

WHY IS THE NONVALENT HPV VACCINE SO IMPORTANT FOR BRAZIL?

POR QUE A VACINA NONVALENTE CONTRA O HPV É TÃO IMPORTANTE PARA O BRASIL?

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ABSTRACT

Genital Human papillomavirus (HPV) infection is the most common sexually transmitted infection worldwide. It presents from latent infection to anogenital and oropharyngeal carcinoma in both men and women. Cervical cancer is still the most prevalent cancer associated with HPV and in many countries, such as Brazil, is considered an epidemic, although Pap smears are available in public and considered a way of prevention of the disease. However, in Brazil, the coverage of this test is very low, reflecting the maintenance of high mortality for this disease for decades. The most effective way to prevent this disease, of course, is to prevent HPV infection with vaccination. High vaccine coverage using the 4HPV vaccine, which is available in Brazil, would provide a significant reduction in cancer in our country, whereas the use of 9HPV would prevent almost all high-grade lesions, true precursors of cervical cancer.

Keywords: Papillomaviridae; papillomavirus infections; Papanicolaou test; papillomavirus vaccines.

RESUMO

A infecção genital pelo papilomavírus humano (HPV) é a infecção de transmissão sexual mais frequente no mundo inteiro. Ela se apresenta desde a infecção latente até o carcinoma da área anogenital e orofaringe em homens e mulheres. O câncer de colo de útero ainda é o mais prevalente associado ao HPV e em muitos países, como no Brasil, é considerado uma epidemia, apesar de o exame de Papanicolaou estar disponível nas redes públicas e ser considerado uma forma de prevenção da doença. No entanto, no Brasil, a cobertura deste exame é muito baixa, refletindo na manutenção da alta mortalidade por esta doença há décadas. A forma mais eficaz de prevenção desta doença, sem dúvida, é a prevenção da infecção pelo HPV através das vacinas. Uma alta cobertura vacinal, utilizando a vacina 4HPV, que é a disponível no Brasil, proporcionaria uma redução importante do câncer em nosso meio, ao passo que a utilização da 9HPV, preveniria a quase a totalidade das lesões de alto grau, verdadeiras precursoras do câncer de colo de útero.

Palavras-chave: Papillomaviridae; infecções por papillomavirus; teste de Papanicolaou; vacinas contra papillomavirus.

INTRODUCTION

Genital HPV infection is the most frequent Sexually Transmitted Infection (STI) in both women and men⁽¹⁾. It is estimated that at least 50% of sexually active individuals will enter in contact with HPV at some point in their lives, and that 80% of women will have this contact up to 50 years of age⁽²⁾. We can consider this an epidemic infection in Brazil, because there are from 9 to 10 million infected people with this virus, and 700,000 more new cases are found every year⁽³⁾.

Recently, preliminary results of the prevalence of HPV infection in Brazil were published in the POP Study (Papillomavirus Prevalence Study in Brazil), a cross-sectional study with 7,586 individuals sexually active (5,812 women and 1,774 men) from 16 to 25 years old, in the 26 capitals of Brazil and the Federal District. HPV prevalence was 54.6% with positive high-risk HPV in 38.4% of the participants. The highest prevalence was in Salvador City, with a positivity rate of 71.9%, and the lowest rate in Recife, with 41.2%⁽⁴⁾.

Worldwide, 32 million new cases of genital warts are estimated each year (Brazil, around 1.9 million/year), and the vast majority is associated to HPV 6 (70% of cases) and 11 (20% of cases)⁽⁵⁾.

HPV INFECTION AND CANCER

For the biennium 2018-2019, 16,370 new cases of cervical cancer per year in Brazil are estimated, with a risk of 15.43 cases/100,000 women occupying the third position, only after breast and colon/rectum cancer. However, without considering non-melanoma skin cancer, cervical cancer is the first most incident in the Northern region (25.62/100,000 women)⁽⁶⁾. The estimate of deaths is 8,079 cases/year

(7.5/100,000 women)⁽⁷⁾. If we consider other types of HPV-related cancers, we can also consider HPV-induced cancer an epidemic in Brazil (Table 1)⁽⁷⁾.

HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82, 26, 53, 66 and 73 are the most often considered high oncogenic risk, and HPV types 6, 11, 40, 42, 43, 44, 53, 54, 54, 61, 70, 72, 73, 81, CP6108, low risk⁽⁸⁾. In general, HPV 16 and 18 account for 70% of cases of cervical cancer, and 80-90% of cases of HPV cancers induced in other areas, whereas HPV 6 and 11 are the causes of at least 90% of anogenital warts and almost all larynx papillomatoses⁽⁹⁾. High-risk HPV is still responsible for cancer of other organs, such as anus, in 90%; 70% of the vagina, 50% of the penis; 40% of the vulva; and 13-72% of the oropharynx⁽¹⁰⁾.

HPV VACCINE EFFICACY

Currently, the most effective way to prevent infection and HPV-associated diseases is the use of vaccines. Up to date, three vaccines are available on the international market: the bivalent or Cervarix[®] (2HPV — protection against HPV 16 and 18), the quadrivalent or

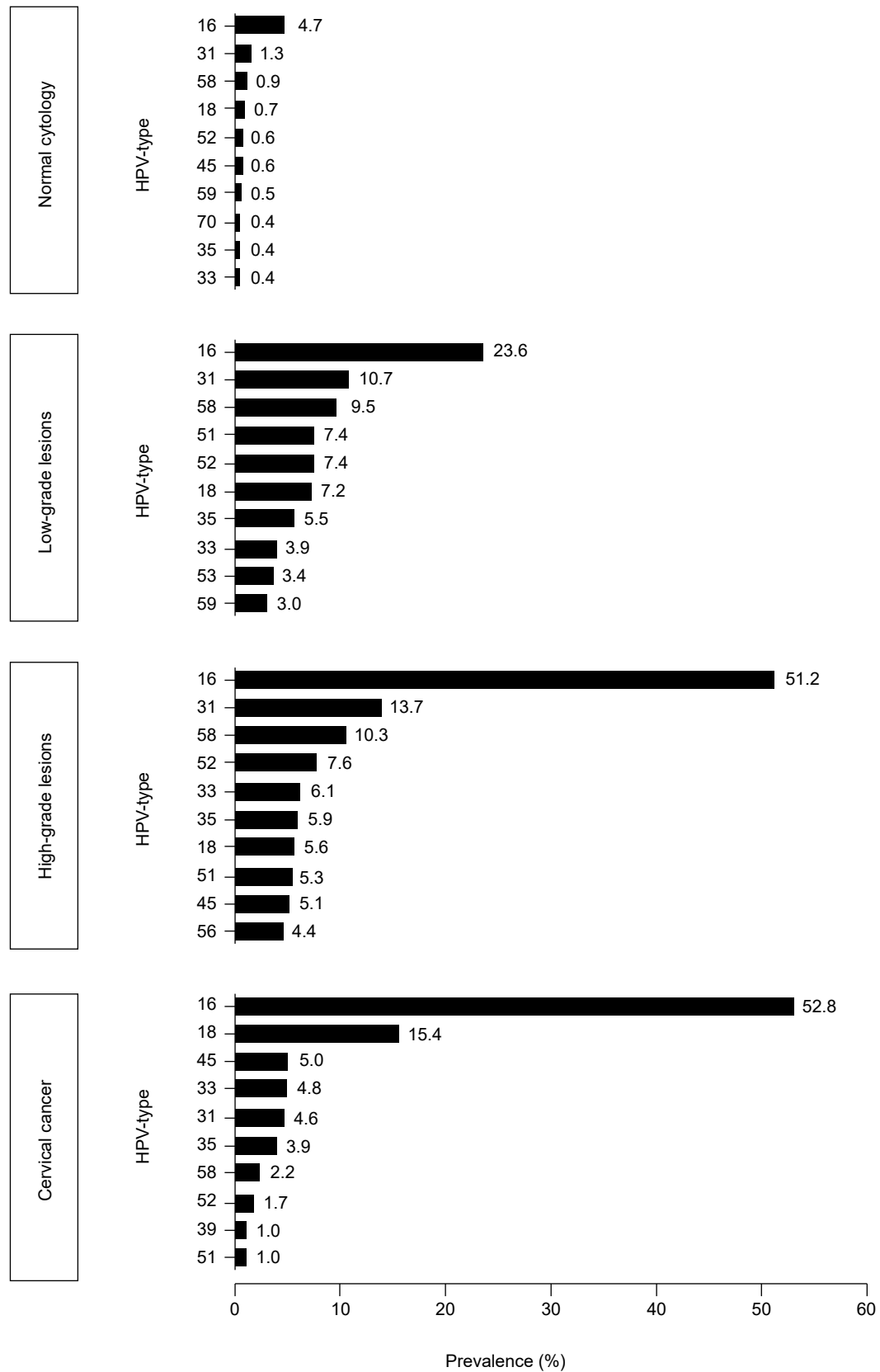
Table 1 – Crude incidence rates of HPV-related cancers/100,000.

	Male	Female
Cervical cancer	-	15.2
Anal cancer	0.3-1.2	0.8-1.7
Vulvar cancer	-	0.8-2.7
Vaginal cancer	-	0.0-0.9
Penile cancer	0.3-2.0	-
Oropharyngeal cancer	3.7	0.8

HPV: Human papillomavirus.

Source: ICO/IARC Information Centre. Human Papillomavirus and Related Diseases Report – Brazil, 2019⁽⁷⁾.

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Source: ICO/IARC Information Centre. Human Papillomavirus and Related Diseases Report – Brazil, 2019⁽⁷⁾.

Figure 1 – Comparison of the ten most frequent human papillomavirus (HPV) oncogenic types in Brazil among women with and without cervical lesions.

Table 2 – Human papillovirus (HPV) types in the cervix with and without lesion in Brazil.

HPV INFECTION	HPV 16, 18 (%)	HPV 16, 18, 31, 33, 45, 52, 58 (%)
Normal Cytology	5.4	9.2
LSIL	30.8	62.3
HSIL	56.8	99.6
Cervical cancer	68.2	86.5

LSIL: low-grade lesion; HSIL: high-grade lesion.
 Source: ICO/IARC Information Centre. Human Papillomavirus and Related Diseases Report – Brazil, 2019⁽⁷⁾.

Gardasil® (4HPV — against HPV 6, 11, 16, and 18), and the nonavalent or Gardasil 9® (9HPV — against HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58), which were highly effective and safe in clinical trials with rates of 95-100% efficacy in the prevention of genital warts and precancerous lesions of the lower genital tract associated to HPV 16 and 18 (2HPV and 4HPV) and for the other five types of high-risk HPV for nonavalent vaccine⁽¹¹⁾. Although the 9HPV vaccine has been approved by the Brazilian National Health Surveillance Agency (ANVISA) in December 2017, it is not available in the national market yet.

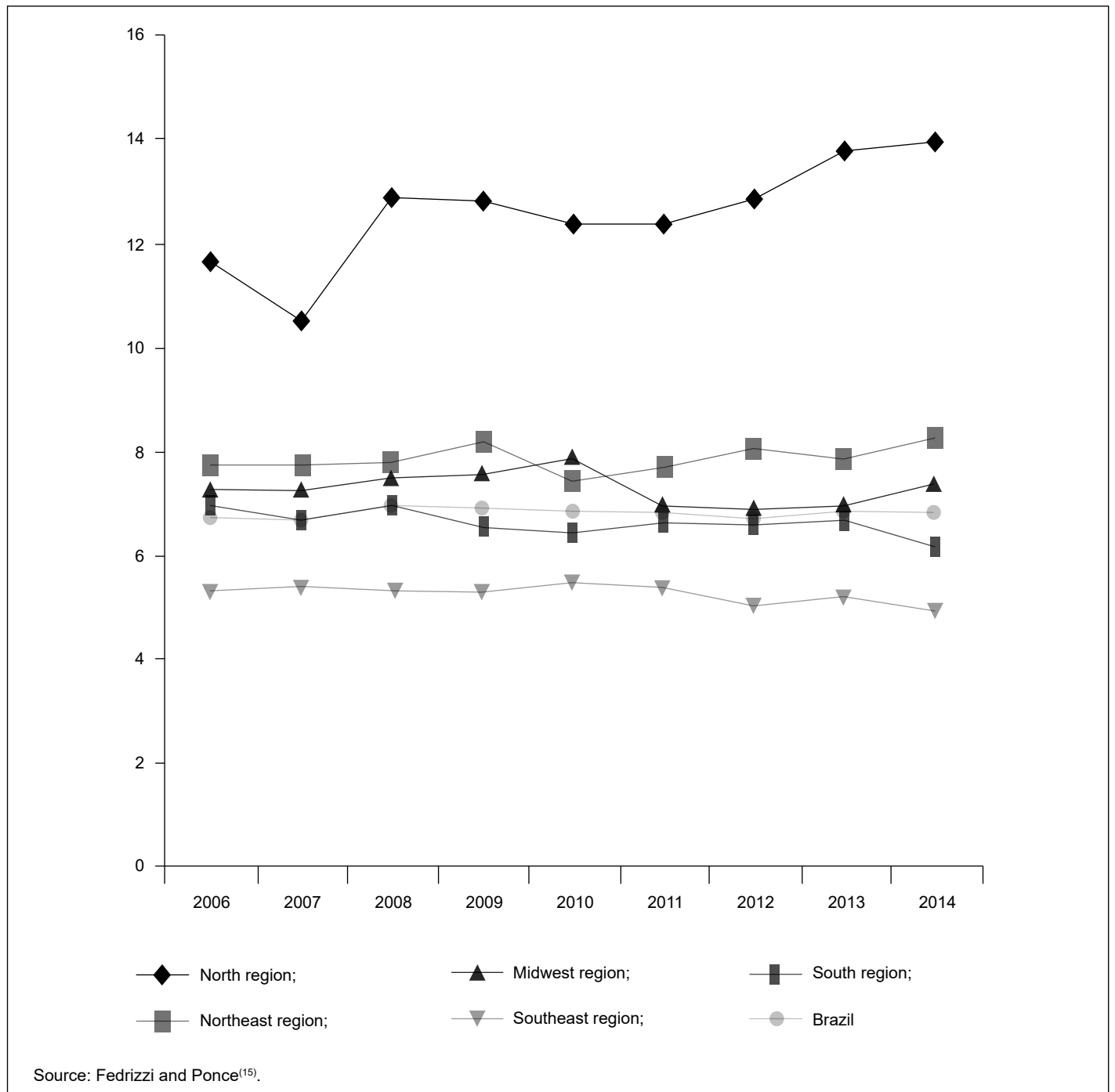


Figure 2 – Comparison of specific mortality coefficient by cervix cancer among the five Brazilian regions and Brazil over nine years (2006 to 2014) per 100,000 women.

The most appropriate moment for the use of HPV vaccine is before exposure to the virus. However, the most recent studies also show benefits for already infected women, including those with cervical intraepithelial neoplasia (CIN) 2/3 lesions, showing a decrease in recurrences of roughly 75–88% for vaccinated women⁽¹²⁾. Although there is an age recommendation for the use of the vaccines in the label, they were highly safe, immunogenic, and effective also in elderly men and women⁽¹²⁾.

HPV DISEASES AND HPV VACCINATION IN BRAZIL

Since March 2014, the 4HPV vaccine is available on the public vaccination calendar in Brazil. Currently, the National Immunization Program (PNI) provides the vaccine to girls aged from 9 to 14, and boys aged from 11 to 14, as well as men and women aged from 9 to 26 years with an immune problem (HIV infection, radio/chemotherapy for cancer, bone marrow and solid organs transplantation^(13,14)).

When we evaluate the Brazilian scenario as to HPV types among women with and without cervical lesion (**Figure 1**), we observe a great variability between the different types of HPV and the severity of lesions⁽⁷⁾.

THE IMPORTANCE OF 9HPV VACCINE

When we classify HPV lesions associated to viruses 16 and 18 (direct protection with the 2HPV and 4HPV vaccine), and viruses 16, 18, 31, 33, 45, 52, and 58 (direct protection with the 9HPV vaccine), we observed a significant increase in the protection of lesions with the 9HPV vaccine. If we do not consider the possible cross-protection and consider a protection of 100% of the vaccine, we will be protecting a low-grade lesion (LSIL) by 30.8% using 2HPV and 4HPV vaccines, whereas we double this protection to 62.3% when we use the 9HPV vaccine. This difference becomes more evident for real precursor lesions of cancer, high-grade lesions (HSIL), where we obtain a protection of 56.8% with 2HPV and 4HPV vaccines, and to virtually, the totality of the cases (99.6%) with the vaccine 9HPV⁽⁷⁾ (**Table 2**).

Unfortunately, the mortality by cervical cancer remained unchanged in several decades in Brazil, regardless of the various programs and campaigns carried out over these years for the Pap smear use, as demonstrated in a recent analysis of nearly 10 years in our country (**Figure 2**)⁽¹⁵⁾. It is quite clear that the most effective way to prevent this disease is with the HPV vaccination. Brazilian health authorities must take urgent actions to get high HPV vaccination coverage again (as occurred with the first dose in the year of implementation of the public vaccination program) by restarting vaccination in schools, spreading information for the public and health professionals, facilitating the access to Basic Health Units (expanding working hours), and adopting the 9HPV vaccine as soon as possible, so that we can definitively change this reality in Brazil, of about 16,000 new cases/year and 8,000 deaths/year by cervical cancer, a disease absolutely preventable.

CONCLUSION

Cervical cancer mortality in Brazil has remained the same for several decades, regardless of public campaigns and programs to encourage it, especially due to its low coverage. One of the best strategies to change this scenario is HPV vaccination, which should achieve high vaccination coverage and replacement of 4HPV vaccine for 9HPV as soon as possible.

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Conflict of interests

Researcher of the quadrivalent and nonavalent vaccine trials in men and women by the company MSD.

Ethics Committee

There is no need for this action.

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