

## Cost-Effectiveness of Primary and Secondary Prevention Strategies for Cervical Cancer in Brazil: A Systematic Review

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### Abstract

**Background:** Although Cervical Cancer (CC) can be effectively prevented, it is still a serious public health problem, especially in developing countries. In Brazil, almost 18,000 new cases are expected in 2013, and it is the type of neoplasia that claims the most lives of young women. New secondary prevention strategies (such as the HPV-DNA test) and primary prevention strategies (vaccination against HPV) have been developed. However, applying these strategies to large populations is costly, and their use is limited in Brazil. Because financial resources are scarce in Brazilian scenario, studies about the economic implications of the new preventative technologies for CC may support rational and evidence-based decisions in public health.

**Methods:** A systematic search of the articles (1970 to 2013) was conducted in MEDLINE, EMBASE, Cochrane Collaboration of Systematic Reviews, and LILACS. The aim was original articles that evaluated the cost-effectiveness of primary and/or secondary prevention strategies for cervical cancer in Brazil.

**Results:** A total of 6 articles were included in this review. Two articles described economic analyses of population screening strategies in comparison to the current strategy in Brazil (oncotic cytology). Four articles evaluated the addition of a vaccine against the HPV (genotypes 16 and 18) for Brazil in comparison to population screening.

**Conclusion:** Despite raising the costs of preventing cervical cancer, new preventive technologies reveal a favorable cost-effectiveness profile for the case of Brazil. Ignoring the new preventative technologies for CC can lead to misguided and perverse consequences in a country where programs based on the Papanicolaou technique have only been partially successful.

**Keywords:** Cervical neoplasia; Primary prevention; Secondary prevention; Cervical cancer prevention; Cost-effectiveness analysis

**Abbreviations:** HPV: Human Papilloma Virus; CC: Cervical Cancer; OC: Oncotic Cytology; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year; ASC-US: Atypical Squamous Cell of Unknown Significance

### Background

Although Cervical Cancer (CC) can be effectively prevented, almost 500,000 new cases are diagnosed each year worldwide [1]. The global reduction in the incidence and mortality from CC over the last four decades did not occur in a homogeneous manner; it was concentrated in the developed countries that were able to implement solid and effective population screening programs [2].

In Brazil, organizational and financial difficulties have compromised the quality of prevention programs based on Oncotic Cytology (OC), and they have not succeeded in controlling the disease; approximately 17,500 new cases of CC are expected in 2013 [3-5]. It is the second most common type of neoplasia in women (excluding non-melanoma skin cancer), and it is the type of neoplasia that claims the most lives of young women (15 to 44 years of age) [1].

These difficulties, which are associated with the inherent limitations of the OC technique, have led many researchers to seek alternative or supplementary techniques for OC for CC screening, such as the hybrid capture test (HPV-DNA), and, more recently, to prepare vaccines against the most carcinogenic genotypes of HPV. These new technologies exhibit better performance and/or effectiveness; however, they would result in higher costs if they were incorporated into Brazil's prevention strategy.

Because of the universal increase in healthcare costs and the growing constraints imposed by the scarcity of resources, there is a greater need to justify the use of a new technique by considering its cost-effectiveness ratio [6]. To handle this growing demand, economic analysis tools can be applied to new healthcare technologies to support decision-making in public health that aims for rational and efficient use of available resources [7,8].

Among the methods of economic evaluation, cost-effectiveness analyses have received special attention [7]. Markov models have been widely used to evaluate new technologies and to compare healthcare strategies around the world. In comparing two strategies, the Markovian model provides the Incremental Cost-Effectiveness Ratio (ICER) as the primary result [8]. This ratio shows the additional cost required to save 1 year of life (adjusted or not by quality of life) using one strategy compared to a baseline strategy. The World Health Organization stipulates that a strategy is considered cost-effective if the

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ICER is less than 1 to 3 times the *per capita* GDP of the country (for Brazil, approximately US\$10,000 to US\$30,000 in 2011) [9].

The objective of this article is to systematically review the studies that have used cost-effectiveness and cost-utility analyses to evaluate the clinical and economic implications of primary (vaccination against HPV) and secondary (population screening strategies) prevention strategies for CC in Brazil.

## Methods

### Search strategy

A systematic search of the articles published from 1970 to 2013 was conducted in MEDLINE (Ovid system), EMBASE, Cochrane Collaboration of Systematic Reviews, and LILACS. The search aimed to identify original articles published in indexed periodicals that evaluated the cost-effectiveness of primary and/or secondary prevention strategies for cervical cancer in Brazil. The terms used for this review search were “human papillomavirus”, “HPV”, “vaccine”, “vaccination”, “prevention”, “screening”, “cost”, “cost-effectiveness”, “cost-utility”, “economic evaluation”, “economic models”, “pharmacoeconomics”, “Brazilian” and “Brazil”.

### Inclusion criteria and quality assessment

Articles in Portuguese and English that evaluated the cost-effectiveness of strategies for preventing CC in Brazil using mathematical cost-effectiveness models were included.

According to the recommendations of Sonnenberg and Becker for evaluating the cost-effectiveness of healthcare, the following criteria were used to evaluate the quality of the articles: 1) to use of a Markov mathematical model or a dynamic transition model; 2) to use a clear point of view of Brazil Unified Health System as the payer; 3) to evaluate a complete and clear economic comparison between at least 2 preventive strategies; 4) to use a base comparison scenario that is compatible with the current environment in Brazil (OC each 3 years for every women between 25-64 years old); 5) to make appropriate measurement of clinical and economic outcomes (as \$/QALY or \$/Years of life saved); 6) to present analysis of the uncertainty of the variables (e.g., a sensitivity analysis of at least 3 variables); 7) to use reliable data sources to estimate variables [9].

### Extracted information

The following information was extracted from each article: the model type, the timeframe of the analysis, the perspective, the baseline scenario, the estimated coverage of the preventative strategy, the need for revaccination, the number of lifetime preventative examinations, the age at which prevention begins, the efficacy of the strategy, the costs, the reduction in mortality attributable to CC, the reduction in the incidence of CC, the incremental cost-effectiveness ratio of the strategy used and the Quality-Adjusted Life Years (QALYs) gained by the strategy.

## Results and Discussion

The literature search identified 11 original articles. Of these articles, 5 were excluded because they did not meet the study criteria of quality. In 3, the point of views as the payer was not the Brazilian Unified Health System. In one study, the compared strategy was not the current in Brazilian scenario, and the other study did not use a validated mathematical model. A total of 6 articles were thus included in the systematic review.

Two articles described economic analyses of population screening strategies in comparison to the current strategy in Brazil (oncotic cytology). Four articles evaluated the addition of a vaccine against the HPV genotypes 16 and 18 for Brazil in comparison to population screening. The selected articles and their sources are described in Table 1.

Caetano et al. and Vanni et al. published studies evaluating the clinical and economic implications of substituting new CC screening technologies for traditional oncotic cytology in Brazil [6,10]. Caetano et al. used a Markov model to simulate the natural history of infection with HPV [6]. Using national epidemiologic data, a hypothetical cohort of women illustrated the risk of HPV infection, spontaneous resolution or progression to CC. The model evaluated the cost-effectiveness of new population-screening technologies in comparison with the methods recommended by the Brazilian government. The health benefit was expressed as the number of detected cases of cervical cancer or precursory lesions with a high degree of malignancy. The theoretical cohort in the model included 10,000 women who were representative of the population that could participate in these programs.

The results indicate that OC has the best ICER among the screening strategies analyzed (Table 2). The negative ICER value found in this study means that screening with OC is far superior to the strategy of not screening for CC in Brazil. That is, the OC screening strategy is cheaper and more effective.

Furthermore, in the study by Caetano et al., hybrid capture strategies (HPV-DNA) and liquid media cytology alone and in combination with the HPV-DNA test are inferior to the Papanicolaou test when the latter is used as a basis for comparison [6]. The authors indicate that the low cost of OC is the main factor responsible for its favorable performance in the cost-effectiveness analysis (10 times cheaper than HPV-DNA), supplanting the negative influence of its relatively lower accuracy. For a sensitivity analysis, the authors repeated the economic analyses with a 20% increase in the cost of OC concomitant with a 20% reduction in the costs of the other tests. In this simulation, screening with HPV-DNA had the best incremental cost-effectiveness ratio, indicating that market prices influence the analysis.

Because of the high cost of administering the HPV-DNA test to a large population, some authors proposed strategies that involve selecting population groups to receive the more expensive and sophisticated techniques, with the objective of better allocating the available resources. Vanni et al. developed and satisfactorily calibrated a Markov model to simulate cervical carcinogenesis based on Brazilian or Latin American studies [10]. The model rigorously followed the Brazilian screening protocol with one exception: the procedure for Atypical Squamous Cells Of Unknown Significance (ASC-US). The authors' objective was to evaluate the impact of other diagnostic strategies in the subgroups of women whose diagnosis and prognosis are uncertain.

When confronted with a patient with ASC-US in oncotic cytology, the model considered the possibility of repeating OC in 6 months (recommended in Brazil), performing the HPV-DNA for all of the women or only those older than 30, or immediately performing a colposcopy for all of the women or only those older than 30 (Table 3). For ASC-US, the developed model showed that the current strategy (repeat OC in 6 months) would be the cheapest and the least effective. Using the HPV-DNA for women older than 30 who showed ASC-US in the OC test was more expensive and more effective and had the greatest probability of cost-effectiveness (US\$1,914 per year of life saved) compared with the current protocol. If this strategy were

Study (author, year)	Source (database)	Modeling method	Main strategy tested	Base strategy	Clinical outcome	Economic outcome	Perspective of the paying source	Main result <sup>£</sup>
Caetano et al. (2006) [6]	LILACS	Markov model	Population screening with hybrid capture	Population screening with OC	Number of cases detected	R\$/QALY	Brazilian Unified Health System	Base Strategy
Vanni et al. (2007) [10]	MEDLINE	Markov model	Perform hybrid capture for patients with ASC-US	Repeat OC in 6 months for patients with ASC-US	Years of life saved	US\$/years of life saved	Brazilian Unified Health System	\$ 1,914/year of life saved
Goldie et al. (2007) [19]	MEDLINE	Dynamic transition model	Mass vaccination of pre-adolescents against HPV	Population screening with OC	Years of life saved	US\$/years of life saved	Brazilian Unified Health System	\$ 1,100/year of life saved
Kok et al. (2007) [28]	MEDLINE	Dynamic transition model	Mass vaccination of pre-adolescent boys and girls against HPV	Mass vaccination of only pre-adolescent girls against HPV	Years of life saved	US\$/years of life saved	Brazilian Unified Health System	\$ 37,720/year of life saved
Colantonio et al. (2009) [20]	MEDLINE	Markov model	Mass vaccination of pre-adolescent girls against HPV	Population screening with OC	QALY	US\$/QALY	Brazilian Unified Health System	\$ 10,181/QALY
Kawai et al. (2012) [21]	MEDLINE	Dynamic transition model	Mass quadrivalent vaccination of pre-adolescent girls against HPV	Population screening with OC	QALY	US\$/QALY	Brazilian Unified Health System	\$ 450/QALY

<sup>£</sup>The main result refers to the incremental cost-effectiveness ratio of the main strategy tested in relation to the base strategy, considering the base case described in the article. Legend: OC: Oncotic Cytology For Cervical Cancer; QALY: Quality-Adjusted Life Years; SUS (Brazilian Unified Health System); ASC-US: Atypical Squamous Cells of Unknown Significance

**Table 1:** Summary of 6 articles selected for the systematic review of the medical literature.

Screening Examination	Sensitivity (%)	Accuracy	Cost per exam (R\$)	Cost per case (R\$/case)	ICER (R\$)
Oncotic Cytology	71.4	0.654	27.85	14.586	- 1,575,012.58
Liquid media cytology	66.7	0.565	44.75	19.315	23,918.50
Hybrid capture (HPV DNA)	91.4	0.824	228.13	18.254	146,638.56
Papanicolaou + HPV DNA	97.1	0.823	255.98	20.101	47,805.30
LMC + HPV	90.9	0.711	272.88	23.722	84,434.48

ICER: Incremental cost-effectiveness ratio ( $\Delta$  cost /  $\Delta$  detected case) for implementing the CC screening technique in Brazil compared with not employing population screening; HPV DNA: Hybrid Capture for the Human Papillomavirus; LMC: Liquid Media Cytology.

Source: Caetano et al. [6]

**Table 2:** Performance, cost and cost-effectiveness of CC screening in Brazil.

Strategy with ASC-US cytology	Costs per woman (US\$)	ICER (US\$/years saved)
Repeat OC <sup>#</sup>	140.9	-
HPV-DNA for > 30 years	141.9	1,914.87
HPV-DNA for all	144.1	10,303.54
Colposcopy > 30 years	142.9	inferior
Colposcopy for all	145.9	30,211.19

<sup>#</sup>The strategy of repeating OC does not have comparative analyses because it is the base strategy to which the others are compared. HPV-DNA: hybrid capture for HPV

**Table 3:** Cost-effectiveness analysis of strategies following an OC Exam Revealing A Slight Alteration (ASC-US) in Brazil [42].

expanded to all patients who showed cytology with slight alterations, the ICER would slightly exceed the *per capita* GDP in Brazil but would still be cost-effective according to the authors. The strategies involving immediate colposcopy were either inferior or not cost-effective in this scenario. The results were expressed in the cost per year of life saved, and the sensitivity analysis showed that the variations in the parameters did not alter the results of the base case, confirming that the conclusions are robust.

Vanni et al. concluded that although OC had the best cost-effectiveness profile for general population screening, selecting subgroups for more modern diagnostic methods could guarantee an acceptable cost-effectiveness profile in countries with intermediate income, such as Brazil [10].

In a similar manner, a Canadian study that evaluated various preventative strategies concluded that performing the HPV-DNA test for a selected group of women (i.e., women over 30 years of age with ASC-US) is less costly and more effective, costing US\$16,078 to save 1 QALY [11].

The studies presented in this review provide robust evidence that organized screening with OC is still the most cost-effective option for controlling CC. Some authors have declared their support for this strategy and have suggested that it is necessary to extract all of the benefits of OC before pursuing other screening techniques [12]. However, the data indicate that more expensive and more effective techniques can be used more cost-effectively by reserving their use for specific subgroups at higher risk, depending on the reduction of prices in the health sector [13,14].

The HPV vaccination will significantly reduce the incidence of CC in future decades in countries that have pursued mass vaccination of adolescents and young women [15]. Consequently, the cost-effectiveness of secondary prevention strategies for CC would be significantly altered. That is, the success of primary prevention programs (i.e., the vaccine) might make the screening programs less cost-effective. Therefore, the future cost-effectiveness of strategies that use sophisticated (and expensive) methods for detecting HPV is somewhat uncertain and new studies will be necessary after the effects of the vaccine have been documented.

The first results on the efficacy of prophylactic vaccines were published in 2004. They refer to 2 vaccines: one bivalent vaccine (with viral particles from serotypes 16 and 18) and one tetravalent vaccine (serotypes 6, 11, 16 and 18) [16,17]. The preliminary results from the vaccine studies, combined with the evidence that the HPV vaccines induce highly effective antibodies, suggesting that the immunity is lasting [18], were sufficient for the regulatory agencies of the United States (Food and Drug Administration) to license the vaccine in June 2006; various other countries, including Brazil, followed.

Goldie et al. performed a cost-effectiveness study of the HPV vaccine specific to Brazil. A dynamic model was developed using national data for the morbidity and mortality from CC and assuming that 9-year-old pre-adolescent girls would be vaccinated [19]. The base screening strategy was two-fold: 1) screening women over 30 years old with the hybrid capture test for HPV; 2) administering colposcopic cytology 3 times over the lifespan. Both screening strategies were modeled alone or combined with the vaccination strategy (prior to sexual debut between 9 and 12 years of age). The model assumed an annual discount rate of 3% and that society was the source of funding. Because the price of the vaccine for mass vaccination in Brazil had not been established, the authors varied the price of the vaccination between US \$25 and US \$450 in their analyses.

Assuming 70% vaccine coverage of the target population, vaccination would result in a 42% reduction in CC risk over a lifetime (in isolation, not considering the screening strategy). If associated with the base strategy of 3 oncotic cytology exams over a lifetime, the risk would be reduced 55%; if associated with the base strategy of 3 hybrid capture exams for HPV, the risk would be reduced approximately 61%.

At US \$25 for each vaccinated woman, the vaccine strategy alone would be more effective and less costly than the screening strategies and is therefore considered superior. If applied concomitantly with population screening, vaccination would be associated with an ICER of US \$200 to US \$700 for each year of life saved, depending on the base screening strategy. For a vaccine cost of US \$50, the ICER would reach US \$1,000 for each year of life saved. For a vaccine cost of US \$75, the screening with hybrid capture in isolation would no longer be inferior to vaccination in isolation (with an ICER of US \$500 for each year of life saved). If the vaccine cost more than US \$75, the combination of

vaccination and screening is superior; the ICER for the addition of the vaccine to the screening strategy with hybrid capture varies from US \$1,100 to US \$9,600 for each year of life saved, depending on the cost of the vaccine (Table 4).

Colantonio et al. performed a similar cost-utility study about adding the HPV vaccine to the CC screening programs in 5 Latin American countries: Brazil, Argentina, Peru, Mexico and Chile [20]. Markov models were developed to simulate the natural history of HPV until the genesis of CC for each country. The model assumed that society was the payer, adopted a discount rate of 3% per year for the clinical and economic outcomes and simulated a cohort in which pre-adolescent girls older than 11 either were or were not vaccinated. The study compared the clinical and economic outcomes of adding vaccination to the base strategy (screening) versus the base strategy in isolation.

Considering the current situation in each country, adding the vaccine would substantially reduce the risk of CC over a lifetime compared with the screening strategy alone (Table 3). For Brazil, the cost for each vaccinated women was estimated at US \$210. Vaccination would reduce the incidence of high degree intraepithelial lesions in Brazil by 62.8%, CC by 62.7% and mortality from CC by 62% in relation to the screening strategy in isolation. These figures imply that 643 cases of CC and 309 deaths from CC would be avoided and 29,460 QALYs would be gained for every 100,000 women vaccinated.

According to Colantonio, from an economic point of view, the mass vaccination of Brazilian girls would increase the annual cost of the preventative program from US \$85 million (current strategy) to US \$385 million (an increase of 251%). The cost-utility analysis showed that vaccination would imply an investment of approximately US \$10,000/QALY saved.

Kawai et al. evaluated the cost-effectiveness of introducing the quadrivalent vaccine for preventing CC and genital sores in Brazil [21]. The model simulated a hypothetical cohort over 100 years using Brazilian data about the natural history of infection with HPV and carcinogenesis. Using a dynamic model of transmission, the strategies were the following: 1) routine vaccination of 12-year-old girls; and 2) routine vaccination of 12-year-old girls and catch-up vaccination of 12 to 26-year-old women.

Assuming 85% coverage of the target public and that the cost of vaccination (3 doses) would be US\$45.45, and considering the perennial protection of the vaccine, the authors concluded that the ICER for routine vaccination compared to non-vaccination was US \$219/QALY. The strategy of combined vaccination (routine and catch-up) increased the ICER to US \$450/QALY.

Kawai et al. estimated that routine vaccination of 12-year-old girls would decrease the incidence of CC attributable to HPV 16/18 by 59% to 71% in year 50 and 97% to 99% in year 100 of the hypothetical cohort

Strategies	Incremental cost-effectiveness ratio (US\$/years of life saved)					
	US\$25	US\$50	US\$75	US\$100	US\$450	Risk reduction (%)
Cost of vaccination						
<b>Pap test (3x)</b>	inferior	inferior	inferior	inferior	inferior	21.9
<b>HPV-DNA test (3x)</b>	inferior	inferior	500	500	500	30.7
<b>Vaccine</b>	superior	300	inferior	inferior	inferior	42.7
<b>Vaccine + Pap test (3x)</b>	200	inferior	inferior	inferior	inferior	55.6
<b>Vaccine + HPV test (3x)</b>	700	1,000	1,100	1,700	9,600	60.8

Inferior: more costly and less effective than the alternative strategy; Superior: more effective and less costly than the alternative strategy; Pap 3x: Papanicolaou test performed at 35, 40 and 45 years; HPV-DNA: hybrid capture test performed at 35, 40 and 45 years; Vaccine: vaccination of pre-adolescent girls between 9 and 12 years old

**Table 4:** Cost-effectiveness of preventative methods and combinations for Brazil, strategies estimated for 70% of the population [16].

[21]. In addition, the incidence of genital sores would be reduced by 98%. An estimated 278,283 deaths from CC would be prevented by year 100.

To better understand the clinical and economic implications of mass vaccination against HPV in Brazil, attention should be paid to the cost-effectiveness profile of the vaccine in countries with social and economic characteristics that are different than those available in the literature. One study that evaluated the cost-effectiveness of the HPV vaccine for 72 underdeveloped countries with low or extremely low income showed interesting results [22]. The majority of the countries analyzed were African countries characterized by an elevated incidence of CC (>40 cases per 100,000 women/year). The ACE, which was based on epidemiological data for each country, showed that the ICER for the addition of the vaccine did not exceed US \$200/QALY for 59 of the 72 countries, although there was a large reduction in the mortality and incidence of CC. The study emphasized that the cost-effectiveness profile of the vaccine is extremely favorable in regions where CC is not controlled by conventional screening programs.

On the other hand, in developed countries that have been able to control CC incidence and mortality with solid programs of gynecological screening, the HPV vaccine is not as favorable from a cost-effectiveness point of view. Ireland, Switzerland, the United Kingdom and Finland have gross CC incidence rates of less than 10 cases per 100,000 women per year [23-26]. In these countries, cost-effectiveness studies demonstrated an additional cost of more than US\$20 thousand to save one QALY. In the United States, the ICER for adding the vaccine exceeded US\$43,000/QALY [27]. The case of the Netherlands is worth noting. With an annual incidence rate of CC less than 6 cases per 100,000 women, the ICER for adding the HPV vaccine to the Dutch preventative program was greater than US\$70,000/QALY, making the vaccine cost-ineffective, according to the authors [28].

The studies of cost-effectiveness are based on simplified representations of reality. As such, they must be interpreted in a conservative manner. However, the current evidence consistently classifies the HPV vaccine as cost-effective and beneficial for Brazil. Vaccination has the potential to create opportunities for prevention in regions and areas of the country where traditional preventative programs have failed to control CC incidence and mortality. It is important to note that vaccination does not replace population screening but rather complements it.

Being aware of gender differences, Kim et al. evaluated the cost-utility of a vaccination strategy including boys and girls versus only girls for preventing CC in Brazil [29]. The rationale for this proposition is based on the fact that HPV is sexually transmitted and immunization of boys/men would reduce the risk of infection in vaccinated women. A dynamic model was created to simulate the natural history of HPV infection in both sexes. The model assumed that both sexes would be vaccinated prior to their first sexual intercourse.

The results were compared to the base screening strategy using the Papanicolaou test. The cost of vaccination varied from US \$25 to US \$400. The timeframe of the cohort was the lifetime of the cohort members, and the authors estimated that the vaccine produced long-term immunity. If girls were vaccinated exclusively, the model estimated a 63% reduction in CC risk over a lifetime given 90% vaccine coverage of the target population. If boys were added to the model with the same vaccine coverage rate, an additional 4% reduction in risk was estimated (67% reduction in the risk of CC over the course of a lifetime).

The model also simulated the results assuming lower vaccine coverage. With 50% coverage, including boys in the vaccination strategy would increase the reduction in the risk of CC from 29% to 40% (Table 5).

The economic analysis shows that for the lower cost of vaccination, the vaccination strategy is superior to the non-vaccination strategy (exclusively for the female sex). In other words, the cost of secondary prevention and treatment of CC would be greater than the cost of vaccinating the girls. Vaccination was not superior when boys were included in the strategy. If the cost of vaccination is higher than US \$50, the vaccination strategy is no longer superior, and the ICER varies according to vaccine coverage. For example, assuming the cost of vaccination is US \$100, the ICER for the vaccination strategy for girls only varied from US \$610 to US \$810 for each year of life saved, while the inclusion of boys increased the ICER to US \$2,190 to US \$37,720 for each year of life saved (exceeding the conventional limit for considering a strategy cost-effective).

Vaccinating Brazilian boys against HPV produced a small additional gain in the clinical benefit (an approximately 4% reduction in risk); however, the cost also increased, making the strategy cost-ineffective. The model suggests that efforts should focus on expanding vaccine coverage for girls only.

The HPV vaccine can also be effective in preventing masculine cancers (such as those of the penis and anus) and other female cancers (such as those of the vagina and vulva) in addition to benign diseases such as genital warts and youth laryngeal papillomatosis. It must be noted that the study by Kim et al. did not take into consideration the clinical benefits of vaccination for men (i.e., related to cancers of the penis and anal canal) in its analyses [29]. Depending on the incidence of these diseases, the cost-effectiveness of vaccination could increase with an additional reduction of the ICER from 18% to 31% compared to the effects on CC alone [30].

Currently, the greatest impediment to administering the HPV vaccine is its high cost. The technology involved in the vaccine requires a large investment; it is the most expensive vaccine proposed for mass use. The cost is estimated between US \$300 and US \$400 for three doses [31]. Based on the lessons learned with the Hepatitis B vaccine, which is available today for children in 89% of the countries in the world, including the poorest countries, mass vaccination on a global scale may only be possible after a drastic reduction in the price of the vaccine [32].

Strategy	Reduction in the risk of CC (%) <sup>b</sup>	Cost per individual vaccinated			
		US\$ 25	US\$ 50	US\$ 100	US\$ 400
Coverage					
Girls only	14	Superior <sup>c</sup>	30	610	3450
Both sexes	21	110	810	2,190	9,370
Coverage					
Girls only	29	Superior <sup>c</sup>	70	540	3210
Both sexes	40	660	1,740	3,900	15,120
Coverage					
Girls only	45	Superior <sup>c</sup>	130	740	3,940
Both sexes	57	2,440	2,180	4,860	18,820
Coverage					
Girls only	63	Superior <sup>c</sup>	170	810	4,180
Both sexes	67	9,110	18,650	37,720	136,910

<sup>a</sup>Values represent the additional cost divided by the clinical benefit in terms of years of life saved, compared to the base strategy of not vaccinating (US\$/QALY)

<sup>b</sup>Percent reduction in the risk of CC over a lifetime

<sup>c</sup>Superior means that the vaccine strategy is more efficient and less costly than the alternative

**Table 5:** Clinical benefit and incremental cost-effectiveness ratio for vaccine coverage and for vaccination cost<sup>a</sup> [27].

## Conclusion

Every secondary data analysis has the potential to publish biases related to individual limitations of the selected studies, and therefore, the conclusions should be interpreted cautiously. However, regardless of the types of mathematical model and data sources used, all studies pointed to the similar conclusions, suggesting that they are robust and reliable. Fact is that CC continues to be a serious public health problem in Brazil that claims the lives of young women at a productive age. Ignoring the new preventative technologies for CC can lead to misguided and perverse consequences in countries where programs based on the Papanicolaou technique have only been partially successful. The evidence available in the literature consistently affirms that new preventative technologies for CC, especially the HPV vaccine, are cost-effective for Brazil, leaving the decision about bearing the costs of these new technologies to healthcare managers.

## Authors' contributions

AJF participated in the study design, literature review and writing of the manuscript.

CNR contributed with literature review and writing of the manuscript.

RLGG participated in the literature review and writing of the manuscript.

LCLF participated in the review and critical analysis of the manuscript.

GBN contributed with the study design, literature review and writing of the manuscript.

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