International STD Research & Reviews

6(1): 1-8, 2017; Article no.ISRR.35382
ISSN: 2347-5196, NLM ID: 101666147

A Cost-effectiveness Study of the Quadrivalent HPV6/11/16/18 Vaccination in a Two-dose Scheme in Girls of 9-11 Years Old Compared to Bivalent HPV 16/18 Vaccination in Ecuador and Challenges for Public Health and Screening

Maria Isabel Roldós[1*], Isabel Espinosa[2], Amit Kulkarni[3], Matthew Pillsbury[3], Andrew Pavelyev[4], Homero A. Monsanto[3], Diego Guarín[3] and Miguel Cashat-Cruz[3]

[1]College of Health Sciences, Walden University, USA.
[2]Department of Internal Medicine, Nova Clínica-Santa Cecilia, Quito, Ecuador.
[3]Merck & Co., USA.
[4]HCL América, USA.

Authors' contributions

This work was carried out in collaboration between all authors. Authors MIR, IE and HAM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript in collaboration with authors AK, MP, AP and DG. Authors AP, HAM and MCC managed statistical analysis and model simulations. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/ISRR/2017/35382
Editor(s):
(1) Kailash Gupta, Division of AIDS, NIAID, NIH, USA.
(2) Jose Eduardo Serrao, Department of General Biology, Federal University of Viçosa, Brazil.
Reviewers:
(1) Wagner Loyola, Brazil.
(2) Oroma Nwanodi, A. T. Still University Arizona School of Health Sciences, USA.
Complete Peer review History: http://www.sciencedomain.org/review-history/20743

Original Research Article

Received 10th July 2017
Accepted 14th August 2017
Published 30th August 2017

ABSTRACT

Aims: Assess the incremental cost-effectiveness of the quadrivalent HPV6/11/16/18 vaccination as administered in a two-dose scheme to girls between 9 and 11 years old, as compared to the bivalent HPV 16/18 vaccination administered in Ecuador, and to estimate the cost-saving of preventing GW

**Corresponding author: Email: mariaisabel.roldosprosser@mail.waldenu.edu;*

while preventing cervical cancer with both vaccines.
Study Design: We used a previously developed transmission dynamic mathematical model to evaluate the impact of routine vaccination of 9-11 year-old females. The model assumed coverage of 90% for two doses of HPV6/11/16/18 vaccine at international price rates versus HPV16/18 vaccine and costs for genital warts treatment. Other simulation parameters include: country socio-demographic variables, sexual behavior and screening parameters among Ecuadorian girls.
Results: Over a 100-year period, HPV6/11/16/18 vaccination would result in reductions of HPV 6/11-related disease incidence at the population level as follows: genital warts in females (81.3%), genital warts in males (78.9%) and HPV6/11-related CIN1 (79.7%). These results would translate into a reduction of HPV 6/11-related disease cost of between 52% to 56% for genital warts among females, genital warts among males, and HPV6/11-related CIN1. Under the model assumptions, the estimated net cost of vaccination with the HPV6/11/16/18 vaccine from a public health perspective would be close to -USD$256 million. Adjusted to the net present value, this cost-saving represents USD$180,735,849.09 with a present value interest factor of 0.9512.
Conclusions: In Ecuador, routine vaccination of 9-11 year old females with a quadrivalent HPV6/11/16/18 vaccine is cost-saving compared to a bivalent HPV 16/18 vaccine, which suggests a significant public health and economic impact.

Keywords: HPV prevention; genital warts; ecuador; cost-savings.

1. INTRODUCTION

Human papillomavirus (HPV) infection is the most common sexually transmitted disease (STD) in the world. The W orld Health Organization (W HO) estimates that every year 448 million new cases are detected worldwide, [1] while other sources estimate that a sexually active person will acquire at least one HPV infection during his or her lifetime with the highest transmission rates occurring from female to male partners [2]. Most HPV infections are symptomless; however, at least 13 of the known 100 subtypes may cause cancers of the vulva, penis and oropharynx [3,4]. Persistent HPV infection can also progress to cause genital warts (GW).GW frequently occurs in the vulva and the perianal regions, and close to 90% of such cases are related to HPV subtypes 6 and 11 [1,3,5].

HPV infection and its health consequences can be prevented with vaccination. HPV subtypes 16 and 18 account for approximately 70% of cervical cancers, while subtypes 6 and 11 are responsible for approximately 90% of GW [6,7]. The quadrivalent HPV vaccine protects against HPV types 6, 11, 16, and 18, and it has been licensed in the United States for use on females since June 2006 and on males since 2009 [8]. Bivalent vaccination protects only against types 16 and 18 [9]. Quadrivalent vaccination could prevent cervical, vaginal, and vulvar cancer in women; and anal cancer and GW in both men and women [10]. On October 19, 2016, the Advisory Committee on Immunization Practices (ACIPc) approved a recommendation for the HPV vaccine to be administered on a 2-dose schedule for boys and girls initiating HPV vaccination series at 9 to 14 years (0,6-12 months); a 3-dose schedule for persons initiating HPV vaccination series at older ages; and a 3-dose schedule for immunocompromised persons.

As of 2015, there are 80 national HPV vaccination programs and 37 pilot programs worldwide, funded by Vaccine Alliance, the Pan American Health Organization (PAHO) and others [3]. These programs have used different strategies to reach the targeted population, including school-based efforts, clinic-centered plans, and community programs.

School-based programs have proven to be the most successf ul, while those based in clinics have experienced challenges with dissemination [3].

Official estimates of the incidence of HPV infections are inconsistent in Ecuador. The Ministry of Health's (MOH) estimates suggest cervical cancer as the second most common cancer among women with approximately 1200 new cases every year and close to 300 deaths per year and an incidence of 15,8 cases per 100,000 people in 2012 [11,12]. Meanwhile, international projections estimate about 2,094 new cervical cancer cases are diagnosed annually, with an incidence of 28.3 cases per 100,000 for 2012 [13].

HPV as a sexually transmitted disease is also misclassified in official registries. MOH estimates

9,830 STD cases occurring between 2007-2010; however, their epidemiological surveillance system does not differentiate all types of STDs [14]. Ninety-five percent of STD cases in Ecuador are classified as "other," the remaining 5% appropriately classified as gonorrhea, syphilis, HIV, or herpes. Furthermore, very few studies exist on the prevalent HPV subtypes. For example, an MOH study that explored HPV subtypes in a convenient sample of 555 women suggested that 6% of the women had an HPV infection in their lifetime, 12% had subtype 6; close to 9% had subtype 18; and 6% each had subtypes 58 and 59 [11].

Ecuador's MOH launched in 2012 the national strategy to prevent cervical and vaginal cancer through an Extended Immunization Program. Therefore, 1.4 million bivalent vaccines were purchased—enough to administer two doses only to girls between the ages of 9 and 11 [15]. These vaccines were administered in public schools and were offered in public clinics to people who sought the vaccine. Privately, the vaccines are available to people willing to pay out-of-pocket.

The MOH's goals were to achieve at least 95% coverage of the second dose in girls that initiated the vaccination scheme in 2014, and by 2015 achieve coverage of 95% and above with a third dose [11]. Results of the Extended Immunization Program are unknown. The National Public Health Strategy of technical and operational guidelines to introduce HPV vaccination does not include long- term strategies or programs that specifically address HPV or its consequences with regard to morbidity, such as GW.

2. METHODOLOGY

This study assesses the cost-effectiveness of a quadrivalent HPV6/11/16/18 vaccination program in a two- dose scheme in girls of 9-11 years old compared to the same vaccination schedule of an HPV 16/18 vaccination program in Ecuador and estimates the additional cost savings from interrupting the spread of genital warts while preventing cervical cancer with both vaccines.

We adapted a previously developed transmission dynamic mathematical model for HPV vaccination developed by Elbasha 2008 [16,17]. This is a nonlinear, deterministic, age structured, mathematical model of the transmission dynamics of HPV and disease occurrence in a US population stratified simulation that included gender, age, sexual activity frequency, Group of HPV types (16/18 = 1, 6/11 = 2, joint = 12), Stage of cervical intraepithelial neoplasia (CIN) or cancer, Cervical screening category (never= 1, routine = 2), as well as demographic, behavioral, biological model parameters Elbasha's model assessed both the epidemiologic consequences and cost effectiveness of alternative vaccination strategies in a setting of organized cervical cancer screening in the United States [17].

This study compared routine HPV vaccination of Ecuadorian girls between ages 9 and 11 with a baseline coverage of 90% of all Ecuadorian girls for two doses. The model's assumptions are the following:

- Vaccine dose cost:
  - USD $11/dose for Quadrivalent vaccine
  - USD $8.50/dose for Bivalent vaccine
- GW treatment costs: USD $395 per episode (Assumed equal for females and males) [18].
- Sensitivity analysis: 25% and 50% lower GW treatment costs (USD $296 and USD $198, respectively).

Other input data included demographic, behavioral, epidemiological, and screening parameters, as well as direct treatment costs of HPV-related morbidities at market based prices. Due to the lack of Ecuadorian specif ic data, we used data from Peru and Colombia as a proxy for Ecuador.

3. RESULTS

Results from this simulation suggest that in a 100- year period 90% coverage of the quadrivalent vaccination would result in reductions of subtypes HPV 6 and 11 -related diseases such as genital warts in females in 81.3% and of 78.9% for males, and 79.7% for HPV6/11-related CIN1 among females. These outcomes would translate into a reduction of HPV 6/11-related costs for GW among females and males, and HPV6/11-related CIN1 at rates of 56%, 51.8%, and 51.7%, respectively, over the 100-year period.

The incremental cumulative quality-adjusted life years (QALYs) gained per 100,000 by HPV 6/11/16/18-related disease over 100 years would be 241.44 for the quadrivalent vaccination program when compared with an HPV16/18 vaccination program.

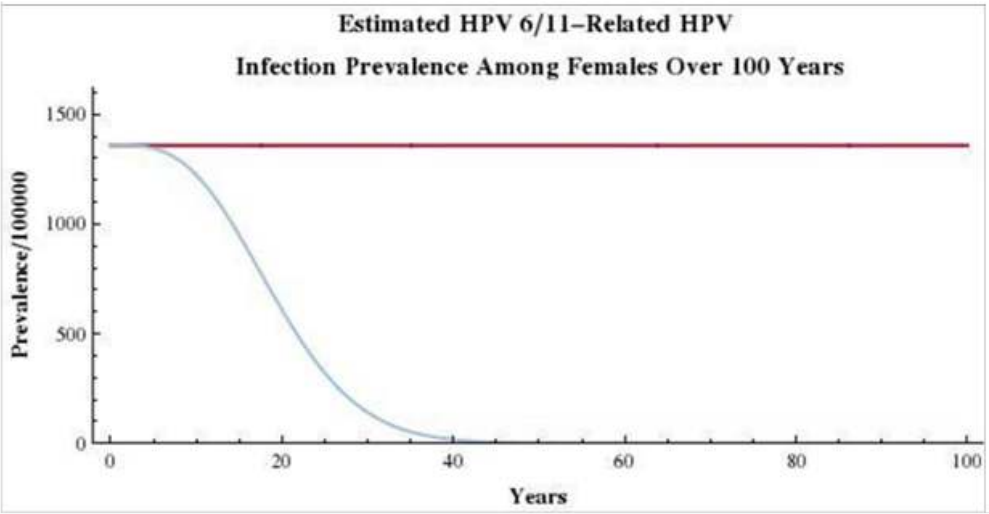

Fig. 1. The estimated HPV 6/11 Infection prevalence among Females over 100 years related to HPV

Under the model assumption, over a 100-year period, the health care (HC) costs averted by the introduction of the quadrivalent vaccination program would exceed the actual cost of the uptake the vaccine. The quadrivalent vaccination program would result in cost-saving of USD $256 million over 100 years adjusted to 2016 dollars.

Sensitivity analysis demonstrated that the quadrivalent vaccination program remained cost-saving at 25% and 50% lower GW treatment costs (USD $296 and USD $198, respectively). The estimated vaccination savings at 25% lower GW treatment cost was USD $190 million, while at 50% lower GW treatment cost it was USD $124 million.

4. DISCUSSION

In Ecuador, routine vaccination of females from age 9 to 11 with a quadrivalent vaccine (HPV6/11/16/18) would result in significant cost savings compared to a bivalent HPV 16/18 vaccine, both monetarily and in terms of public health. The government's annual budget has increased systematically since 2008, from $10.358 million to $36.317 million in 2015, then it decreased 13% in 2016 to $29.835 million [19]. The health budget, by comparison, was approximately $3.413 million in 2015, or 0.5% of the country's gross domestic product (GDP). The Ministry of Health received a direct budget of $289,267,260 million [19]. Exact data on the MOH investment in primary prevention through vaccination schemes is unknown.

According to MOH estimates the Disability Adjusted Life Years (DALYS) adverted because of the introduction of the bivalent vaccine is of $USD 836 from their perspective in the provision of health services and USD$597 from the societal perspective, with 601 cases of cervical cancer and 210 deaths due to cervical cancer averted due to the introduction of the bivalent vaccine program [11]. These estimates may not include the prevention of morbidities associated by HPV. A study by a neighboring country, Colombia, suggested an incremental cost effectiveness ratio (ICER) of US$2.957 per DALY averted with the 4vHPV compared to the 2vHPV [20]. The results of this study suggest that the Ecuadorian economy can reduce its financial burden by an estimated $256 million over 100 years for GW prevention, simply by choosing the 4vHPV over the 2vHPV. These savings can have a positive impact on the Ecuador's public health system as well as the economy at large, assuming the same level of macroeconomic investment in the health sector.

The monitoring of human papillomavirus (HPV) vaccination coverage is imperative to evaluate the potential impact of HPV vaccines on HPV-related diseases. Since the vaccine was approved for use in 2006, HPV vaccines have been progressively introduced in many developing countries, mainly targeting young adolescent girls aged 10–14 years [21]. Best practices of effectiveness suggest that vaccination coverage at a 70% threshold in women is the most cost-effective [22]. A meta-

analysis showed that a vaccination coverage of at least 50% delivered a 68% reduction in HPV types 16 and 18 and a 61% reduction in anogenital warts between the pre-vaccination and post- vaccination periods [23]. The results from the simulation model assumed 90% coverage with an increase of 27.123 QALYs for Ecuador when the quadrivalent vaccine is applied. Some evidence suggests that at 70% coverage, a herd protection reduction in prevalence can be observed in HPV types 16 and 18 among non-vaccinated women [21,24]. Furthermore, other studies suggest a possible decrease in the incidence of GW in women younger than 35 and in men from ages 12 to 29, based on the introduction of an HPV vaccination program in Denmark that indicated substantial herd protection [25].

In countries like Ecuador, protection of the non-vaccinated population from infection from HPV types 6, 11, 16 or 18 is equally important as vaccination programs given the challenges of implementing consistent vaccination programs nationwide over time, threats to the MOH budgets, stigma associated with STD prevention, and the absence of vaccination programs targeting young men. Evidence gathered from program implementations in Australia showed that four years after introducing the quadrivalent HPV vaccine the country experienced significant declines in proportions of under 21 years old (81.8%) and 21-30 year old (51.1%) heterosexual men diagnosed as having genital warts in the vaccination period-from 12.1% in 2007 to 2.2% in 2011 (P<0.001) and from 18.2% in 2007 to 8.9% in 2011 (P<0.001), respectively [26].

In order to monitor vaccinated and non-vaccinated populations and HPV infections in both early and recurrent cases, the epidemiological surveillance system of Ecuador's MOH must track the occurrence of sexually transmitted diseases appropriately and create policies to secure the necessary resources to combat it, along with the human capital required to maintain those resources.

4.1 Recommendations for Ecuador

In countries such as Ecuador, where HPV vaccine was introduced only recently, screening programs need to be developed or strengthened. Vaccination is a primary prevention strategy and does not replace cervical cancer screenings. Best practices for the prevention of cervical cancer include working with women across the course of their lives with a multidisciplinary set of programs and services that include education programs, pap tests in primary care, and civil society organizations that provide complementary services and palliative care. Ecuador may achieve these goals if the Model for Comprehensive Family, Community and Intercultural Health (MAIS) developed in the last decade is implemented appropriately. MAIS is based on the belief that a psychosocial, multidisciplinary and intercultural approach will respond more effectively to the needs of individuals, families and communities, to ultimately improve quality of life by reducing morbidity and mortality. Services for screening are particularly important to Ecuador's healthcare system given the unique characteristics of the country's population and their risk to HPV-related diseases. More than 50% of Ecuador's population is 24 years old and under. Thirty percent is 15 years old or younger [27]. However, MAIS' health promotion programs are deficient in addressing the risk of HPV-related diseases and it fails to record the results of their screening and vaccination programs.

Although the MOH has a legal mandate to serve the population with preventive programs and screening services, civil society organizations (CSOs) and other levels of government also have a role. Worldwide, CSOs and nonprofit organizations have focused on preventive interventions for boys and girls and addressing safe sexual practices and the use of condoms; delaying the start of sexual activity; and distilling the myths and stigma associated with male circumcision. Nonprofits are in a unique position to address issues of sex education and to portray the diversity of opinions and positions. Ecuador's

Table 1. Cost effectiveness analysis bivalent versus quadrivalent vaccination programs (Cost/QALYs)

	Cost/Person (USD*)	QALYs/Person (Year**)	Cost/QALYs (USD/Year***)
Bivalent vaccination program	$68.92	27.12349	Strongly Dominated
Quadrivalent vaccination program	$57.05	27.12590	

**Costs rounded to 0.01, **QAL Ys rounded to 0.01, ***Costs/QAL Y rounded to 1*

Table 2. Cost saving comparison of bivalent vaccination program versus the quadrivalent HPV vaccination program

Estimated Cost of Vaccination (Vaccine + Administration)	15,496,352 USD*
Estimated HPV 6/11/16/18 Disease Cost Avoided	271,947,526 USD*
Estimated Net Cost of Quadrivalent HPV Vaccination Program	-256,451,173 USD*

**Costs rounded to 0.01*

Table 3. Cost-effectiveness analysis of HPV vaccination strategies – ecuador

Scenario	Cost/ Person (USD)*	QALYs/person (year)~	Cost/ person (USD)*	QALYs person (year)~	Cost/QALYs (USD/year)^
Ecuador GW $395 Bivalent $8.50	76.33	27,123 49	-	-	Strongly dominated
Ecuador GW $395 Quadivalent $11	60.08	27,125 90	(16.26)	0.00241	

** Cost rounded to 0.01, ~ QALYs rounded to 0.00001, ^ Cost/QALY rounded to 1*

MOH stance toward sex education has been inconsistent over the last five years, at times promoting the use of condoms, sexual freedom, and reproductive rights, while at other times condemning sex among adolescents [28]. It is clear that CSOs and nonprofits can only offer complementary services, and that the MOH's leadership and resources are necessary to protect the population from infectious diseases, such as HPV. To this date, delivery using the public network schools are irregular. According to the Ministry of Education, the potential number of education circuit districts is of 1,117 units divided in 140 circuits and 9 zonal coordination offices. [29] Using the school health systems to carry out vaccinations within a school environment is known overwhelmingly improve the uptake of vaccination programs [30,31]. In most cases, successf ul uptakes of vaccination programs include a vested involvement of school nurses and educators to gather consents, speak to parents and ensure the two or three doses are applied. For example, in Uganda, the results of the HPV vaccination project held in 2008 - 2009 showed a high uptake of 99.6% of the girls targeted, and 87.8% completed all 3 doses; while in 2009 93.2% of girls received their first dose, and 86.3% completed all 3 doses [32]. Ecuador would benefit from alliances between the Ministry of Education and the MOH to improve the current HPV uptake and of information about the vaccine, provide funding, and regulate private insurance coverage and by combining strategies between Ministries and require vaccination for school entry reach the 95% coverage goal. To do so, the Ecuadorian government should introduce policies designed to increase 4vHPV availability.

5. CONCLUSION

The burden and cost of HPV-associated disease and cancer remain an important public health problem in Ecuador. With a female population of childbearing age remaining highly susceptible to contracting STDs—and specifically to developing a pathology of genital wart HPV, the cost to society of this disease is particularly high. Reducing the burden of HPV-associated cancer and disease, including GW, through vaccination requires an integrated approach that includes clinical medicine and public health policies that are implemented effectively and given the necessary resources to ensure their success. The aforementioned analysis suggests that a quadrivalent HPV vaccination program would be cost- saving within the context of the Ecuador health care system.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. World Health Organization. Sexually transmitted diseases; 2011 [Agosto 2011].

Available:http://www.who.int/mediacentre/factsheets/ fs110/es/

2. Park IU, Introcaso C, Dunne EF. Human papillomavirus and genital warts: A review of the evidence for the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. Clinical Infectious Diseases. 2015;61(Suppl. 8):S849-S55.
3. W igle J, Fontenot HB, Zimet GD. Global delivery of human papillomavirus vaccines. Pediatric Clinics of North America. 2016; 63(1):81-95.
4. Muñoz N, Castellsagué X, de González AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. Vaccine. 2006; 24(Supplement 3):S1-S10.
5. Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine. 2006; 24(Supplement 3(0):S11-S25.
6. Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: A meta-analysis. Bristish Journal of Cancer. 2003;88(1):796.
7. Garland SM, Steben M, Sings HL, James M, Lu S, R R. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. Journal of Infectious Diseases. 2009;199(6):805-14.
8. Centers for Disease Control and Prevention. FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). MMW R Morbidty Mortal Weekly Report. 2010; 59(20):630.
9. Centers for Disease Control and Prevention. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). MMWR Morbidity Mortality Weekly Report. 2010;59(20):626.
10. Centers for Disease Control. HPV Vaccines: Vaccinating Your Preteen or Teen; 2016
Available:https://www.cdc.gov/hpv/parents/vaccine.html
(August, 27, 2016)
11. Ministry of Health. Technical and administrative guidelines to introduce HPV vaccine in the public health care services. Quito, Ecuador; 2013.
12. National Tumor Registry. Uterous Cancer Epidemiologic Surveillance; 2012.
Available:http://www.solcaquito.org.ec/index.php/en/el-cancer/tipos-de-cancer/cancer-de-cuello-uterino
13. Bruni L, Barrionuevo-Rosas AG, Aldea M, Serrano B, Valencia S, Brotons M, et al. Human Papillomavirus and Related Diseases in Ecuador. ICO Information Centre on HPV and Cancer (HPV Information Centre); 2016.
14. Castellsagué A. Xavier, San Martín B. María, González B. Antonio, Casado C. Miguel Ángel. Epidemiology of precancer lesions and genital warts associated with Human papilloma virus infection in Spain. Progresos de Ginecologia y Obstetricia. 2010;53(03).
15. Ministry of Health. Guide for HPV vaccine to prevent uterous cancer in Ecuador Quito, Ecuador; 2012.
Available:http://www.salud.gob.ec/vacuna-contra-el-virus-del-papiloma-humano-previene- cancer- uterino-en-el-ecuador/
16. Elbasha E, Dasbach E, Insinga RP. Model for Assessing Human Papillomavirus Vaccination Strategies. Emerging Infectious Diseases. 2007;13(1):28.
17. Elbasha E, Dasbach E, Insinga RP. A Multi- Type HPV Transmission Model. Bulletin of Mathematical Biology. 2008;70: 2126.
18. Roldos MI, Bustamante V. Consensus of clinical practices and associated costs to diagnose and treat genital warts caused by Human Papilloma Virus in Ecuador: Results from a panel of experts. Journal of Health, Sport and Tourism. 2014;5(1):11-7.
19. Ministry of Finance. General Budget General Description; 2016.
20. Morales Vasquez RC, Rios Romero OG, Alvis Guzmán NRA. Determinación de costo-efectividad de la vacunación contra VPH en Cartagena de Indias: Universidad de Cartagena; 2013.
21. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: A pooled analysis. The Lancet Global Health. 2016;4(7):e453-e63.
22. Canfell K, Chesson H, Kulasingam S, Berkhof J, Diaz M, Kim J. Modeling preventative strategies against human papillomavirus-related disease in

developed countries. Vaccine. 2010;30: F157–F67.
23. Kury CMH, Kury MMH, Silva RMH, Oliveira FAS, de Moraes JC, De Moraes JGSA, et al. Implementation of the quadrivalent vaccine against HPV in the Municipality of Campos dos Goytacazes, Brazil – A combination of strategies to increase immunization coverage and early reduction of genital warts. Trials in Vaccinology. 2013;2:19-24.
24. Cameron RL, Kavanagh K, Pan J, Love J, Cuschieri K, Robertson C, et al. Human Papillomavirus Prevalence and Herd Immunity after Introduction of Vaccination Program, Scotland, 2009–2013. Emerging Infectious Diseases. 2016;22(1):56-64.
25. Bollerup S, Baldur-Felskov B, Blomberg M, Baandrup L, Dehlendorff C, Kjaer SK. Significant reduction in the incidence of genital w arts in young men 5 years into the danish human papillomavirus vaccination program for girls and women. Sexually Transmitted Diseases. 2016; 43(4):238-42.
26. Ali H, Donovan B, W and H, Read TRH, Regan DG, Grulich AE, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: National surveillance data. BMJ: British Medical Journal. 2013;346.
27. National Institute of Census and Statistics. Population descriptive projection by area and sex 2010-2020. Quito, Ecuador; 2013.
28. Ministry of Health. National Program to prevent and control HIV and ETS 2007-2015. Quito, Ecuador; 2011.
29. Education Mo. New Educational Model by zone, district and circuits Quito, Ecuador; 2013.
Available:https://educacion.gob.ec/zonas-distritos-y- circuitos/
30. Whelan NW, Steenbeek A, Martin-Misener R, Scott J, Smith B, D'Angelo-Scott H. Engaging parents and schools improves uptake of the human papillomavirus (HPV) vaccine: Examining the role of the public health nurse. Vaccine. 2014;32(36):4665-71.
31. Laugesen MJ, Mistry R, Carameli KA, Ribisl KM, Needleman J, Bastani R. Early policy responses to the human papillomavirus vaccine in the United States, 2006–2010. Journal of Adolescent Health. 2014;55(5):659-64.
32. Moodley I, Tathiah N, Mubaiwa V, Denny L. High uptake of Gardasil vaccine among 9-12-year-old schoolgirls participating in an HPV vaccination demonstration project in KwaZulu-Natal, South Africa. SAMJ: South African Medical Journal. 2013;103(5):313-7.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/20743