua, we assumed that a histologic diagnosis of CIN1 was followed by cryotherapy and CIN2/3 was followed by LEEP at a secondary facility. In Uganda, we assumed that, upon a histologic diagnosis of CIN1, women received cryotherapy at a secondary facility; a histologic diagnosis of CIN2/3 was followed by cryotherapy for approximately 80% of women, and

Table A8
Women's Time Spent Receiving Care [a].

Procedure	Time Spent Receiving Care (min)		
	Hyderabad [7,60]	Nicaragua [7,62]	Uganda [7,60]
Screening			
Wait time	60	15	90
Procedure time	15	20	15
Transport time (round-trip)	60	90	220
Receiving results (negative)[b]	5	2	10
Receiving results (positive)	15	5	15
Diagnosis			
Wait time	120	150	180
Procedure time	42	37	35
Transport time (round-trip)	240	90	340
Treatment of precancer: screen-and-treat cryotherapy[c]			
Wait time	60	150	90
Procedure time	30	35	30
Transport time (round-trip)	60	90	220
Treatment of precancer: LEEP			
Wait time	NA	150	180
Procedure time	NA	25	25
Transport time (round-trip)	NA	90	340

[a] I$: international dollars. LEEP: loop electrosurgical excision procedure.
[b] Applicable to careHPV and Pap screening.
[c] We assumed most eligible women received cryotherapy in the same visit they received screening results (i.e., initial screening visit with VIA; second visit for HPV testing). Thus, additional transportation time was only accrued for women who delayed cryotherapy. Screen-and-treat cryotherapy was assumed to take place at a primary facility. For women who received cryotherapy following diagnostic confirmation of CIN, wait time and transport time were the same as for LEEP, as cryotherapy was assumed to take place at a secondary facility.

Table A7
Location of Service Delivery for Screening, Diagnosis, and Treatment of Precancerous Lesions and Cancer[a].

Procedure	Location of services
HPV DNA test	Primary facility
Cytology test	Primary facility
VIA test	Primary facility
Colposcopy/biopsy	Secondary facility
Cryotherapy	Primary facility (for women eligible for screen-and-treat cryotherapy) Secondary facility (for women ineligible for screen-and-treat cryotherapy
LEEP	Secondary facility
Follow-up visits (after cryotherapy or LEEP)	Primary facility (for examinations and Pap) Secondary facility (if colposcopy is necessary)
Cancer treatment	Tertiary facility

[a] HPV: human papillomavirus; LEEP: loop electrosurgical excision procedure; VIA: visual inspection with acetic acid.

LEEP for approximately 20% of women, and treatment occurred at a secondary facility.

We assumed cytology required separate visits for screening (primary facility), receiving results (primary facility), colposcopy (secondary facility), and subsequent treatment (secondary facility).

Loss-to-follow-up rates impact cost accrual in the microsimulation model, and we have the flexibility to input differential loss-to-follow-up for each visit (i.e., results, cryotherapy (if delayed), diagnostic confirmation, and treatment following diagnostic confirmation). In the base case, we assumed 10% of women would be lost to follow-up if subject to delayed cryotherapy in a screen-and-treat strategy (i.e., VIA or HPV testing). We assumed visits for screening results, diagnostic confirmation, and treatment following diagnostic confirmation were each associated with 15% loss-to-follow-up.

Following treatment of precancerous lesions with either cryotherapy or LEEP, we assumed the setting-specific follow-up protocols as used in the START–UP demonstration studies (Table A9). We included direct medical costs of each procedure, as well as women's time and transportation costs (as shown in Table 1 of the main manuscript). While women in the START–UP studies could be seen prior to scheduled follow-up visits as necessary, we did not have data on these unscheduled visits. Treatment complications in each site were very rare, so we did not consider these costs in the base case analysis.

Supplementary results

Reduction in cancer risk

The health impact of screening two and three times in a lifetime for each screening test and age combination considered is displayed in Figs. A7–A12.

Cost-effectiveness results, all screening tests, start ages, and frequencies

Fig. 2 from the main text is displayed in tabular form in Tables A10–A12.

Cost-effectiveness results for careHPV, by frequency of screening

Table A13 displays the health benefits and cost-effectiveness assuming each country has decided *a priori* to screen either once in a lifetime; twice in a lifetime; or three times in a lifetime at specific targeted age(s) with the dominant strategy *care*HPV (cervical sampling). In India, assuming screening will take place once in a lifetime, screening at either 45, 40, or 35 years (in order of increasing effectiveness) had ICERs that were well-below India's per capita GDP and therefore would be considered very cost-effective. Assuming

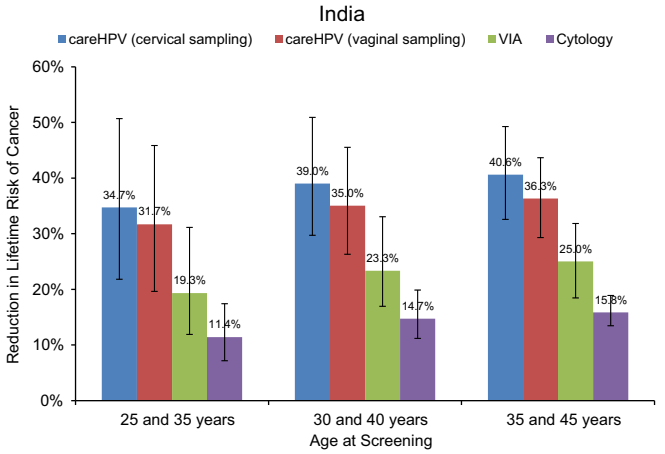

Fig. A7. Reduction in lifetime risk of cancer, screening twice in a lifetime, India. Reduction in lifetime risk of cancer (*y*-axis) is displayed for each age combination at which twice in a lifetime screening was considered (*x*-axis) for India. Cancer reduction associated with *care*HPV (cervical sampling) is displayed by the blue bars; *care*HPV (vaginal sampling) by the red bars; VIA by the green bars; and cytology by the purple bars. Error bars display the range in cancer reduction across the 50 good-fitting input parameter sets. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

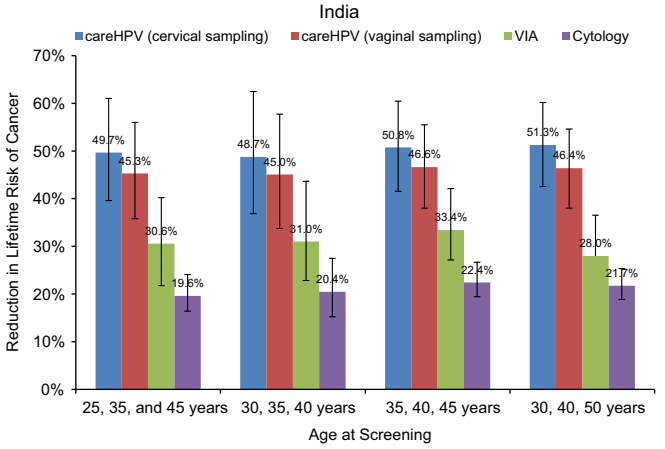

Fig. A8. Reduction in lifetime risk of cancer, screening three times in a lifetime, India. Reduction in lifetime risk of cancer (*y*-axis) is displayed for each age combination at which three screenings in a lifetime were considered (*x*-axis) for India. Cancer reduction associated with *care*HPV (cervical sampling) is displayed by the blue bars; *care*HPV (vaginal sampling) by the red bars; VIA by the green bars; and cytology by the purple bars. Error bars display the range in cancer reduction across the 50 good-fitting input parameter sets. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table A9
Follow-up protocols after treatment of precancerous lesions[a].

Treatment	Hyderabad	Nicaragua	Uganda
Cryotherapy	1 year Cytology/Colposcopy	1 year Cytology	6 week exam 1 year Cytology/Colposcopy[b]
LEEP	NA	1 year Cytology	6 week exam 1 year Cytology 1 year Colposcopy, as needed[b]

[a] LEEP: loop electrosurgical excision procedure. Follow-up protocols were based on the START–UP demonstration study in each setting. We included direct medical costs and women's time and transportation costs for each procedure. A 6 week visual exam was associated with the same costs as VIA at the primary facility. Cytology was assumed to take place at a primary facility, while colposcopy was assumed to take place at a secondary facility.

[b] Colposcopy at 1 year was performed as needed in Uganda. Approximately 15% of women who received treatment required a colposcopy and biopsy at 1 year for suspected recurrence.

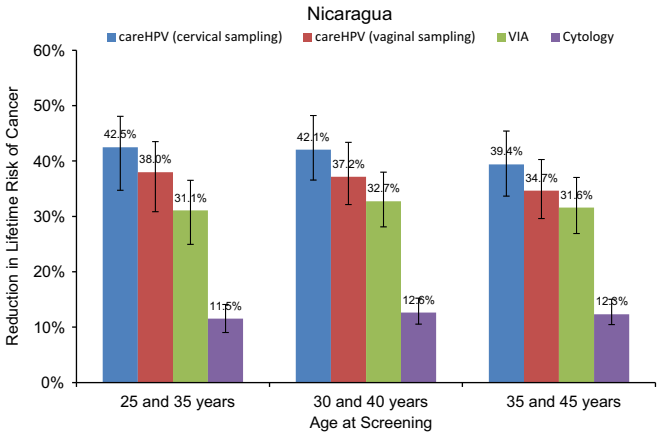

Fig. A9. Reduction in lifetime risk of cancer, screening twice in a lifetime, Nicaragua. Reduction in lifetime risk of cancer (*y*-axis) is displayed for each age combination at which two screenings in a lifetime were considered (*x*-axis) for Nicaragua. Cancer reduction associated with *care*HPV (cervical sampling) is displayed by the blue bars; *care*HPV (vaginal sampling) by the red bars; VIA by the green bars; and cytology by the purple bars. Error bars display the range in cancer reduction across the 50 good-fitting input parameter sets. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

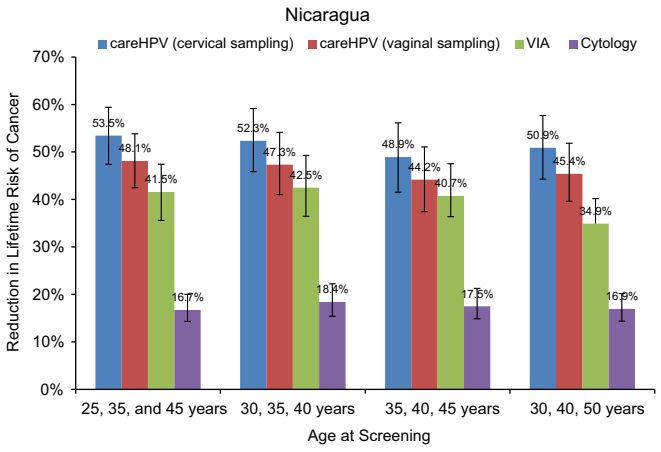

Fig. A10. Reduction in lifetime risk of cancer, screening three times in a lifetime, Nicaragua. Reduction in lifetime risk of cancer (*y*-axis) is displayed for each age combination at which three screenings in a lifetime were considered (*x*-axis) for Nicaragua. Cancer reduction associated with *care*HPV (cervical sampling) is displayed by the blue bars; *care*HPV (vaginal sampling) by the red bars; VIA by the green bars; and cytology by the purple bars. Error bars display the range in cancer reduction across the 50 good-fitting input parameter sets. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

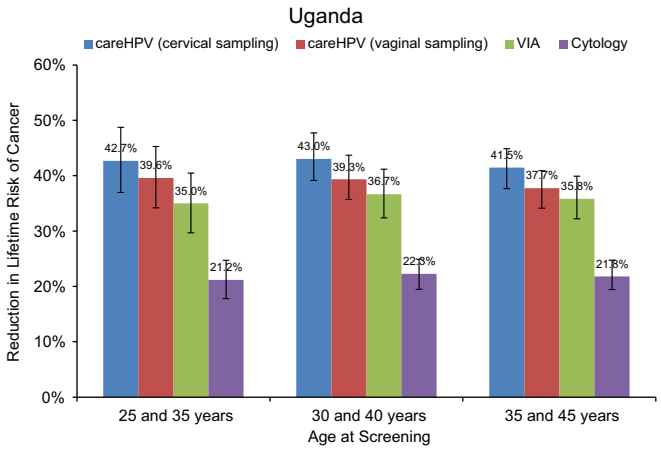

Fig. A11. Reduction in lifetime risk of cancer, screening twice in a lifetime, Uganda. Reduction in lifetime risk of cancer (*y*-axis) is displayed for each age combination at which two screenings in a lifetime were considered (*x*-axis) for Uganda. Cancer reduction associated with *care*HPV (cervical sampling) is displayed by the blue bars; *care*HPV (vaginal sampling) by the red bars; VIA by the green bars; and cytology by the purple bars. Error bars display the range in cancer reduction across the 50 good-fitting input parameter sets. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

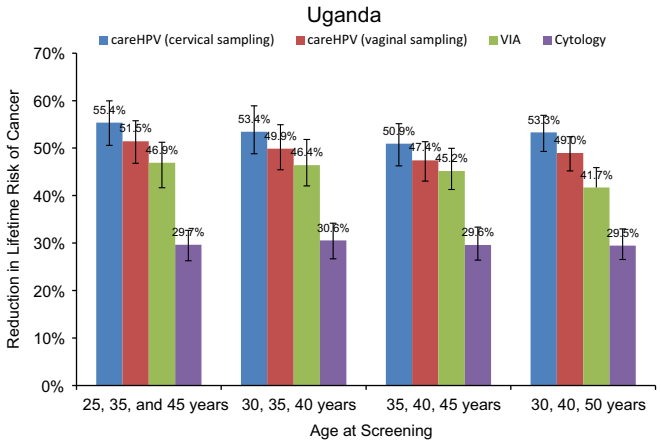

Fig. A12. Reduction in lifetime risk of cancer, screening three times in a lifetime, Uganda. Reduction in lifetime risk of cancer (*y*-axis) is displayed for each age combination at which three screenings in a lifetime were considered (*x*-axis) for Uganda. Cancer reduction associated with *care*HPV (cervical sampling) is displayed by the blue bars; *care*HPV (vaginal sampling) by the red bars; VIA by the green bars; and cytology by the purple bars. Error bars display the range in cancer reduction across the 50 good-fitting input parameter sets. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

screening will take place twice per lifetime, screening at either 35 and 45 years, or 30 and 40 years (in order of increasing effectiveness) would be very cost-effective. Assuming screening will take place three times per lifetime in India, it would be very cost-effective at either 30, 40, and 50 years, or 30, 35, and 40 years (in order of increasing effectiveness). Assuming all ages and frequencies considered are available, screening once in a lifetime at 35 years becomes dominated by screening once at 40 years, and screening twice in a lifetime at 30 and 40 years becomes dominated by screening twice at 35 and 45 years. Screening three times in a lifetime at 30, 35, and 40 years is associated with the highest population-level gains in life expectancy, and with an ICER of I$1600 per YLS is very cost-effective.

In Nicaragua, assuming screening is available only once per lifetime, screening at age 35 will be cost-saving. Screening once at age 30 will be more effective, and with an ICER of I$60 per YLS is very cost-effective. Screening once at age 25 is associated with the highest gains in life expectancy, and would be considered cost-effective with an ICER of I$5750 per YLS. Assuming screening is available twice per lifetime, screening at 35 and 45 years would be cost-saving, and screening at 25 and 35 years will cost I$360 per YLS. If screening is available three times per lifetime, screening at 30, 40, and 50 years would be I$30 per YLS, while screening at 30, 35, and 40 years or 25, 35, and 45 years (in order of increasing effectiveness) would be very cost-effective. Assuming all ages and frequencies considered are available, screening once at age 35 will be cost-saving and screening twice per lifetime at 30 and 40 years

Table A10
Cost-effectiveness of screening by age, frequency, and interval in India (GDP per capita: I$5240)[a].

Strategy[b]	Discounted lifetime cost per woman (I$)[c]	Discounted life expectancy (years)[c]	ICER (I$/YLS)[d]
*care*HPV (cervical) at 50 years	10.82	27.7950	Dom
VIA at 50 years	10.89	27.7883	Dom
*care*HPV (vaginal) at 50 years	10.92	27.7936	Dom
***care*HPV (cervical) at 45 years**	**11.24**	**27.7982**	**190**
*care*HPV (vaginal) at 45 years	11.37	27.7963	Dom
VIA at 45 years	11.40	27.7933	Dom
***care*HPV (cervical) at 40 years**	**11.97**	**27.8000**	**330**
VIA at 40 years	11.97	27.7945	Dom
*care*HPV (vaginal) at 40 years	12.08	27.7983	Dom
Cytology at 50 years	12.46	27.7900	Dom
VIA at 35 years	12.74	27.7949	Dom
*care*HPV (cervical) at 35 years	13.06	27.8017	Dom
Cytology at 45 years	13.13	27.7911	Dom
*care*HPV (vaginal) at 35 years	13.13	27.7997	Dom
VIA at 30 years	13.66	27.7948	Dom
Cytology at 40 years	13.97	27.7918	Dom
*care*HPV (cervical) at 30 years	13.99	27.8018	Dom
*care*HPV (vaginal) at 30 years	14.02	27.7996	Dom
VIA at 25 years	14.97	27.7926	Dom
Cytology at 35 years	15.01	27.7920	Dom
VIA at 35 & 45 years	15.45	27.8000	Dom
***care*HPV (cervical) at 35 & 45 years**	**15.88**	**27.8105**	**390**
*care*HPV (vaginal) at 35 & 45 years	15.96	27.8076	Dom
Cytology at 30 years	16.22	27.7919	Dom
*care*HPV (vaginal) at 25 years	16.62	27.7919	Dom
*care*HPV (cervical) at 25 years	16.71	27.7997	Dom
VIA at 30 & 40 years	16.93	27.8024	Dom
*care*HPV (cervical) at 30 & 40 years	17.53	27.8126	Dom
*care*HPV (vaginal) at 30 & 40 years	17.55	27.8095	Dom
Cytology at 25 years	17.88	27.7897	Dom
VIA at 35, 40, & 45 years	18.96	27.8068	Dom
VIA at 30, 40, & 50	18.96	27.8068	Dom
Cytology at 35 & 45 years	19.33	27.7970	Dom
*care*HPV (vaginal) at 35, 40, & 45 years	19.87	27.8138	Dom
*care*HPV (cervical) at 35, 40, & 45 years	19.91	27.8168	Dom
*care*HPV (vaginal) at 30, 40, & 50 years	20.06	27.8142	Dom
***care*HPV (cervical) at 30, 40, & 50 years**	**20.07**	**27.8178**	**580**
VIA at 30, 35, & 40 years	21.20	27.8081	Dom
*care*HPV (vaginal) at 25 & 35 years	21.23	27.8091	Dom
*care*HPV (cervical) at 25 & 35 years	21.34	27.8116	Dom
Cytology at 30 & 40 years	21.37	27.7977	Dom
VIA at 25 & 35 years	21.52	27.7983	Dom
VIA at 25, 35, & 45 years	21.77	27.8067	Dom
*care*HPV (vaginal) at 30, 35, & 40 years	22.50	27.8164	Dom
***care*HPV (cervical) at 30, 35, & 40 years**	**22.62**	**27.8194**	**1600**
*care*HPV (vaginal) at 25, 35, & 45 years	24.22	27.8157	Dom
*care*HPV (cervical) at 25, 35, & 45 years	24.35	27.8189	Dom
Cytology at 35, 40, & 45 years	24.57	27.8019	Dom
Cytology at 30, 40, & 50 years	25.04	27.8025	Dom
Cytology at 30, 35, & 40 years	27.65	27.8025	Dom
Cytology at 25, 35, & 45 years	28.39	27.8009	Dom

[a] Dom: dominated strategy (i.e., those that are more costly and less effective, or have higher ICERs than more effective options); GDP: gross domestic product; ICER: incremental cost-effectiveness ratio; I$: 2011 international dollars; YLS: year of life saved.
[b] Strategies are listed in order of increasing cost.
[c] Discounted costs and life expectancies starting from age 9.
[d] ICERs are presented as the ratio of the mean costs divided by the mean effects of one strategy versus another across the top 50 input parameter sets.

will cost I$50 per YLS; screening three times at 30, 35, and 40 years or 25, 35, and 45 years are associated with ICERs of I$180 per YLS and I$1200 per YLS, respectively, and would be very cost-effective.

In Uganda, if screening is only available once in a lifetime, screening would be very cost-effective at either age 40, 35, or 30 years (in order of increasing effectiveness), with an ICER of I$260 per YLS or less. If screening is available twice in a lifetime, all age combinations and intervals would be very cost-effective, with the highest life expectancy gains associated with screening at 25 and 35 years. If screening is available three times in a lifetime, it would be very cost-effective at either 30, 40 and 50 years; 30, 35, and 40 years; or 25, 35, and 45 years (in order of increasing effectiveness), with an ICER of I$1370 per YLS or less. Assuming all ages and frequencies considered are available, screening once in a lifetime at age 30 years, and screening twice in a lifetime at ages 35 and 45 years or 25 and 35 years are now dominated. The most effective strategy is screening three times in a lifetime at 25, 35, and 45 years, which would be very cost-effective with an ICER of I$1370 per YLS.

Budget impact

For the analysis of budget impact, we converted the direct medical costs associated with *care*HPV (cervical sampling), colposcopy and biopsy, cryotherapy, and LEEP from local

Table A11
Cost-effectiveness of screening by age, frequency, and interval in Nicaragua (GDP per capita: I$4220) [a].

Strategy[b]	Discounted lifetime cost per woman (I$)[c]	Discounted life expectancy (years)[c]	ICER (I$/YLS)[d]
***care*HPV (cervical) at 35 years**	**40.98**	**28.6404**	**CS**
*care*HPV (cervical) at 40 years	41.41	28.6290	Dom
*care*HPV (cervical) at 30 years	41.47	28.6483	Dom
*care*HPV (cervical) at 45 years	42.03	28.6174	Dom
*care*HPV (vaginal) at 35 years	42.08	28.6322	Dom
*care*HPV (vaginal) at 40 years	42.33	28.6223	Dom
*care*HPV (cervical) at 35 & 45 years	42.59	28.6627	Dom
*care*HPV (vaginal) at 30 years	42.60	28.6390	Dom
VIA at 35 years	42.63	28.6283	Dom
*care*HPV (cervical) at 50 years	42.66	28.6070	Dom
VIA at 40 years	42.74	28.6204	Dom
*care*HPV (vaginal) at 45 years	42.78	28.6122	Dom
***care*HPV (cervical) at 30 & 40 years**	**42.98**	**28.6790**	**50**
VIA at 45 years	43.05	28.6114	Dom
*care*HPV (vaginal) at 50 years	43.22	28.6033	Dom
VIA at 30 years	43.52	28.6329	Dom
*care*HPV (vaginal) at 35 & 45 years	43.82	28.6527	Dom
*care*HPV (cervical) at 25 years	44.17	28.6488	Dom
*care*HPV (vaginal) at 30 & 40 years	44.27	28.6671	Dom
VIA at 35 & 45 years	44.47	28.6491	Dom
VIA at 50 years	44.75	28.5877	Dom
*care*HPV (vaginal) at 25 years	44.84	28.6407	Dom
VIA at 30 & 40 years	45.29	28.6611	Dom
*care*HPV (cervical) at 30, 40, & 50 years	45.48	28.6905	Dom
Cytology at 50 years	45.78	28.5909	Dom
*care*HPV (cervical) at 25 & 35 years	45.91	28.6871	Dom
VIA at 25 years	46.00	28.6264	Dom
*care*HPV (cervical) at 35, 40, & 45 years	46.04	28.6827	Dom
Cytology at 45 years	46.23	28.5941	Dom
*care*HPV (vaginal) at 30, 40, & 50 years	46.75	28.6779	Dom
Cytology at 40 years	46.80	28.5975	Dom
*care*HPV (vaginal) at 25 & 35 years	46.84	28.6753	Dom
*care*HPV (vaginal) at 35, 40, & 45 years	47.04	28.6722	Dom
***care*HPV (cervical) at 30, 35, & 40 years**	**47.21**	**28.7030**	**180**
Cytology at 35 years	47.62	28.6001	Dom
VIA at 35, 40, & 45 years	47.80	28.6687	Dom
VIA at 30, 40, & 50 years	47.84	28.6642	Dom
*care*HPV (vaginal) at 30, 35, & 40 years	48.27	28.6907	Dom
***care*HPV (cervical) at 25, 35, & 45 years**	**48.46**	**28.7040**	**1200**
Cytology at 30 years	48.84	28.6011	Dom
VIA at 30, 35, & 40 years	49.22	28.6844	Dom
*care*HPV (vaginal) at 25, 35, & 45 years	49.41	28.6912	Dom
VIA at 25, 35, & 45 years	50.21	28.6798	Dom
Cytology at 25 years	51.03	28.5966	Dom
Cytology at 35 & 45 years	51.34	28.6110	Dom
VIA at 25 & 35 years	51.94	28.6379	Dom
Cytology at 30 & 40 years	53.17	28.6155	Dom
Cytology at 35, 40, & 45 years	55.93	28.6235	Dom
Cytology at 25 & 35 years	56.09	28.6136	Dom
Cytology at 30, 40, & 50 years	56.54	28.6229	Dom
Cytology at 30, 35, & 40 years	58.50	28.6299	Dom
Cytology at 25, 35, & 45 years	59.91	28.6240	Dom

[a] CS: cost-saving; Dom: dominated strategy (i.e., those that are more costly and less effective, or have higher ICERs than more effective options); GDP: gross domestic product; ICER: incremental cost-effectiveness ratio; I$: 2011 international dollars; YLS: year of life saved.
[b] Strategies are listed in order of increasing cost.
[c] Discounted costs and life expectancies starting from age 9.
[d] ICERs are presented as the ratio of the mean costs divided by the mean effects of one strategy versus another across the top 50 input parameter sets.

currency units to 2013 US$ using GDP deflators and official exchange rates. We assumed the cost of the test kit was stable at a cost of US$5. The expected direct medical costs per woman screened are presented in Table A14.

Alternative natural history inputs, India

For the majority of good-fitting input parameter sets in the India model, model-projected cancer incidence fell below the 95% confidence interval suggested by registry data for age 40 and above. We explored alternative scoring algorithms that emphasized fit to cancer incidence at older ages, but this resulted in HPV prevalence projections above the target bounds. To assess the impact of this uncertainty in cancer incidence, we repeated the analysis with 3 alternative parameter sets that had either (1) reduced HPV incidence for non-HPV16/18/33 types and reduced CIN3 regression for non-HPV16 types; or (2) reduced HPV incidence for non-HPV16/18/33 types and reduced CIN3 regression for all high-risk types. Model projections for high-risk HPV prevalence and cancer incidence, relative to the calibration targets

Table A12
Cost-effectiveness of screening by age, frequency, and interval in Uganda (GDP per capita: I$1370) [a].

Strategy[b]	Discounted lifetime cost per woman (I$)[c]	Discounted life expectancy (years)[c]	ICER (I$/YLS)[d]
VIA at 50 years	14.98	25.2122	Dom
*care*HPV (cervical) at 50 years	15.60	25.2249	Dom
*care*HPV (vaginal) at 50 years	15.67	25.2221	Dom
VIA at 45 years	16.23	25.2312	Dom
*care*HPV (cervical) at 45 years	16.49	25.2345	Dom
*care*HPV (vaginal) at 45 years	16.58	25.2306	Dom
VIA at 40 years	17.13	25.2402	Dom
***care*HPV (cervical) at 40 years**	**17.60**	**25.2454**	**120**
*care*HPV (vaginal) at 40 years	17.70	25.2405	Dom
VIA at 35 years	18.36	25.2476	Dom
***care*HPV (cervical) at 35 years**	**19.14**	**25.2548**	**160**
*care*HPV (vaginal) at 35 years	19.23	25.2492	Dom
VIA at 30 years	20.06	25.2518	Dom
Cytology at 50 years	20.12	25.2155	Dom
*care*HPV (cervical) at 30 years	20.55	25.2602	Dom
*care*HPV (vaginal) at 30 years	20.62	25.2540	Dom
Cytology at 45 years	22.15	25.2204	Dom
VIA at 25 years	22.36	25.2469	Dom
VIA at 35 & 45 years	22.65	25.2675	Dom
*care*HPV (cervical) at 35 & 45 years	23.77	25.2755	Dom
*care*HPV (vaginal) at 35 & 45 years	23.83	25.2684	Dom
*care*HPV (vaginal) at 25 years	23.86	25.2548	Dom
*care*HPV (cervical) at 25 years	23.92	25.2595	Dom
Cytology at 40 years	24.51	25.2256	Dom
VIA at 30 & 40 years	25.35	25.2789	Dom
***care*HPV (cervical) at 30 & 40 years**	**26.42**	**25.2889**	**210**
*care*HPV (vaginal) at 30 & 40 years	26.45	25.2808	Dom
Cytology at 35 years	27.43	25.2299	Dom
VIA at 30, 40, & 50	28.22	25.2845	Dom
VIA at 35, 40, & 45 years	28.46	25.2848	Dom
*care*HPV (vaginal) at 35, 40, & 45 years	30.03	25.2856	Dom
*care*HPV (cervical) at 35, 40, & 45 years	30.10	25.2925	Dom
*care*HPV (vaginal) at 30, 40, & 50 years	30.26	25.2912	Dom
***care*HPV (cervical) at 30, 40, & 50 years**	**30.27**	**25.2998**	**350**
Cytology at 30 years	30.88	25.2318	Dom
*care*HPV (vaginal) at 25 & 35 years	31.33	25.2874	Dom
*care*HPV (cervical) at 25 & 35 years	31.44	25.2948	Dom
VIA at 30, 35, & 40 years	32.59	25.2993	Dom
VIA at 25, 35, & 45 years	33.41	25.2972	Dom
*care*HPV (vaginal) at 30, 35, & 40 years	34.36	25.3018	Dom
***care*HPV (cervical) at 30, 35, & 40 years**	**34.48**	**25.3099**	**420**
Cytology at 25 years	35.15	25.2281	Dom
*care*HPV (vaginal) at 25, 35, & 45 years	36.15	25.3029	Dom
***care*HPV (cervical) at 25, 35, & 45 years**	**36.31**	**25.3112**	**1370**
Cytology at 35 & 45 years	37.29	25.2447	Dom
VIA at 25 & 35 years	39.64	25.2662	Dom
Cytology at 30 & 40 years	43.16	25.2519	Dom
Cytology at 35, 40, & 45 years	49.75	25.2606	Dom
Cytology at 25 & 35 years	50.35	25.2519	Dom
Cytology at 30, 40, & 50 years	51.09	25.2614	Dom
Cytology at 30, 35, & 40 years	58.60	25.2699	Dom
Cytology at 25, 35, & 45 years	60.33	25.2654	Dom

[a] Dom: dominated strategy (i.e., those that are more costly and less effective, or have higher ICERs than more effective options); GDP: gross domestic product; ICER: incremental cost-effectiveness ratio; I$: 2011 international dollars; YLS: year of life saved.
[b] Strategies are listed in order of increasing cost.
[c] Discounted costs and life expectancies starting from age 9.
[d] ICERs are presented as the ratio of the mean costs divided by the mean effects of one strategy versus another across the top 50 input parameter sets.

and the 50 good-fitting input parameter sets used for the main analysis, are displayed in Figs. A13 and A14.

When screening with *care*HPV (cervical sampling) was compared at various ages assuming a set frequency, ICERs were generally similar to results from 50 sets (Table A15). For screening three times in a lifetime, screening at 30, 35, and 40 was no longer attractive, but screening at 25, 35, and 45 was a ranking strategy, albeit with a high ICER. For screening once, twice, or three times in a lifetime, screening once at 40 years was no longer a ranking strategy, and screening three times at 30, 35, and 40 was not a ranking strategy, but screening at 25, 35, and 45 years was a ranking strategy (again, with a high ICER). Findings indicate that results are robust for the 50 parameter sets in the main analysis.

Sensitivity analyses

We explored the impact of varying the proportion of eligible women receiving immediate cryosurgery following *care*HPV results, setting the base case proportion of 0.8 to 0.7, to be consistent with VIA (in the main analysis, we assumed women

Table A13
Cost-effectiveness of screening with careHPV (cervical sampling) by frequency in India, Nicaragua, and Uganda [a].

Strategy[b]	Discounted lifetime cost per woman (I$)	Discounted life expectancy (years)	ICER (I$/YLS)[c]
	India (GDP per capita: I$5240)		
Screening once in a lifetime[d]			
*care*HPV (cervical) at 50 years	10.82	27.7950	Dom
*care*HPV (cervical) at 45 years	11.24	27.7982	190
*care*HPV (cervical) at 40 years	11.97	27.8000	330
*care*HPV (cervical) at 35 years	13.06	27.8017	780
*care*HPV (cervical) at 30 years	13.99	27.8018	22,410
*care*HPV (cervical) at 25 years	16.71	27.7997	Dom
Screening twice in a lifetime[e]			
*care*HPV (cervical) at 35 & 45 years	15.88	27.8105	280
*care*HPV (cervical) at 30 & 40 years	17.53	27.8126	760
*care*HPV (cervical) at 25 & 35 years	21.34	27.8116	Dom
Screening three times in a lifetime[f]			
*care*HPV (cervical) at 35, 40, & 45 years	19.91	27.8168	Dom
*care*HPV (cervical) at 30, 40, & 50 years	20.07	27.8178	350
*care*HPV (cervical) at 30, 35, & 40 years	22.62	27.8194	1600
*care*HPV (cervical) at 25, 35, & 45 years	24.35	27.8189	Dom
Screening once, twice, or three times in a lifetime[g]			
*care*HPV (cervical) at 50 years	10.82	27.7950	Dom
*care*HPV (cervical) at 45 years	11.24	27.7982	190
*care*HPV (cervical) at 40 years	11.97	27.8000	330
*care*HPV (cervical) at 35 years	13.06	27.8017	Dom
*care*HPV (cervical) at 30 years	13.99	27.8018	Dom
*care*HPV (cervical) at 35 & 45 years	15.88	27.8105	390
*care*HPV (cervical) at 25 years	16.71	27.7997	Dom
*care*HPV (cervical) at 30 & 40 years	17.53	27.8126	Dom
*care*HPV (cervical) at 35, 40, & 45 years	19.91	27.8168	Dom
*care*HPV (cervical) at 30, 40, & 50 years	20.07	27.8178	580
*care*HPV (cervical) at 25 & 35 years	21.34	27.8116	Dom
*care*HPV (cervical) at 30, 35, & 40 years	22.62	27.8194	1600
*care*HPV (cervical) at 25, 35, & 45 years	24.35	27.8189	Dom
	Nicaragua (GDP per capita: I$4220)		
Screening once in a lifetime[d]			
*care*HPV (cervical) at 35 years	40.98	28.6404	CS
*care*HPV (cervical) at 40 years	41.41	28.6290	Dom
*care*HPV (cervical) at 30 years	41.47	28.6483	60
*care*HPV (cervical) at 45 years	42.03	28.6174	Dom
*care*HPV (cervical) at 50 years	42.66	28.6070	Dom
*care*HPV (cervical) at 25 years	44.17	28.6488	5750
Screening twice in a lifetime[e]			
*care*HPV (cervical) at 35 & 45 years	42.59	28.6627	CS
*care*HPV (cervical) at 30 & 40 years	42.98	28.6790	20
*care*HPV (cervical) at 25 & 35 years	45.91	28.6871	360
Screening three times in a lifetime[f]			
*care*HPV (cervical) at 30, 40, & 50 years	45.48	28.6905	30
*care*HPV (cervical) at 35, 40, & 45 years	46.04	28.6827	Dom
*care*HPV (cervical) at 30, 35, & 40 years	47.21	28.7030	140
*care*HPV (cervical) at 25, 35, & 45 years	48.46	28.7040	1200
Screening once, twice, or three times in a lifetime[g]			
*care*HPV (cervical) at 35 years	40.98	28.6404	CS
*care*HPV (cervical) at 40 years	41.41	28.6290	Dom
*care*HPV (cervical) at 30 years	41.47	28.6483	Dom
*care*HPV (cervical) at 45 years	42.03	28.6174	Dom
*care*HPV (cervical) at 35 & 45 years	42.59	28.6627	Dom
*care*HPV (cervical) at 50 years	42.66	28.6070	Dom
*care*HPV (cervical) at 30 & 40 years	42.98	28.6790	50
*care*HPV (cervical) at 25 years	44.17	28.6488	Dom
*care*HPV (cervical) at 30, 40, & 50 years	45.48	28.6905	Dom
*care*HPV (cervical) at 25 & 35 years	45.91	28.6871	Dom
*care*HPV (cervical) at 35, 40, & 45 years	46.04	28.6827	Dom
*care*HPV (cervical) at 30, 35, & 40 years	47.21	28.7030	180
*care*HPV (cervical) at 25, 35, & 45 years	48.46	28.7040	1200

Table A13 (*continued*)

Strategy[b]	Discounted lifetime cost per woman (I$)	Discounted life expectancy (years)	ICER (I$/YLS)[c]
	Uganda (GDP per capita: I$1370)		
Screening once in a lifetime[d]			
*care*HPV (cervical) at 50 years	15.60	25.2249	Dom
*care*HPV (cervical) at 45 years	16.49	25.2346	Dom
*care*HPV (cervical) at 40 years	17.60	25.2454	120
*care*HPV (cervical) at 35 years	19.14	25.2548	160
*care*HPV (cervical) at 30 years	20.55	25.2602	260
*care*HPV (cervical) at 25 years	23.92	25.2595	Dom
Screening twice in a lifetime[e]			
*care*HPV (cervical) at 35 & 45 years	23.77	25.2755	160
*care*HPV (cervical) at 30 & 40 years	26.42	25.2889	200
*care*HPV (cervical) at 25 & 35 years	31.44	25.2948	840
Screening three times in a lifetime[f]			
*care*HPV (cervical) at 35, 40, & 45 years	30.10	25.2925	Dom
*care*HPV (cervical) at 30, 40, & 50 years	30.27	25.2999	180
*care*HPV (cervical) at 30, 35, & 40 years	34.48	25.3099	420
*care*HPV (cervical) at 25, 35, & 45 years	36.31	25.3112	1370
Screening once, twice, or three times in a lifetime[g]			
*care*HPV (cervical) at 50 years	15.60	25.2249	Dom
*care*HPV (cervical) at 45 years	16.49	25.2346	Dom
*care*HPV (cervical) at 40 years	17.60	25.2454	120
*care*HPV (cervical) at 35 years	19.14	25.2548	160
*care*HPV (cervical) at 30 years	20.55	25.2602	Dom
*care*HPV (cervical) at 35 & 45 years	23.77	25.2755	Dom
*care*HPV (cervical) at 25 years	23.92	25.2595	Dom
*care*HPV (cervical) at 30 & 40 years	26.42	25.2889	210
*care*HPV (cervical) at 35, 40, & 45 years	30.10	25.2925	Dom
*care*HPV (cervical) at 30, 40, & 50 years	30.27	25.2999	350
*care*HPV (cervical) at 25 & 35 years	31.44	25.2948	Dom
*care*HPV (cervical) at 30, 35, & 40 years	34.48	25.3099	420
*care*HPV (cervical) at 25, 35, & 45 years	36.31	25.3112	1370

[a] CS: cost saving; Dom: dominated strategy (i.e., those that are more costly and less effective, or have higher ICERs than more effective options); GDP: gross domestic product; ICER: incremental cost-effectiveness ratio; I$: 2011 international dollars; YLS: year of life saved.
[b] Strategies are listed in order of increasing cost. For this table, we have assumed only *care*HPV (cervical sampling), the dominant screening strategy, was available.
[c] ICERs are presented as the ratio of the mean costs divided by the mean effects of one strategy versus another across the top 50 input parameter sets.
[d] Assuming screening will take place once in a lifetime, at one of the ages evaluated.
[e] Assuming screening will take place twice in a lifetime, at one of the age combinations considered.
[f] Assuming screening will take place three times in a lifetime, at one of the age combinations considered.
[g] Assuming screening will take place once, twice, or three times in a lifetime, at one of the age combinations considered.

Table A14
Budget impact: Expected direct medical cost per woman screened, by country and age, 2013 US$.

Age	Expected direct medical cost per woman screened		
	India	Nicaragua	Uganda
25	7.14	12.41	7.87
30	6.73	11.57	7.34
35	6.73	11.30	7.12
40	6.56	10.91	6.63
45	6.37	10.53	6.12
50	6.17	10.15	5.57

might be more likely to delay cryotherapy after VIA than with 2-visit HPV testing, when they would have already received counseling in the screening visit). Varying the proportion receiving immediate cryosurgery during the results visit had no impact on the rank order of strategies, and *care*HPV (cervical sampling) remained the dominant strategy. The ICERs associated with *care*HPV (cervical sampling) changed little. In Uganda, the ICER

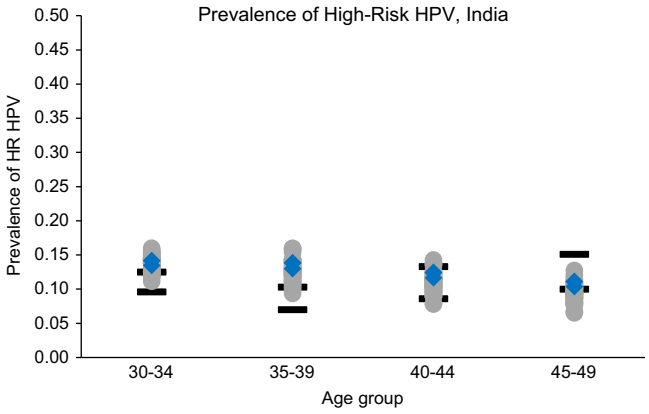

Fig. A13. Model fit of 3 alternative input parameter sets, India: high-risk HPV prevalence. The black lines represent the 95% confidence interval around the empirical data [7], and the gray dots represent model-predicted prevalence of high-risk HPV from the 50 good-fitting input parameter sets used in the main analysis. Blue diamonds represent the fit of the alternative 3 sets used for sensitivity analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

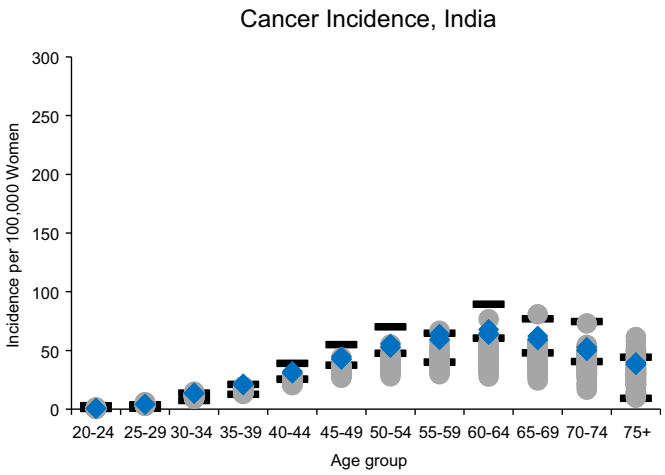

Fig. A14. Model fit of 3 alternative input parameter sets, India: cancer incidence. The black lines represent the 95% confidence interval around the empirical data [57], and the gray dots represent model-predicted cancer incidence from the 50 good-fitting input parameter sets used in the main analysis. Blue diamonds represent the fit of the alternative 3 sets used for sensitivity analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

for screening with *care*HPV (cervical sampling) at ages 25, 35, and 45 years increased from I$1370 per YLS to I$1520, which given Uganda's per capita GDP of I$1370 would be considered cost-effective, but no longer very cost-effective.

When we varied loss to follow-up associated with each clinical encounter relative to the previous visit (including the results visit for HPV testing, or diagnostic confirmation and treatment visits for women who are ineligible for cryosurgery in a screen-and-treat approach) from 15% in the base case to 30%, *care*HPV (cervical sampling) remained the dominant strategy in India and Nicaragua, with ICERs increasing slightly as screening costs were more frequently incurred without corresponding health benefits. In Uganda, where VIA test sensitivity in the START–UP project was higher than other sites (74%), VIA became the dominant screening strategy.

Supplementary discussion

There are several limitations to this analysis, which are primarily documented in the paper. We elaborate further here. With regards to potential interaction between HIV and cervical cancer, we did not explicitly model an altered natural history in HIV-infected women due to data limitations. Instead, we calibrated our model to the general population of women in Uganda, assuming the model output reflects the course of HPV natural history at the population level, including high-risk subgroups.

Regarding costing estimates, we did not include the cost of treatment-associated complications, as these were very rare in the START–UP studies. As primary data on cancer costs in Nicaragua and Uganda were unavailable, these were extrapolated from primary data in El Salvador and Kenya, respectively, as described above. While our extrapolation technique explicitly considered differences in health care costs and GDP per capita between Nicaragua and El Salvador, the cancer costs in Nicaragua were relatively high compared to screening costs, and thus screening with *care*HPV was either cost-saving or had a very low ICER. If cancer costs in Nicaragua are in fact lower, screening would appear somewhat less attractive.

Data on loss to follow-up between screening and treatment are limited, so we assumed that 15% of women were lost between each subsequent visit to receive screening results or diagnostic confirmation and treatment of histologically confirmed lesions (when applicable). This may be an underestimate, if attrition rates are closer to 40% suggested by a study from South Africa [63]; however, the same study found that community health worker contact improved follow-up rates substantially.

Cancer incidence data for Nicaragua were drawn from GLOBOCAN, rather than a cancer registry. Cancer incidence data for India (Hyderabad) were based on the Nagpur registry, which may not reflect cancer incidence in Hyderabad, although cancer incidence in Nagpur appears to be similar to incidence rates documented by several other urban registries in northern and central India (i.e., Bhopal and Delhi).

Table A15
Cost-effectiveness of screening by frequency in India, sensitivity analysis (50 good-fitting sets vs. 3 selected parameter sets)[a].

Strategy[b]	India (GDP per capita: I$5240)	
	ICER (I$/YLS),[c] 50 sets	ICER (I$/YLS),[c] 3 sets
Screening once in a lifetime[d]		
*care*HPV (cervical) at 50 years	Dom	Dom
*care*HPV (cervical) at 45 years	190	100
*care*HPV (cervical) at 40 years	330	430
*care*HPV (cervical) at 35 years	780	5550
*care*HPV (cervical) at 30 years	22,410	Dom
*care*HPV (cervical) at 25 years	Dom	Dom
Screening twice in a lifetime[e]		
*care*HPV (cervical) at 35 & 45 years	280	190
*care*HPV (cervical) at 30 & 40 years	760	2090
*care*HPV (cervical) at 25 & 35 years	Dom	Dom
Screening three times in a lifetime[f]		
*care*HPV (cervical) at 35, 40, & 45 years	Dom	Dom
*care*HPV (cervical) at 30, 40, & 50 years	350	240
*care*HPV (cervical) at 30, 35, & 40 years	1600	Dom
*care*HPV (cervical) at 25, 35, & 45 years	Dom	11,600
Screening once, twice, or three times in a lifetime[g]		
*care*HPV (cervical) at 50 years	Dom	Dom
*care*HPV (cervical) at 45 years	190	100
*care*HPV (cervical) at 40 years	330	Dom
*care*HPV (cervical) at 35 years	Dom	Dom
*care*HPV (cervical) at 30 years	Dom	Dom
*care*HPV (cervical) at 35 & 45 years	390	300
*care*HPV (cervical) at 25 years	Dom	Dom
*care*HPV (cervical) at 30 & 40 years	Dom	Dom
*care*HPV (cervical) at 35, 40, & 45 years	Dom	Dom
*care*HPV (cervical) at 30, 40, & 50 years	580	430
*care*HPV (cervical) at 25 & 35 years	Dom	Dom
*care*HPV (cervical) at 30, 35, & 40 years	1600	Dom
*care*HPV (cervical) at 25, 35, & 45 years	Dom	11,600

[a] Dom: dominated strategy (i.e., those that are more costly and less effective, or have higher ICERs than more effective options); GDP: gross domestic product; ICER: incremental cost-effectiveness ratio; I$: 2011 international dollars; YLS: year of life saved.
[b] Strategies are listed in order of increasing cost.
[c] ICERs are presented as the ratio of the mean costs divided by the mean effects of one strategy versus another across the top 50 input parameter sets, or the 3 selected input parameter sets.
[d] Assuming screening will take place once in a lifetime, at one of the ages evaluated.
[e] Assuming screening will take place twice in a lifetime, at one of the age combinations considered.
[f] Assuming screening will take place three times in a lifetime, at one of the age combinations considered.
[g] Assuming screening once, twice, or three times in a lifetime will take place, at one of the age combinations considered.

References

[1] J. Ferlay, I. Soerjomataram, M. Ervik, et al., GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet], International Agency for Research on Cancer, Lyon, France, 2013.

[2] L. Denny, Control of cancer of the cervix in low- and middle-income countries, Ann. Surg. Oncol. 22 (3) (2015) 728–733.
[3] R. Sankaranarayanan, B.M. Nene, S.S. Shastri, et al., HPV screening for cervical cancer in rural India, N. Engl. J. Med. 360 (14) (2009) 1385–1394.
[4] S.S. Shastri, I. Mittra, G.A. Mishra, et al., Effect of VIA screening by primary health workers: randomized controlled study in Mumbai, India, J. Natl. Cancer Inst. 106 (3) (2014), dju009.
[5] S.J. Goldie, L. Gaffikin, J.D. Goldhaber-Fiebert, et al., Cost-effectiveness of cervical-cancer screening in five developing countries, N. Engl. J. Med. 353 (20) (2005) 2158–2168.
[6] M. Diaz, J.J. Kim, G. Albero, et al., Health and economic impact of HPV 16 and 18 vaccination and cervical cancer screening in India, Br. J. Cancer 99 (2) (2008) 230–238.
[7] J. Jeronimo, P. Bansil, J. Lim, 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 24 (3) (2014) 576–585.
[8] Y.L. Qiao, J.W. Sellors, P.S. Eder, 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. 9 (10) (2008) 929–936.
[9] F.H. Zhao, M.J. Lin, F. Chen, 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. 11 (12) (2010) 1160–1171.
[10] N.G. Campos M. Maza, K. Alfaro, J. Gage, P.E. Castle, J.C. Felix, M. Cremer, J.J. Kim. The comparative and cost-effectiveness of HPV-based cervical cancer screening algorithms in El Salvador. Int. J. Cancer 137 (2015) 893-902.
[11] World Health Organization, WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention, World Health Organization, Geneva, 2013.
[12] World Heath Organization, Comprehensive Cervical Cancer Control: A Guide to Essential Practice, second ed., World Health Organization, Geneva, 2014.
[14] N.G. Campos, E.A. Burger, S. Sy, et al., An updated natural history model of cervical cancer: derivation of model parameters, Am. J. Epidemiol. 180 (5) (2014) 545–555.
[15] J.J. Kim, K.M. Kuntz, N.K. Stout, et al., Multiparameter calibration of a natural history model of cervical cancer, Am. J. Epidemiol. 166 (2) (2007) 137–150.
[16] N.G. Campos, J.J. Kim, P.E. Castle, et al., Health and economic impact of HPV 16/18 vaccination and cervical cancer screening in Eastern Africa, Int. J. Cancer 130 (11) (2012) 2672–2684.
[17] S.J. Goldie, J.J. Kim, K. Kobus, et al., Cost-effectiveness of HPV 16, 18 vaccination in Brazil, Vaccine 25 (33) (2007) 6257–6270.
[18] M. Mvundura, V. Tsu, Estimating the costs of cervical cancer screening in high-burden Sub-Saharan African countries, Int. J. Gynaecol. Obstet. 126 (2) (2014) 151–155.
[19] World Health Organization, Macroeconomics and Health: Investing in Health for Economic Development: Report of the Commission on Macroeconomics and Health, World Health Organization, Geneva, 2001.
[20] T. Tan-Torres Edejer, R. Baltussen, T. Adam, R. Hutubessy, A. Acharya, D. B. Evans, C.J.L. Murray (Eds.), Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis, World Health Organization, Geneva, 2003.
[21] Disease Control Priorities in Developing Countries, in: D.T. Jamison, J. G. Breman, A.R. Measham, G. Alleyne, M. Claeson, D.B. Evans, P. Jha, A. Mills, P. Musgrove (Eds.), second ed.,Oxford University Press and The World Bank, Washington, DC., 2006.
[22] M.R. Gold, J.E. Siegel, L.B. Russell, M.C. Weinstein, eds. Cost-effectiveness in Health and Medicine, Oxford University Press, New York, NY, 1996.
[23] N. Munoz, F. Mendez, H. Posso, et al., Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results, J. Infect. Dis. 190 (12) (2004) 2077–2087.
[24] R. Herrero, A. Hildesheim, A.C. Rodriguez, et al., Rationale and design of a community-based double-blind randomized clinical trial of an HPV 16 and 18 vaccine in Guanacaste, Costa Rica, Vaccine 26 (37) (2008) 4795–4808.
[25] M.R. McCredie, K.J. Sharples, C. Paul, et al., Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study, Lancet Oncol. 9 (5) (2008) 425–434.
[26] Surveillance, Epidemiology, and End Results (SEER) Program. SEERStat Database: Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases Nov 2011 Sub (1973–2009 varying) – Linked to County Attributes – Total U.S., 1969–2010 Counties.
[27] R. Sankaranarayanan, R. Swaminathan, H. Brenner, et al., Cancer survival in Africa, Asia, and Central America: a population-based study, Lancet Oncol. 11 (2) (2010) 165–173.
[28] J.D. Goldhaber-Fiebert, N.K. Stout, J. Ortendahl, et al., Modeling human papillomavirus and cervical cancer in the United States for analyses of screening and vaccination, Popul. Health Metr. 5 (2007) 11.
[29] A.A. Stinnett, A.D. Paltiel, Estimating CE ratios under second-order uncertainty: the mean ratio versus the ratio of means, Med. Decis. Making 17 (4) (1997) 483–489.
[30] P.D. Blumenthal, L. Gaffikin, S. Deganus, et al., Cervical cancer prevention: safety, acceptability, and feasibility of a single-visit approach in Accra, Ghana, Am. J. Obstet. Gynecol. 196 (4) (2007) e408–409 407 e401-408; discussion 407.
[31] P.E. Castle, Y.L. Qiao, F.H. Zhao, et al., Clinical determinants of a positive visual inspection after treatment with acetic acid for cervical cancer screening, BJOG 121 (6) (2014) 739–746.
[32] M. Cremer, E. Conlisk, M. Maza, et al., Adequacy of visual inspection with acetic acid in women of advancing age, Int. J. Gynaecol. Obstet. 113 (1) (2011) 68–71.
[33] N. Li, J.F. Shi, S. Franceschi, et al., Different cervical cancer screening approaches in a Chinese multicentre study, Br. J. Cancer 100 (3) (2009) 532–537.
[34] M. Cremer, K. Bullard, M. Maza, et al., Cytology versus visual inspection with acetic acid among women treated previously with cryotherapy in a low-resource setting, Int. J. Gynaecol. Obstet. 111 (3) (2010) 249–252.
[35] Z.M. Chirenje, S. Rusakaniko, L. Kirumbi, et al., Situation analysis for cervical cancer diagnosis and treatment in east, central and southern African countries, Bull. World Health Organ. 79 (2) (2001) 127–132.
[36] C. Sauvaget, R. Muwonge, R. Sankaranarayanan, Meta-analysis of the effectiveness of cryotherapy in the treatment of cervical intraepithelial neoplasia, Int. J. Gynaecol. Obstet. 120 (3) (2013) 218–223.
[37] United Nations Development Programme. International Human Development Indicators. Available from: ⟨http://hdr.undp.org/en/data⟩ [September 14, 2014].
[38] World Health Organization, WHO Guidance Note: Comprehensive Cervical Cancer Prevention and Control: A Healthier Future for Girls and Women, World Health Organization, Geneva, 2013.
[39] World Health Organization Statistical Information System: CHOICE (CHOosing Interventions that are Cost Effective). Available from: ⟨http://www.who.int/choice/en/⟩ [October 17, 2007].
[40] E. Marseille, B. Larson, D.S. Kazi, et al., Thresholds for the cost-effectiveness of interventions: alternative approaches, Bull. World Health Organ. 93 (2) (2015) 118–124.
[41] Human papillomavirus vaccines: WHO position paper, October 2014. Wkly. Epidemiol. Rec. 2014;89(43):465–491.
[42] FDA approves Gardasil 9 for Prevention of Certain Cancers Caused by Five Additional Types of HPV.. FDA News Release December 11, 2014; Available from: ⟨http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426485.htm⟩[February 4, 2015].
[43] S.R. Skinner, A. Szarewski, B. Romanowski, et al., Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study, Lancet 384 (9961) (2014) 2213–2227.
[44] X. Castellsague, N. Munoz, P. Pitisuttithum, et al., End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24–45 years of age, Br. J. Cancer 105 (1) (2011) 28–37.
[45] S. Arrossi, L. Thouyaret, R. Herrero, 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 Global Health 3 (2) (2015) e85–94.
[46] C.S. Racey, D.R. Withrow, D. Gesink, Self-collected HPV testing improves participation in cervical cancer screening: a systematic review and meta-analysis, Can. J. Public Health 104 (2) (2013) e159–166.
[47] United States Census Bureau. International Data Base. 2013; Available from: ⟨http://www.census.gov/population/international/data/idb/informationGateway.php⟩ [April 14, 2015].
[48] N.G. Campos, E.A. Burger, S. Sy, M. Sharma, M. Schiffman, A.C. Rodriguez, et al., An updated natural history model of cervical cancer: derivation of model parameters, Am. J. Epidemiol. 180 (2014) 545–555.
[49] N. Munoz, F. Mendez, H. Posso, M. Molano, A.J. van den Brule, M. Ronderos, et al., Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results, J. Infect. Dis. 190 (2004) 2077–2087.
[50] R. Herrero, A. Hildesheim, A.C. Rodriguez, S. Wacholder, C. Bratti, D. Solomon, et al., Rationale and design of a community-based double-blind randomized clinical trial of an HPV 16 and 18 vaccine in Guanacaste, Costa Rica, Vaccine 26 (2008) 4795–4808.
[51] M.R. McCredie, K.J. Sharples, C. Paul, J. Baranyai, G. Medley, R.W. Jones, et al., Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study, Lancet Oncol. 9 (2008) 425–434.
[52] F.L. Meyskens Jr., E. Surwit, T.E. Moon, J.M. Childers, J.R. Davis, R.T. Dorr, et al., Enhancement of regression of cervical intraepithelial neoplasia II (moderate dysplasia) with topically applied all-trans-retinoic acid: a randomized trial, J. Natl. Cancer Inst. 86 (1994) 539–543.
[53] K.A. Keefe, M.J. Schell, C. Brewer, M. McHale, W. Brewster, J.A. Chapman, et al., A randomized, double blind, Phase III trial using oral beta-carotene supplementation for women with high-grade cervical intraepithelial neoplasia, Cancer Epidemiol. Biomarkers Prev. 10 (2001) 1029–1035.
[54] P.E. Castle, M. Schiffman, C.M. Wheeler, D. Solomon, Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2, Obstet. Gynecol. 113 (2009) 18–25.
[55] S.M. Wang, D. Colombara, J.F. Shi, F.H. Zhao, J. Li, F. Chen, et al., Six-year regression and progression of cervical lesions of different human papillomavirus viral loads in varied histological diagnoses, Int. J. Gynecol. Cancer 23 (2013) 716–723.
[56] A.B. Moscicki, Y. Ma, C. Wibbelsman, T.M. Darragh, A. Powers, S. Farhat, et al., Rate of and risks for regression of cervical intraepithelial neoplasia 2 in adolescents and young women, Obstet. Gynecol. 116 (2010) 1373–1380.
[57] Cancer Incidence in Five Continents, in: D. Forman, F. Bray, D.H. Brewster, C. Gombe Mbalawa, B. Kohler, M. Piñeros, E. Steliarova-Foucher,

R. Swaminathan, J. Ferlay (Eds.), International Agency for Research on Cancer, Lyon, France, 2013.
[58] J. Ferlay, I. Soerjomataram, M. Ervik, R. Dikshit, S. Eser, C. Mathers, et al., GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet], International Agency for Research on Cancer, Lyon, France, 2013.
[59] World Bank. (2013) World Development Indicators. Available from: http://data.worldbank.org/data-catalog/world-development-indicators [July 24, 2014].
[60] S.J. Goldie, L. Gaffikin, J.D. Goldhaber-Fiebert, A. Gordillo-Tobar, C. Levin, C. Mahe, et al., Cost-effectiveness of cervical-cancer screening in five developing countries, N. Engl. J. Med. 353 (2005) 2158–2168.
[61] N.G. Campos, J.J. Kim, P.E. Castle, J.D. Ortendahl, M. O'Shea, M. Diaz, et al., Health and economic impact of HPV 16/18 vaccination and cervical cancer screening in Eastern Africa, Int. J. Cancer 130 (2012) 2672–2684.
[62] N.G. Campos, M. Maza, K. Alfaro, J.C. Gage, P.E. Castle, J.C. Felix, et al., The comparative and cost-effectiveness of HPV-based cervical cancer screening algorithms in El Salvador, Int. J. Cancer (2015).
[63] J.D. Goldhaber-Fiebert, L.E. Denny, M. De Souza, T.C. Wright Jr., L. Kuhn, S. J. Goldie, The costs of reducing loss to follow-up in South African cervical cancer screening, Cost Eff. Resour. Alloc. 3 (2005) 11.