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

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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 careHPV (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 careHPV (cervical sampling) was the most effective and cost-effective strategy in all settings; careHPV (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%.

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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 careHPV (QIAGEN, Gaithersburg, MD), a lower-cost DNA test that can be used in clinics that lack reliable clean water or electricity; the performance of careHPV 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...
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 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 careHPV (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 careHPV 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

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

* 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.

* 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 careHPV 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 careHPV testing]).

* 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.

* 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.

* All costs are in 2011 international dollars (I$).

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

* 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).

* All costs presented include the value of women’s time spent pursuing care and transportation to health facilities.

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 supplies, and laboratory equipment. In the START-UP sites, because women self-collected a vaginal sample for careHPV 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 across countries, taking into account differences in purchasing power; we assumed the careHPV 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).
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 careHPV (cervical sampling) is displayed by the blue bars; careHPV (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 \textit{care}HPV (cervical sampling) yielded the greatest mean reductions in lifetime risk of cancer relative to other screening tests. Self-collected vaginal sampling with \textit{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 \textit{care}HPV testing, particularly in India, where VIA test sensitivity (CIN2+ threshold) was approximately 20% lower than \textit{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 \textit{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 \textit{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, \textit{care}HPV (vaginal sampling) was the second most effective, with mean reductions in cancer risk just a few percentage points below \textit{care}HPV (cervical sampling). Screening twice in a lifetime with \textit{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 \textit{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.](image-url)

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. IS: 2011 international dollars; VIA: visual inspection with acetic acid; YLS: year of life saved.

\textit{Care}HPV: Human Papillomavirus; CIN2+: Cervical intraepithelial neoplasia grade 2 or worse; VIA: Visual Inspection with Acetic Acid; Cytology: Cervical cytology; YLS: Year of Life Saved.
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., careHPV with cervical sampling at age 45 years), the direct medical costs associated with screening alone would be an estimated US$342.2 million in 2015. The most effective strategy in India with an ICER below the country's per capita GDP (i.e., careHPV 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 careHPV 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 careHPV at ages 25, 35, and 45 years, would cost an estimated US$1.1 million in 2015. Once in a lifetime screening with careHPV 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.

### 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, careHPV (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].

### Table 2

| Age group in 2015, by country | Number of women in target age group in 2015 | Cost of screening 70% of the target population with careHPV (US$) |
|-----------------------------|------------------------------------------|---------------------------------------------------------------|
| India                      |                                           |                                                               |
| 45 years                   | 7,657,000                                 | 34,167,000                                                   |
| 40 years                   | 8,446,000                                 | 38,708,000                                                   |
| 35 & 45 years              | 16,996,000                                | 76,740,000                                                   |
| 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, 35, & 40 years         | 460,000                                   | 2,190,000                                                    |
| 30, 35, & 40 years         | 554,000                                   | 2,750,000                                                    |
| 25, 35, & 45 years         | 607,000                                   | 3,116,000                                                    |

* We considered non-dominated strategies from Fig. 2.
* The number of women in the target age group includes only those at target age(s) in 2015.
* US$. 2013 US$. As described in the Methods, the expected cost per woman screened (including direct medical costs associated with careHPV [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.

### 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., careHPV with cervical sampling at age 45 years), the direct medical costs associated with screening alone would be an estimated US$342.2 million in 2015. The most effective strategy in India with an ICER below the country's per capita GDP (i.e., careHPV 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 careHPV 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 careHPV at ages 25, 35, and 45 years, would cost an estimated US$1.1 million in 2015. Once in a lifetime screening with careHPV at age 40 years in Uganda, the strategy with the lowest ICER,
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 careHPV 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 careHPV 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.

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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.

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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 core 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.

| 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)   |

* HPV positivity was based on a cut-off of 0.5 relative light units.
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$) to facilitate comparisons across regions. The relevant GDP deflators were applied to local currency units to inflate to year 2011 levels, and local currency units were then converted to international dollars by means of purchasing power parity (PPP) exchange rates [59]. The exceptions were for equipment, which was generally procured in the United States, and the cost of the careHPV test kit, which was assumed to be US$. 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

| Table A2 | Age-specific prevalence of high-risk HPV, Nicaragua [57]. |
| --- | --- |
| 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) |

* 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]. |
| --- | --- |
| 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) |

* 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]. |
| --- | --- |
| 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) |

* 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 cervical 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.
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. 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. 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. 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. 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. 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 (Nyadondo 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 Indicators, “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 30% would delay treatment. We assumed HPV DNA testing was primarily a one-visit strategy, with women receiving screening results (i.e., initial screening visit with VIA; second visit for HPV testing). Thus, additional transportation time was only accrued for women who received screening results (negative) and preferences for treatment options. In Hyderabad, we assumed that a histologic diagnosis of CIN1 was followed by cryotherapy and a histologic diagnosis of CIN2/3 was followed by LEEP at a secondary facility. In Nicaragua, we assumed that a histologic diagnosis of CIN1 was followed by cryotherapy and a histologic diagnosis of CIN2/3 was followed by cryotherapy for approximately 80% of women, and

**Table A7**

| 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) |
| LEEP                              | Secondary facility (for women ineligible for screen-and-treat cryotherapy) |
| Follow-up visits (after cryotherapy or LEEP) | Primary facility (for examinations and Pap) |
| Cancer treatment                  | Tertiary facility                            |

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

**Table A8**

| 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)      | 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 | | | |
| 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            |

- I$: international dollars. LEEP: loop electrosurgical excision procedure.
- Applicable to careHPV and Pap screening.
- 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.
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 careHPV (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

| Age at Screening | 25 and 35 years | 30 and 40 years | 35 and 44 years |
|------------------|----------------|----------------|----------------|
| India            | -              | -              | -              |

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 careHPV (cervical sampling) is displayed by the blue bars; careHPV (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.)

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 careHPV (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

Table A9

Follow-up protocols after treatment of precancerous lesions1.

| Treatment | Hyderabad | Nicaragua | Uganda |
|-----------|-----------|-----------|--------|
| Cryotherapy | 1 year Cytology/Colposcopy | 1 year Cytology | 6 week exam |
| LEEP | NA | 1 year Cytology | 6 week exam |

1 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.

2 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.
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 25 and 35 years will cost I$360 per YLS. If screening is available three times per lifetime, screening at 25, 35, and 45 years will cost I$360 per YLS. If screening is available three times per lifetime, screening at 30, 35, and 50 years would cost I$360 per YLS. If screening is available three times per lifetime, screening at 30, 35, and 40 years would cost I$360 per YLS. If screening is available three times per lifetime, screening at 30, 35, and 40 years would be cost-saving at either 35 and 40 years (in order of increasing effectiveness) would be very cost-effective. Assuming 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 25 and 35 years will cost I$360 per YLS. If screening is available three times per lifetime, screening at 25, 35, and 45 years will cost I$360 per YLS. If screening is available three times per lifetime, screening at 30, 35, and 50 years would cost I$360 per YLS. If screening is available three times per lifetime, screening at 30, 35, and 40 years would be cost-saving at either 35 and 40 years (in order of increasing effectiveness) would be very cost-effective. Assuming 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 25 and 35 years will cost I$360 per YLS. If screening is available three times per lifetime, screening at 25, 35, and 45 years will cost I$360 per YLS. If screening is available three times per lifetime, screening at 30, 35, and 50 years would cost I$360 per YLS. If screening is available three times per lifetime, screening at 30, 35, and 40 years would be cost-saving at either 35 and 40 years (in order of increasing effectiveness) would be very cost-effective. Assuming 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.
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 30 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 careHPV (cervical sampling), colposcopy and biopsy, cryotherapy, and LEEP from local

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

| Strategy | Discounted lifetime cost per woman (I$) | Discounted life expectancy (years) | ICER (I$/YLS) |
|----------|----------------------------------------|----------------------------------|--------------|
| careHPV (cervical) at 50 years | 10.82 | 27.7950 | Dominated |
| VIA at 50 years | 10.89 | 27.7883 | Dominated |
| careHPV (vaginal) at 50 years | 10.92 | 27.7936 | Dominated |
| careHPV (cervical) at 45 years | 11.24 | 27.7982 | 190 |
| VIA at 45 years | 11.37 | 27.7963 | Dominated |
| careHPV (vaginal) at 45 years | 11.40 | 27.7933 | Dominated |
| VIA at 35 years | 11.97 | 27.8000 | 330 |
| careHPV (cervical) at 35 years | 12.08 | 27.7945 | Dominated |
| VIA at 35 years | 12.46 | 27.7983 | Dominated |
| careHPV (vaginal) at 35 years | 12.74 | 27.7949 | Dominated |
| VIA at 30 years | 13.06 | 27.8017 | Dominated |
| careHPV (cervical) at 30 years | 13.13 | 27.7911 | Dominated |
| VIA at 25 years | 13.33 | 27.7997 | Dominated |
| careHPV (vaginal) at 30 years | 13.66 | 27.7948 | Dominated |
| VIA at 35 & 45 years | 13.97 | 27.7918 | Dominated |
| careHPV (cervical) at 35 & 45 years | 14.02 | 27.8018 | Dominated |
| VIA at 30 & 45 years | 14.97 | 27.7996 | Dominated |
| careHPV (vaginal) at 30 & 45 years | 15.01 | 27.7926 | Dominated |
| VIA at 35 & 45 years | 15.45 | 27.8000 | Dominated |
| careHPV (cervical) at 35 & 45 years | 15.88 | 27.8105 | 390 |
| VIA at 35 & 45 years | 15.96 | 27.8076 | Dominated |
| careHPV (vaginal) at 30 years | 16.22 | 27.7919 | Dominated |
| VIA at 25 years | 16.62 | 27.7919 | Dominated |
| careHPV (cervical) at 25 years | 16.71 | 27.7997 | Dominated |
| VIA at 30 & 40 years | 16.93 | 27.8024 | Dominated |
| careHPV (cervical) at 30 & 40 years | 17.53 | 27.8126 | Dominated |
| VIA at 35 & 40 years | 17.55 | 27.8095 | Dominated |
| careHPV (vaginal) at 30 & 40 years | 17.88 | 27.7897 | Dominated |
| VIA at 35, 40, & 45 years | 18.96 | 27.8068 | Dominated |
| VIA at 30, 40, & 50 years | 18.96 | 27.8068 | Dominated |
| careHPV (cervical) at 35 & 45 years | 19.33 | 27.7970 | Dominated |
| VIA at 35 & 45 years | 19.87 | 27.8138 | Dominated |
| careHPV (vaginal) at 35, 40, & 45 years | 19.91 | 27.8168 | Dominated |
| VIA at 30, 40, & 50 years | 20.06 | 27.8142 | Dominated |
| careHPV (cervical) at 30, 40, & 50 years | 20.07 | 27.8178 | 580 |
| VIA at 30, 35, & 40 years | 21.20 | 27.8081 | Dominated |
| careHPV (vaginal) at 35, 40, & 45 years | 21.23 | 27.8091 | Dominated |
| VIA at 30 & 35 years | 21.34 | 27.8116 | Dominated |
| careHPV (cervical) at 25 & 35 years | 21.37 | 27.7977 | Dominated |
| VIA at 25 & 35 years | 21.52 | 27.7983 | Dominated |
| VIA at 25, 35, & 45 years | 21.77 | 27.8067 | Dominated |
| careHPV (vaginal) at 30, 35, & 40 years | 22.50 | 27.8164 | Dominated |
| VIA at 25, 35, & 45 years | 22.62 | 27.8194 | 1600 |
| careHPV (vaginal) at 25, 35, & 45 years | 24.22 | 27.8157 | Dominated |
| VIA at 25, 35, & 45 years | 24.25 | 27.8189 | Dominated |
| careHPV (cervical) at 25, 35, & 45 years | 24.57 | 27.8019 | Dominated |
| VIA at 30, 40, & 50 years | 25.04 | 27.8025 | Dominated |
| Cytology at 30, 35, & 40 years | 27.65 | 27.8025 | Dominated |
| Cytology at 25, 35, & 45 years | 28.39 | 27.8009 | Dominated |

* 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.

* Strategies are listed in order of increasing cost.

* Discounted costs and life expectancies starting from age 9.

* 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.

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For the analysis of budget impact, we converted the direct medical costs associated with careHPV (cervical sampling), colposcopy and biopsy, cryotherapy, and LEEP from local
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 above, are shown in Table A12.

### Table A12

| Strategy                        | Discounted lifetime cost per woman (I$) | Discounted life expectancy (years) | ICER (I$/YLS) |
|---------------------------------|----------------------------------------|-----------------------------------|--------------|
| core HPV (cervical) at 35 years | 40.98                                  | 28.6404                           | CS           |
| core HPV (cervical) at 40 years | 41.41                                  | 28.6290                           | Dom          |
| core HPV (cervical) at 30 years | 41.47                                  | 28.6483                           | Dom          |
| core HPV (cervical) at 45 years | 42.03                                  | 28.6174                           | Dom          |
| core HPV (vaginal) at 35 years  | 42.06                                  | 28.6222                           | Dom          |
| core HPV (vaginal) at 40 years  | 42.33                                  | 28.6223                           | Dom          |
| core HPV (cervical) at 35 & 45 years | 42.59     | 28.6627                           | Dom          |
| VIA at 35 years                 | 42.60                                  | 28.6390                           | Dom          |
| core HPV (cervical) at 50 years  | 42.63                                  | 28.6283                           | Dom          |
| VIA at 40 years                 | 42.66                                  | 28.6070                           | Dom          |
| core HPV (vaginal) at 45 years  | 42.74                                  | 28.6204                           | Dom          |
| core HPV (cervical) at 30 & 40 years | 42.98     | 28.6790                           | 50           |
| VIA at 45 years                 | 43.05                                  | 28.6114                           | Dom          |
| core HPV (vaginal) at 50 years  | 43.22                                  | 28.6033                           | Dom          |
| VIA at 30 years                 | 43.52                                  | 28.6329                           | Dom          |
| core HPV (vaginal) at 35 & 45 years | 43.82     | 28.6527                           | Dom          |
| core HPV (cervical) at 25 years  | 44.17                                  | 28.6488                           | Dom          |
| core 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          |
| core HPV (vaginal) at 25 years  | 44.84                                  | 28.6407                           | Dom          |
| VIA at 30 & 40 years            | 45.29                                  | 28.6611                           | Dom          |
| core HPV (cervical) at 30, 40, & 50 years | 45.48     | 28.6905                           | Dom          |
| Cytology at 50 years            | 45.78                                  | 28.5909                           | Dom          |
| core HPV (cervical) at 25 & 35 years | 45.91     | 28.6871                           | Dom          |
| VIA at 25 years                 | 46.00                                  | 28.6264                           | Dom          |
| core HPV (cervical) at 35, 40, & 45 years | 46.04     | 28.6827                           | Dom          |
| Cytology at 45 years            | 46.23                                  | 28.5941                           | Dom          |
| core HPV (vaginal) at 30, 40, & 50 years | 46.75     | 28.6779                           | Dom          |
| Cytology at 40 years            | 46.80                                  | 28.5975                           | Dom          |
| core HPV (vaginal) at 25 & 35 years | 46.84     | 28.6753                           | Dom          |
| core HPV (vaginal) at 35, 40, & 45 years | 47.04     | 28.6722                           | Dom          |
| core 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          |
| core HPV (vaginal) at 30, 35, & 40 years | 48.27     | 28.6907                           | Dom          |
| Cytology at 30 years            | 48.84                                  | 28.6011                           | Dom          |
| VIA at 30, 35, & 40 years       | 49.22                                  | 28.6844                           | Dom          |
| core 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                                  | 28.5986                           | Dom          |
| Cytology at 35 & 45 years       | 51.34                                  | 28.6130                           | 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.
and the 50 good-fitting input parameter sets used for the main analysis, are displayed in Figs. A13 and A14.

When screening with careHPV (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 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 careHPV 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 A12
Cost-effectiveness of screening by age, frequency, and interval in Uganda (GDP per capita: $1370) *.

| Strategy                        | Discounted lifetime cost per woman (I$) | Discounted life expectancy (years) | ICER (I$/YLS) |
|---------------------------------|----------------------------------------|-----------------------------------|---------------|
| VIA at 50 years                 | 14.98                                  | 25.2122                           | Dom           |
| careHPV (cervical) at 50 years  | 15.60                                  | 25.2249                           | Dom           |
| careHPV (vaginal) at 50 years   | 15.67                                  | 25.2221                           | Dom           |
| VIA at 45 years                 | 16.23                                  | 25.2312                           | Dom           |
| careHPV (cervical) at 45 years  | 16.40                                  | 25.2345                           | Dom           |
| careHPV (vaginal) at 45 years   | 16.58                                  | 25.2306                           | Dom           |
| VIA at 40 years                 | 17.13                                  | 25.2402                           | Dom           |
| careHPV (cervical) at 40 years  | **17.60**                              | **25.2454**                       | 120           |
| careHPV (vaginal) at 40 years   | 17.70                                  | 25.2405                           | Dom           |
| VIA at 35 years                 | 18.36                                  | 25.2476                           | Dom           |
| careHPV (vaginal) at 35 years   | 19.14                                  | 25.2548                           | 160           |
| VIA at 30 years                 | 20.06                                  | 25.2492                           | Dom           |
| Cytology at 50 years            | 20.12                                  | 25.2518                           | Dom           |
| careHPV (vaginal) at 30 years   | 20.55                                  | 25.2602                           | Dom           |
| VIA 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           |
| careHPV (cervical) at 35 & 45 years | 23.77                              | 25.2755                           | Dom           |
| careHPV (vaginal) at 35 & 45 years | 23.83                              | 25.2684                           | Dom           |
| careHPV (vaginal) at 25 years   | 23.86                                  | 25.2548                           | Dom           |
| careHPV (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           |
| careHPV (cervical) at 30 & 40 years | 26.42                              | 25.2889                           | 210           |
| careHPV (vaginal) at 30 & 40 years | 26.45                              | 25.2608                           | 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           |
| careHPV (vaginal) at 35, 40, & 45 years | 30.03                              | 25.2856                           | Dom           |
| careHPV (cervical) at 35, 40, & 45 years | 30.10                              | 25.2925                           | Dom           |
| careHPV (vaginal) at 30, 40, & 50 years | 30.26                              | 25.2912                           | Dom           |
| careHPV (cervical) at 30, 40, & 50 years | 30.27                              | 25.2998                           | 350           |
| Cytology at 30 years            | 30.88                                  | 25.2318                           | Dom           |
| careHPV (vaginal) at 25 & 35 years | 31.33                              | 25.2874                           | Dom           |
| careHPV (cervical) at 25 & 35 years | 31.44                              | 25.3098                           | 420           |
| VIA at 30, 35, & 40 years       | 32.59                                  | 25.2939                           | Dom           |
| VIA at 25, 35, & 45 years       | 33.41                                  | 25.2972                           | Dom           |
| careHPV (vaginal) at 30, 35, & 40 years | 34.36                              | 25.3018                           | Dom           |
| careHPV (cervical) at 30, 35, & 40 years | 34.48                              | 25.3099                           | 350           |
| Cytology at 25 years            | 35.15                                  | 25.2281                           | Dom           |
| careHPV (vaginal) at 25, 35, & 45 years | 36.15                              | 25.3029                           | Dom           |
| careHPV (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       | 50.53                                  | 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           |

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

| Strategy                                                                 | India (GDP per capita: I$5240) | Nicaragua (GDP per capita: I$4220) |
|-------------------------------------------------------------------------|---------------------------------|-------------------------------------|
| **Screening once in a lifetime**                                         |                                 |                                     |
| careHPV (cervical) at 50 years                                          | 10.82                           | 40.98                               |
| careHPV (cervical) at 45 years                                          | 11.24                           | 41.41                               |
| careHPV (cervical) at 40 years                                          | 11.97                           | 41.47                               |
| careHPV (cervical) at 35 years                                          | 13.06                           | 42.03                               |
| careHPV (cervical) at 30 years                                          | 13.99                           | 42.66                               |
| careHPV (cervical) at 25 years                                          | 16.71                           | 44.17                               |
| **Screening twice in a lifetime**                                        |                                 |                                     |
| careHPV (cervical) at 35 & 45 years                                     | 15.88                           | 42.59                               |
| careHPV (cervical) at 30 & 40 years                                     | 17.53                           | 42.98                               |
| careHPV (cervical) at 25 & 35 years                                     | 21.34                           | 45.91                               |
| **Screening three times in a lifetime**                                  |                                 |                                     |
| careHPV (cervical) at 35, 40, & 45 years                                | 19.91                           | 45.48                               |
| careHPV (cervical) at 30, 40, & 50 years                                | 20.07                           | 46.04                               |
| careHPV (cervical) at 30, 35, & 40 years                                | 22.62                           | 47.21                               |
| careHPV (cervical) at 25, 35, & 45 years                                | 24.35                           | 48.46                               |
| **Screening once, twice, or three times in a lifetime**                 |                                 |                                     |
| careHPV (cervical) at 35 & 45 years                                     | 15.88                           | 42.59                               |
| careHPV (cervical) at 30 & 40 years                                     | 17.53                           | 42.98                               |
| careHPV (cervical) at 25 & 35 years                                     | 21.34                           | 45.91                               |
| **Screening once in a lifetime**                                         |                                 |                                     |
| careHPV (cervical) at 35 years                                          | 11.24                           | 41.41                               |
| careHPV (cervical) at 45 years                                          | 11.97                           | 41.47                               |
| careHPV (cervical) at 40 years                                          | 13.06                           | 42.03                               |
| careHPV (cervical) at 35 years                                          | 13.99                           | 42.66                               |
| careHPV (cervical) at 30 years                                          | 16.71                           | 44.17                               |
| careHPV (cervical) at 25 years                                          | 21.34                           | 45.91                               |
| **Screening twice in a lifetime**                                        |                                 |                                     |
| careHPV (cervical) at 35 & 45 years                                     | 15.88                           | 42.59                               |
| careHPV (cervical) at 30 & 40 years                                     | 17.53                           | 42.98                               |
| careHPV (cervical) at 25 & 35 years                                     | 21.34                           | 45.91                               |
| **Screening three times in a lifetime**                                  |                                 |                                     |
| careHPV (cervical) at 35, 40, & 45 years                                | 19.91                           | 45.48                               |
| careHPV (cervical) at 30, 40, & 50 years                                | 20.07                           | 46.04                               |
| careHPV (cervical) at 30, 35, & 40 years                                | 22.62                           | 47.21                               |
| careHPV (cervical) at 25, 35, & 45 years                                | 24.35                           | 48.46                               |
| **Screening once, twice, or three times in a lifetime**                 |                                 |                                     |
| careHPV (cervical) at 35 years                                          | 11.24                           | 41.41                               |
| careHPV (cervical) at 45 years                                          | 11.97                           | 41.47                               |
| careHPV (cervical) at 40 years                                          | 13.06                           | 42.03                               |
| careHPV (cervical) at 35 years                                          | 13.99                           | 42.66                               |
| careHPV (cervical) at 30 years                                          | 16.71                           | 44.17                               |
| careHPV (cervical) at 25 years                                          | 21.34                           | 45.91                               |
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 remained the dominant strategy. The ICERs associated with care HPV (cervical sampling) changed little. In Uganda, the ICER

**Table A13 (continued)**

| Strategy | Discounted lifetime cost per woman (I$) | Discounted life expectancy (years) | ICER (I$/YLS) |
|----------|----------------------------------------|-----------------------------------|---------------|
| Screening once in a lifetime | | |
| 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 | 17.50 | 25.2454 | 120 |
| care HPV (cervical) at 35 years | 18.14 | 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 | | |
| 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 | 25.3112 | 840 |

| Screening three times in a lifetime | | |
| 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 | | |
| 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 | 18.14 | 25.2548 | 160 |
| care HPV (cervical) at 30 years | 20.55 | 25.2602 | Dom |
| care HPV (cervical) at 25 & 35 years | 23.77 | 25.2755 | Dom |
| care HPV (cervical) at 30, 35, & 40 years | 31.44 | 25.2925 | Dom |
| care HPV (cervical) at 30, 35, & 40 years | 34.48 | 25.2999 | 350 |
| care HPV (cervical) at 30, 35, & 40 years | 36.31 | 25.3099 | 420 |
| care HPV (cervical) at 25, 35, & 45 years | 36.31 | 25.3112 | 1370 |

| Prevalence of High-Risk HPV, India |
|-----------------------------------|
| Age group | Prevalence of HR HPV |
|-----------|---------------------|
| 30-34     | 0.10 |
| 35-39     | 0.15 |
| 40-44     | 0.20 |
| 45-49     | 0.25 |

**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   |

* 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.
* 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.
* 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.
* Assuming screening will take place once in a lifetime, at one of the ages evaluated.
* Assuming screening will take place twice in a lifetime, at one of the age combinations considered.
* Assuming screening will take place three times in a lifetime, at one of the age combinations considered.
* Assuming screening will take place once, twice, or three times in a lifetime, at one of the age combinations considered.
for screening with careHPV (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%, careHPV (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 careHPV 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).

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