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Cost effectiveness of high-risk HPV DNA testing for cervical cancer screening in South Africa

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ABSTRACT

Objective. To determine the cost effectiveness of several cervical cancer screening strategies utilizing HPV testing in South Africa.

Methods. We developed a lifetime Markov model of the costs, quality of life, and survival associated with screening and treating cervical cancer and its precursors. Screening strategies evaluated included: 1) conventional cytology, 2) cytology followed by HPV testing for triage of equivocal cytology, 3) HPV testing, 4) HPV testing followed by cytology for triage of HPV-positive women, and 5) co-screening with cytology and HPV testing. Primary outcome measures included quality-adjusted life-years saved (QALYs), incremental cost-effectiveness ratios, and lifetime risk of cervical cancer. Costs are in 2006 South African Rand (R).

Results. In a cohort of 100,000 women, starting at age 30 and screening once every 10 years reduced the lifetime risk of cervical cancer by 13–52% depending on the screening strategy used, at an incremental cost of R13,000–R42,000 per QALY. When strategies were compared incrementally, cytology with HPV triage was less expensive and more effective than screening using cytology alone. HPV testing with the use of cytology triage was a more effective strategy and costs an additional R42,121 per QALY. HPV testing with colposcopy for HPV-positive women was the next most effective option at an incremental cost of R1541 per QALY. Simultaneous HPV testing and cytology co-screening was the most effective strategy and had an incremental cost of R25,414 per QALY.

Conclusions. In our model, HPV testing to screen for cervical cancer and its precursors is a cost-effective strategy in South Africa.

Introduction

Invasive cervical cancer is the second most common cancer among South African women, with an incidence rate of 30 per 100,000 women per year [1]. The incidence of human papillomavirus (HPV), the causative agent for cervical cancer, is also high; HPV has been detected in approximately 7% of women aged 35–39 years and 10% of women aged 60–65 years [2]. In addition, the prevalence of human immunodeficiency virus (HIV) infection among South African adults aged 15–49 years is approximately 18%, and there are an estimated 5.4 million HIV-positive adults, the highest number anywhere in the world [3]. HIV-positive women are about three times more likely to have an HPV infection, 4.5 times more likely to develop cervical intraepithelial neoplasia (CIN), [4] and three to five times more likely to develop invasive cervical cancer compared to HIV-negative women [5,6]. Therefore, the high prevalence of HIV in South Africa is likely a contributing factor to the high rates of both HPV and cervical cancer.

Current South African guidelines in the public sector recommend screening once every 10 years using conventional cytology (Pap smear) [7]. Women are entitled to three free lifetime Pap smears beginning at age 30 years. Although HPV testing has shown promise as a tool for primary cervical screening and is more sensitive in detecting CIN lesions than cytology alone, [8,9] HPV testing is currently not offered in the public sector in South Africa, and the economic implications of this approach require additional investigation.

Our objective was to use a lifetime Markov simulation model to determine the cost effectiveness of several cervical cancer screening strategies utilizing conventional cytology and HPV testing in South Africa.

Methods

We developed a lifetime Markov Monte Carlo simulation model to simulate the natural history of cervical cancer and the impact of screening and treatment on disease progression and cost. The model was used to evaluate the following cervical cancer screening strategies:

- No screening;
- Conventional cytology every 10 years with repeat screening for women with equivocal (Atypical Squamous Cells of Undetermined

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Significance (ASCUS)) cytology and follow-up colposcopy for women with low-grade squamous intraepithelial lesions (LSIL) or worse cytology;
- Conventional cytology followed by HPV testing to triage women with ASCUS cytology results every 10 years;
- HPV testing for all patients followed by colposcopy for HPV-positive women every 10 years;
- HPV testing followed by cytology for triage of HPV-positive women every 10 years;
- Co-screening with both cytology and HPV testing every 10 years.

We adopted a societal perspective and as such included direct medical and indirect costs. Future costs and health outcomes were discounted at a rate of 3%. Primary outcome measures included quality-adjusted life-years saved (QALYs), total costs, and lifetime risk of cervical cancer. Screening strategies were compared using the incremental cost-effectiveness ratio (ICER), defined as the ratio of the difference in costs to the difference in effectiveness between two alternative screening strategies. We adhered to the recommendations of the Panel on Cost Effectiveness in Health and Medicine [10]. All modeling was conducted using TreeAge Pro 2007 release 1.5 (TreeAge Software, Williamstown, MA).

Natural history model

The model follows a hypothetical cohort of 100,000 South African women over their lifetimes beginning at age 13 years. We modeled the natural history of cervical neoplasia using eight health states (Fig. 1). Women could transition between health states based on probabilities obtained through extensive literature reviews and expert clinical opinion (Table 1). Cervical disease was classified as CIN (CIN 1, CIN 2/3) or cervical cancer, which was further sub-classified into four stages according to the International Federation of Gynecology and Obstetrics (FIGO) recommendations [32].

The incidence of HPV infection was estimated based on the prevalence of HPV in South Africa [2,11,15]. Women with HPV infection or cervical disease could progress to higher-grade cervical disease, while women infected with CIN could regress to normal health or have persistent HPV infection without CIN (Table 1) [12–16].

HIV infection and cervical neoplasia

Women in any health state in the model could become infected with HIV. CD4 cell counts and viral load levels were used to model risk of disease progression [19–22,33]. We assumed that 50% of patients with acquired immunodeficiency syndrome (AIDS) (defined as CD4 count <200 cells/mm^3) would receive antiretroviral therapy (ART). Based on input from clinical experts, we assumed that the relative risk of progression and regression of HPV and CIN among patients receiving ART for HIV infection is mid-way between the relative risk for HIV-negative patients and untreated HIV-positive patients [34–36]. Natural history data were used to estimate risk of death due to AIDS (Table 1) [23,37]. Women could die during any cycle of the model from cervical cancer, AIDS, or other causes. Table 1 shows selected variables that were used to model the correlation between HIV and cervical cancer precursors [4,24–28].

Screening strategies and diagnostic follow up

In the base case, we assumed that women would be screened every 10 years, starting at age 30 [7]. Cytology test results were classified according to the 2001 Bethesda system [38]. HPV testing was used to identify the 13 known high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Women with abnormal screening results were referred for follow-up colposcopies or repeat screening, and the presence of a cervical lesion was confirmed using colposcopy and biopsy [29–31,39,40]. The number of clinic visits varied from 1 to 3 visits, based on screening strategy and test results. Each screening and diagnostic test involved a separate clinic visit, except in the co-screening strategy where both HPV and cytology samples were collected during one visit. In our base-case analysis, we assumed no loss to follow up among any of the strategies, but we incorporated loss to follow up of 15% per clinic visit in sensitivity analysis. Screening was discontinued at age 55 years for women who had had no prior abnormal screening test results [39].

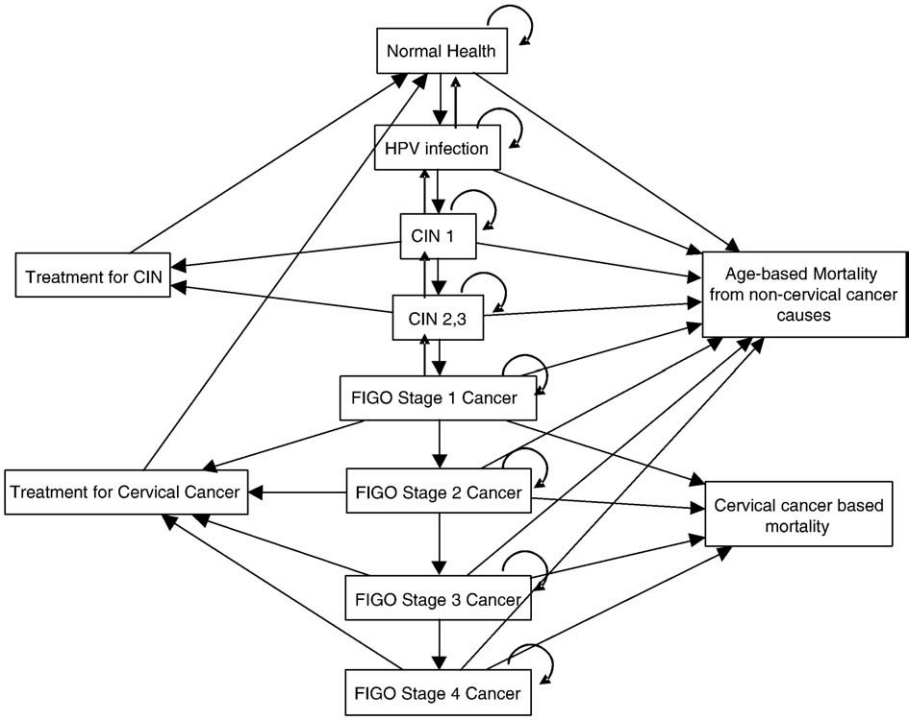

Fig. 1. Schematic representation of the model. All patients start the model in normal health and can transition to other health states as shown. Impact of HIV infection is not shown.

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Table 1
Input variables and sources[a]

Clinical variable	Base-case value	Range	Source
Population variables			
Age at start of sexual activity (years)	15	13–18	Assumption
Prevalence of HPV infection[b] (%)	4.5–16.5	0.5–2× baseline	[2], [11]
Probability of disease progression (%)			
HPV infection progressing to CIN I	8.1	5.4–15.0	[12], [13], [14]
HPV infection progressing to CIN 2,3	0.56	0.54–1.5	[12], [15]
Progression from CIN 1 to CIN 2,3[b]	1.7–5.7	1.7–8.3	[15]
Progression from CIN 2,3 to FIGO Stage I cervical cancer	3.8	3–6.2	[16]
Progression of cervical cancer (%)			[16]
FIGO Stage I to Stage II cervical cancer	43.7	40–45	
FIGO Stage II to Stage III cervical cancer	53.5	50–55	
FIGO Stage III to Stage IV cervical cancer	68.3	65–70	
Probability of disease regression (%)			
Regression of HPV infection[b]	3.3–37.3	1.7–60.0	[12], [15]
Regression of CIN 1[b]	2.7–14.2	2–16	[16]
Patients regressing to HPV infection without lesion (%)	10	0–20	
Regression of CIN 2,3[b]	3.7–5.8	3–7	[15], [16]
Patients regressing to normal (%)	45	40–50	[16]
Patients regressing to HPV infection without lesion (%)	5	0–10	
Patients regressing to CIN 1 (%)	50	40–60	
Annual symptom detection probability for cervical cancer (%)			[16]
FIGO Stage I	15	12–18	
FIGO Stage II	23	20–25	
FIGO Stage III	60	67–73	
FIGO Stage IV	90	87–93	
Mortality data			
5-year survival rates (% alive at 5 years)			
FIGO Stage I	85	84–86	[17]
FIGO Stage II	55	53–58	
FIGO Stage III	41	39–44	
FIGO Stage IV	12	10–15	
Data on HIV/AIDS in South Africa			
Rate of HIV infection among South African women[b] (%)	0.03–3.2	0.5–2× baseline	[18]
Percentage of eligible patients receiving ART	50	0–100	Assumption
Percentage of patients with virological failure	15.8	6–30	[19], [20], [21]
Increase in CD4 count after initiating ART (cells/mm^3)	184	30–212	[19], [21]
Median viral load for patients with HIV (log copies/ml)	4.75	–	[22]
Annual mortality rate for untreated patients with AIDS (CD4<200)[b] (%)	34–52	17–100× baseline	[23]
Relative risk of HPV and CIN progression/regression for patients with HIV			
Incidence of HPV infection	2.64	2–3	[24]
HPV infection progressing to CIN I	3.34	2.16–5.5	[4], [25]
HPV infection progressing to CIN 2,3	3.34	2.16–5.5	
HPV infection regressing	0.84	0.31–1.0	[24]
CIN 1 progressing to CIN 2,3	2.3	1.67–6.68	[26], Assumption
CIN 1 regression	0.33	0.17–0.52	[26], [27], [28]
CIN 2,3 progression	1.0	0–1	Assumption
CIN 2,3 regression	0	0–1	Assumption
Utilities			
HPV infection	1	0.8–1	[16]
CIN 1	0.97	0.8–1	
CIN 2,3	0.97	0.5–1	
FIGO Stage I cervical cancer	0.79	0.25–1	
FIGO Stage II–IV cervical cancer	0.62	0.25–1	
Initial efficacy of treatment			
Probability HPV persists after effective treatment (%)			[16], Assumption
CIN 1	10	0–25	
CIN 2,3	10	0–25	
Cervical cancer	0	–	
Screening tests	Sensitivity	Specificity	
Conventional cytology			[29], [30]
CIN 1 or worse	45	94	
CIN 2,3 or worse	56	93	
HPV positive			[31]
CIN 1 or worse	88	94	
CIN 2,3 or worse	98	92	
Triage tests			
Conventional cytology among HPV-positive patients			[30]
CIN 1 or worse	47	55	
CIN 2,3 or worse	52	55	

[a] All variables are annual unless otherwise noted. CIN denotes Cervical Intraepithelial Neoplasia, HPV Human Papillomavirus, FIGO International Federation of Gynecology and Obstetrics, HIV Human Immunodeficiency Virus, AIDS Acquired Immune Deficiency Syndrome, and ART Antiretroviral Therapy.
[b] These data vary based on age. The range of values is shown.

Impact of treatment

All women diagnosed with CIN or cervical cancer were eligible for treatment. Women diagnosed with CIN 2+ could undergo either loop electrode excision procedure or cryotherapy. Women diagnosed with cervical cancer could undergo hysterectomy, chemotherapy, and/or radiation therapy. Women with persistent cervical cancer could receive a second cycle of chemotherapy. This treatment was considered palliative in nature and did not improve survival [41,42].

Costs

Micro-costing methods were used to calculate the direct medical costs of cervical cancer screening, diagnostic tests, and treatment. Unit costs were obtained from the South African Uniform Patients Fee Schedule (October 2005 Edition). Cost of HPV DNA testing was obtained from the manufacturer [Roche Products (Pty) Ltd., Randburg, South Africa, December 2006]. Patient time costs included time spent for cervical cancer screening, diagnosis, and treatment. Indirect costs resulting from morbidity were incorporated as utilities [16,43]. All costs are expressed in 2006 South African Rand (Table 2).

Sensitivity analysis

We conducted one-way sensitivity analyses to assess the robustness of model results. Ranges for the sensitivity analysis for clinical variables were based on the literature and input from clinical experts (Table 1). The range of values for cost variables represents a variation of 25% above and below the base-case estimates.

Results

Model validation

For the base-case analysis, we calculated the margin of error (standard deviation) using a sequence of 10 simulations with 50,000

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patients each. In these simulations, the lifetime cost per patient and average life expectancy varied by less than 0.13% (R91,767 122) and 0.05% (23.68 0.03 years), respectively.

The age-specific prevalence of HPV infection was within plausible ranges observed in the literature. Fig. 2 shows the age-specific prevalence of CIN and cervical cancer predicted by the model. The peak annual prevalence of cervical cancer was 0.28% at age 41 years.

Base-case analysis

The reduction in lifetime risk of cervical cancer ranged from 13% to 52%, depending on the screening strategy used. In a cohort of 100,000 women, screening every 10 years with conventional cytology prevented approximately 330 cases of cervical cancer and 180 deaths. Use of HPV testing instead of conventional cytology decreased the incidence of cervical cancer and death further by 41% and 47%, respectively. In comparison, simultaneous cytology and HPV testing was the most effective strategy and resulted in an additional 6% decrease in the incidence of cervical cancer (Table 3).

In the absence of screening, the total lifetime cost per woman was R91,767 and quality-adjusted life expectancy (QALE) was 23.68 years. Screening using conventional cytology increased QALE by 4.12 days resulting in an ICER of R41,977 per QALY gained. Conventional cytology with the use of HPV testing for triage of equivocal (ASCUS) cytology was a dominant strategy, i.e., less expensive and more effective than screening using cytology alone. In comparison, HPV testing with the use of cytology for triage of HPV-positive women increased life expectancy by an additional 2.4 days resulting in an ICER of R42,121 per QALY. HPV testing followed by colposcopy for all HPV-positive women was the next most effective option with an ICER of R1541 per QALY. Co-screening with simultaneous cytology and HPV testing was the most effective strategy and had an ICER of R25,414 per QALY (Tables 4, 5).

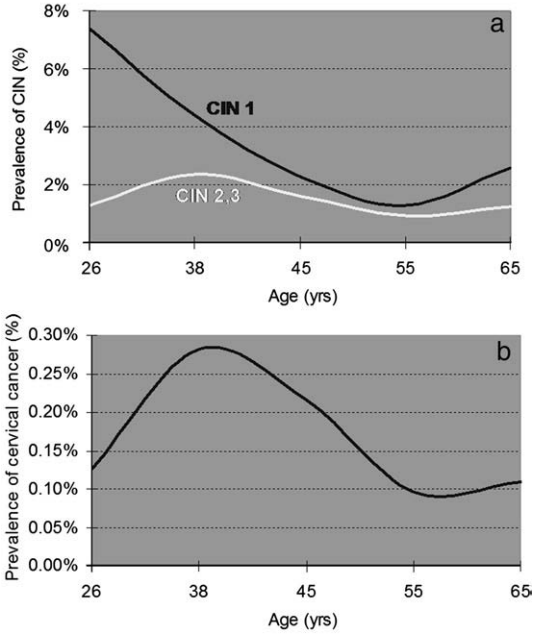

Fig. 2. (a) Prevalence of CIN among unscreened South African women. (b) Prevalence of cervical cancer among unscreened South African women.

Sensitivity analysis

Fig. 3 shows the cost effectiveness of screening at different intervals using HPV testing alone compared with conventional cytology. Screening every 5 years using HPV DNA testing instead of cytology prevented 544 deaths per 100,000 women and was cost effective, with an ICER of R6907 per QALY. Annual screening was the most effective strategy but resulted in high ICERs (R51,211 to R95,525 per QALY compared to no screening). We also examined the impact of loss to follow up among different screening approaches. Assuming that 15% of patients would be lost to follow up at each clinic visit increased all of the ICERs, and in particular increased the ICERs of three-visit strategies compared to two-visit strategies. Screening using cytology followed by HPV triage resulted in an ICER of

Table 2
Cost variables[a]

Variable	Base-case value		Source
	SA Rand	US Dollars[b]	
Cost per clinic visit	R163	$24	UPFS, October 2005 edition www.doh.gov.za/programmes/upfs/docs/2005/userguide/cover.pdf
Diagnostic tests			
Conventional cytology test	R65	$10	Government cytology laboratory
HPV DNA testing	R200	$30	Roche Diagnostics
Colposcopy/biopsy	R280	$42	UPFS, October 2005 edition
Treatment options			UPFS, October 2005 edition
LEEP	R696	$104	
Cryotherapy	R696	$104	
Hysterectomy	R7644	$1141	
Chemoradiation	R60,362	$9009	
Radiotherapy	R58,843	$8783	
Treatment[c]			UPFS, October 2005 edition
CIN 1	R696	$104	
CIN 2,3	R1390	$207	
FIGO Stage I cancer	R59,942	$8947	
FIGO Stage II cancer	R59,942	$8947	
FIGO Stage III cancer	R59,411	$8867	
FIGO Stage IV cancer	R58,803	$8777	
Non-HPV medical costs	R2607	$389	WHOSIS health indicators (2001) http://www3.who.int/whosis/core/core_select_process.cfm

[a] UPFS denotes Uniform Patient Fee Schedule, LEEP Loop Electrode Excision Procedure, CIN Cervical Intraepithelial Neoplasia, HPV Human Papillomavirus, FIGO International Federation of Gynecology and Obstetrics. All costs are in 2006 South African Rand.

[b] Using a conversion rate of 6.7 Rand = 1.00 US$ (http://www.oanda.com/convert/fxhistory).

[c] Costs were calculated based on treatment options.

Table 3
Cervical cancer cases and deaths per 100,000 South African women[a]

Screening strategy	Number of cervical cancer cases per 100,000 women	Number of cervical cancer deaths per 100,000 women
No screening	2580	1348
Conventional Cytology	2249	1169
Conventional Cytology followed by HPV triage for equivocal cytology results	2216	1127
HPV DNA testing followed by cytology for HPV-positive women	1602	756
HPV DNA testing followed by colposcopy for all HPV-positive women	1318	619
Simultaneous HPV DNA testing and conventional cytology co-screening	1242	586

[a] HPV denotes human papillomavirus.

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Table 4
Lifetime risk of cervical cancer-related death, quality-adjusted life expectancy, average lifetime costs, and cost-effectiveness ratios associated with different cervical cancer screening strategies[a]

Screening strategy	Lifetime risk of cervical cancer-related death	QALY (years)	Average lifetime costs (Rand)	ICER (Rand/QALY)[b]	ICER (US$/QALY)[c]
No screening	0.0135	23.6811	R91,767	–	–
Conventional cytology	0.0117	23.6924	R92,241	R41,977	$6263
Conventional cytology followed by HPV triage for equivocal cytology results	0.0113	23.7126	R92,185	(Dominates)[d]	(Dominates)[d]
HPV DNA testing followed by cytology for HPV-positive women	0.0076	23.7192	R92,463	R42,121	$6287
HPV DNA testing followed by colposcopy for all HPV-positive women	0.0062	23.7286	R92,477	R1541	$230
Simultaneous HPV DNA testing and conventional cytology co-screening	0.0059	23.7318	R92,557	R25,414	$3792

[a] QALY denotes quality-adjusted life year, HPV human papillomavirus, and ICER incremental cost-effectiveness ratio.
[b] The ICER is calculated as the ratio of the difference in costs to the difference in effectiveness between two alternative screening strategies. The ICER of each strategy is compared to the strategy listed just above it and represents the incremental cost associated with moving from one strategy to the next most effective strategy.
[c] Using a conversion rate of 6.7 Rand = 1.00 US$ (http://www.oanda.com/convert/fxhistory).
[d] Conventional cytology with use of HPV testing for triage of abnormal cytology is less expensive and more effective than screening using cytology alone and is thus a dominant strategy.

R36,463 per QALY compared to cytology alone, while the ICER of HPV testing followed by cytology also increased to R21,540 per QALY. HPV testing followed by colposcopy and co-screening remained cost-effective strategies with ICERs of R10,887 and R13,604 per QALY respectively.

One-way sensitivity analyses were used to determine the effect of individual parameters on the ICER (Fig. 4). Results were most sensitive to the rate of progression/regression of CIN, quality of life, and cost of colposcopy/biopsy. However, HPV testing remained the most cost-effective option under most scenarios.

We conducted threshold analyses on the sensitivity and specificity of cytology and HPV testing. As the sensitivity of conventional cytology testing increased, both costs and life-expectancy outcomes increased. If the sensitivity of HPV testing decreased by more than 55%, using HPV testing became less effective and more expensive than conventional cytology.

In our model, 40% of cervical cancer deaths occurred among HIV patients. Decreasing HIV treatment coverage rates increased HIV-related mortality and resulted in fewer deaths due to cervical cancer. If all HIV-positive women received ART, HPV testing remained a cost-effective strategy with an ICER of R8598 per QALY compared to conventional cytology while assuming that women did not receive ART resulted in an ICER of R2462 per QALY. HPV testing remained a cost-effective option when we varied the relative risk of progression and regression of HPV and CIN among patients receiving ART over the entire range of possible values with ICERs of R9079 to R8032 compared to the conventional cytology strategy.

Table 5
Incremental cost effectiveness of cervical cancer screening strategies[a]

Screening strategy	ICER compared to no screening (Rand/QALY)[b]	ICER compared to conventional cytology (Rand/QALY)[c]
No screening	–	–
Conventional cytology	R41,977	–
Conventional cytology followed by HPV triage for equivocal cytology results	R13,270	Dominates[d]
HPV DNA testing followed by cytology for HPV-positive women	R18,258	R8286
HPV DNA testing followed by colposcopy for all HPV-positive women	R14,947	R6534
Simultaneous HPV DNA testing and conventional cytology co-screening	R15,596	R8040

[a] QALY denotes quality-adjusted life year, ICER incremental cost-effectiveness ratio, and HPV human papillomavirus.
[b] Incremental cost effectiveness of each screening strategy compared to the "no screening" option.
[c] Incremental cost effectiveness of each screening strategy compared to the current clinical practice of using conventional cytology alone.
[d] Conventional cytology with use of HPV testing for triage of abnormal cytology is less expensive and more effective than screening using cytology alone and is thus a dominant strategy.

Discussion

This study was designed to evaluate the cost effectiveness of several cervical cancer screening strategies using conventional cytology and HPV testing in South Africa. Compared to the current practice of screening with conventional cytology, screening using HPV testing prevented approximately 650 to 1000 new cases of cervical cancer and 400 to 600 deaths for each 100,000 women screened, depending on the screening strategy used. These results are driven primarily by the increased sensitivity of HPV testing for CIN 2+ lesions, which is particularly important over a 10-year screening interval. For South African women similar to those in our model, use of HPV testing to triage ASCUS Pap smears was less expensive and more effective than cytology testing alone, and all 3 HPV screening strategies had lower ICERs than conventional cytology.

According to the Commission on Macroeconomics and Health guidelines, interventions with an ICER between one and three times per capita GDP are considered cost effective [44]. In our analysis, HPV-based screening strategies (either alone or in conjunction with Pap

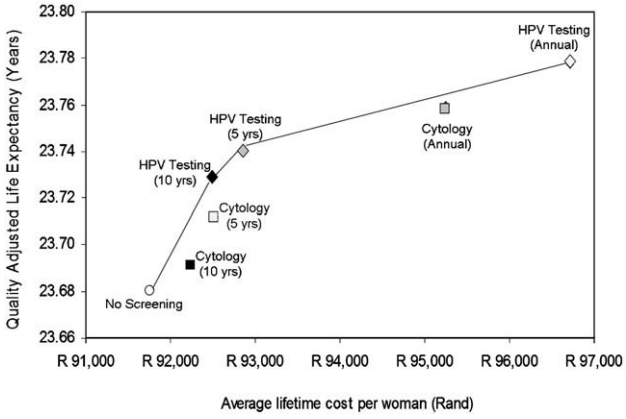

Fig. 3. Impact of screening frequency. Costs and outcomes associated with no screening and screening using conventional cytology or HPV testing alone are shown.

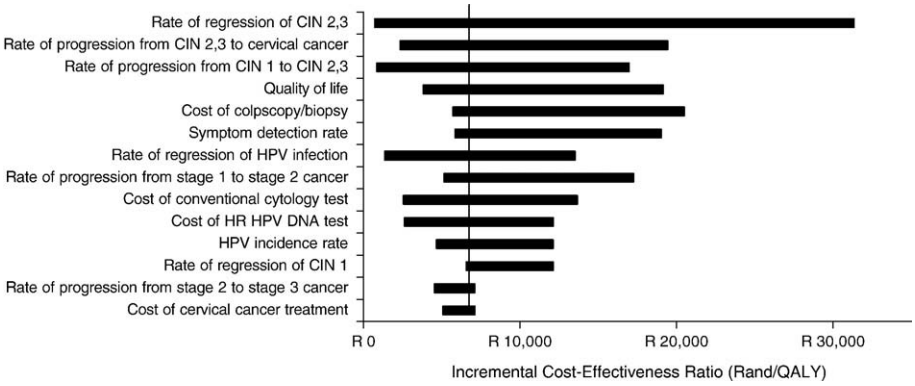

Fig. 4. Sensitivity analysis. One-way sensitivity analysis showing the range of incremental cost-effectiveness ratios comparing current clinical practice (conventional cytology every 10 years) and screening using HPV testing every 10 years. Ranges are shown in Table 1. The vertical line represents the base-case analysis ICER. A wide horizontal bar indicates that the associated variable has a large effect on the results of the model.

testing) had ICERs in the range of R6534 to R8286 per QALY, compared with the current screening paradigm of conventional cytology. This represents a factor of 1.2 to 1.5 times the per capita GDP in South Africa (R5380 in 2006) [45,46], suggesting that HPV-based screening in South Africa would be a cost-effective option.

Our findings are similar to other published reports on the cost effectiveness of HPV testing in developing countries. Goldie et al. [47] found that cervical cancer screening strategies incorporating HPV testing were cost-effective alternatives to conventional cytology-based screening programs in India, Kenya, Peru, South Africa, and Thailand. This study found that using HPV testing instead of conventional cytology increased life expectancy by 0.01 years compared to 0.04 years in our model. Their incremental costs where higher than ours resulting in higher ICERs. The higher effectiveness in our model may be due to the availability of ART for HIV-positive women in our model. The difference in cost is most likely due to the higher cost of colposcopy/biopsy in the study by Goldie et al. A second study by Goldie et al. in South Africa [48] that compared screening using direct visual inspection of the cervix, conventional cytology, and HPV testing found that HPV testing was always more effective and less costly than cytology. Our analysis also found that HPV testing was always more effective than cytology. However, we found that HPV testing was also more expensive than cytology. This difference may be due to assumptions on the costs of the screening tests, with Goldie et al. assuming that the HPV test was less expensive than a cervical cytology test whereas we assumed the HPV test was about three times as expensive as conventional cytology, a relative pricing relationship that is more consistent with other markets where both technologies are reimbursed. While both these studies incorporated some screening strategies using cytology and HPV testing, our analysis compares additional strategies that are currently used in the developed world, including cytology followed by HPV testing and co-screening with both cytology and HPV testing.

The risk of cervical cancer in HIV-positive women depends on a number of factors, such as the incidence of HIV infection, the impact and availability of ART, and the AIDS-related mortality rate. As HIV treatment becomes more widely available, AIDS-related deaths may decrease, resulting in an increase in cervical cancer mortality. There are conflicting data on the impact of ART on HPV infection, CIN, and cervical cancer. While some studies have shown a slight reduction in CIN and cervical cancer rates among HIV-positive patients receiving ART, it is likely that this benefit depends on viral load and CD4 count [34–36,49]. However, our analysis suggests that cervical cancer screening using HPV DNA testing remains cost effective over the entire possible range of assumptions on this issue. Additional studies should be undertaken to find the optimal interval for cervical cancer screening in HIV-positive women.

In resource-constrained settings such as South Africa, cost-effectiveness analyses only provide guidance in one aspect of decision-making. Practical considerations might lead clinicians and policy-makers to favor one strategy over another. For instance, referring all HPV-positive women to colposcopy may overwhelm currently available colposcopy resources and lead to dislocation of cytology resources, whereas use of cytology to triage HPV-positive women may be simpler to implement logistically while still yielding a substantial benefit versus cytology-based screening strategies [9,50].

Our analysis has several limitations. First, as with most modeling studies, data were combined from multiple sources with varied study designs. However, we used data from published literature wherever possible and any assumptions were based on input from clinical experts. In addition, we varied all model inputs across wide ranges to determine their impact on the model results. Second, although we found the use of HPV testing to be cost effective in South Africa, there may be areas of the country where the infrastructure is not sufficiently developed to allow for HPV testing at this time. However, HPV testing requires less skilled technicians and is easier to perform than cervical cytology [2] so it should be feasible to incorporate HPV testing in screening programs going forward. In addition, although an instant HPV test is likely to be a cost-effective option, this test is not currently available, so we chose not to include it in the model [47]. Third, given the long screening interval in South Africa, we chose to model only strategies that improved upon the sensitivity of conventional cytology. As a result we have excluded screening methods such as direct visual inspection and liquid-based cytology, as these approaches have demonstrated sensitivity comparable to conventional cytology [51]. Finally, our results may not be generalizable to countries other than South Africa since our model relied on country-specific data and assumptions regarding epidemiology, infrastructure, and costs [52,53].

Our study shows that cervical cancer screening strategies incorporating HPV testing would be cost effective in South Africa. Given the high incidence of HPV and cervical cancer in South Africa and the role that high HIV prevalence rates may play in the development of these cancers, expanding the cervical cancer screening strategies beyond those currently offered may have a significant public health impact.

Conflict of interest statement

This study was funded by a grant from Roche Molecular Systems, Inc., Pleasanton, CA, USA (Roche). AV, ME, and CS have received honoraria or consultancy fees from Roche. Representatives from Roche were allowed to review model results as well as a draft of the manuscript, but all final decisions regarding model calculations and manuscript content were made by the authors.

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