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Economic evaluation of strategies for managing women with equivocal cytological results in Brazil

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In Brazil, current management of women with screening results of atypical squamous cells of undetermined significance (ASC-US) is to offer repeat testing at 6-month intervals. Alternative management strategies that have been adopted in many high-income settings are to offer immediate colposcopy referral or to utilise human papillomavirus (HPV) DNA testing as a triage for colposcopy referral, and to consider different strategies according to women's age. The objective of our study was to evaluate the lifetime cost effectiveness in terms of cost per years of life saved (YLS) of these alternative strategies for a middle income setting. A Markov model was developed using data from the Ludwig-McGill cohort and calibrated to independent observational datasets and local cost estimates obtained. In the base-case analysis, repeat cytology was the least costly strategy but also the least effective. Based on the WHO threshold for very cost-effective interventions, HPV triage for women above 30 years-old was the strategy with the highest probability of being cost effective. HPV triage including younger women with ASCUS results would also be a cost-effective option. Whilst there was a slight further gain in effectiveness with immediate colposcopy referral, it was also more expensive and did not appear to be cost effective. Threshold analysis indicated that an HPV test would have to be more than twice as expensive as a cytology test for HPV triage to no longer be cost effective. In conclusion, our results indicate that in middle income settings HPV triage is likely to be the optimal strategy for managing women presenting with ASC-US results.

Although screening has reduced the incidence of cervical cancer worldwide, it remains a leading cause of death among women in middle- and low-resource settings.[1,2] In most countries in the Latin American and the Caribbean region, despite investments in cytology based screening the impact in reducing cervical cancer rates has been less than expected.[3] In Brazil, cervical cancer is the second leading cause of cancer among women and the fourth leading cause of cancer-related deaths in this group.[4,5]

Whilst the recently developed human papillomavirus (HPV) vaccine represents an important tool to reduce cervical cancer incidence, it is only recommended for young women[6] and it has not yet been incorporated in most low- and middle-income countries vaccination schedules. An alternative option is to improve the efficiency of cervical cancer screening, for example, by changing the management of women with equivocal cytology results. Previous studies in the US and the UK have shown that the HPV DNA test for high-risk genotypes is cost effective for this purpose.[7,8] In low- and middle-income countries, no cost-effectiveness analysis has been published targeting management strategies for women presenting with equivocal results.

The current practice in Brazil is that women with atypical squamous cells of undetermined significance (ASC-US) results are recalled for repeat smears every 6 months and only return to routine screening intervals after two consecutive negative test results. Those that favor the use of repeat

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cytology argue that most women have either no lesion or a lesion that is likely to regress in the absence of treatment. Since HPV is present in all cases of cancer and precancer lesions, an alternative is to test ASC-US results with HPV DNA testing (for high-risk genotypes) which is more sensitive than cytology and to perform colposcopy only in women with positive test results.[7–9] A further option is to offer immediate colposcopy to manage these women, since more than one-third of all biopsy-confirmed high grade cervical neoplasia are identified in women with ASC-US cytology results.[10] Despite having a high sensitivity in identifying cervical neoplasia, colposcopy is more costly and potentially raises more anxiety in women when compared to repeat cytology and HPV testing. Determining the most advantageous management for ASC-US requires a formal setting-specific analysis of costs and health outcomes of alternative strategies.

The objective of our study was to identify the optimal strategy for the management of women having ASC-US at routine cytological screening in Brazil as a case study. We developed a mathematical model to compare the lifetime effects, costs, and cost effectiveness of strategies involving the cervical cytology, HPV DNA with the Hybrid Capture 2 assay (Qiagen, Hilden, Germany) and colposcopy.

Material and Methods

Mathematical model

We used a Markov model which simulates the natural history of cervical carcinogenesis using a sequence of transitions among health states (Fig. 1). The model was developed in TreeAge Pro 2009 (Willianstown, MA). For our analyses, a hypothetical cohort of women age 18 were entered into the model and followed until age 80. The model reflects current scientific understanding of preinvasive and invasive disease.[8,11] Health states in the model, descriptive of the patient's underlying true health, were defined to include HPV infection status, grade of cervical intraepithelial neoplasia (CIN), and stage of invasive cancer. HPV infection was stratified by HPV type categorized as (*i*) high risk types (HR HPV), including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68; and (*ii*) low risk types (LR HPV), including 6, 11, 26, 32, 34, 40, 42, 44, 53, 54, 55, 57, 62, 64, 67, 69, 70, 71, 72, 81, 83, 84, 89 and others.[12] The classification between high and low risk was used because of its strong empirical value in stratifying risk predictions.[11,13]

The incidence rates of HPV as well as clearance rates were obtained from the Ludwig–McGill cohort study, a longitudinal study of the natural history of the HPV infection and cervical neoplasia in the city of São Paulo, Brazil.[13–15] Prevalence rates and transition probabilities between health states were obtained from the literature. Where available, estimates were based on published studies conducted in Brazil or Latin America.[15–17] Supporting Information Appendix Table 1 shows the values of these and other variables used in the model precalibration. All probabilities of transition were calculated for a 6-month time frame, which is the cycle length of the model. This cycle length was chosen because most of events in the management of this disease occur either in 6-month intervals or on an annual basis.[5]

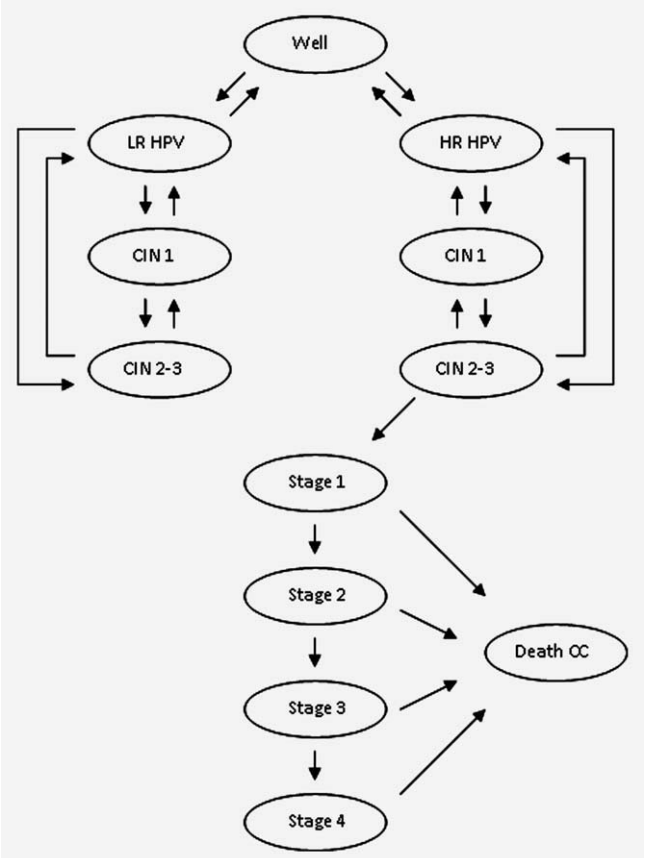

Figure 1. Natural history model. *Both the possibility of dying from other causes and of staying in the same state apply to all states, but were not shown in this figure. LR HPV: low risk type human papillomavirus; HR HPV: high risk type human papillomavirus; CIN: cervical intraepithelial lesion; CC: cervical cancer; Stage: FIGO invasive cancer stage.

Invasive cancer was stratified according to the cancer staging system of the International Federation of Gynaecology and Obstetrics (FIGO).[18] The probability of survival was based on stage and time postdiagnosis.[19] Alongside the probability of dying from cervical cancer, the probability of women dying from other causes was also explicitly modelled as a competing risk, using life tables for the female population of Brazil.[20]

Assumptions were necessary for the model:

- All cases of precancer lesions begin with an HPV infection.[7,8,21]
- Consistent with the latest scientific evidence, it was assumed that invasive cancer could not occur in the absence of infection with a HR HPV type.[11]
- Because most of the epidemiological studies classify women as having HR or LR HPV types and because the natural history implications of multiple infections are

uncertain and occur in less than 10 percent of our study population, we elected to model women as having either HR or LR HPV types.[11]

- Following the structure of previous models,[7,8,11,22] we assumed that an individual can only acquire either a HR or LR HPV type, only once this current HPV type infection has resolved can they change risk groups, as can be seen in Figure 1.
- Conventional cytology could only result in: negative, ASC-US, LSIL (low grade squamous intraepithelial lesion), HSIL (high grade squamous intraepithelial lesion). Although other cytology results are possible, the cytology results were simplified as above, in the same manner as previous modeling studies, because most test accuracy studies present their results in a similar way.[5,7,23,24]
- Women who survive after 5 years are assumed to have the same life expectancy as women in the general population.[19,25]

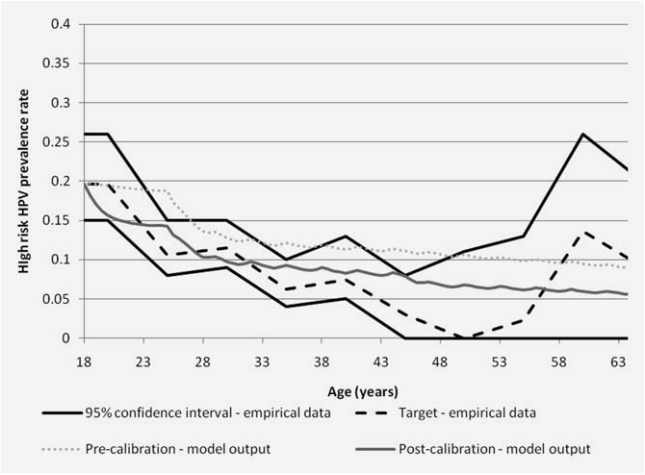

Figure 2. Age-specific HR HPV prevalence rate (calibration process). The calibration target and the 95% CI are based on data from the literature.[15,16]

Model calibration

Calibration of the model was conducted using a random search algorithm programmed in Microsoft Excel Visual Basic for Applications.[26,27] First, we estimated initial plausible ranges for each natural history parameter based on primary data from Brazil and published literature (Supporting Information Appendix Table 1).[11,14–16,28] These ranges were used to assign uniform distributions to these parameters. About 10,000 sets of input parameters values were randomly sampled, and the residuals between the model predictions for each input parameter set and published age-specific HR-HPV prevalence and age-specific CIN 1 prevalence were used to calculate the chi-squared goodness-of-fit (GOF).[15,16,29,30] We selected the best input parameter set based on the estimates of the GOF. Pre- and postcalibration age-specific HR-HPV prevalence rates predicted by the model as well as calibration targets with 95% confidence intervals (CI) can be observed in Figure 2. Additional figures showing the calibration results can be found in the Supporting Information Appendix Figures 1 and 2.

Screening protocol and modeling

In Brazil, routine cervical cytology is performed once a year on women aged 25 to 60, and after two consecutive negative results, every 3 years.[5] In our model, women had the possibility to move among health states that represented both their underlying disease state and their previous screening history within that screening round. Using this approach, the model tracked women's previous screening story (within that screening round) and, depending on the strategy used, either direct them to colposcopy, HPV testing, or repeat cytology. The probability of a test result was determined by the underlying disease state, in other words sensitivity and specificity. This allowed us to deal with the lack of data on regression and progression rates of the lesions of women presenting ASC-US results, since these rates were dependent on the underlying disease states (Fig. 1). The screening result would only change the underlying disease state, if it led to a positive triage test and, consequently, to successful treatment interventions. We assumed that HPV DNA testing was undertaken using hybrid capture 2 assay for HPV DNA; Qiagen, Hilden, Germany). The hybrid capture 2 method (HC2) was chosen for being the most widely used method in HPV screening worldwide. Since according to Brazilian guidelines[5] women could not return to routine screening until they have had two consecutive negative smears this meant that the model had to be large to accommodate all the potential health states. Consequently, our model included 51 underlying states.

Strategies evaluated

Given an ASC-US result in routine screening, five management strategies were evaluated.

Strategy A. Repeat cytology every 6 months. Return to routine screening (every 3 years) only after two consecutive negative cytology results. In case of a second abnormal smear, patients were referred to colposcopy.

Strategy B. Referral to colposcopy.

Strategy C. Referral for HPV testing. In case of a positive result they were referred to colposcopy, otherwise they had to repeat cytology (as in Strategy A).

Strategy D. If women were 30 years old or more they were referred to colposcopy (as in Strategy B), otherwise they had to repeat cytology (as in Strategy A).

Strategy E. If women were 30 years old or more they were referred to HPV testing (as in Strategy C), otherwise they had to repeat cytology (as in Strategy A).

In all strategies, women with HSIL cytology results were referred directly for colposcopy, and negative cytology results

Table 1. Main parameters used in the base-case and sensitivity analysis

Parameter	Mean	Minimum	Maximum	Reference
Screening coverage[1]	63%	50%	75%	33
Sensitivity of HPV test[1]	94%	92%	96%	34
Specificity of HPV test[1]	67%	58%	76%	34
Sensitivity of colposcopy[1]	96%	95%	97%	35
Specificity of colposcopy[1]	48%	47%	49%	35
Discount rate[1]	5%	0%	10%	36
Cost of pap smear[1]	13.67	10.94	16.41	37
Cost of colposcopy[1]	25.42	20.34	30.51	37
Cost of HPV testing[2]	13.67	–	–	37
Cost of biopsy	65.70	–	–	37
Cost of staging invasive cancer	246.64	–	–	37
Cost invasive cancer Stage 1	6,171.42	–	–	37
Cost invasive cancer Stage 2	17,225.92	–	–	37
Cost invasive cancer Stage 3	17,517.7	–	–	37
Cost invasive cancer Stage 4	13,929.41	–	–	37
Cost of invasive cancer follow-up exams	61.63	–	–	37

[1]Parameters varied in the one-way sensitivity analysis. [2]Parameter varied in the threshold analysis.All costs are aggregate costs in US dollars, index year 2008. The costs variation was assumed to be ±20% of the mean value.[37] Invasive cancer was stratified according to the cancer staging system of the International Federation of Gynaecology and Obstetrics.[18]

followed the routine screening schedule. Women having LSIL results were referred to repeat cytology in 6 months, as in Strategy A. The 30-years cut-off was chosen because studies have shown that above this age the incidence of CIN 2–3 and cervical cancer increase markedly, and because, even though HPV infection is common in younger women, it is likely to regress naturally.[31,32] The values of the parameters related to the screening strategies in evaluation are presented in Table 1. The test characteristics of cervical cytology were derived from Goldhaber-Fiebert *et al.*[23,24]

According to the Brazilian Guideline for Cervical Cancer Screening, if no lesion was found at colposcopy the patient would be referred to repeat cytology in 6 months time (as in strategy A).[5] If a lesion was found at colposcopy and the cytology result was HSIL the "see and treat" approach was adopted, otherwise a biopsy was performed. The sensitivity and specificity of colposcopy used in the model were based on a meta-analysis conducted by Mitchell *et al.*[35] Those patients presenting a biopsy compatible with CIN 1 or negative diagnosis were referred to repeat cytology in 6 months or routine screening, respectively. All the patients presenting a biopsy showing cervical cancer would be subjected to clinical staging work-up.[18]

Costs and health outcomes

The perspective of the analysis was the health system. Table 1 includes the cost parameters used in the model. All costs were adjusted to year 2008. The monetary unit was the US dollar (US$) according the annual average exchange rate of US$1 = R$1.86.[38] The costs were mainly obtained from the Classificação Hierarquizada de Procedimentos Médicos—Asssociação Médica Brasileira.[37,39] The cost of a medical visit, a nurse visit and a hospitalization day were provided by Hospital de Clínicas de Porto Alegre – Universidade Federal do Rio Grande do Sul, one of the main university public hospitals in Brazil. Since the HPV HC2 test is not currently performed in Brazilian public hospitals, we had to assume a plausible cost for the test in the public system in the base-case analysis and to explore its variation in the sensitivity analysis. For the base-case analysis, we consider the cost of HPV HC2 test to be the same as the cost of pap smear, since similar or lower prices have been achieved in other settings.[8] Our model was able to predict the proportion of patients in each health state for all the cycles. This information was used to calculate the expected costs and expected years of life of hypothetical cohorts subjected to different screening strategies. The main health outcome modeled was years of life saved (YLS) that was obtained by subtracting the expected years of life of a screening strategy in respect to the next least costly strategy. Quality-adjusted life years (QALYs) were not used in our study, because no studies measuring the quality of life in patients with precancer or cancer lesions of the cervix in the Brazilian population were found. Expected costs and years of life were discounted at an annual rate of 5%, in concordance with Brazilian guidelines.[36]

Base-case analysis

Using the best set of natural history input parameters obtained through calibration, we estimated the expected costs and effectiveness of each strategy in the base-case and

Table 2. Base-case incremental cost effectiveness results

Strategy	Expected costs (US$)	Incremental cost (US$)	Expected effect (YL)	Incremental effect (YLS)	ICER (US$/YLS)
Strategy A—repeat cytology	140.9404	–	18.83023	–	–
Strategy E—HPV test $\geq$ 30	141.9783	1.037864	18.83077	0.000542	1,914.87
Strategy D—colposcopy $\geq$ 30	142.9630	–	18.83081	–	Dom.
Strategy C—HPV test to all	144.1832	2.204957	18.83098	0.000214	10,303.54
Strategy B—colposcopy to all	145.9959	1.812672	18.83104	0.00006	30,211.19

Strategy A—repeated cytology, Strategy B—immediate colposcopy to all, Strategy C—HPV test to all, Strategy D—immediate colposcopy to those age 30 or more, Strategy E—HPV DNA test to those age 30 or more.
US$: US dollars; YL: years of life; YLS: years of life saved; ICER: incremental cost effectiveness ratio; Dom.: dominated.

sensitivity analysis. We calculated the incremental cost-effectiveness ratios (ICER) by the dividing the difference in cost between strategies by the difference in effectiveness.[40] Options that were dominated (*i.e.,* they are more costly but less effective than another alternative or a combination of alternatives) were excluded. Since in the Brazilian Guidelines for Health Technology Assessment, there is no recommended threshold to determine whether an intervention is cost effective (*i.e.,* represents good value for money), one heuristic has evolved from the Commission on Macroeconomics and Health[41] and was used to extrapolate a threshold for Brazil. This Commission suggested that a cost-effective interventions would avert one additional disability-adjusted life year (DALY) for less than three times the average per capita gross domestic product (GDP) and a very cost-effective intervention would avert one additional DALY for less than the average per capita GDP for a given country or region. We extrapolated these thresholds and assumed that what society's willingness to pay (WTP) for one DALY is equivalent to its WTP for one YLS. This has been the approach used in previous economic evaluations performed in Brazil and other developing countries.[29,42,43] According to the International Monetary Fund 2008 estimates,[44] this infers a threshold of 25,876 US$/YLS for a cost-effective intervention and a threshold of 8,625 US$/YLS for a very cost-effective intervention.

Sensitivity analysis

To access parameter uncertainty, one-way, scenario, threshold and probabilistic sensitivity analysis were conducted. In the one-way sensitivity analysis key parameters were varied using minimum and maximum estimates, as shown in Table 1. To evaluate the best and the worst scenario in terms of sensitivity and specificity of each screening test, the sensitivity and specificity were varied together, minimum value of both and maximum value of both. Given that the HPV vaccine may be introduced in the Brazilian health system in the medium or long run, an attempt was made to explore how the vaccine may affect the results of this analysis, considering a decrease in the incidence of HR HPV of 70%.[11] As the final cost for the HPV HC2 test for Brazil is not established, we undertook a threshold analysis to explore the maximum price at which HPV triage would still be deemed cost effective. To explore the joint uncertainty across parameters a probabilistic sensitivity analysis was also conducted. Gamma distributions were assigned to all cost parameters, since they are restricted from 0 to positive infinity. Beta distributions were assigned to diagnostic accuracy estimates and coverage, since they are restricted from 0 to 1. By sampling from the above distribution, 10,000 estimates for the costs and effects of each strategy were generated. Cost-effectiveness acceptability curves were used to depict the level of uncertainty for the optimal strategy at different WTP thresholds for an additional YLS.[45]

Results

Base-case analysis

Table 2 presents the base-case incremental cost-effectiveness results. When we look at the expected years of life estimates of the five strategies, like in previous studies we notice that the differences between strategies are very small.[7,8] However, there is a substantial difference in terms of expected lifetime costs. To identify which strategy represents better value for money, we have to consider the costs and effectiveness of the strategies in relative terms by considering the ICER in respect to the threshold. As illustrated in Figure 3 and Table 2, the cheapest and least effective strategy was repeat cytology (Strategy A). Adopting HPV triage for women over 30 (Strategy E) was slightly more expensive but also more effective in terms of YLS. At an ICER of $1,915, this is very cost-effective option for Brazil. Moving to a strategy of also including HPV triage for women under 30 (Strategy C) would also be cost effective at an additional $10,304 per year of life saved. Whilst immediate colposcopy for all women gave a slight additional gain in life years, the additional cost led to an ICER higher than is considered to be cost effective for this setting.

Sensitivity analysis

In the one-way analysis, the ranking of the strategies remained unchanged for almost all input parameters. The results were most sensitive to changes in the cost of colposcopy and the diagnostic accuracy of HPV testing. Only when considering the lowest cost for colposcopy or the worst combination of

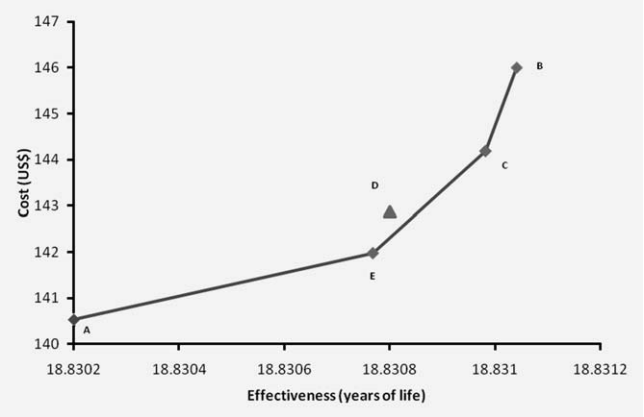

Figure 3. Cost-effectiveness plane (base-case). A—Repeated cytology, B—Immediate colposcopy to all, C—HPV DNA test to all, D—Immediate colposcopy to those age 30 or more, E—HPV DNA test to those age 30 or more.

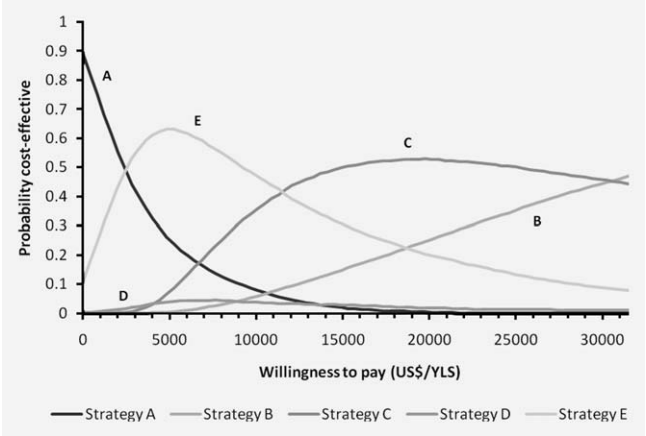

Figure 4. Cost-effectiveness acceptability curve. A—Repeated cytology, B—Immediate colposcopy to all, C—HPV DNA test to all, D—Immediate colposcopy to those age 30 or more, E—HPV DNA test to those age 30 or more.

sensitivity and specificity of HPV testing does immediate colposcopy become the most cost-effective option. Whilst the discount rate seemed to play an important role in determining the magnitude of the ICER of the different strategies,[46] it did not change the conclusions. When considering the possible effect of the HPV vaccine by decreasing the incidence of HR HPV by 70%, HPV triage for all women remained the optimal strategy. In the threshold analysis, if the cost of HPV HC2 test was more than twice the cost of cytology (over 26 US$), all strategies involving HPV testing become dominated. In this scenario, the optimal strategy would be immediate colposcopy.

Figure 4 reports the results of the probabilistic sensitivity analysis. This shows a high degree of certainty about the conclusions. If we consider the threshold recommended by the Commission for Macroeconomics in Health for very cost-effective interventions (8,625 US$/YLS), HPV triage for women above 30 years-old was the strategy with the highest probability of being cost effective, 53% of the simulations. When we consider a cost-effective threshold of three times the GDP for Brazil (25,876 US$/YLS), HPV triage for all women is the strategy with the highest probability of being cost effective, 49% of the simulations.

Discussion

Our results suggest that although HPV testing to triage women with ASC-US results is a more costly strategy than repeated cytology (current protocol), it also saves slightly more years of life. This small gain in life years is likely to occur due to earlier referral of at risk women and also the losses to follow-up that occur with repeat screening protocols. The additional cost of HPV testing strategies is mainly due to the fact that more women that need colposcopy are detected and referred. Colposcopy is costly because it is performed by a trained physician. If we consider a very cost-effective threshold given by Brazil's GDP per capita, HPV triage for women over the age of 30 is the strategy with best cost-effectiveness profile (ICER below the threshold and highest probability of being cost effective in the probabilistic sensitivity analysis). However, if we consider a cost-effective threshold given by three times Brazil's GDP per capita, HPV triage for all women is the strategy with the best cost-effectiveness profile. In the one-way sensitivity analysis, we showed that the results were insensitive to changes in the input parameters. Even when considering a reduction of HR HPV incidence due to the vaccine, HPV testing for all women remained the optimal strategy. In the threshold analysis, we found that the cost of HPV test would have to be nearly twice the cost of cytology for the strategies involving HPV test no longer be cost effective.

To the best of our knowledge, this is the first cost-effectiveness analysis of strategies for managing women presenting ASC-US smear results in a resource-limited setting. Our model estimates of incremental YLS were similar to those reported in previous studies in high-income countries and we draw the same conclusion about the advantage of HPV triage compared to routine screening.[7–9] While our model was estimated and calibrated from data mostly collected in Brazil and the current Brazilian screening strategy was used as the baseline strategy, it is likely that the results can be extrapolated to other middle-income countries with similar conditions.

Our model estimates of incremental YLS were similar to those reported in previous studies in high-income countries. The HPV HC2 test also presented a better cost-effectiveness profile than other strategies evaluated in those studies. It is worth pointing out that the strategies evaluated in the other studies were also slightly different from our study. For example, in the study conducted by Legood *et al.*[8] liquid-based cytology (LBC) was always used as the method of routine screening. Our decision not to include LBC in the analysis reflected current practice in Brazil (which favors conventional cytology), and

because of a previous economic evaluation conducted in Brazil[39] that had shown it was not cost effective.

An important strength of our model is that the incidence rates of HPV as well as clearance rates were obtained from a cohort study conducted in Brazil, the Ludwig–McGill cohort study.[14] Another distinctive feature of our model is the use of calibration.[7–9] It allowed us to make sure that despite parameter uncertainty, our natural history model was capable of simulating prevalence and incidence rates of key events that fitted targets derived from studies conducted in Brazil and Colombia.[15–17] Unlike other studies,[7,9] in our study a probabilistic sensitivity analysis was conducted and presented, which made it possible to explore in more depth the uncertainty surrounding the cost and tests accuracy parameters and consequently the decision.

An important limitation of our study is that it lacks information on the quality of life related to the different states in the model. Although colposcopy is more accurate than the other tests evaluated, there are potentially negative psychological effect associated with this examination. On one hand, this could represent a decrease in quality of life and, therefore, affect our results. On the other hand, the other strategies studied have longer follow-up periods and also involve colposcopy, which means longer periods of anxiety over the results of the tests and strategies that do not completely avoid the necessity to perform a colposcopy.

The model was calibrated to cross-sectional data from a screened population assuming that each member of the cohort experiences the same pattern of screening and treatment through her lifetime. However, it is likely that older women were subject to different patterns than younger women. This may explain why the model fit was better for younger women than older women. Although the probabilistic sensitivity analysis allows us to investigate the overall impact of parameter uncertainty in the model results, it assumes that parameters are independent not allowing us to explore the correlation of parameters in the model.

This analysis indicates a number of areas requiring further research. It would be valuable to obtain QALYs estimates for screening and cervical cancer management in the Brazilian population that could be used in future economic evaluations. A clear obstacle not only for this analysis but for health decision making in the country is the absence of a cost-effectiveness threshold that directly reflects the preferences of the Brazilian society. Hence, it is important to address this matter in the near future.

The incorporation of the highly efficacious HPV vaccine, which has been strongly endorsed by the Pan American Health Organization,[6] is likely to have major implications in the screening strategies. If the prevalence of HPV, and consequently cervical cancer and its precancerous lesions, is significantly reduced with the introduction of the vaccine, it will be possible to change the routine screening protocol and, for example, extend the screening intervals or use different approaches. Refinements of mathematical and economic models are necessary to better inform vaccination and screening decision in the future.[47,48] A further option not evaluated here is the potential to use HPV testing as a primary screen, triaged by cytology.[49] The use of transmission dynamic models would make it possible to better evaluate the optimal screening strategy in a scenario that includes the HPV vaccine.[50] Also as more data becomes available on the implications of simultaneous infection of multiple types as well as HPV cross-immunity, future models should be able to incorporate these possibilities.

In conclusion, in our analysis repeat cytology for all women with ASC-US results in routine screening was the least costly strategy but also the one with the least YLS. Immediate colposcopy for all these women was the strategy with greater YLS but also the one with the highest costs. HPV testing for all women with ASC-US results was the strategy with the best cost effectiveness profile. These results proved to be robust through an extensive sensitivity analysis.

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