Nonavalent HPV vaccine: what are the advantages?

Vacina nonavalente contra o HPV: quais são as vantagens?

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INTRODUCTION

Sexually transmitted infections caused by the human papillomavirus (HPV) are the most prevalent in the world and can cause from genital warts to premalignant lesions, which can lead to cervical cancer, vaginal and vulvar neoplasms, anal and penile cancer, if left untreated. Non-genital pathologies may also be related to HPV, such as oropharyngeal cancer and recurrent respiratory papillomatosis[1-3].

HPV can be transmitted whenever there is direct contact of infected hair and mucosa during sexual intercourse. It can also occur via the maternal fetal route (pregnancy, intra and peripartum)[4]. The lesions are imperceptible in many cases, without manifestations of infection, which may facilitate transmission.

This virus affects men and women and is found not only in anogenital regions, but also in extragenital ones. Infection can be manifested in clinical, subclinical and latent forms[5], with subclinical and asymptomatic forms predominating in men[6].

Around 90% of the HPV infections are eliminated in almost two years and, therefore, there is no need of any pharmacological treatment[7]. However, when there is a persistent infection, different pathologies may be present depending on the virus sub-genotype. Infections caused by low-risk oncogenic sub-genotypes may be related to genital warts and respiratory papillomatosis, and high-risk oncogenic subtypes may be associated with the pathogenesis of cervical, anal, penile, vulva, and vaginal and oropharyngeal cancer. Studies have also associated HPV with other cancers, such as oral cavity squamous cell carcinoma[8].

In an attempt to reduce the number of HPV-associated pathologies, there are three vaccines present in the world market currently: Cervarix® (bivalent vaccine) produced by GlaxoSmithKline; Gardasil® (quadrivalent vaccine) by Merck, and most recently, the Gardasil 9® (nonavalent vaccine) was released. All three vaccines are highly immunogenic, effective and safe. The only difference between them is the HPV sub-genotypes that are present[9]. HPV vaccination has been known as a mean to significantly reduce the incidence of related anogenital cancers and the appearance of genital warts[10].

In Brazil, the quadrivalent vaccine (Gardasil®) is available free of charge in the Unified Health System (SUS) units for girls aged 9 to 14 and boys aged 11 to 14. In 2018, the second-generation Gardasil, Gardasil9®, was approved by ANVISA (Brazilian Health Surveillance Agency). Considering the world scenario, in which HPV has been associated with pathologies of a large number of morbidities and mortality, does the nonavalent vaccine have advantages over the other vaccines in the market?

This paper aims to evaluate the advantages and/or disadvantages of the nonavalent vaccine in relation to the other two vaccines by performing a literature review, using Scielo and PubMed databases and the keywords: "HPV", "Vaccine and HPV", "Nonavalent Vaccine and HPV", "Quadrivalent Vaccine and HPV", in Portuguese and English.

HUMAN PAPILLOMAVIRUS

HPV are viruses belonging to the *Papillomaviridae* family, which has over 39 genera. The classification by type is based on the comparison of L1 gene nucleotide sequences of the various HPVs, each type differs from the other types by at least 10% in the sequence of L1 nucleotides.[11,12]. Papillomaviruses that share an identity of 60 to 70% in this gene are designated as species, while types in a given species have show an identity between 71 and 89%[1,13]. The genera *Alpha*, *Beta*, *Um* and *Nupapillomavirus* are capable of infecting humans and have more than 200 types[12-14]. They are viruses of about 55 nm long, with a double-stranded DNA genome of approximately 5 to 8 Kb that is not coated with a lipoprotein envelope. The viral genome may be present in the episomal (circular) form associated with nuclear histones in benign lesions, or it may be integrated into the host cell genome as in malignant lesions. In the latter case, there is a greater risk of cell transformation as a result of early viral protein expression[15].

The genome has about ten open reading frames (ORF) that consist of an early region (E) formed by proteins expressed in the early phase of the replicative cycle, responsible for viral transcription and replication. The late region (L), responsible for the proteins expressed in the later phase of the HPV cycle, are the structural proteins. There is also a long control region (CSF), which is important for the regulation of viral genome transcription and replication events and where the origin of replication is located. The early proteins are E1, E2, E4, E5, E6, and E7. These proteins can interfere in the host cell to the point of immortalizing it. The E6 and E7 oncoproteins direct the degradation of tumor suppressor proteins p53 and pRB, respectively. Therefore, they can contribute to the progression of the carcinogenesis process and genomic instability[16,17]. Late proteins are L1 and L2. They are structural proteins that form the capsid and are responsible for the virus immunogenicity and for carrying gender-specific antigenic determinants[11,12,14].

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HPV has tropism for cutaneous, mucosal, and cervical epithelial cells, preferentially infecting the most basal layers, in which there is greater cell proliferation[15]. Based on the ability to produce malignant lesions, HPV can be divided into low, moderate and high risk types. Persistent HPV-16 infection is the most potent type among the neoplasm-associated viral types. It is known to lead to the development of cancer in various body regions, resulting in infected cells to immortalize genomic instability, inhibit response to DNA damage and escape from apoptosis[18]. Types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are also associated with cancer, especially cervical cancer.

Type 68 has limited evidence in human studies, but strong mechanistic evidence of cervical cancer. Types 26, 53, 66, 67, 70, 73 and 82 present limited evidence in humans in the development of cervical cancer. Finally, types 6 and 11, which belong to the alpha papillomavirus ten species, are classified as non-carcinogenic to humans based on epidemiological evidence and absence of carcinogenic potential in the studied mechanisms[18].

Epidemiology

Around 15% of all human cancers are believed to be caused by viral infections, and 5% may be attributed to HPV infection. Regarding cervical cancer, about 99% of cases are related to HPV[1-3,7-9]. This persistent infection, in turn, can lead to the development of several neoplastic forms, in addition to cervical cancer, such as vagina, vulva, penile, anus, and oropharynx[1-3,7-9]. Cervical cancer is among the most prevalent cancers in the world, with 530,000 new cases per year[19].

In Brazil, cervical cancer is the third most common tumor in the female population and the fourth leading cause of death in women, with 16,340 (7.9%) new cancer cases of cervical cancer and 5,430 deaths of women per year, according to the National Cancer Institute[20].

Around half of women diagnosed with cervical cancer are under 50 years old, and more than two thirds are diagnosed in less developed countries. Southeast Asia (especially India), Latin America, and sub-Saharan Africa are areas with the highest percentages of cases. HPV 16 and 18 together account for 71% of cervical cancer globally. This percentage increases to 90% when we include HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58[19].

Recent studies have been conducted to evaluate the prevalence of the young Brazilian population. The study population conducted by the Brazilian Department of Health consisted of 5,812 women and 1,774 men, with a mean age of 20.6. The city of Salvador had 71.9% of HPV-positive participants, and the lowest rate was in the city of Recife, with 41.2% of survey participants[21].

The distribution and prevalence of HPV types vary based on the degree of cervical disease, age, and geographic location of patients[22-25]. The prevalence of HPV 16 and 18 has been observed in more severe lesions, but they are also the most frequent types observed in women with normal cytology[26]. A recent study carried out in Ghana showed that infection with high-risk types alone was seen in 32.3% of participants, while infection with multiple high-risk types was 9.7%.

The five most common HPV types detected were: 16 (7.4%), 52 (7.2%), 35 (4.8%), 59 (4.7%), 56 (3.9%)[27]. HPV-18 has been found in many regions as the second most common and in some Brazilian studies as well[28-31]. HPV-31 ranks second in frequency in Europe, HPV-52 is especially frequent in Africa and North America, and HPV-45 is in third place in Africa, Central/West Asia, North America, and Oceania[28,32]. In Brazil, HPV 31 and 33 are the second most prevalent types in the Northeast and Central regions[33,34].

In Mato Grosso do Sul, HPV-66 was detected in 22% of HPV-positive samples[35], and HPV-58 was the most frequent type (19.8%) in HIV-infected women followed by HPV-53 (15.5%) in Rio de Janeiro[36]. HPV DNA was detected in 67.5% of women. In a study in the state of São Paulo, HPV-16 (40%) was the most prevalent type in most patients with lesions, followed by HPV 31 (13.3%), 45 (13.3%) and 18 (4.1%). Multiple infections occurred in 15% of the cases, and infections with other types of HPV were detected in 14% of the samples. Thus, HPV 16 and 18 infections do not always occur in a solitary manner (single infection) and are associated with other types of HPV on several occasions[37].

HPV VACCINES

Three types of the HPV vaccine are available for the prevention of HPV-related diseases nowadays. The bivalent vaccine (Cervarix®) acts against HPV types 16 and 18. The quadrivalent vaccine targets types 6, 11, 16 and 18 (Gardasil®). More recently, the nonavalent vaccine (Gardasil 9®), which includes the most oncogenic genotypes prevalent and relevant low risk types 6, 11, 16, 18, 31, 33, 45, 52 and 58[38], was released.

Bivalent vaccine

This vaccine contains the viral capsid protein L1 and is produced by recombinant DNA technology using the *Trichoplusnia ni* insect cell baculovirus expression system to obtain VLPs, which are analogous viral particles of the two most common types present in neoplasms, cervical lesions, HPV-16 and HPV-18, accounting for 70% of the cases of this type of cancer[38].

Stimulation to the organism by the viral subtypes present in the VLP triggers the production of neutralizing antibodies against them, which provides the protection by the vaccine[39]. The adjuvant used in this vaccine is ASO4 with 500 µg aluminum hydroxide and 50 µg 3-deacylated monophosphoryl lipid-A[38]. Cervarix® is not a replicative vaccine and may be given together with other inactivated or replicative vaccines. However, its use is not recommended in pregnant women[38].

Side effects include injection site reactions, such as pain (91.8%), redness (48%), and edema (44.1%). Some people who received the vaccine described fatigue (55%), myalgia (49%), arthralgia (21%), and hives (7%) after immunization. In approximately 6,400 patients who received the vaccine, 28% reported gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal pain, and 13% developed fever within seven days after vaccination[40].

Quadrivalent vaccine

The quadrivalent HPV vaccine (Gardasil-4®) is also produced by a recombinant DNA technique in *Saccharomyces cerevisiae* yeast using the virus capsid protein L1, resulting in the production of

virus-like particles (VLP). These VLP resemble the virus, with the same shape and size, but are not infectious because they do not have genetic material. The quadrivalent vaccine is composed of HPV 6, 11, 16, and 18 capsid L1 proteins[39,41]. Protection is conferred by stimulating the body's production of neutralizing antibodies against viral subtypes present in the VLP[39].

It is known that the vaccine protects the HPV genotypes present in its cross-protection between other viral types due to gene similarity. The quadrivalent vaccine appears to provide partial cross-protection (around 59%) against types 31 and 45. Although these data have not been confirmed yet, there is also evidence of cross-protection against types 33, 52, and 58[41]. Studies have also shown a 38% efficacy of this vaccine against subtypes 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 in preventing cervical intraepithelial neoplasms 2 and 3 and adenocarcinoma *in situ*[42].

The quadrivalent vaccine, or Gardasil®, was approved by Anvisa in 2006. Brazil was one of the first countries to approve the HPV vaccine. It was implemented in the national immunization program by the Brazilian Department of Health in SUS in 2014. When it was released, the vaccine was recommended only for girls aged 11 to 13, but it has been currently applied to girls aged between 9 and 14 and boys from 11 to 14 years old[41].

Nonavalent vaccine

Following the first licensed Gardasil-4® (first generation vaccine), the second generation vaccine was Gardasil-9®, which covers types 6, 11, 16, 18, 31, 33, 45, 52, and 58, and these types together account for 90% of cervical cancer cases and other intraepithelial neoplasms. This increases the protection of the population against persistent infections that could lead to some mucous or skin cancers[43].

It is also produced by a recombinant DNA technique through expression in *Saccharomyces cerevisiae* yeasts, and VLP formed by capsid proteins of nine distinct viral subtypes will protect against the HPV types associated with approximately 90% of cervix cancer cases in women and 80 to 95% of other HPV-associated anogenital cancers in men and women[43-45].

The nonavalent vaccine, or Gardasil-9®, was approved by the US Food and Drug Administration (FDA) in 2014. In 2017, the second-generation vaccine was approved and registered by Anvisa and was indicated for girls and women, as well as for boys and men aged 9 to 26[46].

In a study by the Merck Sharp & Dohme Pharmaceuticals, comparing the two vaccines and highlighting the advantages of the second-generation vaccine, the Gardasil-9® not only presents the same benefits as Gardasil-4®, it also promotes immunization of the population of five types. This is more than the first-generation vaccine, showing better results against HPV 31, 33, 45, 52 and 58 related to undetermined atypical squamous cells and positive high-risk HPV or worse abnormality in the Pap smear[47]. A major advantage is also the extended age range indicated for vaccination, as the age range for Gardasil-4® vaccination is 9 to 26 years and is indicated for women and men older than 45[48].

In Brazil, surveys were conducted to estimate the prevalence of new cases per 100,000 inhabitants, with the highest prevalence recorded in states with the lowest level of regional development. This is a national profile that follows the world profile, where the highest prevalence rates are found in the in the Midwest, North, Northeast, Southeast and South regions, respectively. The most common oncogenic viral types in Brazil are HPV 6, 11, 16, 18, and 31[49].

COST-EFFECTIVENESS

There are 13 types of HPV known to cause cervical cancer and contribute to cancer in the anogenital region, vagina, vulva, anus, and penis, as well as in the oropharynx, mainly tonsillar region and tongue base[19,50]. Estimates of the possible health and economic effects of HPV vaccination provide vital evidence to support the introduction of the vaccine into national programs[51]. To assess the cost and benefit ratio of HPV vaccination, a quality-adjusted incremental cost per year of life (QALY) calculation is made from the expanded scenario, assessing the vaccination costs and those related to associated pathologies[52]. Recent work has shown a gain in QALY, and when vaccination occurs in both men and women, this gain is even greater[51-53].

Thus, vaccination, even with all related expenses, leads to a gain in public health. The nonavalent vaccine is an important advance, as the nine types present in the vaccine account for about 90% of cervical cancer cases. Non-vaccination vaccination can bring substantial additional public health benefits and is a very positive cost-effective intervention.

CONCLUSION

The great advantage of the nonavalent vaccine is protection of types that are represented among the most prevalent in some Brazilian regions, which were not present in the quadrivalent vaccine. Thus, it is believed that the nonavalent vaccine may present a new tool to control cases of persistent infections by high-risk types not covered by the quadrivalent vaccine and, in the long term, lead to a decrease in the number of cases of cervical cancer and other HPV-related cancers. We hope this paper will be important to disseminate knowledge of the new HPV vaccine efficacy. Further studies are expected to be conducted so this vaccine may be soon implemented in the National Immunization Program, replacing the quadrivalent vaccine, protecting the population against the most common infections and preventing injuries caused by HPV.

Participation of each author

Aislan Cristina Rheder Fagundes Pascoal was responsible for project design, literature review, manuscript writing. Marília Barcelos Marqui, Luana Tiuma Borba and Luiza de Souza Duarte were responsible for literature review and manuscript writing. Vinicius D'Ávila Bitencourt Pascoal and Fabiana Nunes Germano were responsible for manuscript revision.

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Conflict of interests

The authors declare no conflict of interests.

Ethics Committee Approval for Human Research

It is not applicable because it is a bibliographic review.

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