Early impact in reducing cervical abnormalities in Campos dos Goytacazes, RJ, Brazil, after introduction of the quadrivalent HPV vaccine for girls 11–15: is it time to think about HPV vaccine in boys?

Impacto precoce na redução de anormalidades cervicais em Campos dos Goytacazes, RJ, Brasil, depois da introdução de vacina quadrivalente de HPV em meninas de 11 a 15 anos: é hora de pensar em vacinas HPV para rapazes?

Charbell Miguel Haddad Kury[1], Abdalla Dib Chacur[2], Cristiano Salles Rodrigues[3], Hugo Oliveira Freixo[4], Andrei Vargas Vieira Lopes[4], Renata Louzada de Moraes[4], Verônica França Misse[4], Leonardo Cordeiro Abreu[4], Melissa Martins Barbosa[4], Marcus Miguel Haddad Kury[4], Sílvia Baeta Cavalcanti[5], Oswaldo Gonçalves Cruz[6]

ABSTRACT

Introduction: Human papillomavirus (HPV) is a huge concern in public and private health. The prevention of this condition is the combination of the use of Papanicolaou smear test, condoms and HPV vaccines. Campos dos Goytacazes, RJ, is the first Brazilian municipality to implement in September 2010 the quadrivalent HPV vaccine (Gardasil®) for girls in the age group of 11–15 years, in a hybrid strategy of vaccination (schools and health centers). In 2014, the vaccination was started also for boys, at the same time that the Ministry of Health introduced it for girls. **Objective:** The aim of the study was to analyze the trends in reduction of low-grade cervical abnormalities five years after the introduction of the quadrivalent HPV vaccine in this municipality (primary outcome). Furthermore, this study evaluated the relative risk (RR) of each of the groups studied, in order to explain the protective effect of the vaccine (secondary outcome). **Methods**: The ecological analysis evaluated the impact of HPV vaccination as a protective factor against low risk of HPV abnormalities. Results of the Pap smear test obtained from the Brazilian Ministry of Health's Sistema de Informação do Câncer do Colo do Útero (SISCOLO) were categorized in low-grade abnormalities (LGA) and high-grade abnormalities (HGA). This preliminary study focused in LGA rates, which were estimated for a 1-month period and then stratified by four age groups (<20; 20–24; 25–30; >30 years) from 2007 to 2014. A quantitative comparison of LGA temporal trends before and after vaccination was done with Quasi-Poisson regression analysis. The protective effect of the vaccine over time was evaluated by calculating the RR in each age group. **Results:** The study showed significant decrease of more than 60% in LGA in women <20 years old, and less, almost 50% for the other groups. HPV vaccine was a protective factor, because the RR result was <0.0001 in all age groups. **Conclusions:** Although the studies show that the pre-HPV neoplastic lesions may be reversible spontaneously, it is undeniable that the vaccine contributes greatly to the high reduction rates, associated with high vaccination coverage. These results are the first in Brazil and in future may address the necessity to discuss the vaccination for boys in the context of the same results obtained in Australia.

Keywords: Papillomaviridae; human papillomavirus recombinant vaccine quadrivalent, types 6, 11, 16, 18; Papanicolaou test; immunization coverage; uterine cervical neoplasms.

RESUMO

Introdução: O papilomavírus humano (HPV) é uma grande preocupação na saúde pública e privada. A prevenção dessa condição é a combinação do uso do exame de Papanicolaou, de preservativos e de vacinas contra o HPV. Campos dos Goytacazes é o primeiro município brasileiro a implementar em setembro de 2010 a vacina quadrivalente contra o HPV (Gardasil®) para meninas de 11 a 15 anos de idade em uma estratégia híbrida de vacinação (escolas e centros de saúde). Em 2014, a vacinação começou para os meninos na mesma época em que o Ministério da Saúde introduziu a vacina para as meninas. **Objetivo:** O objetivo do estudo foi analisar as tendências na redução de anormalidades cervicais de baixo grau cinco anos depois da introdução da vacina quadrivalente de HPV na cidade (resultado primário). Além disso, esta investigação avaliou o risco relativo de cada grupo analisado, de maneira a explicar o efeito protetor da vacina (resultado secundário). **Métodos:** A análise ecológica avaliou o impacto da vacinação contra o HPV como um fator protetor contra o baixo risco de anormalidades pelo HPV. Os resultados do teste de Papanicolaou, obtidos por meio do Sistema de Informação do Câncer do Colo do Útero (Siscolo) do Ministério da Saúde, foram categorizados em anormalidades de baixo grau (LGA) e anormalidades de alto grau (HGA). Este estudo preliminar foi centrado nas taxas de LGA, as quais foram estimadas para o período de um mês e estratificadas por quatro grupos etários (<20; 20-24; 25-30; >30 anos) de 2007 a 2014. A comparação quantitativa das tendências temporais de LGA antes e depois da vacinação foi feita com análise de regressão de Quase-Poisson. O efeito protetor da vacina ao longo do tempo foi avaliado por cálculo do risco relativo em cada grupo de idade. **Resultados:** O estudo mostrou diminuição significativa de mais de 60% em LGA em mulheres de <20 anos de idade e de pelo menos cerca de 50% para os outros grupos. A vacina contra o HPV foi um fator de proteção, por causa do resultado do risco relativo de <0,0001 em todas as idades. **Conclusões:** Embora os estudos mostrem que as lesões pré-neoplásicas do HPV possam ser reversíveis espontaneamente, é inegável que a vacina contribuiu grandemente para as taxas elevadas de redução, associadas com a alta cobertura vacinal. Esses resultados são os primeiros no Brasil e podem dirigir no futuro a necessidade de discutir a vacinação dos meninos no contexto dos mesmos resultados obtidos na Austrália.

Palavras-chave: Papillomaviridae; vacina quadrivalente recombinante contra HPV tipos 6, 11, 16, 18; teste de Papanicolaou; cobertura vacinal; neoplasias de colo de útero.

INTRODUCTION

The human papillomavirus (HPV) is the most common infection of the genital tract. It is a sexually transmitted virus with a high outcome of morbidity and mortality, accounting for about 270,000 deaths of cervical cancer annually in women worldwide, 85% of them in low- and middle-income countries[1].

According to the World Health Organization (WHO), more than 819 million men and women (11.7% of the world population) are infected with this virus[2]. In Brazil, it is estimated that there are approximately 10 million infected with HPV and that 700,000 cases occur each year, and it is considered therefore an epidemy[3]. The risk of acquiring HPV infection during their lifetime for sexually active men and women is at least 50%. At age 50, at least 80% of women will have acquired genital HPV infection[4].

HPV is non-enveloped viruses with an icosahedral capsid, presenting circular double-stranded DNA encoding growth proteins. It belongs to a heterogeneous family of more than 100 different genotypes. Among these genotypes, 40 of them can infect the anogenital region[5]. They are classified as high-risk and low-risk HPV.

In molecular epidemiology, the most important HPV types are 16 and 18 (high risk), responsible for 70% of cases of cervical cancer, and types 6 and 11 (low risk), which account for 90% of cases of genital warts[6-8]. This virus can be also associated with other types of cancer, in addition to affecting the anogenital tract, such as the cancer on the laryngeal, respiratory, and digestive tracts[9,10].

The portfolio for the protection against HPV considers the combination of Papanicolaou smear (preventive) associated with the use of condoms and vaccination as state of the art in preventing the HPV infection. Currently, the Ministry of Health provides the vaccine freely for the entire country since 2014, only for girls. Alternatively, the municipality of Campos dos Goytacazes, in the state of Rio de Janeiro, Brazil, began in September 2010 free vaccination for all girls between 11 and 15 years old, living in the city, and expanded this statement to the boys in 2014[11]. Interestingly, Campos dos Goytacazes followed the national program protocol immunization against HPV in Australia.

OBJECTIVE

The aim of the study was to analyze the trends in the reduction of low-grade cervical abnormalities five years after the introduction of the quadrivalent HPV vaccine in this municipality (primary outcome). Furthermore, this investigation evaluated the relative risks (RR) of each of the groups studied in order to explain the protective effects of the vaccine (secondary outcome).

METHODS

Characteristics of the city

Campos dos Goytacazes is the municipality with the largest jurisdiction in the state of Rio de Janeiro, comprising 4,026 km^2 of territorial distribution, with an estimated population of 483.970 individuals according to the latest demographic census[12] (**Figure 1**). The economic activity is mainly supported by petroleum extract, which represents 80% of the Brazilian production.

Study description

An historical cohort was formed to evaluate the impact of HPV vaccination as a protective factor against low-risk HPV abnormalities. The results of the Pap smear test obtained from the Brazilian Ministry of Health database (SISCOLO system), were categorized in low-grade abnormalities (LGA) and high-grade abnormalities (HGA). This preliminary study focused in LGA rates, which were estimated for 1-month period and stratified by four age groups (<20; 20–24; 25–30; >30 years) from 2008 to 2014.

Place and duration of the study

The study was conducted at the Hospital Escola Álvaro Alvim (HEAA), the only hospital of the municipality responsible for conducting cervical smear tests by the Unified Health System (SUS). It is known for its total number of scans each year. An active research was carried out within each test in these eight years. In the case of presence of a positive test for low- or high-grade lesions, we categorized it according to the year of realization, age and degree of this lesion.

Ethical consideration

The study was conducted in compliance with the ethical principles originating in, or derived from, the Declaration of Helsinki, and in compliance with all Good Clinical Practices. The study was approved by the Ethical Committee of the Faculdade de Medicina de Campos (Protocol No. 33063214.4.0000.5244).

This is the first Brazilian ecological analysis of reduction of low-grade abnormalities related to HPV vaccination in the first city in Brazil that introduced the quadrivalent vaccine against HPV.

[1]Professor responsável de Microbiologia e Bioquímica da Faculdade de Medicina de Campos (FMC) – Campos dos Goytacazes (RJ), Brasil. Membro do Comitê de Infectologia Pediátrica da Sociedade de Pediatria do Estado do Rio de Janeiro (SOPERJ). Mestre em Microbiologia e Parasitologia Aplicada pela Universidade Federal Fluminense (UFF) – Niterói (RJ), Brasil.

[2]Professor responsável de Ginecologia da FMC – Campos dos Goytacazes (RJ), Brasil. Mestre em Ginecologia pela Universidade Federal do Rio de Janeiro (UFRJ) – Rio de Janeiro (RJ), Brasil.

[3]Professor auxiliar de Ginecologia e Obstetrícia da UFRJ, *Campus* Macaé – Macaé (RJ), Brasil. Professor auxiliar III de Ginecologia e Obstetrícia da FMC – Campos dos Goytacazes (RJ), Brasil. Mestre em Planejamento Regional e Gestão de Cidades pela Universidade Cândido Mendes – Campos dos Goytacazes (RJ), Brasil.

[4]Acadêmico da FMC – Campos dos Goytacazes (RJ), Brasil.

[5]Professora titular da disciplina de Virologia do Departamento de Microbiologia e Parasitologia da UFF – Niterói (RJ), Brasil. Doutora em Ciências (Microbiologia) pela UFRJ – Rio de Janeiro (RJ), Brasil. Mestre em Ciências (Microbiologia) pela UFRJ – Rio de Janeiro (RJ), Brasil.

[6]Doutor em Engenharia Biomédica pela UFRJ – Rio de Janeiro (RJ), Brasil. Mestre em Saúde Pública pela Faculdade de Saúde Pública da Universidade de São Paulo – São Paulo (SP), Brasil. Membro permanente do Programa de Biologia Computacional do Instituto Oswaldo Cruz da Fundação Oswaldo Cruz (IOC/FIOCRUZ) – Rio de Janeiro (RJ), Brasil.

Calculation of vaccination coverage

The coverage calculation was performed using a method described by Moraes et al.[13], which gives a relationship between the number of vaccinated and the total number of individuals of the same age. The female population used in the denominator was calculated for the years 2010, 2011, and 2012, according to Brazilian Institute of Geography and Statistics (IBGE). They were entered in the numerator of immunization data for the first and third doses (full course).

Calculation of the Pap smear coverage

According to the protocol of the Ministry of Health[14], every woman who has or has had sexual life must undergo the preventive periodic review, especially those between 25 and 64 years old. Initially, the test should be done annually. After two consecutive tests (with an interval of one year) with normal results, preventive tests can now be done every three years. Thus, considering the city's population of 119,000 women, it has to be about 4,000 who will be examined in this age group of 25 and 26 years (4,000 per age group). Considering two standard tests and performance after three years, we have a total denominator of 47,000 Pap smears per year to be held in the city to achieve 100% coverage screening.

Study design and data analysis

Data of Pap smears were collected from the HEAA database. The variables analyzed were age and the type of abnormalities grade. Data of Pap smears were collected from the HEAA database. The study included the first Pap smear of the patient in the timeline. The variables analyzed were age and the type of cervical abnormalities. Inclusion criteria were to be a resident of the municipality and a Pap smear with cervical abnormalities classified in low and high; exclusion criteria were indeterminate cervical abnormalities and sequential Pap smear after any cervical intervention.

Statistical analysis included a quantitative comparison of LGA temporal trends before and after vaccination, which was done with Quasi-Poisson regression analysis by using R archive network software®.

The same statistical analysis had calculated the protective effect of the vaccine on the timeline and was assessed by calculating the RR in each age group, and the aim of estimating the protection of the vaccine.

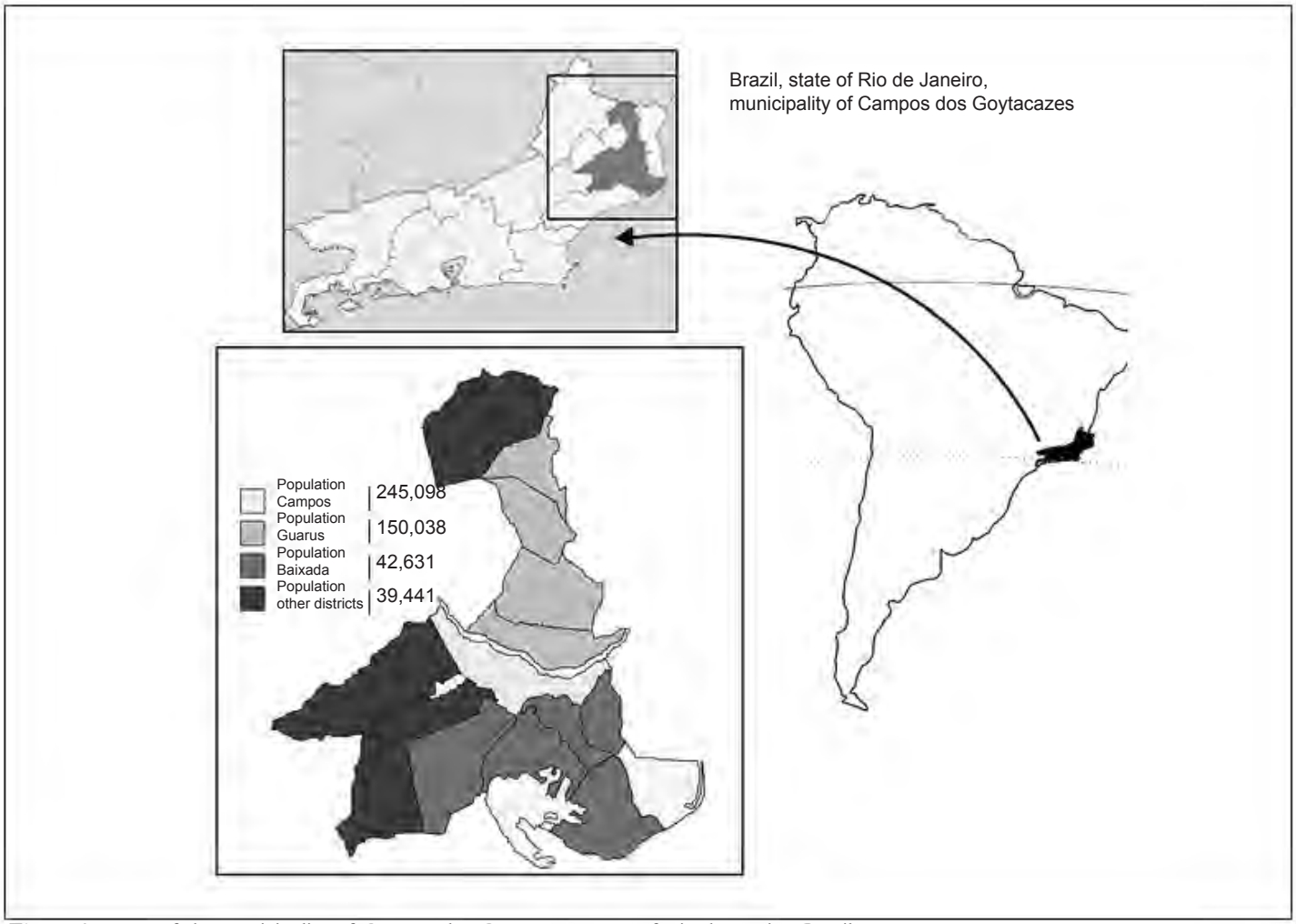


Figure 1 – Map of the municipality of Campos dos Goytacazes, state of Rio de Janeiro, Brazil.

RESULTS

Vaccination coverage

Table 1 summarizes the number of vaccines administered in 2010–2014. In this period, they were applied in about 103,326 doses, vaccination coverage variables. It should be noted that in 2010 the third dose of the vaccine had not been administered because of the beginning of the implementation of the vaccine in September 2010.

Another important comment appears about the period including the end of 2013 and beginning of 2014, with the implementation of the HPV vaccine by the Ministry of Health. Conversely, the federal government HPV vaccine schedule consisted of the alternative scheme of three doses in the time frame of zero, six and 60 months.

Table 2 shows the Pap smear coverage for each year, before and after the vaccination intervention. It should be noted that the Pap smear coverage of the city of Campos dos Goytacazes always had a level below the Brazilian average, which according to Brazilian surveys is about 65%[15].

Table 1 – Quadrivalent HPV vaccine coverage among adolescents by dose and year of vaccination, Campos dos Goytacazes, Brazil.

	11 years (vg/pop=vc)	12 years	13 years	14 years	15 years	AVC (%)
2010						
1st dose	1,583/4,083=38.7%	1,695/3,923=43.2%	2,321/3,969=58.4%	1,930/4,031=47.8%	3,219/4,280=75.2%	52.9%
3st dose	0	0	0	0	0	0.0%
2011						
1st dose	3,756/4,122=91.1%	3,121/3,960=78.8%	3,948/4,007=98.5%	3,210/4,069=78.8%	4,231/4,321=97.9%	89.02%
3st dose	2,650/4,122=64.2%	2,054/3,960=51.8%	3,218/4,007=80.3%	2,430/4,069=59.7%	2,980/4,321=68.9%	65.1%
2012						
1st dose	3,680/4,159=88.4%	3,223/3,996=80.6%	3,890/4,042=96.2%	3,460/4,105=84.2%	4,087/4,359=93.7%	87.9%
3st dose	2,423/4,159=58.2%	3,112/3,996=77.8%	2,980/4,042=73.70%	2,646/4,105=64.4%	2,530/4,359=58%	66.2%
2013						
1st dose	3,025/4,052=74.6%	3,834/4,161=92.1%	2,737/4,177=65.5%	1,995/4,133=48.3%	1,754/4,385=40%	64.1%
3st dose	1,209/4,159=29.8%	1,209/4,161=24.5%	1,366/4,177=32.7%	802/4,133=19.4%	987/4,385=22.5%	25.78%
2014						
1st dose	3,428/4,052=84.6%	3,054/3,996=76.4%	3,525/4,177=84.3%	425/4,133=10.2%	335/4,385=7.6%	52.62%
3st dose	424/4,052=10.2%	3,110/3,996=77.8%	343/4,177=8.2%	120/4,133=2.9%	104/4,359=2.3%	20.28%
Total doses	**22.178**	**22.358**	**21.646**	**16.917**	**20.227**	**103.326 doses**

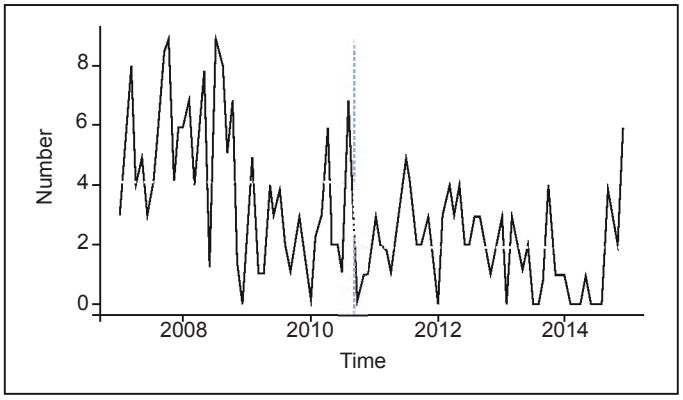
Vg: vaccines given; pop: adolescent population in the years 2010, 2011, 2012, 2013 and 2014; vc: vaccination coverage; AVC: average vaccination coverage.

Table 2 – Pap smear coverage and absolute number of low-grade and high-grade abnormalities, Campos dos Goytacazes, 2010–2014.

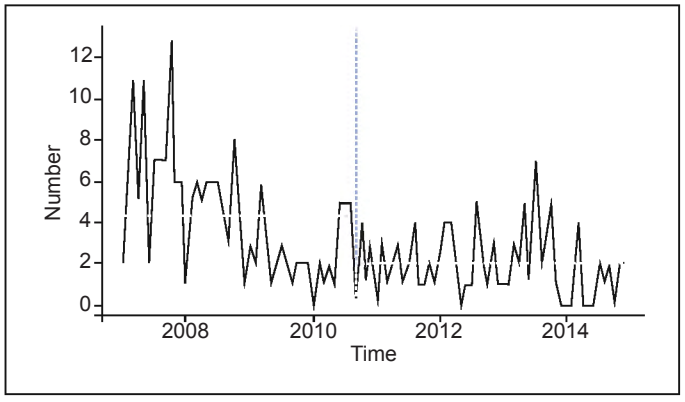
	Years	Pap test	Pap smear coverage (%)	LGA	HGA	LGA + HGA
2008	Total	21,120	44,90	346	78	424
	Up to 20	1,668		71	6	77
	21–30	4,118		117	17	134
	>30	15,334		158	55	213
2009	Total	22,108	47	205	65	270
	Up to 20	1,923		29	7	36
	21–30	3,647		76	13	89
	>30	16,538		100	45	145
2010	Total	24,438	51,90	197	112	315
	Up to 20	2,370		39	7	44
	21–30	4,276		52	24	82
	>30	17,792		106	81	187
2011	Total	27,780	59,10	210	123	334
	Up to 20	2,111		34	6	40
	21–30	4,500		59	29	88
	>30	21,169		117	88	205
2012	Total	18,931	42,40	171	67	238
	Up to 20	1,684		34	5	39
	21–30	3,407		53	10	63
	>30	13,840		84	52	136
2013	Total	27,485	58,40	143	41	184
	Up to 20	2,033		21	1	22
	21–30	4,919		58	2	60
	>30	20,533		64	38	102
2014	Total	24,337	51,70	92	70	160
	Up to 20	2,263		18	2	20
	21–30	4,234		26	7	33
	>30	17,840		48	61	107

LGA: low-grade abnormalities; HGA: high-grade abnormalities.

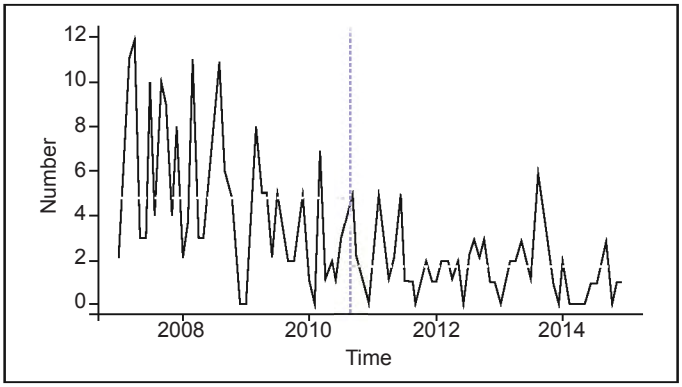
We recorded a significant decrease of 54.2%, considering all ages, in the incidence of LGA, by just comparing three years before and three years after the implementation of the quadrivalent vaccine (**Graphics 1, 2, 3 and 4**). However, the most important reduction was observed in the age group between 21 and 30 years (55.2%), followed by the age group above 30 years (53.2%), and at last the age group comprising the girls until 19 years old.



Graphic 1 – Low-grade abnormalities reduction in women aged up to 19 years old.



Graphic 2 – Low-grade abnormalities reduction in women aged 20–24 years old.



Graphic 3 – Low-grade abnormalities reduction in women aged 25–29 years old.

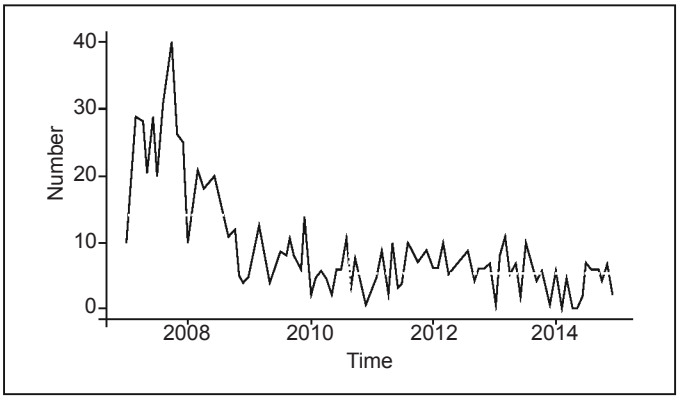
The next analysis comprised the RR evaluation, which can be observed in **Graphic 5**. In that analysis, it is undeniable that the vaccination played an important role in the reduction of the cervical preneoplastic abnormalities, with RR <0.0001 in all age groups. Again, it is not a surprise that the vaccination is a protective intervention mainly in the group with the women between 25 and 29 years old.

DISCUSSION

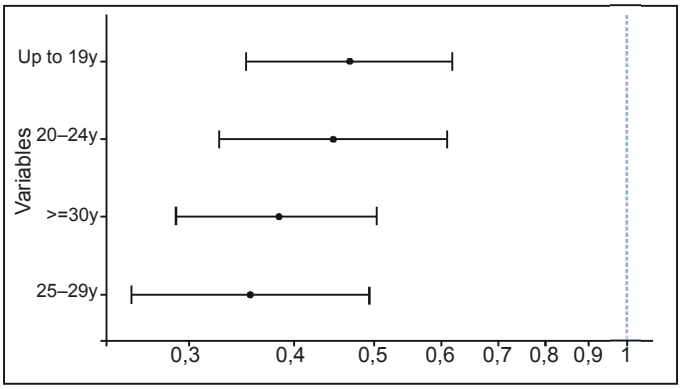
In this study, we sought to determine the possible effect of the HPV vaccine by reducing LGA in a middle city of the countryside of Brazil. So far, Campos dos Goytacazes was the first city in Brazil that implemented HPV vaccine until March 2014 with its own resources when the Ministry of Health introduced the vaccine for girls. In the same time the municipality introduced the vaccine for boys.

From 2010 to 2014, more than 100,000 doses of Gardasil® were administered and the technicians of the public health overcame some challenges, like the "hybrid" strategy of vaccination by using schools and public sites; the prejudice that the parents and relatives had associated with the vaccination, like sexual issues, among others. This strategy showed the reduction in genital warts, but the reduction in LGA was being conducted[16].

Once again, the implementation of this vaccine was challenging, but we tried to overcome it by reducing the LGA in at least 50% for all age groups. These findings are close to the preliminary study in Victoria, Australia, which showed some findings that allowed



Graphic 4 – Low-grade abnormalities reduction in women aged 30 years old and above.



Graphic 5 – Relative risk in purchasing low-grade abnormalities in women by age group.

reduction from 40,80 to 47,49% in some age groups. The same article showed the protective role of the HPV vaccine by the reduced RR[17].

After that, other studies showed similar results. In the United States of America, Hariri et al.[18] evaluated the effectiveness of Gardasil® in women who received more than one dose of vaccination. This interesting study showed the reduction in prevalence of the cervical abnormalities from 53.6% to 28.4% in women who were vaccinated at least 24 months before the trigger test.

A recent study from Sweden showed more important results in women aged 13–29 years old who were vaccinated for HPV and were followed for a HPV screening. In this investigation, the effectiveness of the vaccine was about 75% for those girls initiating vaccination before 17 years old[19].

There are several limitations in this study. First, there are some publications that address the role of the natural immunity in the regression of LGA. According to Schiffman and colleagues[20], the immune response to HPV naturally leads to virus destruction in three years; it is expected that there may be influence of chance in the improvement of the cases and this factor must be carefully excluded from the study. Another factor that should be carefully analyzed is the vaccination coverage, important to the achievement of successful strategies against HPV unfavorable outcomes. Finally, we must infer the role played by the coverage of the Pap smear test, we should monitor this indicator carefully to properly assess the impact of vaccination in improving the incidence of LGA and HGA.

CONCLUSION

Although the studies showed that the cervical LGA and HGA lesions might be reversible spontaneously, it is undeniable that the vaccine contributed greatly to the high reduction rates, associated with high vaccination coverage. These results are the first in Brazil and may address in the future the necessity to discuss the vaccination of boys in the context of the same results obtained in Australia.

Funding source

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Conflict of interests

The authors reported no conflict of interests.

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Address for correspondence:
CHARBELL MIGUEL HADDAD KURY
Rua Camara Junior, 42, apto 102 – Campos dos Goytacazes
Rio de Janeiro (RJ), Brazil.
CEP: 28035-135
E-mail: charbellkury@hotmail.com

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