The impact of the HPV vaccine on the world: initial outcomes and challenges

O impacto da vacina contra o HPV no mundo: resultados iniciais e desafios

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ABSTRACT

Introduction: Human papillomavirus (HPV) infection can be considered an epidemic in the world and in Brazil. This infection accounts for virtually all cases of cervical cancer, most malignant anal, vaginal and oropharyngeal tumors, and a large number of cases of cancer of the penis and vulva. The most effective way to prevent this infection is through vaccination. Several countries, including Brazil, have already introduced this vaccine into the public vaccination programs and are observing the real-life results of decreasing HPV-associated diseases. **Objective:** To evaluate the effectiveness of HPV vaccination in preventing virus-induced diseases in countries that have adopted it for a longer time, in a different scenario from clinical studies. **Methods:** This is a bibliographic review study in journal databases PubMed, LILACS, SciELO and Scopus, with publications dated from 2000 to 2019. The research was restricted to articles in English and Portuguese and studies conducted in humans. Ten studies that were considered relevant were selected. Furthermore, additional articles found by free search were selected. After this phase, the chosen publications were obtained in full for reassessment of their methodology and results. **Results:** The HPV vaccine demonstrated its effectiveness in reducing the incidence of HPV infection and/or anogenital warts and/or precancerous lesions in the seven countries analyzed by the study: Australia, Brazil, Denmark, United States of America, New Zealand, Czech Republic and Sweden. The impact was bigger in countries that introduced it earlier, such as Australia, where the vaccine virtually eliminated the incidence of genital warts in women aged under 21 years. Although Brazil implemented the vaccine a few years ago, a preliminary study was conducted in Campos dos Goytacazes, RJ, where the vaccine was implemented in 2010, showing a 55% reduction in the incidence of genital warts for women aged under 21 years old, between 2007 and 2012. **Conclusion:** The HPV vaccine is highly effective in protecting against HPV infection and disease in the countries where it has been implemented, with better results than those seen in clinical trials.

Keywords: HPV; vaccination; precancerous conditions; cervical cancer; vaccination coverage.

RESUMO

Introdução: A infecção pelo papilomavírus humano (HPV) pode ser considerada uma epidemia no mundo e no Brasil. Essa infecção responde por virtualmente todos os casos de câncer de colo de útero, pela maioria dos tumores malignos anais, vaginais e orofaríngeos e por um grande número dos casos de câncer de pênis e vulva. A forma mais eficaz de prevenção dessa infecção é por meio da vacinação. Vários países, entre eles o Brasil, já introduziram essa vacina na rede pública e começaram a observar os resultados na vida real de diminuição das doenças HPV induzidas. **Objetivo:** Avaliar a eficácia da vacinação contra o HPV na prevenção de doenças induzidas pelo vírus em países que a adotaram há mais tempo, em um cenário diferente dos estudos clínicos. **Métodos:** Estudo de revisão bibliográfica em bases de dados de periódicos PubMed, LILACS, SciELO e Scopus, com publicações no período de 2000 a 2019. A pesquisa restringiu-se a artigos de língua inglesa e portuguesa e com estudos realizados em seres humanos. Foram selecionados dez trabalhos considerados relevantes. Além disso, foram escolhidos artigos adicionais pesquisados por busca livre. Após essa fase, as publicações selecionadas foram obtidas na íntegra para reavaliação da metodologia e dos resultados. **Resultados:** A vacina contra o HPV demonstrou sua eficácia na redução da incidência de infecção pelo HPV e/ou verrugas anogenitais e/ou lesões pré-cancerosas nos sete países analisados pelo estudo: Austrália, Brasil, Dinamarca, Estados Unidos da América, Nova Zelândia, República Tcheca e Suécia. O impacto foi maior em países que introduziram a vacina mais precocemente, como na Austrália, onde ela virtualmente eliminou a incidência de verrugas genitais em mulheres abaixo de 21 anos. Ainda que o Brasil tenha implementado a vacina há poucos anos, um estudo preliminar foi realizado no município de Campos dos Goytacazes (RJ), onde a vacina foi introduzida em 2010, demonstrando redução na incidência de verrugas genitais em 55% para mulheres abaixo de 21 anos de idade, no período entre 2007 e 2012. **Conclusão:** A vacina contra o HPV é muito eficaz na proteção contra a infecção e as doenças induzidas pelo HPV nos países em que foi implementada, com resultados melhores que os observados nos ensaios clínicos.

Palavras-chave: HPV; vacinação; lesões pré-cancerosas; câncer de colo uterino; cobertura vacinal.

INTRODUCTION

Human papillomavirus (HPV) is responsible for the most common sexually transmitted infection in the world, being an important cause of morbidity and mortality due to its relationship with different types of cancer[1]. In 2017, a Brazilian study with men and women aged 16 to 25 years pointed out an estimated prevalence of HPV of 54.6% among the participants, with 38.4% of them presenting the types of HPV with high risk for the development of cancer[2].

HPV infection is known to be responsible for virtually all cases of cervical cancer and high-grade intraepithelial lesions, in addition to about 90% of malignant anal tumors, 70% of vaginal tumors, 50% of penile tumors, 40% of vulvar tumors and between 13 and 72% of oropharyngeal tumors[3].

HPV types are classified, according to their oncogenic potential, into high and low risk. The most prevalent representatives of the first category are types 16 and 18, which account for 70% of cervical cancer cases and 80 to 90% of HPV-related neoplasms elsewhere. The most common low-risk types are 6 and 11, which are

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responsible for 90% of anogenital warts and practically all cases of laryngeal papillomatosis[3].

Until recently, the best tool for preventing pre-cancerous lesions and cervical cancer was periodic screening with a cytopathological examination of the cervix, popularly known as the preventive test or Pap smear[4].

This prevention program, however, has its limitations. The first one is that it only contemplates women, when we know that men can also be carriers of the virus, being able to transmit it to their partners and to also develop precancerous lesions and cancer[5]. The second limitation is that research is restricted to the disease that manifests in the cervix, while HPV-induced lesions can occur elsewhere[6]. The third is that, as in any complementary exam, its accuracy is limited, because the greater the specificity of the technique adopted, the lower the sensitivity, resulting in a greater number of false negatives[7]. Finally, the fourth — and perhaps the most critical limitation — is the need for high coverage and follow-up of women with periodic examinations in the health system. A form of longitudinal prevention makes adherence by the target population difficult[8].

Unfortunately, mortality from cervical cancer has remained unchanged in recent decades in Brazil, regardless of the various Pap smear programs and campaigns carried out over the years, as demonstrated in a recent analysis of almost ten years in Brazil. Taking into account the population data from the Brazilian Institute of Geography and Statistics and the Cervical Cancer Information System (SISCOLO) of the Ministry of Health, this study demonstrated an extremely low coverage of the Pap smear by the Unified Health System (SUS) — from 14 to 17%, depending on the region — and high mortality, maintained in the ten years evaluated (**Figure 1**)[9].

The consequence of all these limitations is that, despite the indisputable progress that has been made with cervical cancer screening, there are still people who are only diagnosed with HPV-related cancer in advanced stages[10]. In Brazil, the forecast of the National Cancer Institute (INCA) for this year is about 16,000 cases of cervical cancer, causing 8,000 deaths[11]. Therefore, another form of prevention against cancerous lesions associated with HPV is needed which includes men and women, prevents the disease in all its infection sites, and is simple to perform, to facilitate adherence by the population. Currently, all of these needs can be met by HPV vaccination[12,13].

The HPV vaccine has emerged as a primary way of preventing diseases caused by these viruses. Its initial models were monovalent and bivalent vaccines, contemplating, respectively, type 16 and types 16 and 18, the most prevalent high risk types. The other is the quadrivalent vaccine, which in addition to protecting against these two types, also provides protection against types 6 and 11, the most prevalent low risk types[3,14].

The bivalent and quadrivalent vaccines have already been implemented in other countries, such as Australia and Denmark, in the past decade. Brazil took a longer time to do so, including them in the Public Vaccination Program only in 2014[15]. Recently, the nonavalent vaccine (against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58) was developed. It's already being commercialized in North America, Australia, Europe and Asia, but still in the process of implementation in Brazil[16,17].

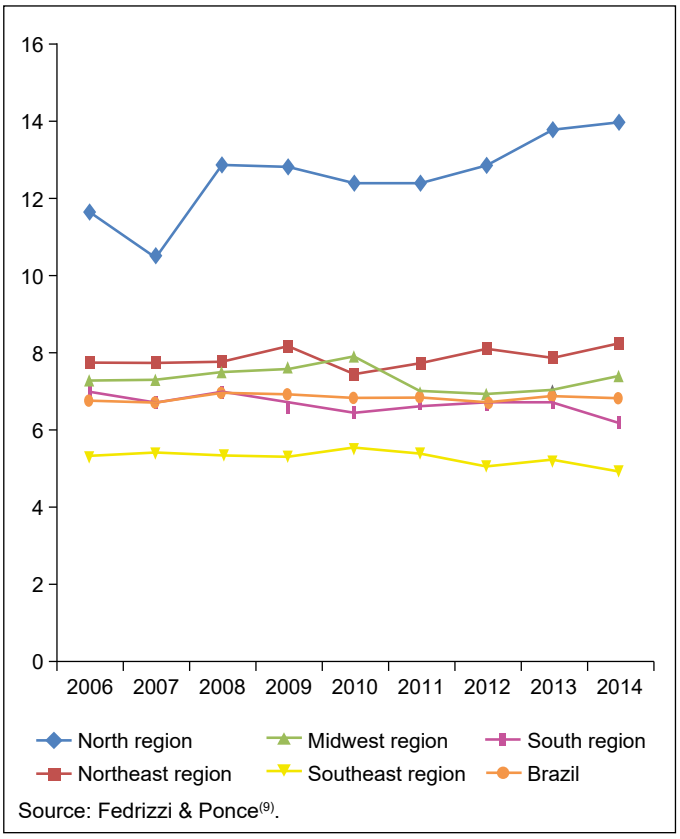

Figure 1 – Comparison of the specific mortality coefficient for cervical cancer between the five Brazilian regions and Brazil, over nine years (2006 to 2014), for every 100,000 women.

In Brazil, the vaccine offered by Public Vaccination Program is quadrivalent, which is available for girls aged 9 to 14 years (14 years, 11 months and 29 days) and boys aged 11 to 14 years (14 years, 11 months and 29 days), with a two-dose vaccination schedule (0 and 6 months). In addition, it also contemplates men and women aged 9 to 26 years with human immunodeficiency virus/AIDS, transplant recipients of solid organs and bone marrow, and cancer patients, who must undergo a three-dose schedule (0, 2 and 6 months)[18].

Although it is too early to fully observe the effects of vaccination on the Brazilian population, its impact in countries that implemented it in the past decade can already be analyzed. This is because we know that the average time between HPV infection and the manifestation of condyloma is shorter, usually up to four years; manifestation time between infection and precancerous lesions is around five to seven years; and between infection and cancer, about 10 to 15 years[19].

OBJECTIVE

To evaluate the effectiveness of the HPV vaccine in preventing diseases induced by the virus in real life, that is, in countries that have adopted it for a longer time, in a different scenario from clinical

studies. To this end, the results of epidemiological bases that support its efficacy and effectiveness were discussed.

METHODS

A bibliographic review was carried out in journal databases MEDLINE, LILACS, SciELO and Scopus, with publications dated from 2000 to 2019, using the following keywords and free combinations: "HPV" AND "vaccine" OR "vacina", "HPV" AND "immunization" OR "imunização", "HPV" AND "prevention" OR "prevenção", "HPV" AND "vaccination" OR "vacinação" AND "Brazil" OR "Brasil". The search was restricted to articles in English and Portuguese and studies carried out in humans. In this search, 24 articles were found, of which ten were selected, and works were considered relevant according to the criteria of: analyzed outcome, publication date and time elapsed since implementation of the vaccine. In addition, additional articles were found and selected by free search. After this phase, the chosen publications were obtained in full for reassessment of their methodology and results. A summary of the articles selected for the study can be seen in **Table 1**.

Table 1 – Summary of articles selected for the study.

Outcome analyzed	Authors	Country	Year of publication	Vaccine implementation year	Vaccine schedule	Result
HPV infection	Markowitz et al.[20]	USA	2016	2006	Boys and girls aged 11 or 12 years; women aged up to 26 years and men aged up to 21 years not previously vaccinated; three doses.	64% drop in the prevalence of infection by the four types of HPV vaccine for girls aged 14 to 19 years; drop of 34% for women aged 20 to 24 years.
Anogenital warts	Petráš et al.[21]	Czech Republic	2015	2006	Women aged 16 to 40 years; three doses.	Reduction in the occurrence of genital warts by 90.6%, when comparing immunized and non-immunized women.
Anogenital warts	Ali et al.[22]	Australia	2013	2007	Women aged 12 to 26 years; three doses.	No anogenital warts diagnosed in women aged under 21 years who have been vaccinated.
Anogenital warts	Baandrup et al.[23]	Denmark	2013	2006	Girls aged 12 to 15 years; three doses.	Elimination of the incidence of genital warts in women aged 16 and 17.
Anogenital warts	Leval et al.[24]	Sweden	2012	2007	Girls aged 13 to 17 years; three doses.	Decline greater than 25% of genital warts in women aged 17 and 18.
Anogenital warts	Oliphant et al.[25]	New Zealand	2011	2008	Girls in the eighth grade (about 11 or 12 years old).	13% drop per quarter in the prevalence of genital warts in women aged under 20 years.
Anogenital warts	Bauer et al.[26]	USA	2012	2006	Boys and girls aged 11 or 12 years; women aged up to 26 years and men aged up to 21 years not previously vaccinated; three doses.	35% drop in the prevalence of genital warts for women aged under 21 years.
High-grade cervical lesions	Crowe et al.[27]	Australia	2014	2007	Women aged 12 to 26 years; three doses.	46% efficacy for preventing high-grade injuries and 34% for other cervical abnormalities in women immunized with three doses of the vaccine.
High-grade cervical lesions	Baldur-Felskov et al.[28]	Denmark	2015	2006	Girls aged 12 to 15 years; catch-up in 2012 for women aged up to 27 years; three doses.	Reduction in the incidence of high-grade injuries for the age group of 12 to 20 years.
Anogenital warts	Kury et al.[29]	Brazil	2013	2010* *Only in the municipality of Campos de Goytacazes (RJ).	Girls aged 11 to 15 years; three doses.	55% reduction in the incidence of genital warts for women aged under 21 years.

RESULTS

When reviewing the international literature, the first outcome to be analyzed is the vaccine's effectiveness in fighting HPV infection, whether symptomatic or not. In this sense, a cross-sectional study published in 2016 compared the prevalence of HPV in years before and after vaccine implementation in the United States of America (USA): 2003–2006 and 2009–2012, respectively. The method used to determine the prevalence was the search for HPV deoxyribonucleic acid in cervicovaginal collections from women aged between 14 and 34 years. The study showed that, between the pre- and post-vaccination years, there was a drop in the prevalence of the four types of HPV prevented by the vaccine (6, 11, 16 and 18). Among women aged 14 to 19 years, the drop was 11.5 to 4.3%, resulting in an adjusted prevalence ratio of 0.36 (95% confidence interval [95%CI] from 0.21 to 0.61). In the age group of 20 to 24 years, the drop was from 18.5 to 12.1%, with a prevalence ratio of 0.66 (95%CI 0.47–0.93). Therefore, the observed drop in prevalence was 64 and 36%, respectively, for the two age groups surveyed, which were those covered by the vaccine[20].

The second relevant outcome to be considered about HPV vaccination is its impact on the incidence of genital warts. A case-control study conducted in the Czech Republic investigated the occurrence of genital warts in women aged between 16 and 40 years, from January 2013 to March 2014. The study showed a significant reduction in the occurrence of genital warts by 90.6% (95%CI 80.1–95.6) in the comparison between women immunized for at least one year and non-immunized women. The prevalence of recurrent genital warts was 1.1% (95%CI 0.0–5.9) and 10.9% (95%CI 9.1–12.9), respectively, for immunized and non-immunized women, resulting in a vaccine effectiveness of 89% (95%CI 38.6–98.0%)[21].

Another important study, conducted in Australia, compared the prevalence of genital warts between the periods before and after vaccination, respectively, 2004–2007 and 2007–2011. The decline found was drastic: less than 1% of women aged under 21 years who sought sexual health services were diagnosed with condyloma in 2011, compared to 10.5% in 2006. An even more striking finding was that, in 2011, no anogenital wart was diagnosed in women aged under 21 years who had been vaccinated[22].

The impact on the occurrence of anogenital warts was also seen in other countries, which carried out preliminary studies a few years after the implementation of the HPV vaccine in their territories. In Denmark, where vaccination coverage for women aged 16 and 17 years was greater than 85%, cases of genital warts in this age group were virtually eliminated in 2011[23]. In Sweden, a study showed a drop of over 25% in condylomas diagnosed in women aged 17 to 18 years, between 2006 and 2010[24]. In New Zealand, there was a 13% drop per quarter in the prevalence of condyloma in women aged under 20 years, in the period between 2007 and 2010[25]. In the same period, in the USA, the prevalence of condylomas dropped by 35% among women aged under 21 years[26]. All of these studies showed statistical significance.

Finally, the third outcome analyzed is the vaccine's impact on precancerous lesions. In this sense, we found a large study carried out in Australia that dealt with the prevalence of high-grade cervical lesions among women vaccinated and not vaccinated against HPV. A case-control study dating from 2014 separated the participating women into three groups, according to different results on Pap smear exams (high-grade cervical lesions; non-high-grade cervical abnormalities and normal cytology), carried out between 2007 and 2011. Then, the administration of one, two or three vaccine doses was evaluated, compared to that of no dose, relating this data to the outcome of abnormal findings in the Pap smear. The primary analysis of the data showed that, for women who had never been screened by Pap smear, the odds ratio of exposure to the three doses of the HPV vaccine, compared to non-exposure, was 0.54 (95%CI 0.43–0.67) for high-grade lesions and 0.66 (95%CI 0.62–0.70) for other cervical abnormalities compared to the normal cytology control group. These numbers represent 46% effectiveness for preventing high-grade lesions and 34% for other cervical abnormalities[27].

A second study that evaluated the incidence of cervical lesions was conducted in Denmark, analyzing data from 2000 to 2013, in a population whose vaccination started in 2008. The contrast between the periods before and after vaccination was striking: cervical atypias and more serious lesions increased in all age groups between 2000 and 2010; whereas, in the following years, these same lesions showed a gradual reduction in incidence in the age group between 12 and 20 years. Even though the period between the vaccine implementation and the incidence study was short, this drop was statistically significant. The study pointed out the high vaccination coverage in this age group, which had been covered by the vaccine for free, as a justification for this phenomenon[28].

In relation to Brazil, a preliminary study was carried out in Campos dos Goytacazes (RJ), where the vaccine was implemented in September 2010, even before it was added to the National Vaccination Calendar. The study compared the period between 2007 and 2012, showing a 55% reduction in the incidence of genital warts for women aged under 21 years. This was the first published article to verify the vaccine's effectiveness in Brazil[29].

DISCUSSION

The impact of the vaccine on morbidity and mortality by human papillomavirus

A few years after its implementation, the HPV vaccine demonstrated its effectiveness on three of the main outcomes analyzed, the first being HPV infection itself, which is a determining condition for the occurrence of cervical cancer and high-grade intraepithelial lesions, in addition to being a risk factor for genital warts and anal, vaginal, penile, vulvar and oropharyngeal tumors[3]. The reduction in the prevalence of HPV infection was demonstrated by a cross-sectional study in the USA[15].

With regard to anogenital warts, the literature has been ample in demonstrating the effectiveness of the HPV vaccine, with decreases in the incidence of condyloma observed in the Czech Republic, Australia, Denmark, Sweden, New Zealand, in the USA and in Brazil[21-26].

The third outcome analyzed was that in which the HPV vaccine must have had the greatest impact on morbidity and mortality:

the reduction of high-grade cervical lesions, which are closely related to cervical cancer. Studies in Australia and Denmark have shown a statistically significant association between the vaccine and the reduction in the prevalence of high-grade lesions[27,28]. Since these lesions take an average time of up to seven years to appear, the trend is for new studies on the subject to be published in the coming years, with the implementation of the vaccine in other countries.

As expected, the magnitude of the impact was related to two main factors: the time elapsed since the vaccine was implemented and the population coverage achieved. Countries with free distribution of the vaccine and high vaccine coverage, such as Australia and Denmark, presented earlier and more significant results[22,23,27,28]. The experience of these countries should serve as a model for Brazil, where the vaccine is also offered for free by Public Vaccination Program, but has an unfortunately low coverage[15].

The Brazilian reality: vaccination cost-effectiveness and coverage

When talking about primary prevention in public health, a discussion that should not be left out is about the cost-effectiveness of the measure to be implemented. In 2008, a survey analyzed the estimated cost of the HPV vaccination program in order to assess its viability in the Brazilian economic scenario. In the study, the cost per vaccinated woman was estimated at less than USD 25, considering that the cost of the dose is around USD 5, vaccination before 12 years of age, and screening on three occasions between 35 and 45 years. It was found that a vaccination coverage of 70% would be able to prevent about 100,000 new cases of invasive cervical cancer in a period of five years. Thus, the study inferred that, for a country with Brazil's Gross Domestic Product, the benefits of the HPV vaccination would be sufficient to justify the economic investment of its implementation[30].

Thus, in 2014, vaccination against HPV was implemented in the Brazilian public health system, with a dose cost of BRL 31.02. The plan was to acquire 41 million doses of the vaccine over the following five years, adding up to a total investment of BRL 1.1 billion, and to transfer the technology of vaccine production to the Butantan Institute in Brazil. The investment would be heavy, but rewarding in case of efficient vaccination coverage[31].

The most recent data on HPV vaccination coverage dates from January 15, 2019. According to the Ministry of Health, 6 million girls aged between 9 and 14 years completed the HPV vaccination schedule, corresponding to 47.4% of the female population in the country in that age group. Among boys aged 11 to 14 years, only 2 million received both doses, corresponding to only 28.6% of this target population[32]. It is worth mentioning that the vaccine started to be made available to boys in 2017. Even so, inferring only on girls, 47.4% of coverage is an advance, but far from the goal of 70% established by the cost-effectiveness study[30].

Thus, actions are needed to increase population adherence to the HPV vaccine. According to a study published on Cochrane, some of the strategies that can improve child immunization coverage in low and middle income countries are to better inform parents and other members of the community about vaccines and to promote integration of vaccination with other health services[33]. In addition, the Primary Health Care model of SUS allows more active strategies to increase adherence, such as more flexible opening hours for the Basic Health Units, vaccinations at home or at schools and periodic home visits by community health agents, aimed at verifying the vaccination status of the population and providing it with information on the importance of preventing HPV infection[32].

Future perspectives

One limitation observed in the Brazilian campaign for primary prophylaxis against HPV is the use of the quadrivalent vaccine, which is the model offered today by the National Immunization Program of the Ministry of Health. Although the quadrivalent vaccine protects the individual against both types of HPV with higher prevalence of cervical cancer (16 and 18), it does not protect against infection by other HPV types that also have a strong association with this type of cancer[34].

A study published by the HPV Information Center in 2019 found that 52.8% of cervical cancer cases in Brazil are associated with HPV-16, and 15.4% with HPV-18, adding up to 68.2% of all cervical cancer cases. Among the remaining 31.8%, the most prevalent types were 45 (5.0% prevalence), 33 (4.8%), 31 (4.6%), 35 (3.9%), 58 (2.2%), 52 (1.7%), 39 (1.0%) and 51 (1.0%), that is, 18.3% associated with the other five types of HPV contained in the nonavalent vaccine (HPV 31, 33, 45, 52 and 58)[17,34]. When we analyze the proportion of high-grade cervical lesions associated with the seven types of high-risk HPV contained in the nonavalent vaccine, which is 99.6%, we can infer that an almost complete prevention of these lesions, which are the true precursors of cancer, is possible in Brazil (**Figure 2**)[34].

As previously mentioned, the nonavalent vaccine is still being implemented in Brazil. Despite being licensed by the National Health Surveillance Agency in December 2017, its commercialization has not started yet[16]. The importance of this measure is evident when we analyze the prevalence data exposed previously. Although the quadrivalent vaccine against types 16, 18, 6 and 11 can promote cross-immunization against other types of HPV, data are lacking to verify its protection against the other most prevalent oncogenic types, for how long, and in which women[35].

A positive point of this literature review that can be highlighted is that the positive results of HPV vaccine efficacy in clinical trials showed no inferior or even better results in real life when evaluating short-term endpoints, such as HPV infection and genital warts. However, some limitations must be considered: first, the effectiveness of the HPV vaccination in real life could not be evaluated in many countries due to the non-publication or the poor publication of this data; second, HPV-associated cancer prevention claims are still premature, despite evident protection against precancerous lesions, depending on how long the vaccine has been used in all countries; third, the analysis of the reduction of high-grade intraepithelial lesions was demonstrated in a very young population, usually adolescents, whose natural history of regression is quite frequent; fourth, the reduction in HPV lesions induced in Brazil has yet to be demonstrated due to the low vaccination coverage.

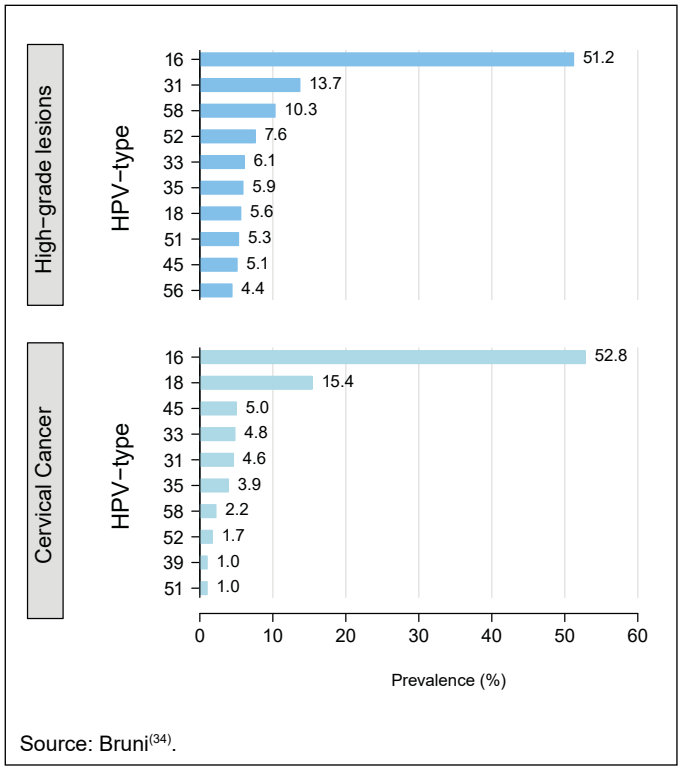

Figure 2 – Comparison of the ten most common oncogenic types of human papillomavirus in Brazil, among women with high-grade cervical lesion and cervical cancer (data updated on June 11, 2019).

CONCLUSION

The HPV vaccination has shown to be effective in preventing HPV infection, genital warts and high-grade cervical lesions in countries that have adopted it in the past decade. Such results were observed in the first year of implantation for HPV infection and genital warts, and after about five years for high-grade lesions.

Even though the efficacy of the vaccine against genital warts has already been demonstrated in Brazil in only a few years, the expectation is that the results will be even better over time, if we follow the example of countries with high vaccine coverage. The main goals that the country must establish in order to observe a significant reduction in HPV-induced diseases are to expand vaccination coverage and introduce the nonavalent vaccine into the vaccination calendar of children and adolescents, as it capable of preventing almost all pre-cancerous high-grade lesions in Brazil and, consequently, preventing cervical cancer.

Participation of each author

The authors declare that all authors were active participants.

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Conflict of interests

Dr. Edison Natal Fedrizzi participated in the clinical trials of the Merck Sharp & Dohme Laboratory's quadrivalent and nonavalent vaccine against HPV in men and women.

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