

# Why should boys and men receive HPV vaccine?

## INTRODUCTION

Human papillomavirus (HPV) is one of the most common sexually transmitted infections and a major cause of various types of cancers, as well as of anogenital warts and oral lesions in both the genders. In women, HPV is strongly related to cervical, vaginal, vulvar, and anal cancers, and is also considered the agent responsible for precursor lesions<sup>(1)</sup>. HPV infection in men is a major concern owing to its infectivity potential. It may occur in anal and urethral area, on the penis, oral cavity, and larynx<sup>(2)</sup>. Currently, the clinical manifestations caused by HPV are considered vaccine-preventable diseases.

The scientific community and the medical societies question the ethics of HPV immunization strategies directed exclusively to women. Historically, vaccinations based on risk or gender were not successful in reducing the disease<sup>(3)</sup>. Although vaccination in women can substantially reduce the incidence of diseases related to HPV in women (and, to some extent, in men, as known as “herd protection” effect), vaccination programs based on gender and with low coverage have slowed the impact of the diseases. The women vaccination has been leading to a limited effect of the “herd protection,” so that the true potential of the HPV vaccine is not fully achieved. Therefore, the gender-neutral vaccination (for female and male) in adolescents would be the adequate manner to achieve the actual herd protection against HPV infection<sup>(4,5)</sup>.

Vaccines are considered to be one of most effective measures of public health. Some diseases are controlled, and others were eradicated owing to vaccination. From the individual perspective, vaccination can determine the difference between health and sickness, life and death.

## PAPILLOMAVIRUS AND MAN

Sexually transmitted diseases (STDs) are among the most common public health issues around the world<sup>(6,7)</sup>. According to the World Health Organization (WHO), the estimated number of curable STDs worldwide oscillates around 498.9 million new cases per year<sup>(8)</sup>. HPV is the most common sexually transmitted infection among the STDs, of which approximately 25% are easily disseminated by direct skin contact during sexual intercourse (vaginal, oral, and anal), although this is not the only route of transmission<sup>(9)</sup>.

Estimates suggest that there are approximately 20 million people infected with HPV in the United States of America, and approximately 5.5 million new cases occur in the country every year. Over 7% of adolescents reported sexual initiation under 13 years of age. In Brazil, studies show that more than 30% of women and approximately 50% of men become sexually active before 14 years of age. What concerns us the most is the fact the age group more often affected by STIs, including HPV is adolescents aged up to 19 years<sup>(10,11)</sup>.

HPV infections in men are most often asymptomatic, and prevalence rates are poorly understood, but some studies are available.

Man presents a lower immune response to natural infection with low levels, or often null, antibodies; subsequently, there is poor protection against infections. This is corroborated by frequent relapses and persistence of the lesions in men. Moreover, a man plays a role of reservoir and transmitting agent of this STD, indicating that the penis and urethra are the most frequent sites. It is believed that male infection contributes significantly to the infection and subsequent cervix uteri disease in women, and it is estimated that over 70% of partners of women with cervical HPV infection are carriers of the virus DNA.

Worldwide, approximately 1.9 million people have genital condylomata acuminata. It is estimated that 1% of sexually active adults have had some visible genital warts, whereas 15% had a sub-clinical infection. Overall, a probable share of 75% of the sexually active population is estimated to have been exposed to the virus at some point.

Condyloma, or genital warts, is the most common disease found in the anogenital region. These lesions are not evenly distributed over the genitalia, and the most frequently affected locations in men are the frenulum, the balanopreputial sulcus, the glans, and the foreskin – areas which are often difficult to handle and to adhere to treatment. Warts are generally caused by HPV types 6 and 11, and rarely have oncogenic potential<sup>(2,12,13)</sup>. However, psychosocial issues are significant sources of morbidity among men and women. Patients report feeling ashamed after diagnosis and with a high level of anxiety, which impacts their sexuality and their social relationships<sup>(14-16)</sup>.

In the head and neck, injuries can also appear as recurrent respiratory papillomatosis (RRP), which affects adults and children. RRP is a benign tumor that is characterized by the presence of epithelial lesions of verrucous aspect, which can be pedunculated, isolated, or multiple, depending on their evolution. Such lesions may trigger severe manifestations, such as respiratory insufficiency owing to the obstruction mechanism of the upper, and sometimes lower, airways, which also may cause death. It is considered one of the most difficult diseases to control owing to its high recurrence<sup>(14,17,18)</sup>. Injuries can affect the mouth, nose, pharynx, esophagus, and the whole tracheobronchial tree. The laryngeal location (most frequent, with 50% of cases) is the state of the glottis. However, the subglottic location has the worst prognosis as it may cause dyspnea and sometimes requires an emergency tracheotomy, which may be tracheobronchial, and even lung, extension factor. About the rino-pharyngo-esophageal location, warts may appear on the uvula, the tonsils, the soft palate, the base of the tongue, hypopharynx, and esophagus<sup>(19,20)</sup>.

Data show that 5.2% of all cancers worldwide are caused by HPV, and types 16 and 18 are primarily responsible for a substantial number of alterations. In addition to cervical cancer, other

regions may be involved, such as anal cancer in 90%, vulvar and vaginal cancer in 40%, penile cancer in 30–50%, and oropharyngeal cancer in 33–72%<sup>(2,20)</sup> (**Chart 1**).

The annual load of penile cancer was estimated at 22,000 cases worldwide (correlating strongly with cervical cancer rates). This disease is a public health problem; however, studies on the association of HPV with penile carcinomas are still rare, because this type of cancer is rare in developed countries. However, in developing countries, this statistic changes significantly as it represents up to 10% of male cancers in some parts of Africa, South America, and Asia<sup>(26)</sup>. In Brazil, incidence rates vary from 5.5 to 16%, being higher in the north and northeast regions in 1% and the south and southeast regions in 4%, primarily affecting men in the fifth and sixth decades of life (**Table 1**).

Men who have sex with men (MSM) and individuals living with HIV represent the population at greatest risk for persistent infection, and there is a greater chance of developing anal cancer<sup>(31)</sup>. Since 2005, a prospective multicenter study (Brazil, Mexico, USA) is being conducted with men to assess the prevalence of HPV infection in men aged 18–70 years. The prevalence of infection with the types of high and low risk of multiple infections was not different in the three countries. The prevalence of HPV infection in Brazil was 72.3%; in the United States of America it was 61.3%, and in Mexico, the prevalence was 61.9%.

The prevalence of HPV in the anal canal is not restricted to the group of MSM: the researchers found that among men who have sex with women (MSW) the prevalence was 12.2%, and among MSM it was 47.2%. It is worth noting that the prevalence of HPV

16 was twice as common among MSM with relation to MSW group (the potential high risk of the HPV 16 was identical in the anal area when compared to the cervix). The infection by various types of HPV was also ten times more frequent in MSM compared to MSW group<sup>(32)</sup>.

## VACCINATION AGAINST HPV – STRATEGIES, GENDER, AND RISKS

The HPV vaccines have been licensed since 2006 in more than 129 countries for women aged 09–26 years after consistent results were demonstrated in clinical studies, according to which the vaccine is effective in preventing HPV infections (depending on the producer and clinical outcome analyzed). They are also prevented by virus-like particles (VLPs) included in vaccines: genital warts (VLP 6 and 11) and intraepithelial lesions of the cervix, vagina, and vulva (VLP 16 and 18), according to **Figure 1**.

Approximately 60 countries included HPV vaccine in their national immunization programs<sup>(33)</sup>. The strategies of the global implementations of HPV vaccination are based on gender and risk (women, reduction of cervical cancer). That was the right and proper way precisely because it is a new prevention tool, which until then was driven by several hypothetical mathematical analyses of gains in quality of life and cost-effectiveness.

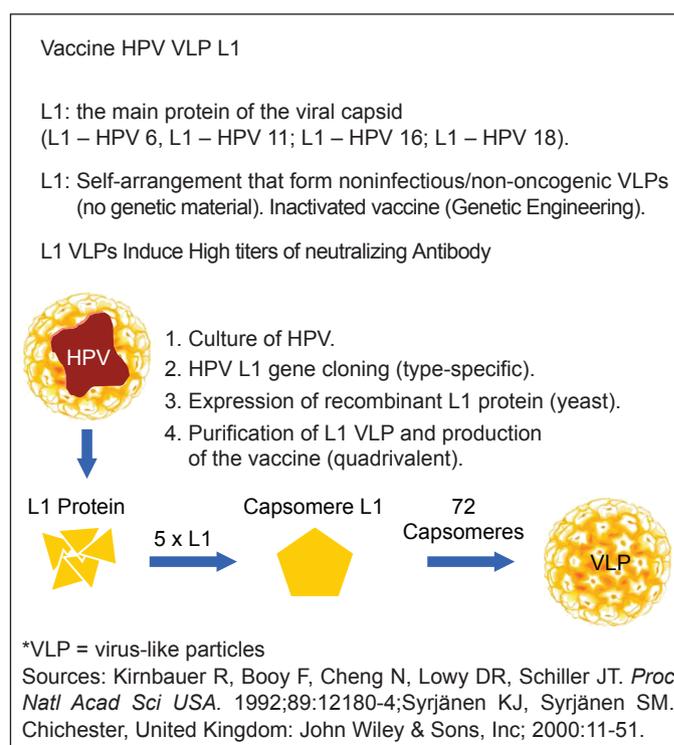
In June 2016, Garland et al.<sup>(34)</sup> published a systematic review on the impact and effectiveness of quadrivalent HPV vaccine (6, 11, 16, and 18) in the period of 10 years, showing the real world experience. The authors evaluated the use of the HPV quadrivalent vaccine in immunization programs nationwide, as well as its effectiveness and safety in nine countries: Australia, Germany, Belgium,

**Chart 1** – Impact of type-specific HPV disease.

Types	Female	Male
6 and 11	>90% of genital warts <sup>(22,26)</sup> ~25% of low-grade cervical lesions <sup>(23,26)</sup> RRP intrauterine transmission from mother to child and/or at the birth canal <sup>(24,25)</sup>	>90% of genital warts <sup>(22,26)</sup> Transmission to women <sup>(21)</sup> RRP vertical transmission <sup>(24,25)</sup>
16 and 18	~25% of low-grade cervical lesions <sup>(23,26)</sup> ~50% of high-grade cervical lesions <sup>(26,27)</sup> ~70% of cervical cancers <sup>(26-28)</sup> ~70% of high-grade vulvar/vaginal lesions <sup>(26,29)</sup> ~40% of vaginal and vulva cancers <sup>(21,26,30)</sup>	~90% of anal cancers <sup>(21,26)</sup> ~30% of penile cancers <sup>(21,26,30)</sup> ~33–72% of oropharyngeal cancers <sup>(21,26,30)</sup> Transmission to women <sup>(21)</sup>

**Table 1** – Crude incidence rates of HPV-associated cancers (Brazil).

	Men	Women
Cervical cancer	-	18.4
Anal cancer	0.3–1.0	0.8–1.4
Vulvar cancer	-	0.3–1.8
Vaginal cancer	-	0.4–1.2
Penile cancer	0.7–2.3	-
Oropharyngeal cancer (excluding nasopharynx)	4.7	0.9



**Figure 1** – HPV vaccine: production technology.

Canada, Denmark, USA, France, New Zealand, and Sweden in the period from 2007 to 2016.

In a short period, the first impact observed in all nine countries was genital warts decrease. Three to five years after the introduction of the vaccine, and when the vaccinated girls were in the age to start undergoing routine screening tests, a significant decrease in the prevalence of infections induced by HPV (6, 11, 16, and 18) in the regions of the cervix and vagina was observed. The incidence rates of genital warts, abnormal cytology, high-grade lesions, and AIS (*adenocarcinoma in situ*) have also declined.

The real world has shown robust results of effectiveness and safety in girls and young women. However, although there is the possibility of “herd protection,” the infection and disease rates in men still prevail. Moreover, the group of MSM would not benefit from such programs and would also cease to receive this protection.

In April 2007, the Australian government was the first and most successful country to implement a national vaccination program against HPV (Immunise). The program was gradually launched in the second quarter of 2007, focusing on girls aged 12–18 years; from the third quarter of the same year until the end of 2009, the program covered (catch-up) young women aged 18–26 years. In 2010, after the phases of catch-up (12–18 years) of women, the vaccination program started to be extended to girls aged 12–13 years. The coverage has averaged 72.5% for the group of girls aged 12–17 years. However, when young women aged 18–26 years were assessed, the coverage in the group was between 38 and 53%. The study revealed that immunization coverage registered an important decline owing to the removal of the vaccination program from the schools.

The infection by HPV 6 and 11 decreased from approximately 75 to 88% in women aged 25 years or less, with a reduction of up to 92.6% in cases of genital warts diagnosed among women aged less than 21 years after four years of implementation of the vaccination program. The percentage of new cases per year of genital warts in men, according to age in the preceding period (04 years) of the implementation of the vaccination program, was 13.7%. After four years of program implementation, the percentage was 6.3%, showing a reduction of 54%. A significant reduction of 72.3% in heterosexual men aged less than 21 years and no reduction for heterosexual men aged over 21 years or MSM was observed.

Despite the high vaccination coverage and evidence of “herd protection,” in 2013 the vaccination program included boys in the first year of high school (aged 12–13 years). In 2013 and 2014, the program intended to cover boys between 14 and 15 years of age<sup>(35)</sup>. The overall results in women, and preliminary results in men are not yet available.

Several reasons were raised by the group responsible for the program to continue with the vaccination program:

- Evidence of clinical efficacy of HPV vaccine from the vaccination program in women was an important factor to extend it to men.
- Gender-neutral vaccination strategy ensures greater equity in the prevention of diseases related to HPV.
- Men should have the opportunity to reduce the individual risk of HPV disease through vaccination. n.

Vaccination of men, in addition to preventing the HPV-induced alterations, will bring the benefit of reducing the male virus reservoir, which will lead indirectly to a reduction in the risk of cervical cancer in women, breaking the chain of contamination.

## CONCLUSION

Considering all the aspects mentioned in this editorial, we must return to the main question:

### Why should boys and men receive a vaccine against HPV?

- HPV is worrying various agencies committed to sexual and reproductive health worldwide and in our country. In this context, man has been presented as a vector and reservoir of infection by HPV.
- There is no risk group for HPV.
- The main target groups for vaccination against HPV should be adolescent boys and girls.
- Preteens should receive full scheme before the onset of sexual activity; thus, they would be immunized if in contact with the viruses included in the vaccine, which would prevent being infected by HPV.
- Boys showed a better immunological response (that is, produced more antibodies to fight infection) when receiving the vaccine, compared to young adults. When we do an evaluation of natural infection and immune response induced by the vaccine, it is observed that boys had a better immune response. In other words, they developed more antibodies than girls and women.
- Men do not respond adequately to natural HPV infection and often do not generate immunological memory (B) and may be susceptible to other types of infection and the same type of virus of the previous infection.
- Men who have sex with unvaccinated women will not be protected.
- MSM are completely unprotected owing to vaccination programs exclusive for women.
- Vaccination of adolescents is a challenge in public health. However, the availability of vaccination campaigns in schools was effective and the most efficient way to achieve high vaccination coverage.
- Discussions on the ethics of immunization strategies against HPV targeted exclusively to women.
- Men should have the opportunity to reduce the risk of individual HPV diseases through vaccination, ensuring greater equity in the prevention of diseases related to HPV. Examples are seen in the past, such as immunization against rubella performed only in the female population, did not lead to the disease reduction. Many of these strategies were later replaced by universal vaccination of young people, regardless of gender (gender neutral), to achieve high levels of protection and indeed reduce the congenital rubella syndrome.
- With HPV vaccination available for boys in the public health network, we will enable a discussion (health education) for this

segment of the population. Men very often are disconnected from the actions on sexual and reproductive health education, such as consistent condom use, family planning, testing for syphilis, HIV, and hepatitis B (including vaccination), among many other actions. Prevention methods may be complementary and not mutually exclusive.

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