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Original article

Cost-effectiveness of the vaccine against human papillomavirus in the Brazilian Amazon region☆

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ABSTRACT

Objective: To assess the cost-utility of the human papillomavirus (HPV) vaccination on the prevention of cervical cancer in the Brazilian Amazon region.
Methods: A Markov cohort model was developed to simulate the natural evolution of HPV and its progress to cervical cancer, considering the current preventive programs and treatment costs. The one-year transition probabilities were mainly based on empirical data of local and national studies. The model evaluated the addition of the vaccine to three cervical cancer-screening scenarios (0, 3 or 10 exams throughout life).
Results: The scenario of three Pap tests resulted in satisfactory calibration (base case). The addition of HPV vaccination would reduce by 35% the incidence of cervical cancer (70% vaccination coverage). The incremental cost-effectiveness ratio was US$ 825 for each quality-adjusted life year gained. The sensitivity analysis confirms the robustness of this result, and duration of immunity was the parameter with greater variation in incremental cost-effectiveness ratio.
Conclusion: Vaccination has a favorable profile in terms of cost-utility, and its inclusion in the immunization schedule would result in a substantial reduction in incidence and mortality of invasive cervical cancer in the Brazilian Amazon region.

Custo-efetividade da vacina contra o papilomavírus humano na região Amazônica brasileira

Palavras-chave:
Câncer de colo de útero
Custo-efetividade
Papilomavírus humano

RESUMO

Objetivo: Avaliar a custo-efetividade da vacinação contra o papilomavírus humano (HPV) na prevenção do câncer de colo de útero na região Amazônica brasileira.
Métodos: Um modelo de coorte Markov foi desenvolvido para simular a história natural do HPV e seu progresso para câncer de colo de útero, considerando os atuais programas de

☆ Study conducted at the Universidade Federal de Rio Grande do Sul, Porto Alegre, RS, Brazil, and at the Fundação de Medicina Tropical, Manaus, AM, Brazil.

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Vacina
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Região amazônica

prevenção e os custos de tratamento. As probabilidades de um ano de transição foram baseadas principalmente em dados empíricos de estudos locais e nacionais. O modelo avaliou a adição da vacina a três cenários de rastreio de câncer de colo de útero (0, 3 ou 10 exames ao longo da vida).

Resultados: O cenário de três exames de Papanicolau resultou em calibração satisfatória (caso base). A adição de vacinação contra o HPV reduziria em 35% a incidência de câncer de colo de útero (70% de cobertura de vacinação). A razão incremental de custo-efetividade foi US$ 825 para cada ano de vida ajustado para qualidade ganho. A análise de sensibilidade confirma a robustez deste resultado, e a duração de imunidade foi o parâmetro com maior variação na razão incremental de custo-efetividade.

Conclusão: A vacinação tem um perfil favorável em termos de custo-utilidade, e sua inclusão no calendário de imunização resultaria em redução substancial de incidência e de mortalidade relacionadas ao câncer de colo de útero na região Amazônica brasileira.

Introduction

The implementation of screening programs for precursor lesions has reduced mortality due to cervical cancer (CC) in developed countries in recent decades; however, infrastructure weaknesses and financing difficulties for this strategy have limited CC control in developing countries.[1,2]

In Brazil, CC represents an important public health problem. It is estimated that 22,000 new cases of CC will be diagnosed in 2013,[3] corresponding to an incidence rate of 17.5 cases per 100,000 women and to a mortality rate of 10.2 deaths per 100,000 women.[2] In the Brazilian Amazon region, the problem is even more serious. Due to a low screening coverage for CC in the target population (less than 25%), a high incidence of the disease has been registered in that area (up to 46 cases/100,000 women), similar to the incidence rates in low-income countries, such as Uganda and Mali.[4]

The finding that 70% of CC cases are caused by two viral serotypes motivated the establishment of preventive strategies based on vaccination against HPV.[5] Currently, two vaccines are available against HPV serotypes 16 and 18.[6–8] Vaccines are recommended for girls before they engage in sexual intercourse, and they appear to have a satisfactory effectiveness. The quadrivalent vaccine induces antibodies of high efficacy against HPV and sustains stable levels for at least five years, in addition to inducing robust immune memory, suggesting that immunity is enduring.[9] Vaccine cross-immunity has also been documented, with a 40% reduced incidence of pre-malignant cervical lesions induced by other oncogenic HPV serotypes (serotypes 31 and 45).[10]

Many questions have been raised about the role of vaccination in CC preventive strategies, such as its clinical effectiveness, target population, and duration of immunity, but the main concern addresses the economic implication of the vaccine. Unfortunately, the real effects of HPV vaccination on the incidence and mortality rates of CC won't be available for decades. In the absence of longitudinal clinical studies that evaluate all of these variables, economic models of analytical health decisions can be useful tools for the evaluation of preventive strategies, by transporting data from empirical studies into real-world simulations, allowing for the management of uncertainties and variations. Therefore, cost-effectiveness analyses play a key role in the evaluation and selection of strategies that should be implemented.

Until the present time, there have been limited data on the clinical and economic impacts of HPV vaccination in Brazil, particularly in the Amazon region, where screening programs have historically not been able to overcome geographical isolation and significant cultural barriers, as in the case of native indigenous populations. The present study aimed to conduct a cost-effectiveness and cost-utility analysis of HPV vaccination in the Brazilian Amazon region, an area with high CC incidence.

Methods

Analytical decision model

A Markov cohort model was developed as a dynamic, closed, and deterministic decision analysis tool for the evaluation of cost-effectiveness and cost-utility in preventive vaccination (Fig. 1), using the TreeAge software (2009 version) (TreeAge Software Inc. - Williamstown, MA, USA).

The analysis was performed from the provider's perspective (Brazilian Unified Health System). The target population was preteen girls (12 years of age), independent of previous sexual contact or HPV infection. The cohort time horizon was lifetime. The model simulated the natural course of HPV infection until its progression to invasive cervical cancer, taking into account the current prevention programs (Pap test) in Brazil. For each strategy (screening plus vaccination or screening only), the model incorporated health state transition probabilities, and the target population was followed-up from adolescence until death in a hypothetical cohort.

The model incorporated the transition probabilities of mutually exclusive health states that refer to one-year cycles. The model simulated the transition probabilities for 70 years from the age of vaccination (12 years of age). At each transition, the model attributed the costs, quality of life, and death expectation according to the individual's health condition. The transition probabilities were based on empirical data from the medical literature and referred to transitions from a healthy state to a possible HPV infection and low-grade squamous intraepithelial lesion (LSIL) induction, which could regress over time to normality, persist, or progress to

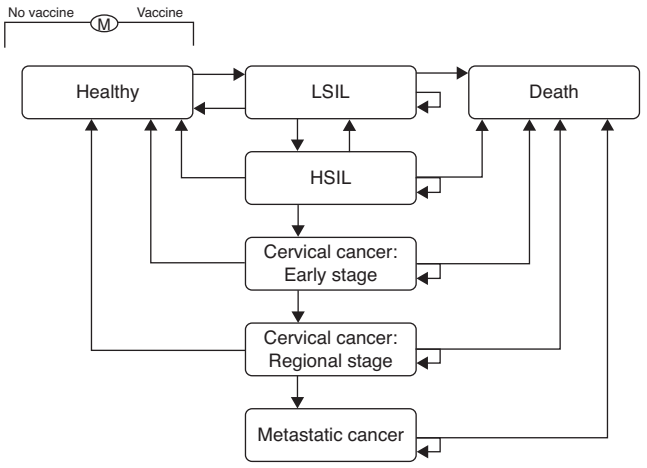

Fig. 1 – Structure of the Markov decision model. The circle above represents the decision of whether or not to vaccinate. The squares represent the states of health, and the arrows represent the transition probabilities. Each individual is followed-up from 12 years of age until death. At each one-year cycle, the individuals are at risk of developing precursor lesions, cancer, or death.

high-grade squamous intraepithelial lesion (HSIL). This, in turn, could persist, regress to normality, or progress to localized, regional, or metastatic invasive cancer (Fig. 1). Given the development of cancer, each individual could continue to suffer from the disease, evolve to death, or evolve to a disease-free state. Each year, individuals would be under an age-specific risk of death that is unrelated to cancer. The odds of death unrelated to cancer are based on the life expectancy and mortality curves of Northern Brazil.[11] The probability of death unrelated to cancer was calculated through the following formula:

$$\text{Probability of death (age)} = 1 - [\text{survival probability (age} + 1)/\text{survival probability (age)}]$$

Due to the low coverage of typical preventive vaginal cytological screening strategies of the Amazonian population, the model was evaluated in three independent scenarios of vaccination or non-vaccination.[4] The scenario with no cytological screening throughout life (natural history of HPV infection) was compared with the scenarios for three and ten Pap smear exams throughout a woman's life. At each screening event, cervical lesions would be found according to the criteria (Pap test sensitivity and specificity) described by national studies. The detection of cervical lesions would require follow-up evaluations or treatment (colposcopy, cryosurgery, and/or surgery), for which they have been assigned a likelihood of success, costs, and implications for the quality of life of the individuals of the cohort model. The economic analysis adopted a 5% annual discount rate for the cost and outcome, with the intent to convert future values into present values.[12]

Model parameters and presumption of base case

The cohort's transition probabilities from a state of health to another were established based on data from published studies. Data from studies that evaluated epidemiology of CC in the Brazilian population were preferably used to calibrate the model, particularly when addressing the Brazilian Amazon population. The supplementary data illustrate the values of the base case, variations of the sensitivity analysis, and the data source used in the model. The base case values represent the best estimate for each variable.

Where necessary, the model was calibrated by adjusting the incidence of precursor lesions of CC to adequately simulate the results of cancer incidence as recorded in the Brazilian Amazon region.

Precursor lesions

The likelihood of oncogenic HPV-induced precursor lesions was defined in accordance with a Brazilian study that assessed the incidence of squamous intraepithelial lesion in adolescents who were followed up annually.[13]

For simplification, LSIL was defined as grade I lesions, and HSIL was defined as grade II and III lesions and in situ carcinoma. The age of sexual initiation was assumed to be 13 years according to a local epidemiological study,[4] and the incidence of LSIL peaked one year after the initiation of sexual intercourse.

Due to the paucity of epidemiological studies evaluating progression probabilities and the regression of precursor lesions, this model used transition probabilities reported in classic international studies adjusted for one year (one cycle), assuming that the mechanism of evolution of the disease is universal.[14,15] The probability of precursor lesion regression to normality was greater in younger women (< 30 years) compared to those who were older than 30 years, reflecting more persistent infections in older women.[16]

Cytological screening tests

The probability of detecting an asymptomatic cervical lesion is a function of the percentage of women who undergo Pap smear screening and the sensitivity and specificity of the test. Incremental evaluations of vaccinations of the population were performed for a non-screening scenario and for scenarios in which individuals were screened three and ten times throughout their lifetimes.

In the scenario of three screening exams throughout an individual's lifetime, the individuals from the model were subjected to the Pap test randomly within the second, fourth, and sixth decades of life. In the scenario of ten lifetime exams, individuals were subjected to testing every five years from the ages of 25 to 40, and then every three years until the age of 55, with a final exam at 65 years of age, in accordance with a Brazilian study that demonstrated that the frequency of preventive examinations tends to be higher between 40 and 59 years of age and decreases after 60 years of age.[16]

The sensitivity of the Pap test was estimated at 70% for LSIL and 80% for HSIL. The specificity ranged from 80% to 90%, according to Brazilian studies.[17–20]

The fundamental structure of the model is based on clinical practice consistent with the clinical program procedures advocated by VIVA MULHER, a program from the Brazilian Ministry of Health.[21] Abnormal screening examinations were forwarded to colposcopy, and tissues were evaluated by biopsy. If HSIL was histologically confirmed, then the patient would be subjected to cryotherapy treatment or surgery. LSIL cases underwent new screening tests after six months.

The costs related to each procedure were derived from the funds allocation table of the Brazilian Ministry of Health.[21,22]

Invasive cervical cancer

Given the progression to cervical invasive cancer, the probabilities of its detection in the asymptomatic, early, regional, or metastatic stages were derived from a local epidemiological study, as were the costs allocated to the initial treatment of cancer.[4] The tumor stages were simplified as localized cancer (FIGO stage I and IIA), regional cancer (FIGO IIB to IVA), or metastatic cancer (FIGO IVB). The standardized treatment was surgery for localized cancer, chemotherapy combined with radiotherapy for regional cancer, and palliative chemotherapy for metastatic cancer.[4]

The probabilities of death by cancer at each stage were extracted from the global survival curves of longitudinal studies.[23] The five-year survival rate ranged from 92.0% for localized cancer to 55.7% for regional cancer and 16.5% for metastatic cancer. The annual incremental costs were estimated at 10% of the initial value of the cancer treatment and refer to screening examinations, control of sequelae, and treatment-related toxicities or costs related to tumor recurrence. Only direct costs that were assigned to cancer were computed, and were expressed in American dollars (US$).

Quality of life

Utility is a measure of the quality of life; it varies on a scale from 0 to 1, where 0 represents death and 1 represents ideal health. The model multiplies the years of life by the utility implicated in the health status to adjust survival by quality of life; the final outcome of effectiveness is quality-adjusted life years (QALYs). The supplementary data illustrate these values.

The completion of the Pap test implied a slight decrease in the quality of life during the year of examination (0.99), as did colposcopy examinations and conization (0.95). Cancer precursor lesions of the uterine cervix were considered asymptomatic and caused no reduction in quality of life. The quality of life (utility) related to each tumor stage was based on an international study that specifically addressed this topic using a validated analog scale, and ranged from 0.48 (metastatic cancer) to 0.76 (localized cancer).[24] The use of utility parameters from international studies as a reference in the present model can be explained by the absence of Brazilian studies addressing this issue, but may be supported by the concept of universality of human suffering.[24]

Vaccination characteristics

The goal of this model is to evaluate the impact of the vaccine on the incidence of CC exclusively. It was not developed to distinguish the effect of the bivalent from the quadrivalent vaccine. The reduction in the incidence of CC-inducing lesions as a result of vaccination was based on studies that originally reported the effectiveness of the vaccine.[6–8]

The vaccination coverage was assumed at 90% of the target population, based on the results of a recently conducted vaccination campaigns against rubella in Brazil (in 2008 and 2011).[25] In this nationwide vaccination strategy held in a similar population, the a 95% coverage was achieved among females aged between 12 and 19 years. Whereas HPV vaccine requires three applications (unlike rubella vaccine, which requires only one dose), the assumed coverage for this model was slightly lower (90%).

In the base case of this model, it was determined that the vaccine provided immunity throughout life after three doses. However, there are major concerns regarding the duration of immunity, with significant impact on the economic outcomes of vaccination. Simulations on the need for booster doses to maintain immunity (one to four doses throughout life) were also performed. Booster vaccination required only one dose; therefore, its cost was estimated at a third of the initial vaccination.

There are no references for the price of the vaccine in Brazil for the large-scale public sector, since the vaccine has not yet been incorporated into public health protocols. A study conduct by the Brazilian Ministry of Health estimated the price of vaccination at approximately US$ 180 (US$ 57 for each dose + US$ 9 as cost of the applications).[26] The Rotative Fund (Pan-American Health Organization) for vaccine purchases has been a technical cooperation mechanism for the expansion of vaccination coverage.[27] According to the Rotative Fund, the cost of the vaccine dose to Brazil would be approximately US$ 60 (US$ 17 for each dose + US$ 9 as cost of the applications). In the present model, the cost of initial vaccination (three doses + implementation costs) for the base case was estimated at US$150.

However, it was reported that the average price of vaccination (three doses) in the American market is US$ 360.[28] For the public sector, the value negotiated by the Centers for Disease Control and Prevention in the United States was US$ 290.[29]

Measurement of outcomes

The results of the effectiveness were shown as the number of cancer cases prevented and deaths avoided, and the utility outcomes were shown as QALYs. The incremental cost-effectiveness ratio (ICER) was calculated by the ratio of the difference in the cumulative total costs divided by the total QALYs obtained per woman that are attributed to the addition of vaccination to the existing screening program. As a threshold for judgment, the international convention that a strategy can be considered cost beneficial if the ICER is less than the value of GDP per capita (i.e., if the additional cost of a strategy is less than the value of GDP *per capita* to save a QALY) was followed.[30,31]

Sensitivity analysis

All economic assessments show a certain degree of uncertainty, inaccuracy, or methodological controversy.[12,31]

Table 1 – Health and economic outcomes for the addition of vaccination to the screening strategy (Pap test).

Preventive strategies	Cost per individual (US$)	Quality-adjusted life years (QALYs)	Incremental cost (US$)	QALYs saved per individual	ICER (US$/QALY)
Non-screening scenario					
Vaccination	270	24.8	-25	0.2	Dominant
No vaccination (natural course)	295	24.6			
Scenario of three screenings throughout the lifetime (base case)					
Vaccination + screening	320	29.6	165	0.2	825
Only screening	155	29.4			
Scenario of ten screenings throughout the lifetime					
Vaccination + screening	448	34.5	255	0.2	1,275
Only screening	193	34.3			

Therefore, sensitivity analyses (one-way) were performed for variables with uncertainty over the base case values to assess the robustness of the present study findings. These analyses recalculate the ICER considering the variations in a given parameter.

The evaluated variables were cost of vaccination, effectiveness of vaccination, scenario of the pre-existing screening program, vaccination coverage, time of immunity, annual discount rate, and characteristics of the Pap test (sensitivity). For such analyses, the variation values represent the authors' judgment regarding the uncertainty of the study parameter or the variations in the results that have been published in the medical literature.

Results

Model calibration

The primary outcome for the calibration of the model was the incidence of invasive cancer. In the scenario of the natural course of HPV infection, without screening exams, the model simulated a 4.2% lifetime risk of cancer, which equates to 34.1 invasive CC cases per 100,000 women, considering the demographic structure of the region studied.[11] In the scenario with screening three times throughout an individual's lifetime, the risk of cancer was estimated at 3.4% (equivalent to 27.5 cases per 100,000 women).

The model was well-calibrated to reported data of incidence of CC in the Brazilian Amazon. The prediction in the three-screenings scenario corresponded satisfactorily to the gross incidence rate of invasive CC as recorded in the Brazilian Amazon region in 2010 (28.2 cases per 100,000 women), and was considered as the baseline strategy to be compared with the addition of vaccination.[4]

Base case analysis

With a vaccination coverage rate of 90%, the vaccination strategy for preteen girls of the Brazilian Amazon region would reduce the lifelong incidence of CC by 42% in this population, and would reduce the mortality due to CC by approximately 43.4%. The addition of the vaccine would generate an incremental cost of approximately US$ 165 per woman to the current strategy. The incremental cost-effectiveness ratio was US$ 825/QALY saved, given the base case parameters.

This assessment can be compared to the addition of the vaccine in other hypothetical scenarios of baseline cytological screening in Table 1.

Fig. 2 compares the reduction in the incidence of CC for the various strategies (combination of cytological screening and vaccination), given the different vaccine coverage levels simulated by this model. It is noteworthy that the goal of a 50% reduction in CC incidence could be achieved by combining high vaccination coverage (> 70%) with existing screening procedures (> 3 Pap tests during lifetime).

Simulation of uncertainties

The sensitivity analyses reveal that vaccination tends to provide a favorable profile regarding cost-effectiveness, despite changes in the base case parameters proposed by the sensitivity analysis (Fig. 3).

The population vaccination coverage implies wide variations in ICER, surpassing US$ 2,000/QALY for vaccine coverage levels of less than 50%. In a vaccination coverage of 100%, the ICER would be approximately US$ 500/QALY. The vaccination strategy tends to dominate the cytological screening (3x) in isolation, i.e., it is less costly and more effective (ICER $\leq$ 0) for vaccination costs lower than US$ 40 (all doses for primary immunization). For vaccination costs above US$ 500, the vaccination strategy requires approximately US$ 2,200 to save one QALY. A vaccination effectiveness (reduction in the incidence

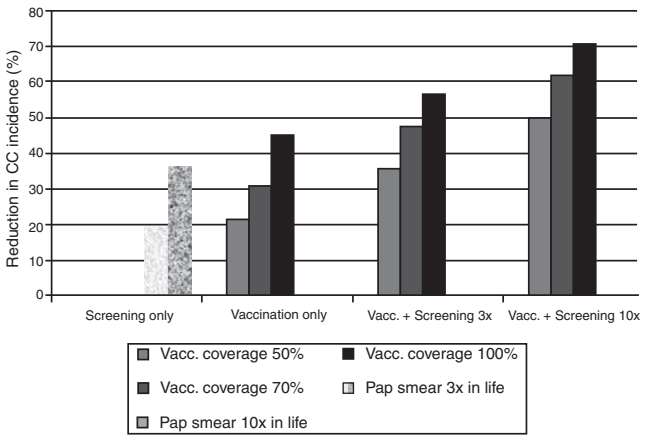

Fig. 2 – Effectiveness of strategies in the prevention of cervical cancer. Additional effect of vaccination in different vaccine coverage levels and preventive strategies.

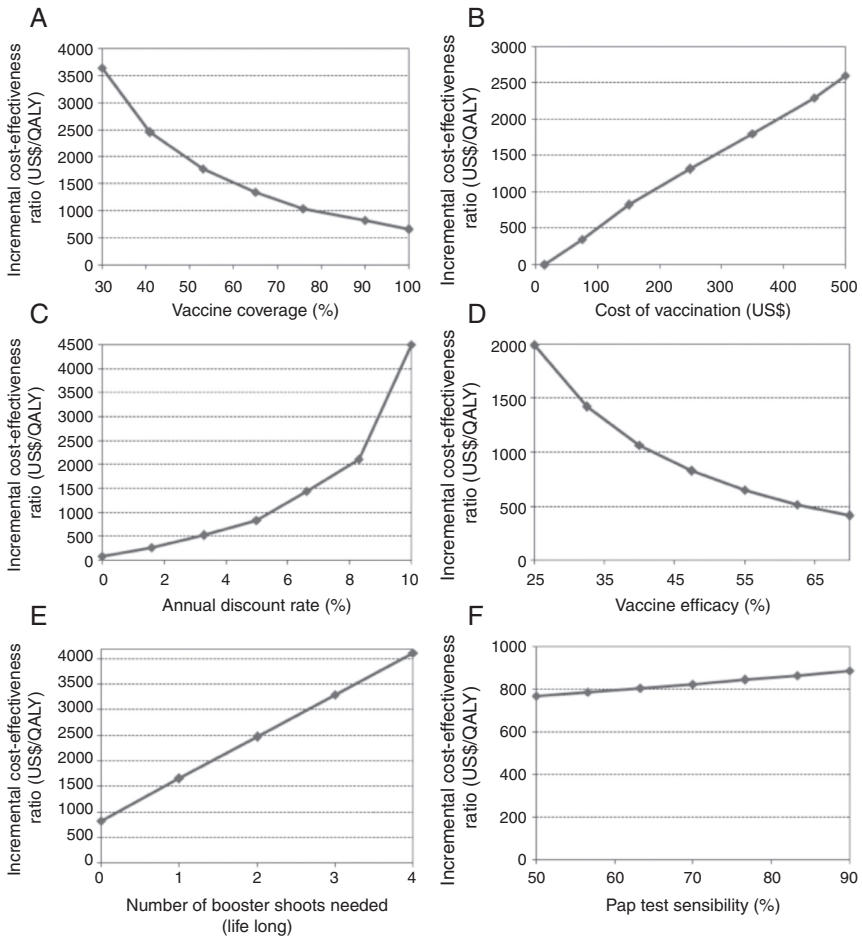

Fig. 3 – Sensitivity analysis. (A) Variation in vaccination coverage (30% to 100%); (B) variation in vaccination cost (US$ 15 to US$ 500); (C) annual discount rate variation (0% to 10%); (D) variation in vaccine effectiveness in reducing the incidence of pre-malignant lesions (25% to 70%); (E) variation in the number of lifetime booster shots (1-4 booster shots); (F) variation in the sensitivity of the Pap test (50% to 90%).

of precursor lesions) of above 40% maintains the ICER below US$1,000/QALY compared to the basal strategy. Increases in the sensitivity of the Pap test tend to modestly increase the ICER of added vaccination by improving the efficiency of the baseline strategy, leading to a relative reduction in the additional benefit of the vaccine.

If revaccination is needed (at least one lifetime booster dose) for the maintenance of immunity, the ICER would be US$ 1,650/QALY for the vaccination strategy, considering the cost of the vaccine booster at US$ 50 per dose. The need of extra doses substantially raises the costs of vaccine strategy without improving clinical effects, negatively altering the cost-effectiveness profile of vaccination. In the case of the need for three booster doses, the ICER would reach US$ 3,200/QALY. The ICER would surpass US$ 4,000/QALY for the hypothesis of a booster dose every 10 years (four booster doses throughout life).

The parameter variation with the greatest impact in the ICER was the annual discount rate. In an analysis without a discount rate, the ICER would be approximately US$ 30/QALY, which is substantially less than a discount rate of 10% (ICER = US$ 4,500/QALY). These results are consistent with a lifetime horizon cohort, as proposed in the present study.

Discussion

Due to increasing healthcare costs worldwide and the growing constraints arising from the scarcity of resources, healthcare demands have increasingly sought to justify the incorporation of a new technique based on its cost-effectiveness or cost-utility. To address this growing demand over the past few decades, methodological tools that promote rationality in decision-making in healthcare were proposed, aiming to achieve efficient use of available resources.

The present study revealed that the addition of HPV vaccination to the existing preventive strategy exhibits a favorable cost-effectiveness and cost-utility profile in the Brazilian Amazon region. Even when simulating a pessimistic vaccination coverage rate (approximately 30%), the ICER of the addition of vaccination does not exceed the conventional limit of the GDP value per capita (about US$ 12,000 for Brazil in 2012) for any other uncertainty simulation. The ICER values resulting from the sensitivity analysis confirms the favorable profile of vaccination even if the limit value used were the GDP per capita in the Amazon region (US$ 6,350 per capita). If the cost of vaccination is reduced to US$ 40 or less, with a vaccination coverage

rate of 90%, then adding vaccination tends to dominate the cytological screening strategy used alone.

Some authors have proposed a different limit parameter for developing countries, suggesting that an expense of one to three times the value of GDP per capita for each QALY saved would represent a good use of resources in these countries.[30] Although there is no consensus in Brazil regarding the limit for a strategy to be considered cost-effective, the present study confirms the favorable profile of the addition of HPV vaccination in Brazilian regions with poor prevention programs and a high incidence of CC according to the proposed criteria.

To better understand the implications of the HPV vaccine, cost-effectiveness analyses published in countries facing opposing economic situations can be enlightening. Goldie et al. studied the cost-effectiveness of the HPV vaccine in 72 low-income countries, mostly countries in Africa, which are characterized by high CC incidence rates.[32] The analysis showed that the ICER of adding vaccinations in these countries did not surpass US$ 200/QALY in 59 of the 72 countries, but had a major impact on the reductions in mortality and incidence rates of CC after the vaccination of preteens. The analysis also showed the favorable cost-effectiveness profile of the vaccine in regions where CC was not controlled by conventional screening programs.

Conversely, in developed countries that succeeded in controlling CC incidence and CC-related mortality with solid gynecological screening programs, the HPV vaccine is not as favorable from a cost-effectiveness standpoint Ireland, the United Kingdom, Switzerland, and Finland have gross incidence rates under 10 cervical cancer cases per 100,000 women. In these countries, cost-effectiveness studies showed an additional cost of over US$ 20,000/QALY.[33–36] In the United States, the ICER of adding vaccination exceeded US$ 43,000/QALY[37]. In the Netherlands, the CC incidence rate is less than six cases per 100,000 women; however, the ICER of adding the HPV vaccine to the existing Dutch preventive program was greater than US$ 70,000/QALY, classifying the vaccination strategy, according to the authors, as non-cost-effective.[38]

These evidences suggest that the greatest benefit of the vaccine does not lie in its synergy with the basal population screening programs, rather in their replacement in countries or regions whose programs are insufficient and poorly structured, and have a high prevalence of oncogenic HPV infection.

Despite the favorable economic profile, the costs involved in the vaccination of preteen girls have caused widespread concern, especially in developing countries. The HPV vaccine (16 and 18) is one of the most expensive vaccines on the market, hindering its incorporation in the healthcare systems of countries that would most benefit from this technology. According to the lesson learned from the vaccine against hepatitis B, which is now available for children in 89% of the world's countries, including the poorest countries, only after a drastic reduction in its price was vaccination in global proportions possible.[39]

Although the cost of the vaccine is the main barrier to its introduction in Latin America, other factors are also important, such as the feasibility of vaccinating the target population, the competition with other vaccines, and its acceptance. The cultural acceptance of the vaccine has not been evaluated in Brazil. It is worth noting that the general public and health managers' knowledge of HPV and its implications are factors that strongly influence the acceptance of the vaccine by a population. Accordingly, strategies of communication and education regarding the subject would be crucial to the success and effectiveness of any public health policy for the introduction of the HPV vaccine in Brazil, particularly in the Amazon region.

There are limitations to the present study. First, due to lack of national data, some parameters have been calibrated based on international data. Second, the Markov assumption itself establishes that transition probabilities depend exclusively on the current health state, not on a sequence of past health states. Indeed, dynamic transmission models represent an economic evaluation methodology that uses probabilistic variations to more reliably simulate the natural course of diseases such as CC, but requires large and robust epidemiological data for its preparation (not commonly available). Finally, the present study considered only the effects of the vaccine on the magnitude of CC, without considering the effects of the vaccine in reducing other types of cancer, such as those of the vulva, vagina, anus, or head and neck, nor the benefits of the quadrivalent vaccine on genital warts.

A recent study evaluated the cost-effectiveness of the quadrivalent HPV vaccine in Brazil, using a dynamic transmission model to assess the effects on CC and genital warts.[40] Kawai et al. estimated that the ICER of vaccination strategy varied from US$ 448 to US$ 698/QALY when considering only the bivalent vaccine (16 and 18) for control of the CC. The study also reported an even better outcome when considering the effect of the quadrivalent vaccine to control CC and genital warts (US$ 219 to US$ 450/QALY). This data suggest that, if the additional benefit of vaccine is considered, a more favorable cost-effectiveness profile may be achieved.

The HPV vaccine may also be effective in preventing male cancers (such as those of the penis and anus). Additionally, male vaccination may improve the protection of women by reducing viral transmission. The cost-effectiveness of including Brazilian boys in HPV vaccination was studied by Kim et al.[41] This strategy rendered a small additional gain in clinical benefit (around 4% reduction in risk of HPV-related cancer), but a high additional cost. The authors judged vaccinating boys as non-cost-effective and recommended that efforts should be focused on expanding the coverage of girls only.

The high risk of invasive CC in the Brazilian Amazon region implies an urgent need to rethink the current preventive policy, especially for underprivileged regions of the country. The present study was the first cost-effectiveness analysis of a CC preventive strategy directed toward a specific region of the country. The cost-effectiveness analysis of HPV vaccine for the Amazon region showed a better profile when compared to studies addressing this topic to Brazil as a whole, as in the analysis published by Colantônio et al. (ICER = US$ 10,181/QALY)[42] and by Goldie et al. (ICER = US$ 9,600/QALY).[43] Regarding public health, these results lead to the conclusion that public policies on women's health, particularly on CC prevention programs, should be decentralized (adjusted to

regional reality) rather than uniform, given the heterogeneity inherent in a country of continental proportions, such as Brazil.

Large-scale preteen vaccination in the Brazilian Amazon region can be considered an investment in the future to prevent, in the coming decades, the premature deaths of hundreds of women who have historically been neglected in preventive government programs.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A.

Model parameters, costs, utilities, variation for the sensitivity analysis, and respective sources

Variables	Base case	Variation[§]	Data source (reference)
Properties of vaccination			
Vaccination coverage – three doses (%)	90	30-100	25
Vaccination age (years)	12		4,13
Duration of immunity (years)	lifetime	10-lifetime	9
Adherence to booster vaccination (%)	90		25
Preventive screening properties			
Number of tests during the lifetime (n)	3	0-10	4
Age screening started (years)	18		estimated
Sensitivity of Pap test (in LSIL scenario) (%)	70	50-90	17,18
Sensitivity of Pap test (in HSIL scenario) (%)	80	60-90	19,20
Specificity of Pap test (%)	90		17,18
Transition probabilities			
Develop LSIL after first sexual intercourse			13
1st year	0.285		4,13
2nd year	0.117		4,13
3rd year	0.114		4,13
4th year	0.075		4,13
5th to 25th year (mean)	0.070 (± 0.022)		4,13
26th to 50th year (mean)	0.053 (± 0.012)		4,13
After 51st year (mean)	0.010 (± 0.008)		4,13
Reduction in the probabilities of developing LSIL attributed to vaccination (%)	50	40-70	6,7,8
LSIL regression (< 30 years old)	0.193		14, 15, 16
LSIL regression (> 30 years old)	0.113		14, 15, 16
Develop HSIL from LSIL	0.110		14, 15
Develop invasive cancer from LSIL	0.00075		14, 15
Regression of HSIL	0.175		14, 15
Develop invasive cancer from HSIL	0.0078		14, 15
Invasive cervical cancer properties			
Probability of localized cancer at diagnosis	0.315		4
Probability of regional cancer at diagnosis	0.488		4
Probability of metastatic cancer at diagnosis	0.197		4
Probability of death – localized	0.0165		23
Probability of death – regional	0.1101		23
Probability of death – metastatic	0.305		23
Precursor lesions treatment properties			
Effectiveness of cryosurgery for LSIL (%)	85		
Effectiveness of cryosurgery for HSIL (%)	75		
Eligibility for cryosurgery (%)	85		estimated

Appendix A (*Continued*)

Variables	Base case	Variation§	Data source (reference)
Others			
Duration of cycle (years)	1		estimated
Age of sexual initiation (years)	13		4
Discount rate (%)	5	0-10	12, 31
Costs (US$)			
Vaccination – three doses	150	15 - 500	26, 27, 28, 29
Booster shot	50		26, 27
Pap test	8		22
Medical appointment	5.5		22
Colposcopy	26.8		22
Cryosurgery	26.8		22
Conization	498		22
Hysterectomy type 1	1,236		22
Localized invasive cancer treatment	3,702		4
Regional invasive cancer treatment	8,420		4
Metastatic cancer treatment	2,625		4
Utilities			
Normal population	1		estimated
Completion of Pap test (for 1 year)	0.99		estimated
Colposcopy and conization (for 1 year)	0.95		estimated
Localized invasive cancer	0.76		24
Regional invasive cancer	0.67		24
Invasive metastatic cancer	0.48		24

§ Range of variation addressed in sensitivity analysis of variables where lies any uncertainty. Costs expressed in American dollars (US$).

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