

Systematic review of the cost-effectiveness of the vaccination against HPV in Brazil

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Abbreviations: HPV, human papillomavirus; CC, cervical cancer; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; ASC-US, atypical squamous cell of unknown significance

In Brazil, almost 16,000 new cases of cervical cancer (CC), the type of neoplasia that claims the more lives of young women than any other, are expected in 2014. Although the vaccine against HPV has been developed, the application of this strategies to large populations is costly, and its use in Brazil is limited. Studies of the economic implications of new preventive technologies for CC may support rational and evidence-based decisions in public health. A systematic search of articles published between 2000 and 2014 was conducted using MEDLINE, EMBASE, the Cochrane Collaboration of Systematic Reviews, and LILACS. The aim of this search was the identification of original articles that evaluated the cost-effectiveness of vaccination against HPV in Brazil. A total of 6 articles are included in this review, evaluating the addition of a vaccine against HPV in comparison to population screening. Although the vaccine against HPV increases the cost of preventing cervical cancer, this new preventive technology presents favorable cost-effectiveness profiles in the case of Brazil. Failure to utilize the newly available preventative technologies against CC can lead to misguided and perverse consequences in a country in which programs based on the Papanicolaou test have been only partially successful.

Background

The global reduction in the incidence of and mortality associated with cervical cancer (CC) that has occurred over the last 4 decades has not occurred in a homogeneous way but, rather, has been concentrated in developed countries that have been able to implement solid and effective population screening programs.¹ In Brazil, approximately 15,500 new cases of CC are expected in 2014 (15.3 cases/100,000 population).² Excluding non-melanoma skin cancer, CC is the second most common type of

neoplasia in women, and it is the type of neoplasia that claims the most lives of women 15 to 44 y of age.³ Currently, the Brazilian program to control CC is based on population screening using the Pap test for women between 25 to 64 y old; this test is provided annually (or once every 3 y after 2 normal tests) and is followed by colposcopy for HSIL, carcinoma, or persistent LSIL or ASC-US.²

Multiple factors may explain the partial success that has been achieved in controlling CC in Brazil. Organizational and financial difficulties may have compromised the quality of prevention programs. In addition, evidence suggests a low capacity of the laboratory network of the Unified Health System in Brazil for identifying intraepithelial lesions,⁴ a lack of specialized human resources,⁵ failure in the following of positive cases,⁶ and irregular screening coverage.⁷ The estimated cost of the current Brazilian strategy for controlling CC is US\$250 million per year, and the coverage varies among Brazilian regions (85% in the Southeast region, which is the most developed region, and 70% in the Amazonian region, the least developed region).^{2,3} These problems, in addition to the inherent limitations of the Pap test, have led many researchers in Brazil to evaluate alternative or supplementary techniques such as the hybrid capture test (HPV-DNA test) and the currently available vaccine against the most carcinogenic genotypes of HPV. Although the vaccination offers better performance and/or effectiveness than secondary prevention strategies alone, it will result in higher costs when incorporated into Brazil's prevention program for CC. While some authors support the inclusion of mass vaccination in Brazilian scenario, others have suggested that the benefits of cervical cytology should be fully utilized before pursuing a new strategy.⁸

Due to the universal recent increase in healthcare costs and the growing constraints imposed by a scarcity of resources, there is a great need to justify the use of a new technique by considering its cost-effectiveness ratio.⁹ In making such a consideration, economic analysis tools may be used to support decision-making in public health and to target the rational use of available resources.¹⁰ Among the available methods of economic evaluation, cost-effectiveness analyses have been widely used to evaluate new technologies and to compare healthcare strategies around the world. When used to compare 2 strategies, the cost-effectiveness analysis model provides the incremental cost-effectiveness ratio (ICER) as the primary outcome.¹¹ This ratio shows the

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additional cost required to save 1 y of life (adjusted or not by quality of life) using a new strategy compared to a baseline strategy. The World Health Organization suggests that a strategy should be considered cost-effective if the ICER is less than 1 to 3 times the *per capita* GDP of the low- or middle- income country for which the strategy is considered (in Brazil, *per capita* GDP was approximately US\$10,000 in 2013).

The objective of this article is to systematically review studies that have used cost-effectiveness analyses to evaluate the clinical and economic implications of the vaccination against HPV in the Brazilian setting compared to the current strategy.

Methods

Search strategy

A systematic search of articles published between 2000 and 2014 was conducted using MEDLINE (Ovid system), EMBASE, the Cochrane Collaboration of Systematic Reviews, and LILACS. The search aimed to identify original articles that had been published in indexed periodicals and that evaluated the cost-effectiveness of vaccination against HPV in Brazil. The terms used for this review search were combinations of (“human papillomavirus” OR “HPV”) AND (“vaccine” OR “vaccination”) AND “prevention” AND (“cost-effectiveness” OR “cost-utility”) AND (“economic evaluation” OR “economic models”) AND “pharmacoeconomics” AND (“Brazilian” OR “Brazil”).

Inclusion criteria

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

According to the recommendations of Jit et al.¹¹ and Barnabas et al.¹² for evaluating the cost-effectiveness of preventive strategies for CC, the following criteria were used to evaluate the quality of the articles: (1) the use of a Markov mathematical model or a transition dynamic model; (2) a clear point of view (the payer); (3) a complete and clear economic comparison between at least 2 strategies; (4) calibration of base case parameters according to Brazilian epidemiological data; (5) the use of a baseline comparison scenario based in cervicovaginal cytology screening; (6) appropriate measurement of clinical and economic outcomes; and (7) analysis of the uncertainty of the variables (e.g., a sensitivity analysis).

Extracted information

The following information was extracted from each article: model type, timeframe of the analysis, perspective, baseline scenario, estimated coverage of the preventative strategy, need for revaccination, age at which vaccination begins, efficacy of the strategy, costs, reduction in mortality attributable to CC, and reduction in the incidence of CC. The principal measures extracted from each article were the ICER of the strategy used and the quality-adjusted life years (QALYs) gained by the strategy.

Results

The literature search identified 6 original articles boarding cost-effectiveness of HPV vaccination in Brazilian scenario. All of them met the study criteria and were included in the systematic review. Data from the selected articles are presented in **Table 1**.

Cost-effectiveness of vaccination strategy against HPV in Brazil

Goldie et al., 2007

Goldie et al.¹³ developed a dynamic model to simulate the natural history of HPV infection, using Brazilian epidemiological data for morbidity and mortality from CC. This model assumed that pre-adolescent girls would be or not vaccinated. The baseline screening strategy was fold2-: (1) screening women over 30 y old by means of the HPV-DNA test; and (2) administering cervical cytology 3 times over each woman’s lifespan. Each screening strategy was modeled alone and in combination with the vaccination strategy (vaccination was assumed to take place occur prior to first sexual intercourse, between 9 and 12 y of age). The model assumed an annual discount rate of 3%. A societal perspective was taken, and the costs to both providers and patients were included. Because the price of the vaccine for mass vaccination in Brazil had not been established, the authors varied the price of the vaccination between I\$25 and I\$450 (international dollars) in their analyses.

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

At I\$25 for each vaccinated woman, the vaccine strategy alone would be more effective and less costly than the proposed screening strategies and is therefore considered superior. If applied concomitantly with population screening, vaccination would be associated with an ICER of I\$200 to I\$700 for each year of life saved depending on the baseline screening strategy employed. For a vaccine cost of I\$50, the ICER would reach I\$1,000 for each year of life saved. For a vaccine cost of I\$75, screening with hybrid capture alone would no longer be inferior to vaccination alone (with an ICER of I\$500 for each year of life saved). If the vaccine cost exceeded I\$75, the combination of vaccination and screening would be superior; the ICER for the addition of the vaccine to the screening strategy with hybrid capture varied from I\$1,100 to I\$9,600 for each year of life saved depending on the cost of the vaccine (**Table 2**).

Colantonio et al., 2009

Colantonio et al.¹⁴ performed a similar cost-effectiveness study of the effects of adding the HPV vaccine to the CC screening programs in 5 Latin American countries: Brazil, Argentina, Peru, Mexico, and Chile. Markov models were

Table 1. Summary of 6 articles selected for the systematic review of cost-effectiveness of vaccination against HPV in Brazil

Study (author, year)	Source (database)	Modeling method	Main strategy tested	Baseline strategy	Clinical outcome	Economic outcome	Currency and base year	Perspective of the paying source	Main result [£]
Goldie et al. (2007)	MEDLINE	Transmission dynamic model	Mass vaccination of pre-adolescents girls against HPV	Population screening with cervical cytology	Years of life saved	\$/years of life saved	2006 I\$	Brazilian Unified Health System	\$ 1,100/year of life saved
Kim et al. (2007)	MEDLINE	Transmission dynamic model	Mass vaccination of pre-adolescent boys and girls against HPV	Mass vaccination of only pre-adolescent girls against HPV	Years of life saved	\$/years of life saved	2007 I\$	Brazilian Unified Health System	\$ 37,720/year of life saved
Colantonio et al. (2009)	MEDLINE	Markov model	Mass vaccination of pre-adolescent girls against HPV	Population screening with cervical cytology	QALY	\$/QALY	2008 US\$	Brazilian Unified Health System	\$ 10,181/QALY
Kawai et al. (2012)	MEDLINE	Transmission dynamic model	Mass quadrivalent vaccination of pre-adolescent girls against HPV	Population screening with cervical cytology	QALY	\$/QALY	2012 US\$	Brazilian Unified Health System	\$ 450/QALY
Vanni et al. (2012)	MEDLINE	Transmission dynamic model	Mass vaccination of pre-adolescents girls against HPV	Population screening with cervical cytology	QALY	\$/QALY	2012 US\$	Brazilian Unified Health System	\$ 5,590/QALY
Fonseca et al. (2013)	MEDLINE	Markov model	Mass vaccination of pre-adolescents girls against HPV in Brazilian Amazonian region	Population screening with cervical cytology	QALY	\$/QALY	2012 US\$	Brazilian Unified Health System	\$ 825/QALY

[£]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: I\$: international dollar; US\$: United States dollar; QALY: quality-adjusted life years; ASC-US: atypical squamous cells of unknown significance.

developed to simulate the natural history of HPV until the genesis of CC for each country. The model assumed a societal perspective, 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 baseline strategy (screening) versus the baseline strategy alone.

Table 2. Cost-effectiveness of preventive methods and combinations for Brazil. Strategies estimated for 70% of the population. Study of Goldie et al.¹³

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

Legend: Inferior: more costly and less effective than the alternative strategy; Superior: more effective and less costly than the alternative strategy; Pap 3×: 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 y of age.

Source: Goldie et al.¹³

Considering the current situation in each country, adding the vaccine would substantially reduce the risk of CC over a woman's lifetime compared with use of the screening strategy alone. 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%, that of CC by 62.7%, and the incidence of mortality from CC by 62.0% relative to the baseline strategy. These figures imply that 643 cases of CC and 309 deaths from CC would be avoided for every 100,000 women vaccinated. Considering the whole cohort of the study, 29,460 QALYs would be gained.

According to Colantonio, mass vaccination of Brazilian girls against HPV would increase the annual cost of the preventative program from US\$85 million (current strategy) to US\$385 million (an increase of 251%) in this model. The cost-effectiveness analysis conducted by these authors indicated that vaccination would entail an investment of approximately US\$10,000/QALY saved at a price of US\$210 and considering coverage of 70% of the targeted population. Based on these findings, vaccination was considered marginally cost-effective.

Kawai et al., 2012

Kawai et al.¹⁵ evaluated the cost-effectiveness of introducing the quadrivalent vaccine for prevention of CC and genital warts in Brazil. Using a dynamic model of transmission, the population was divided into sex and also into 23 age groups to simulate demographic characteristics of the population. Boys and girls were included in this model, which simulated heterosexual transmission of HPV-types 6/11/16/18 and progression to cervical intraepithelial neoplasia (CIN) grades 1, 2, and 3, cervical cancer, and genital warts. Although the model has considered only the vaccination of girls, the clinical outcome of reduction of genital warts was measured for both men and women. Individuals died at sex- and age-specific rates within each group, and individuals were born into the youngest age group at a rate that balanced mortality. The strategies considered were (1) no vaccination; (2) routine vaccination of 12-year-old girls; and (3) 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, a cost of vaccination (3 doses) of US\$45.45 and conferral of long-term protection by 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 but was still considered highly cost-effective by these authors.

Kawai et al.¹⁵ 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 by 97% to 99% in year 100 of the hypothetical cohort. In addition, the incidence of genital warts would be reduced by 94% (both genders). An estimated 278,283 deaths from CC would be prevented by year 100.

Kim et al., 2007

Kim et al.¹⁶ assessed the value of including boys in the vaccination program. The model evaluated the cost-effectiveness of a

vaccination strategy including boys and girls vs. that of a vaccination strategy including only girls for the prevention of CC in Brazil. A dynamic model was created to simulate the natural history of HPV infection in both genders, and it was assumed that both genders would be vaccinated prior to their first sexual intercourse. The rationale for this strategy is based on the fact that HPV is sexually transmitted and that immunization of boys/men would reduce the risk of infection in non-vaccinated women. Unlike the Kawai's study, Kim et al. considered vaccination against HPV 16 and 18 only. Therefore, no clinical outcomes of prevention of genital warts (in men or women) were estimated. In this model, the clinical outcomes were exclusively related to cervical cancer. Therefore, despite been vaccinated, males had no clinical benefits considered in this analysis.

The results were compared to those of a screening strategy involving the Pap test. The cost of vaccination varied from I\$25 to I\$400, each individual. Coverage rates were varied from 0 to 90% in girls and boys independently. The time frame of the cohort was an individual's lifetime, and it was assumed 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 results assuming lower vaccine coverage. With 50% coverage, including boys in the vaccination strategy would increase the reduction in risk of CC from 29% to 40% (Table 3).

The economic analysis conducted in this study shows that for the lower cost of vaccination, the vaccination strategy dominates the non-vaccination strategy when only females are vaccinated. In other words, the cost of secondary prevention and treatment of CC would be greater than the cost of vaccinating girls. However, vaccination did not dominate the baseline strategy when boys were included. Assuming that the cost of vaccination is I\$100 and that the coverage is 90%, the ICER for the vaccination strategy for girls only varied from I\$610 to I\$810 for each year of life saved, while the inclusion of boys increased the ICER to I\$2,190 to I\$37,720 for each year of life saved. The latter values exceed the conventional limits for considering a strategy cost-effective. Vaccinating Brazilian boys against HPV produced a small additional gain in the clinical benefit but a high increase in cost, making the strategy cost-ineffective. The authors suggest that efforts should focus on expanding vaccine coverage for girls only.

Vanni et al., 2012

A dynamic transmission model calibrated with Brazilian epidemiological and demographic data (annual discount rate of 5%) was used by Vanni et al.¹⁷ to assess the cost-effectiveness of the quadrivalent vaccine for Brazilian preteen girls. The analyses performed in this study considered 12 scenarios, combining coverages (50%, 70% and 90%) and costs per vaccinated girl (US\$25, US\$55, US\$125, and US\$556). The results for each scenario ranged from cost-saving (coverage 50% or 70% and cost per

Table 3. Clinical benefits and incremental cost-effectiveness ratios for vaccine coverage and vaccination costa. Study of Kim et al.¹⁶

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

^aValues 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).

^bPer cent reduction in the risk of CC over a lifetime

^cSuperior means that the vaccine strategy is more efficient and less costly than the alternative.

Source: Kim et al.¹⁶

vaccinated woman US\$25) to cost-effective (ICER of US\$5,950/QALY, considering a coverage of 90% and cost per vaccinated, US\$556). In a scenario in which a booster shot was needed after 10 y to secure lifelong protection, the ICER resulted in US\$13,576/QALY. Sensitivity analyses suggested that cost per dose of the vaccine had the most important impact on the results, reinforcing the importance of price negotiation between governments and manufactures as an crucial issue. Vaccination was considered very cost-effective even if a booster shot were necessary.

Fonseca et al. 2013

Considering the heterogeneity of a large country such as Brazil, Fonseca et al.¹⁸ performed a cost-effectiveness analysis of the vaccine for the least developed region, the Brazilian Amazon region; this region has the highest incidence of CC in the country. A Markov model was developed and calibrated with regional clinical and epidemiological data to simulate the natural evolution of HPV. A low adherence of screening was considered in the baseline case

(3 cervical cytology tests throughout life) in accordance with the clinical reality in the Amazonian region. According to the model, addition of HPV vaccination would reduce the incidence of cervical cancer in this region by 35% given 70% vaccination coverage. The incremental cost-effectiveness ratio was US\$825/QALY saved at a vaccination cost of US\$150 (Table 4). The sensitivity analysis confirmed the baseline case outcomes; the duration of immunity was the parameter with the greatest variation in ICER. Even comparing the vaccination strategy with a better and more frequente baseline strategy (10 cervical cytology tests throughout life), use of the vaccine in this Brazilian region would be very cost-effective (US\$1,275/QALY), according to the authors.

Discussion

Despite the differences in the studies presented here, they provide evidence that vaccination of pre-adolescents girls is a cost-

Table 4. Health and economic outcomes for the addition of vaccination to the 3 scenarios of screening strategy (Pap test) in Brazilian Amazonian region. Study of Fonseca, 2013. [¹⁸]

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 history)	295	24.6			
Scenario of 3 screenings throughout the lifetime (base case)					
Vaccination + screening	320	29.6	165	0.2	825
Only screening	155	29.4			
Scenario of 10 screenings throughout the lifetime					
Vaccination + screening	448	34.5	255	0.2	1,275
Only screening	193	34.3			

ICER: incremental cost-effectiveness ratio.

^aDominant means more costly and less effective than the baseline strategy.

effective strategy for controlling CC in Brazil, considering the upper threshold recommended by WHO (for Brazil: US\$10,000/QALY to US\$30,000/QALY). The study by Goldie et al.¹³ deserves special attention in this review. The authors developed a dynamic transmission model, what minimized major limitations inherent to static models (that assume a constant risk of transition between health states, ignoring the multiplicity of factors that influence the health-disease process). The excellent model calibration according to Brazilian epidemiological data, the baseline strategy aligned with the Brazilian reality, and the wide analysis of sensitivity generated the most reliable and robust results of this review.

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 this vaccine in countries with different social and economic characteristics. One study that evaluated the cost-effectiveness of the HPV vaccine for 72 underdeveloped countries with low or extremely low incomes produced interesting results.¹⁹ The majority of the countries analyzed were African countries that were characterized by an elevated incidence of CC (>40 cases per 100,000 women/year). Cost-effectiveness analyses based on epidemiological data for each of these countries showed that the ICER for the addition of the vaccine did not exceed US\$200/QALY for 59 of the 72 countries and that use of the vaccine was associated with 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 in which 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 preventive programs, the HPV vaccine is not as favorable from a cost-effectiveness point of view. Ireland,²⁰ Switzerland,²¹ the United Kingdom,²² and Finland²³ have gross CC incidence rates of less than 10 cases per 100,000 women/year. In these countries, cost-effectiveness studies demonstrated an additional cost of more than US\$20,000/QALY. In the United States, the ICER for adding the vaccine exceeded US\$43,000/QALY.²⁴ The case of the Netherlands is worth noting. With an annual incidence rate of less than 6 cases of CC 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.²⁵

The cost-effectiveness analyses discussed in this work are based on simplified representations of reality. As such, they must be interpreted in a conservative manner. However, all of the studies reviewed here consistently classify the HPV vaccine as cost-effective or highly cost-effective and beneficial for Brazil. HPV vaccination has the potential to create opportunities for prevention in regions and areas of the country in which 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 and that the duration of immunity (the need for booster doses) was the variable that most influenced the cost-effectiveness profile of vaccination in most studies.

The HPV vaccine can also be effective in preventing masculine cancers such as penile and anal cancers and in preventing female cancers of the vagina and vulva in addition to benign diseases such as genital warts and juvenile laryngeal papillomatosis. It must be noted that the studies discussed in this review did not take into consideration these extra benefits in their analyses. Evidence demonstrates that, 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.²⁶

An important point to be considered is the vaccine delivery and its acceptance. Brazil has an Unified Health System that covers all cities and villages, and offers free immunization program to the population. Historically, infant vaccination programs in Brazil has achieved (and often surpassed) its goals, even in the less developed regions (such as Amazonian Region). The cost of vaccine delivery was estimated by most authors, taking into account the pre-existing facilities and infrastructure for mass vaccination in Brazilian scenario. Goldie et al.¹³ have estimated freight and supplies costs of \$1.31, administration of \$1.50, and vaccine support and programmatic costs of \$4.94. Fonseca et al.¹⁸ have estimated the vaccine delivery costs of \$5.00. However, special attention should be given to the fact that the target age of the HPV vaccine is out of the usual range of Brazilian Immunization Program, and its acceptance and perception among parents has never been reported in Brazil. Therefore studies that have assumed a vaccination coverage of 90% or more, should be interpreted cautiously.

Currently, the discussion about administering the HPV vaccine in Brazil are related to its high cost. The vaccine, which is the most expensive vaccine that has ever been proposed for mass use, requires a large investment. Based on the lessons learned from use of the Hepatitis B vaccine, which today is available to children in 89% of the countries in the world, including the poorest countries, mass vaccination on a global scale will only be possible with a drastic reduction in the price of the vaccine.²⁷

This systematic review has limitations and strengths. The studies were conducted in different years, and variations in costs and prices of preventive and diagnostic strategies used to calibrate the models can influence the results, as well as variations in the values of GDP per capita may influence the interpretation of these results. However, the economic stability observed in Brazil in this interval of time does not invalidate the correspondence between the analyzed studies. Besides, all the authors used the same payer perspective (Brazilian Unified Health System). Some studies have evaluated the vaccination of different populations. However, even studies whose focus was the inclusion of boys in the vaccination program also presented a comparative arm based on the vaccinating of girls only, facilitating comparisons. There was no significant discrepancy of targeted age groups among the studies. Moreover, the strong concordance between the results of different studies using such different methods lends more credibility than doubts to the findings of this review.

Conclusions

CC continues to be a serious public health problem in Brazil; as such, it claims the lives of young women at a productive age. Ignoring the new technologies for prevention of CC can lead to misguided and perverse consequences in countries in which programs based on cervical cytology alone have only been partially successful. The evidence available in the literature consistently affirms that the HPV vaccination of girls is cost-effective for Brazil; therefore, decisions

concerning bearing the costs of this new technology are left to healthcare managers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

AJ participated in the study design, literature review and writing of the manuscript. LCLF participated in the literature review and in critical analysis of the manuscript.

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