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Economic modelling assessment of the HPV quadrivalent vaccine in Brazil: A dynamic individual-based approach

Tazio Vanni[a,*], Paula Mendes Luz[b], Anna Foss[a], Marco Mesa-Frias[a], Rosa Legood[a]

[a] Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom
[b] Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

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ABSTRACT

We examined the cost-effectiveness of the quadrivalent HPV vaccine for the pre-adolescent female population of Brazil. Using demographic, epidemiological and cancer data, we developed a dynamic individual-based model representing the natural history of HPV/cervical cancer as well as the impact of screening and vaccination programmes. Assuming the current screening strategies, we calculated the incremental cost-effectiveness ratio (ICER) for cohorts with and without vaccination taking into account different combinations of vaccination coverage (50%, 70%, 90%) and cost per vaccinated woman (US$25, US$55, US$125, US$556). The results varied from cost-saving (coverage 50% or 70% and cost per vaccinated woman US$25) to 5950 US$/QALY (coverage 90% and cost per vaccinated 556 US$). In a scenario in which a booster shot was needed after 10 years in order to secure lifelong protection, the ICER resulted in 13,576 US$/QALY. Considering the very cost-effective and cost-effective thresholds based on Brazil's GDP per capita, apart from the booster scenario which would be deemed cost-effective, all the other scenarios would be deemed very cost-effective. Both the cost per dose of vaccine and discount rate (5%) had an important impact on the results. Vaccination in addition to the current screening programme is likely to save years of life and, depending on the cost of vaccination, may even save resources. Price negotiations between governments and manufacturers will be paramount in determining that the vaccine not only represents good value for money, but is also affordable in middle-income countries like Brazil.

1. Introduction

Cervical cancer is the second most common cause of cancer among women in developing countries [1]. This neoplasm has an especially profound societal impact because it primarily affects women in their 30s to their 50s, a time when they are likely to be raising and supporting families. In the Latin American region, despite the investments in cytology-based screening, the impact in reducing cervical cancer incidence rate has been less than expected [2]. In 2012, a total of 17,540 new cases of cervical cancer are expected in Brazil [2].

Human papillomavirus (HPV) types 16 and 18 are associated with 70% of cervical cancers [3], while types 6 and 11 are associated with 90% of anogenital warts [4]. There are two vaccines currently available that prevent infections by types 16 and 18 [5], and one of them also prevents infections by types 6 and 11 [6]. Clinical trials have shown that these vaccines present excellent immunogenicity and reactogenicity profiles [5,6]. Although having great potential to help reduce cervical cancer incidence in a country like Brazil, neither vaccine has been introduced in the publicly funded national immunization programme.

Determining the most advantageous HPV vaccination and cervical cancer screening strategy for Brazil requires a long-term analysis of costs and health outcomes of vaccination and screening strategies. Mathematical models offer the opportunity to synthesize the best available data and project the impact of the vaccine in order to evaluate its cost-effectiveness over a period of time beyond those used in clinical trials. Dynamic individual-based models allow for more realistic representation of the disease as well as a broader analysis of the benefits of the vaccine. The bivalent vaccine has been previously evaluated for Brazil using a dynamic individual-based model [7], however, the quadrivalent vaccine has not yet been evaluated.

To assess the cost-effectiveness of the quadrivalent HPV vaccine for the pre-adolescent female population of Brazil, we developed a dynamic individual-based model that simulates the natural history of the HPV infection. This analysis is an addition to the previous studies [7,8], as it is a fully integrated individual-based dynamic

* Corresponding author at: Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, 15-17 Tavistock Place, London WC1H 9SH, UK. Tel.: +44 02079272366; fax: +44 02079272701.
E-mail addresses: taziovanni@gmail.com, tazio.vanni@lshtm.ac.uk (T. Vanni).

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model that not only includes the HPV types 16 and 18, but also types 6 and 11, allowing a thorough evaluation of the quadrivalent vaccine.

2. Materials and methods

2.1. HPV/cervical cancer model

We first developed an open dynamic individual-based model representing the HPV transmission and cervical cancer natural history in the heterosexual population of Brazil. The main reason for using of a dynamic model was to capture the herd immunity effect of the vaccine, as it may have an important impact on the cost-effectiveness results [9]. The individual-based model was chosen because, when compared to compartmental models, it is more appropriate to model non-mutually exclusive events and keep track of previous health states as well as screening results.

The model was built in C++ and ran in a computer cluster using OpenMPI. The discrete-time model developed has a cycle length of 1 month. Two important steps occur within each cycle. In the first step, behaviour and biological events occur. In the second step, vaccination, screening and treatment events occur. The analysis of the impact of vaccination and screening only happens once the model has achieved endemic equilibrium. There is considerable uncertainty regarding the level of natural immunity conferred by different HPV-types, as well as the duration of immunity [10–14]. As a reflection of this limited scientific understanding, the model structures adopted in previous modelling studies have varied from susceptible-infected-susceptible [15–17] to susceptible-infected-recovered [18–21]. Following from previous analysis [16,17,22,23], we used a susceptible-infected-susceptible model. The gender, age and sexual behaviour of each individual determine the probability of acquiring different HPV types, in other words the force of infection. More details on how the force of infection was calculated can be found in Appendix.

2.2. Socio-demographic characteristics

The model represents a stable population of 200,000 individuals, which according to Brazil's demographic data are 49.5% men and 50.5% women. Individuals were subjected to age- and gender-specific mortality rates derived from the Brazilian Institute of Geography and Statistics (IBGE) [24]. Individuals younger than 10 years old were not included in the model because they have a negligible prevalence of sexually acquired HPV infection.

2.3. Sexual behaviour

Sexual behaviour was modelled using a structure similar to that previously developed for HIV transmission [25,26] and later applied to HPV transmission [7,20,27]. Briefly, the model population was stratified into four levels of sexual activity according to the rate of sexual partners change and 14 age groups. The number of sexual partners in each sexual activity and age group was determined by a sexual mixing matrix. The parameters of the matrix were governed by two parameters representing the assortiveness of mixing by age and sexual activity groups. Individuals were assumed to be sexually active from age 15 to age 50, as in previous studies [7,20,27].

The force of infection for each age and sexual activity was determined by the distribution of sexual partners for that age and sexual activity group, the number of HPV infected individuals of the opposite sex in those groups and the HPV type-specific transmission probability per partnership.

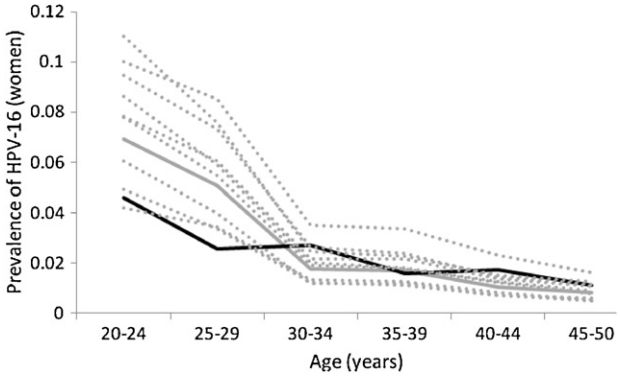

Fig. 1. Prevalence of HPV 16 (women). Full dark lines are the calibration targets, the grey full line is the best calibration set and the dashed grey lines are the other 10 best parameter sets.

2.4. Biological process

The HPV infection was stratified by types in three categories: (a) HPV 16, (b) HPV 18 and (c) HPV 6&11. As in previous models, it was assumed that an individual could only be in one of the three infected categories [7,15,20]. A simplified schematic of the natural history of HPV among men and women are shown in Appendix Figs. S1 and S2 respectively.

Health states in the model, descriptive of the patient's underlying true health, were defined to include HPV infection status, grade of cervical intraepithelial neoplasia (CIN) and presence of genital warts (GW). HPV- and cervical cancer-related progression and regression rates are reported in Table 6 of the Appendix. Men were modelled as being carriers of the infection and did not develop genital warts, as can be seen in Fig. S1 of the Appendix.

2.5. Parameterization and calibration process

The model was initially populated using parameters derived from the published literature. Parameters used and their values can be found in Appendix. The values of seven parameters were explored in the calibration exercise. They were: HPV 16, HPV 18 and HPV 6&11 per partnership transmission probabilities, HPV clearance rate, probability of progression from HPV 6&11 to GW, probability of clearing GW and probability of progression from CIN3 to invasive cancer. The choice of what input parameters to include in the calibration was based on the level of parameter uncertainty as well as the importance of the parameter according to the calibration targets used, as in previous analysis [7,27].

Calibration of the model was conducted using a random search algorithm, as in previous studies [22,28–30]. The residuals between the model outputs for each parameter set and empirical estimates of HPV 16, 18 and 6&11 prevalence, HPV 16&18 cervical cancer incidence rate and HPV 6&11 genital warts incidence rate were used to calculate the chi-squared goodness-of-fit (GOF). The best-input parameter set was selected based on the lowest estimates of the GOF. Pre- and post-calibration age-specific HPV 16, 18, and 6&11 prevalence rates predicted by the model can be observed in Figs. 1–3. The values of inputs, outputs and calibrations targets can be seen in Tables S7 and S8 of the appendix.

2.6. Vaccine and screening characteristics

The parameters related to the interventions can be found in Table 1. In the model, it is assumed that vaccination occurs prior to sexual debut (age 10) and would consist of the three recommended doses. The vaccination would confer type-specific protection. Other parameters subjected to greater uncertainty such as vaccination

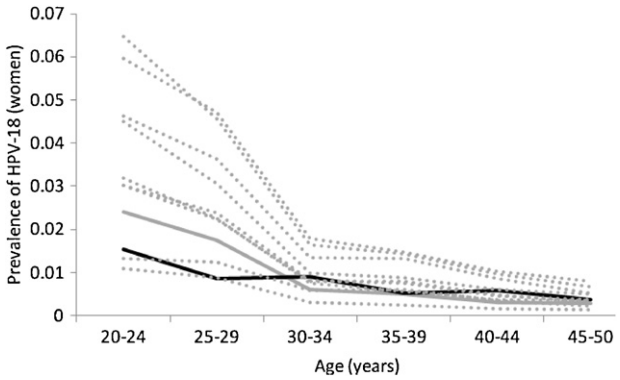

Fig. 2. Prevalence of HPV 18 (women). Full dark lines are the calibration targets, the grey full line is the best calibration set and the dashed grey lines are the other 10 best parameter sets.

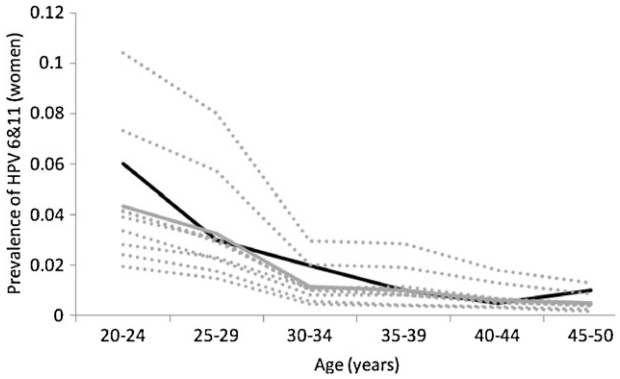

Fig. 3. Prevalence of HPV 6&11 (women). Full dark lines are the calibration targets, the grey full line is the best calibration set and the dashed grey lines are the other 10 best parameter sets.

Table 1
Interventions and economic parameters.

Parameter	Mean	Reference
Vaccination coverage	50–70–90%[a]	[7]
Screening coverage	63%	[53]
Sensitivity/specificity of cytology	58%/95%	[54,55]
Sensitivity/specificity of colposcopy	96%/48%	[56,57]
Cost of vaccine (per dose)	5–12–27–120[a]	[7]
Cost of vaccination (per woman)[b]	25–55–125–556[a]	[7]
Cost of pap smear	13.67	[29,53]
Cost of colposcopy	25.42	[29,53]
Cost of biopsy	65.70	[29,53]
Cost of staging invasive cancer	246.64	[29,53]
Cost invasive cancer stage 1	6171.42	[29,53]
Cost invasive cancer stage 2	17,225.92	[29,53]
Cost invasive cancer stage 3	17,517.7	[29,53]
Cost invasive cancer stage 4	13,929.41	[29,53]
Cost of invasive cancer follow-up exams	61.63	[29,53]
Cost of treating genital warts[b]	65	[58]
Quality of life weight – CIN1	0.91	[58]
Quality of life weight – CIN2/3	0.87	[58]
Quality of life weight – invasive cancer I–II–II–IV	0.65–0.56–0.56–0.48	[20]
Quality of life weight – invasive cancer survivor	0.84	[58]
Quality of life weight – GW	0.91	[58]
Quality of life weight – no condition	0.93–0.69[c]	[58]

All costs are aggregate costs in US dollars, index year 2008.
[a] Parameters varied in combination.
[b] Assumed.
[c] Age- and gender-specific QALY weights varied within this range as in Elbasha et al. [58].

coverage, vaccination cost, and duration of protection had their impact in the cost-effectiveness results explored, as detailed in Section 3.

In both vaccinated and unvaccinated cohorts screening was modelled according to the Brazilian Guideline for Cervical Cancer Screening, in which cytology is performed every 3 years on women aged 25–60 [31]. Invasive cervical cancer cases were treated according to the recommendations of the International Federation of Gynaecology and Obstetrics (FIGO) [32].

2.7. Economic data

The health system perspective was adopted in the cost-effectiveness analysis as recommended by the Brazilian Guidelines for Health Technology Assessment [33]. All costs were adjusted to the year 2008 [29,34]. The monetary unit used was the United States dollar (US$) at the annual exchange rate of US$1 = 1.86 Brazilian reais [35]. Since the HPV quadrivalent vaccine is not currently available in the Brazilian public health system, we decided to explore different costs in a similar fashion as performed in previous studies [7,8]. The highest cost (US$120 per dose) is based on the price approved by the National Health Surveillance Agency (ANVISA) [36]. The other estimates (US$27, US$12 and US$5) that potentially reflect the product of price negotiation are based on the values used in other studies [7,8]. The costs per vaccinated women consider freight, supplies, cold chain maintenance, administration, wastage, vaccine support, and programmatic costs. Quality-adjusted life years (QALYs) were used in order to capture the qualitative gains related to cervical lesions, and particularly those related to genital warts. Both costs and health outcomes were discounted at an annual rate of 5%, as recommended by Brazilian guidelines [33].

Since in the Brazilian guidelines for health technology assessment does not report the threshold to determine whether an intervention is cost-effective (i.e. represents good value for money), a heuristic one was derived from the Commission on Macroeconomics and Health [37]. This Commission proposed that a cost-effective interventions would avert one additional disability-adjusted life year (DALY) for less than three times the average per capita gross domestic product (GDP) and a very cost-effective intervention would avert one additional DALY for less than the average per capita GDP for a given country. We extrapolated these thresholds and assumed that society's willingness to pay (WTP) for one DALY averted is equivalent to its WTP for one QALY, as previous studies [8,38,39]. This presumes a threshold of 25,876 US$/QALY for a cost-effective intervention and a threshold of 8625 US$/QALY for a very cost-effective intervention [40]. The costs and utility weights used in the analysis can be found in Table 1.

3. Results

The effect of the vaccine the prevalence of HPV types in the population can be observed in Fig. 4. Before vaccination starts, the HPV types had reached endemic equilibrium in the population, in other words HPV prevalences are at stable levels only subjected to minor oscillation due to stochasticity. As expected, after vaccination is introduced at a 90% coverage rate we observe a gradual decline in the prevalence rates. This is followed by a rapid drop due to significant reductions in HPV prevalence among highly sexually active young females. After some time only HPV 16, the most virulent, remains endemic at very low levels. These results are similar those found by Van de Velde et al. [22].

Table 2 presents the incremental cost-effectiveness results for different combinations of vaccine coverage and vaccination costs comparing only screening to screening plus vaccination. As expected for the same coverage, as the cost of vaccination

Table 2
Incremental cost-effectiveness ratios by vaccination coverage and cost per vaccinate woman.

Years of life saved (undiscounted)	Cost per vaccinate individual			
	US$25 ($5 per dose)	US$55 ($12 per dose)	US$125 ($27 per dose)	US$556 ($120 per dose)
50% vaccine coverage				
28,608	Cost saving (cost saving) Cost saving	113 US$/QALY (cost saving) 103 US$/YLS	580 US$/QALY (78) 528 US$/YLS	3454 US$/QALY (966) 3146 US$/YLS
70% vaccine coverage				
29,283	Cost saving (cost saving) Cost saving	255 US$/QALY (cost saving) 232 US$/YLS	954 US$/QALY (163) 868 US$/YLS	5258 US$/QALY (1385) 4783 US$/YLS
90% vaccine coverage				
31,642	20 US$/QALY (cost saving) 17 US$/YLS	354 US$/QALY (6) 322 US$/YLS	1136 US$/QALY (243) 1034 US$/YLS	5950 US$/QALY (1701) 5414 US$/YLS

QALY, quality adjusted life years; YLS, life years saved.
All ICER estimates were discounted at 5%, apart from those in parenthesis, which were not discounted.

increases, so does the ICER. When we look at the difference between the US$/QALY and US$/YLS estimates, we can observe that the US$/QALY are slightly higher. This can be explained by the fact that even though QALYs can capture the genital warts prevention gain, this effect is offset by age-specific QALY weights, which give less weight to disease-free years produced by the vaccine, because they account for the impact of co-morbidities." When we look at the differences between discounted and undiscounted estimates, we notice that the vaccination becomes more attractive (i.e. lower ICER) when estimates are not discounted. Discounting does not have great effect in the cost of the vaccine, since vaccination costs incur early in life, however, it does have a great impact in the health gains of the vaccine that occur later in life when individuals become sexually active. In spite of the great uncertainty to which vaccination coverage and cost estimates are subjected, all combinations resulted in ICERs below the very cost-effective threshold. In some cases, as for 50% or 70% coverage at US$25 per vaccinated woman, the vaccine not only saves more QALYs, but it also saves resources as there are less pre-cancer and cancer lesions to be screened and treated. These findings are similar to previous studies [7,21,41].

As expected, considering a higher screening coverage (100%), vaccination becomes less attractive, with an ICER of 8159 US$/QALY at a vaccination cost of US$556, coverage of 90% and discount rate of 5%. This reflects the fact that non-screened women are the ones that benefit the most from the vaccine. Although it is believed that the HPV vaccine provides lifelong immunity, these believes can only be confirmed by follow-up studies currently in progress [42]. Therefore, we evaluated a scenario in which a booster shot was needed after 10 years in order to secure lifelong protection. In this scenario, vaccination costs, coverage and discount rate were considered at the highest values, US$556, 90% and 5% respectively. These assumptions yielded an ICER of 13,576 US$/QALY, which is no longer very cost-effective but still cost-effective. It is safe to infer that using lower input parameters the ICER will be lower than that.

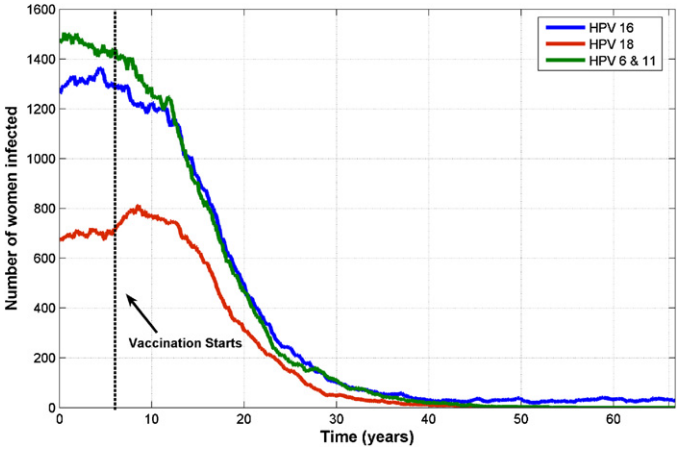

Fig. 4. Prevalence of HPV types before and after vaccination. Coloured full lines represent the prevalence of HPV types at each monthly cycle after endemic equilibrium. Black dashed line mark when vaccination starts. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

HPV vaccination has been incorporated in many high-income countries. For example, Australia, Denmark and France provide the quadrivalent vaccine, while the Netherlands provides the bivalent vaccine for pre-adolescent girls. The UK initially provided the bivalent vaccine [20], however, it has recently announced that it will switch to the quadrivalent vaccine in September 2012 [43,44]. The cost-effectiveness of the bivalent vaccine had already been analyzed for Brazil using a dynamic individual-based model [7]. Nonetheless, the quadrivalent vaccine had never been analyzed for the country using such modelling methods. The goal of our study was to analyze the cost-effectiveness of HPV quadrivalent vaccine for pre-adolescent girls in the Brazilian public health system using robust modelling methods.

We found that over a wide range of coverages vaccination plus screening always yielded more health benefits than just screening. However, the costs of the former strategy were not always higher than latter. When we considered vaccination coverage of 50% or 70% at a cost per dose of US$5, the vaccination plus screening strategy was actually less costly than just screening, given the lower number of pre-cancer and cancer cases to be screened and treated. Taking into account the very cost-effective and cost-effective thresholds based on Brazil's GDP per capita, in almost all scenarios analyzed the vaccination plus screening vaccine strategy would be deemed very cost-effective. Only in the scenario where a booster is needed after 10 years using vaccination coverage of 90% and a cost per dose of US$120, the vaccination plus screening strategy was found to be cost-effective instead of very cost-effective. Our results are consistent with previous analyses [7,21,41,45]. At a cost per vaccinated woman of I$25 and coverage of 50% or 70%, vaccinating girls was also cost saving [7]. Although these models do not have the exact same structure or input parameters, their cost-effectiveness estimates were close to ours. For example, at a cost per vaccinated woman of I$400, coverage of 75% and discounting at 3%, Kim et al.

obtained an ICER of 3940 I$/YLS for the bivalent vaccine [7]. When we considered the same three input parameters, we obtained an ICER of 2301 I$/YLS for the quadrivalent vaccine.

It is important to point out that the cost-effectiveness threshold based on the GDP per capita may be too high for countries in the upper end of the income spectrum. For example, although in the UK the threshold is 30,000£/QALY, the cost-effective threshold based on the GDP per capita would be around 75,000£/QALY. Some argue that the real-world threshold for a new intervention should be the ICER of other intervention competing for the same public investment, for example vaccines already incorporated in the public health system [46]. In this case, the relevant threshold ratio could be as low as 500 US$/YLS. Using this lower threshold would imply that for the vaccine to be considered cost-effective, the cost per vaccinated woman would have to be lower than 125 US$.

Although cost-effectiveness analysis adds information on what constitutes good value for money, it does not take into account other important considerations such as equity, cultural preferences and political circumstances. It also does not take into account the impact to the budget of including the new strategy and which other strategies should be underfunded. In 2007 the Brazilian National Institute of Cancer assessed that the vaccination of all women age 11–12 at a cost of US$120 would incur in a total of 1.857 billion Brazilian reais, approximately 1 billion US$, which was above the budget allocated to all immunization programmes in Brazil together [47].

To our knowledge, there have not been other cost/QALY studies of the HPV quadrivalent vaccine plus screening using a fully integrated dynamic individual-based model for Brazil. Goldie et al. used a static individual-based to analyze the cost-effectiveness (cost/YLS) of the bivalent vaccine [8]. Unfortunately the model used did not capture the herd immunity benefit conferred by the vaccine and the screening strategies considered did not reflect the current practice in Brazil. In another publication by Kim et al., an attempt was made to incorporate the herd immunity effect of the vaccine by linking the static individual-based model to a dynamic compartmental model [7]. However, this study only looked at the bivalent vaccine and reported health gains in YLS. They also used a susceptible-infected-recovered model which is different from our susceptible-infected-susceptible model. An important aspect of this analysis is that it also considered the vaccination of boys among the strategies being evaluated, which did not yield attractive cost-effectiveness results.

There are limitations to our analysis that should be acknowledged. Regarding model assumptions, similar to previous analysis [7,20] we did not considered the cross protection that the vaccine may confer to other HPV types not included in the vaccine. However, it has been pointed out in a recent analysis in the Netherlands that the cost-effectiveness results may be sensitive to changes in the cross-protection assumptions [48]. In respect to the framing assumptions, the model did not consider the development of genital warts among men, therefore undervaluing the overall benefit of the vaccine. The model did not account for other benefits and costs of other diseases associated with HPV such as anal, penile, vaginal, vulvar, head and neck cancers as well as recurrent respiratory papillomatoses.

Following from previous analysis [7,20,27], the model assumes sexual activity only from age 15 to 50. Nonetheless, this could under-estimate the risk of HPV infection for older individuals, what might under-value the impact of vaccination, particularly booster vaccination. A recent study by Insinga et al. has shown that the proportion of infection reappearance for types 6, 11, 16 and 18 after non-detection varies from 8 to 16% by 36 months [49]. These findings confirmed the results of a previous smaller study [50]. Accounting for reappearance could have an impact on the model results, and should be explored in future modelling studies. Nevertheless, we do not anticipate that it would a major impact on the cost-effectiveness estimates of the vaccine.

The model assumes the same clearance rate for the four HPV types. However, recent data suggests a higher clearance rate for HPV 6/11 than for HPV 16 or 18 [51,52], which should be considered in future studies. Country-specific coverage rates were used in the model; therefore, the proportion of non-screened population modelled is likely to match that found in the Brazilian population. Nonetheless, it would be beneficial to add more screening-specific data as calibration targets, in order to increase the level of certainty that the model reflects the screening conditions found in Brazil. This would be particularly useful in further studies exploring different screening strategies for the vaccinated and the non-vaccinated cohorts. It would also be important to include other high-risk HPV types and other low risk types, and to consider HPV-types individually, while accounting for cross-protection. This would allow a more appropriate comparison of the available vaccines.

5. Conclusion

We have demonstrated that adding the quadrivalent vaccination of pre-adolescent girls to the current efforts to control cervical cancer in Brazil can be a highly effective strategy to save years of life as well as quality-adjusted life years and, in some instances, even to save resources. The vaccination strategy seems very cost-effective for most of the scenarios analyzed considering the per capita GDP-based threshold. However, considering the limited vaccination budget, it seems that the inclusion of the vaccine in the national immunization programme will be highly dependent on price negotiations between the government and the manufacturers.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2012.04.087.

References

[1] Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127(12):2893–917.
[2] INCA. Estimativa 2012—Incidencia de Cancer no Brasil; 2011. Available from: http://www.inca.gov.br/estimativa/2012/ [cited 6.12.11].
[3] Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348(6):518–27.
[4] von Krogh G, Lacey CJN, Gross G, Barrasso R, Schneider A. European guideline for the management of anogenital warts. Int J STD AIDS 2001;12(Suppl. 2):40–7.
[5] Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009;374(9686):301–14.
[6] The Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356(May (19)):1915–27.
[7] Kim JJ, Andres-Beck B, Goldie SJ. The value of including boys in an HPV vaccination programme: a cost-effectiveness analysis in a low-resource setting. Br J Cancer 2007;97(November (9)):1322–8.
[8] Goldie SJ, Kim JJ, Kobus K, Goldhaber-Fiebert JD, Salomon J, O'Shea MKH, et al. Cost-effectiveness of HPV 16, 18 vaccination in Brazil. Vaccine 2007;25(33):6257–70.
[9] Edmunds WJ, Medley GF, Nokes DJ. Evaluating the cost-effectiveness of vaccination programmes: a dynamic perspective. Stat Med 1999;18(23):3263–82.
[10] Villa LL, Ault KA, Giuliano AR, Costa RLR, Petta CA, Andrade RP, et al. Immunologic responses following administration of a vaccine targeting human papillomavirus types 6, 11, 16, and 18. Vaccine 2006;24(27–28):5571–83.
[11] Viscidi RP, Schiffman M, Hildesheim A, Herrero R, Castle PE, Bratti MC, et al. Seroreactivity to human papillomavirus (HPV) types 16, 18, or 31 and risk of subsequent HPV infection. Cancer Epidemiol Biomark Prev 2004;13(February (2)):324–7.

[12] Trottier H, Mahmud S, Prado JCM, Sobrinho JS, Costa MC, Rohan TE, et al. Type-specific duration of human papillomavirus infection: implications for human papillomavirus screening and vaccination. J Infect Dis 2008;197(10):1436–47.
[13] Insinga R, Dasbach E, Elbasha E. Epidemiologic natural history and clinical management of human papillomavirus (HPV) disease: a critical and systematic review of the literature in the development of an HPV dynamic transmission model. BMC Infect Dis 2009;9(1):119.
[14] Insinga RP, Dasbach EJ, Elbasha EH. Structural differences among cost-effectiveness models of human papillomavirus vaccines. Expert Rev Vaccines 2008;7(7):895–913.
[15] Kim JJ, Kuntz KM, Stout NK, Mahmud S, Villa LL, Franco EL, et al. Multiparameter calibration of a natural history model of cervical cancer. Am J Epidemiol 2007;166(July (2)):137–50.
[16] Canfell K, Barnabas R, Patnick J, Beral V. The predicted effect of changes in cervical screening practice in the UK: results from a modelling study. Br J Cancer 2004;91(3):530–6.
[17] Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. Emerg Infect Dis 2004;10(November (11)):1915–23.
[18] Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis 2007;13(1):28–41.
[19] Dasbach EJ, Insinga RP, Elbasha EH. The epidemiological and economic impact of a quadrivalent human papillomavirus vaccine (6/11/16/18) in the UK. BJOG: Int J Obstet Gynaecol 2008;115(8):947–56.
[20] Jit M, Choi YH, Edmunds WJ. Economic evaluation of human papillomavirus vaccination in the United Kingdom. BMJ 2008;337(July):a769.
[21] Insinga RP, Dasbach EJ, Elbasha EH, Puig A, Reynales-Shigematsu LM. Cost-effectiveness of quadrivalent human papillomavirus (HPV) vaccination in Mexico: a transmission dynamic model-based evaluation. Vaccine 2007;26(1):128–39.
[22] Van de Velde N, Brisson M, Boily M-C. Understanding differences in predictions of HPV vaccine effectiveness: a comparative model-based analysis. Vaccine 2010;28(33):5473–84.
[23] Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. Emerg Infect Dis 2003;9(January (1)):37–48.
[24] Fontaine J, Hankins C, Mayrand M-H, Lefevre J, Money D, Gagnon S, et al. High levels of HPV-16 DNA are associated with high-grade cervical lesions in women at risk or infected with HIV. AIDS 2005;19(8):785–94.
[25] Garnett GP. An introduction to mathematical models in sexually transmitted disease epidemiology. Sex Transm Infect 2002;78(February (1)):7–12.
[26] Garnett GP. The influence of behavioural heterogeneity on the population level effect of potential prophylactic human immunodeficiency virus type 1 vaccines. J R Stat Soc: Ser A (Stat Soc) 1998;161(2):209–25.
[27] Barnabas RV, Laukkanen P, Koskela P, Kontula O, Lehtinen M, Garnett GP. Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses. PLoS Med 2006;3:e138.
[28] Van de Velde N, Brisson M, Boily M-C. Modeling human papillomavirus vaccine effectiveness: quantifying the impact of parameter uncertainty. Am J Epidemiol 2007;165(April (7)):762–75.
[29] Vanni T, Legood R, Franco EL, Villa LL, Luz PM, Schwartsmann G. Economic evaluation of strategies for managing women with equivocal cytological results in Brazil. Int J Cancer 2011;129(3):671–9.
[30] Vanni T, Karnon J, Madan J, White RG, Edmunds WJ, Foss AM, et al. Calibrating models in economic evaluation: a seven-step approach. Pharmacoeconomics 2011;29(1):35–49, http://dx.doi.org/10.2165/11584600-000000000-00000.
[31] INCA. Nomenclatura brasileira para laudos cervicais e condutas preconizadas: recomendações para profissionais de saúde. Rio de Janeiro, Brazil: Instituto Nacional do Cancer, Ministério da Saude; 2006.
[32] Pecorelli S, Ngan HY, Hacker NF. Staging classification and clinical practice guidelines for gynaecological cancers; third editions. Available from: http://www.figo.org/publications/staging_classifications [cited 29.08.2011].
[33] Methodological guidelines for appraisals on health technology assessment for the Ministry of Health of Brazil; 2008. Available from: http://portal.saude.gov.br/portal/saude/visualizar_texto.cfm?idtxt=26776 [cited 25.07.08].
[34] Vanni T, Luz PM, Grinsztejn B, Veloso VG, Foss A, Mesa-Frias M, et al. Cervical cancer screening among HIV-infected women: an economic evaluation in a middle-income country. Int J Cancer 2011;131(2):E96–104.
[35] Central Intelligence Agency. The World Factbook; 2009. Available from: https://www.cia.gov/library/publications/the-world-factbook/index.html [cited 10.12.09].
[36] National Health Surveillance Agency (ANVISA); 2006. Available from: http://www.anvisa.gov.br/divulga/imprensa/clipping/2006/agosto/290806.pdf [cited 20.10.11].
[37] WHO. Macroeconomics and health: investing in health for economic development: report of the commission on macroeconomics and health. Geneva: World Health Organization; 2001.
[38] Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, Gordillo-Tobar A, Levin C, Mahe C, et al. Cost-effectiveness of cervical-cancer screening in five developing countries. N Engl J Med 2005;353(November (20)):2158–68.
[39] Goldie SJ, Diaz M, Kim S-Y, Levin CE, Van Minh H, Kim JJ. Mathematical models of cervical cancer prevention in the Asia Pacific region. Vaccine 2008;26(Suppl. 12):M17–29.
[40] Popper K. Conjectures and refutations: the growth of scientific knowledge. Oxford: Routledge; 2003.
[41] Colantonio L, Gómez JA, Demarteau N, Standaert B, Pichón-Rivière A, Augustovski F. Cost-effectiveness analysis of a cervical cancer vaccine in five Latin American countries. Vaccine 2009;27(40):5519–29.
[42] Steben M. Update on Gardasil (quadrivalent human papillomavirus [HPV] 6/11/16/18 vaccine) clinical trial efficacy results. In: EUROGIN 2010. 2010.
[43] Jit M, Chapman R, Hughes O, Choi YH. Comparing bivalent and quadrivalent human papillomavirus vaccines: economic evaluation based on transmission model. BMJ 2011;343:d5775.
[44] UK Department of Health. Your guide to the HPV vaccination from September 2012; 2012. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_133345 [cited 06.04.12].
[45] Reynales-Shigematsu LM, Rodrigues ER, Lazcano-Ponce E. Cost-effectiveness analysis of a quadrivalent human papilloma virus vaccine in Mexico. Arch Med Res 2009;40(6):503–13.
[46] Jha P, Bangoura O, Ranson K. The cost-effectiveness of forty health interventions in Guinea. Health Policy Plan 1998;13(January (3)):249–62.
[47] Saúde INdC-Md, editor. Portaria GM/MS No 3.124. Ministério da Saúde; 2006.
[48] Coupé VMH, Bogaards JA, Meijer CJLM, Berkhof J. Impact of vaccine protection against multiple HPV types on the cost-effectiveness of cervical screening. Vaccine 2012;30(10):1813–22.
[49] Insinga RP, Perez G, Wheeler CM, Koutsky LA, Garland SM, Leodolter S, et al. Incidence, duration, and reappearance of type-specific cervical human papillomavirus infections in young women. Cancer Epidemiol Biomark Prev 2010;19(June (6)):1585–94.
[50] Sycuro LK, Xi LF, Hughes JP, Feng Q, Winer RL, Lee S-K, et al. Persistence of genital human papillomavirus infection in a long-term follow-up study of female university students. J Infect Dis 2008;198(October (7)):971–8.
[51] Insinga R, Dasbach E, Elbasha E, Liaw K-L, Barr E. Progression and regression of incident cervical HPV 6, 11, 16 and 18 infections in young women. Infect Agents Dis 2007;2(1):15.
[52] Insinga RP, Wheeler PG, Koutsky CM, Garland LA, Leodolter SM, Joura S, et al. Incident cervical HPV infections in young women: transition probabilities for CIN and infection clearance. Cancer Epidemiol Biomark Prev 2011;20(2):287–96.
[53] Murillo R, Almonte M, Pereira A, Ferrer E, Gamboa OA, Jerónimo J, et al. Cervical cancer screening programs in Latin America and the Caribbean. Vaccine 2008;26(Suppl. 11):L37–48.
[54] Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann Intern Med 2000;132(10):810–9.
[55] Goldhaber-Fiebert JD, Stout NK, Salomon JA, Kuntz KM, Goldie SJ. Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16,18 vaccination. J Natl Cancer Inst 2008;100(5):308–20.
[56] Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol 1998;91(4):626–31.
[57] Pretorius RG, Zhang W-H, Belinson JL, Huang M-N, Wu L-Y, Zhang X, et al. Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. Am J Obstet Gynecol 2004;191(2):430–4.
[58] Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis 2007;13:28–41.