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REVIEW ARTICLE

HPV vaccination programs in LMIC: is it time to optimize schedules and recommendations?

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Abstract
Objectives: Prophylactic HPV vaccines are a fundamental tool to reduce infections and tumors caused by the most prevalent types of these viruses, as this review points out. Several countries have adopted immunization programs that recommend vaccination against HPV for girls and adolescents between 9 and 14 years of age and, in some of them, also for boys. The programs also contemplate the immunization of adults, particularly in the case of individuals with different immunodeficiencies.
Sources of data: The available vaccines are recommended for the prevention of tumors of the uterine cervix, vulva, vagina, penis, and anal canal. Moreover, two of the vaccines prevent the occurrence of genital warts, having been recently indicated for the prevention of oropharyngeal cancer.
Data synthesis: Based on the evidence that antibody responses in girls were non-inferior after two doses when compared to three doses, several countries have decided to reduce the vaccination schedule for girls and boys up to 14 years of age from three to two doses, with an interval of six months between them. Recently, knowledge has been accumulating about the immunogenicity, duration of protection, and efficacy of a single-dose HPV vaccine regimen in girls and young women.
Conclusion: Single-dose HPV vaccination could substantially reduce the incidence of pre-cancer and cervical cancer attributable to HPV, with reduced costs for vaccine delivery and simplified implementation, allowing more countries to introduce HPV vaccination or increase the adherence of the target population.

Epidemiology and disease burden

Infection by the human papillomavirus (HPV) is globally disseminated, being the most frequent sexually transmitted infection worldwide. This happens due to the facilitated

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transmission mechanism of HPV, through sexual contact among other forms of contact. It is estimated that the chance of a person having contact with the virus during their lifetime reaches 80%. Once infected, the person may have spontaneous remission and viral elimination, which occurs in most patients, or progress to persistent infection and later progress to different degrees of dysplasia and cancer. According to the National Cancer Institute of the Brazilian Ministry of Health (INCA, *Instituto Nacional do Câncer*) in 2022, Brazil should record 16,710 new cases of cervical cancer, which represents a considered risk of 15.38 cases per 100,000 women.[1]

Prophylactic vaccines against HPV

The numerous clinical trials of recombinant prophylactic vaccines containing VLPs (virus-like particles) of the HPV types most commonly found in cancer, conducted from the 2000s onwards, revealed that they are safe, highly immunogenic, and effective vaccines in preventing infections and lesions caused by the HPVs contained in vaccines.[2] Therefore, these vaccines were recommended by the World Health Organization as an effective strategy to control infections and tumors caused by HPV, especially cervical cancer.[3] Four prophylactic vaccines have been approved to be used in humans: the vaccine against four types of HPV: 6, 11, 16, 18 (Gardasil®, Merck & Co.), the vaccine against two types of HPV: 16 and 18 (Cervarix®, Glaxo Smithkline, UK), the vaccine against nine types of HPV: 6, 11, 16, 18, 31, 33, 45, 52, 58 (Gardasil9®, Merck & Co., USA), and the vaccine against two types of HPV: 16 and 18 (Cecolin®, Xiamen Innovax Biotech. China). All of them are exclusively prophylactic and can be administered to a wide age range of women and men but are more effective when administered to individuals not yet exposed to HPVs. Therefore, children and adolescents (9 to 14 years old) are the target population of the national immunization programs with these vaccines. In Brazil, the Ministry of Health National Immunization Plan adopted the vaccine against four types of HPV (Gardasil®, Merck & Co.). It is recommended that this age group receive two doses of the vaccine, with an interval of 6 to 15 months between them, according to studies that compared the levels of immune responses triggered by two or three doses of the vaccine. However, it is recommended for those over 15 years of age, for any adult individual in any age group, including immunocompromised ones (iatrogenically, or due to HIV, or those with congenital immunodeficiency) should receive three doses of the vaccine, using the 0, 1—2, 6—12 month schedule). There is no contraindication for breastfeeding women, but HPV vaccines should not be given to pregnant women. Moreover, co-administration with other attenuated or recombinant vaccines is safe.[3]

Results after vaccine implementation

A few years after the introduction of prophylactic vaccines against HPV in the national immunization programs, articles from different countries were accrued, disclosing the reduction of infections by vaccine HPV types. Even more relevant was the demonstration of the reduction of benign tumors caused by low-risk HPV, in addition to dysplastic cancer precursor lesions, caused by high-risk HPV, mainly types 16 and 18.[4] Even more important are the results published in 2020, which show a reduction in the risk of cervical cancer in Swedish women vaccinated with Gardasil®.[5] This confirms the great potential for a significant reduction in these tumors, and potentially in other tumors caused by HPVs, with the perspective of observing its elimination in countries with high immunization coverage of the population.

Despite such positive results, the best perspective of cervical cancer control, under ideal conditions of coverage and high effectiveness, would not exceed 70% of cases, considering that the main world epidemiological studies calculate the proportion of cancer attributed to HPV by 40—50% for HPV 16 and 15—20% for HPV 18. Therefore, at the end of the 2000s, the results of a vaccine containing 5 additional types of high-risk HPVs (31, 33, 45, 52, and 58) (Gardasil9®, Merck & Co., USA) were accrued, which, together with types 16 and 18, are responsible for approximately 90% of cases of cervical cancer.[6] This vaccine, approved in Brazil in 2017 but not yet available, was recommended for children and women aged 9 to 45 years for the prevention of cervical, vulvar, vaginal, anal cancer and its precursor lesions (such as dysplasia of different degrees) caused by HPV types 16, 18, 31, 33, 45, 52 and 58. In males, the vaccine is indicated between 9 and 45 years of age for the prevention of penile and anal cancer, and its precancerous or dysplastic lesions caused by HPV types 16, 18, 31, 33, 45, 52, and 58. Moreover, this vaccine is recommended for the prevention of genital and anal warts caused by HPV types 6 and 11. As with the quadrivalent vaccine, Gardasil9® can be co-administered with other vaccines such as those against meningococcus, tetanus, diphtheria, and acellular pertussis vaccine (bacterial triple - dTpa).

It is important to highlight that the high-risk HPV types are also related to a significant proportion of oropharyngeal cancers, mainly caused by HPV16. A significant increase in its incidence has been observed in males, which is attributed to infections by HPV 16 in the oropharynx, which includes the base of the tongue, the soft palate, the lateral and posterior walls of the throat, and the palatine tonsils. In the USA, according to the most recent estimates made by the Centers for Disease Control and Prevention (CDC, USA), oropharyngeal cancer attributable to HPV has surpassed cervical cancer as the most prevalent type of HPV-related cancer in that country.[7] In view of the above, and considering the preliminary results of clinical trials, which have not yet been completed, the US Food and Drug Administration (FDA) has recently approved a new indication for the nonavalent vaccine (Gardasil9®, Merck & Co., USA) for the prevention of oropharyngeal cancer and other tumors of the head and neck caused by HPV types 16, 18, 31, 33, 45, 52 and 58.[8]

It is clear, therefore, that the benefit of these vaccines should also be extended to men since they suffer from benign lesions and tumors caused by HPV. In addition, despite the proof of herd immunity induced by these vaccines, protection is limited to heterosexual women and men, in situations of high vaccination coverage, not benefiting homosexual and bisexual individuals. Thus, several countries in the world, including most Latin American countries, have introduced the vaccination of boys, aiming at extending the benefit and accelerating the reduction of the viral

load which, ultimately, will contribute to the reduction of HPV infections and associated diseases for all, contributing to the reduction of inequalities in public health.

HPV vaccines have also shown to be very interesting for use in populations that are especially vulnerable to HPV-related infection, disease, and cancer. Thus, currently in Brazil, the quadrivalent HPV vaccine is available at the Reference Center for Special Immunobiologicals (CRIEs, *Centro de Referência de Imunobiológicos Especiais*) for adults regardless of gender, up to the age of 45, cancer patients, solid organ transplant recipients, hematopoietic cell transplant recipients and patients living with HIV/AIDS. In these special situations, regardless of age, a three-dose schedule (0, 2 and 6 months) is recommended.

Other special situations would also benefit from vaccination, due to the greater risk of acquisition and exposure to HPV, such as victims of sexual abuse and men who have sex with men, but vaccination for these situations has not yet been incorporated in Brazil.[9,10]

The safety of HPV vaccines has been extensively studied using experience accumulated in clinical trials and immunization programs already implemented in several countries in the last decade.[10] To date, the WHO and several Scientific Societies and Organizations consider them to be safe and not associated with the development of autoimmune diseases, thromboembolism, neurological diseases, Bell's palsy, Guillain—Barré syndrome, complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS) or death.[11,12] Despite this, the identification of isolated cases of adverse effects in some countries, including Brazil, combined with the indiscriminate dissemination of rumors in the media and social networks, generated a feeling of insecurity. Furthermore, the growth of anti-vaccine movements has a negative influence on population coverage rates.

New vaccination schedules

Based on evidence that antibody responses in girls were non-inferior after two doses compared to three doses,[13] several countries have decided to reduce the vaccination schedule for girls and boys up to 14 years of age from three to two doses, with a six-month interval between them.[14] Recently, knowledge has been accumulating about the immunogenicity, duration of protection, and efficacy of single-dose HPV vaccine regimens in girls and young women.[15] Single-dose vaccination against HPV, if effective, would be tremendously advantageous, simplifying the implementation of national programs, improving vaccine coverage, and decreasing costs.

The main study comes from Kenya, where a randomized, double-blind trial using single-dose, nine-valent (infection by HPV 16/18/31/33/45/52/58/6/11) or bivalent (infection by HPV 16/18) vaccine against HPV was compared to meningococcal vaccination in Kenyan women aged 15 to 20 years.[16] The primary outcome was incident persistent vaccine-type HPV infection at month 18 post-randomization. A single dose of the HPV vaccine has been shown to be about 98% effective in preventing persistent HPV infections caused by HPV-16/18, the most common HPV type, responsible for 70% of cervical cancer cases.[17] Two high-quality observational studies in India and Costa Rica show that protection against HPV infections after the administration of a single dose is similar to two or three doses and lasts for at least 10 years after the vaccination.[18,19]

A single-dose HPV vaccination schedule is further supported by model-based evidence that consistently shows that single-dose vaccination, in settings that have not yet introduced HPV vaccines, will lead to a substantial reduction in uterine cervical cancer cases. Furthermore, reaching more cohorts of girls with a single dose will prevent many more cases of cervical cancer than vaccinating fewer girls with a second dose.

Another randomized clinical trial carried out in Tanzania (Dose Reduction Immunobridging and Safety Study — DoRIS) evaluated the protective immune response for the prevention of cervical cancer in HIV-negative girls aged 9 to 14 years, with different vaccines and vaccination schedules. Bivalent and nonavalent vaccines against HPV were used, in schedules of one, two or three doses (six different arms). The time of follow-up was at least 36 months, and observation should continue. The results obtained so far with the analysis using "immunobridging" showed that a single dose schedule proved to be protective against persistent HPV infection in the studied group.[20]

After review and evaluation by the technical group, current evidence supports the conclusion that single-dose HPV vaccination of the bivalent (Cervarix®), quadrivalent (Gardasil®), and nonavalent (Gardasil®9) vaccines provide protection equivalent or nearly equivalent to the two-dose vaccination schedule. Data accumulated to date and the recent recommendation by SAGE/WHO - Strategic Advisory Group of Experts on Immunization of the World Health Organization - are promising for countries that have not yet introduced it or are struggling to reach all eligible populations.[21] With greatly reduced costs for vaccine supply and delivery and simplified implementation, allowing more countries to introduce HPV vaccination or increase acceptance, single-dose HPV vaccination could substantially reduce the incidence of pre-cancer and cervical cancer attributable to HPV.

Data accumulated to date on single-dose HPV vaccination provide strong evidence that this strategy will have a strong impact on the fight against cervical cancer. Therefore, in April 2022, SAGE recommends updating the dose schedules for HPV as follows:

- One- or two-dose schedule for the primary target of girls aged 9 to 14 years.
- One- or two-dose schedule for young women aged 15 to 20 years.
- Two doses with a 6-month interval for women over 21 years.

Immunocompromised individuals, including those with HIV, should receive three doses if possible, and if not, at least two doses. There is limited evidence on the effectiveness of a single dose in this group.

Regarding Brazil and the possibility of implementing a single-dose recommendation for young people in the PNI, the authors believe it will have to be discussed that, despite the obvious advantages in terms of public health in a large country such as Brazil, there is still a lack of data on the persistence of protection and long-term follow-up. In fact, there are clinical trials being carried out in several countries

worldwide aimed to compare the effectiveness of one-dose compared to two- or three-dose schedules. These results, expected in the coming years, may guide decisions taken by public immunization programs in different countries. In any case, it is very important to establish epidemiological monitoring and surveillance strategies aiming to have an adequate follow-up of this cohort of girls who will receive a single-dose schedule.

Another aspect to consider is the recommendations related to the application of vaccines against HPV with different compositions. Thus, in cases of vaccination schedules initiated with other types of vaccines against HPV, the 9-valent vaccine can be used to continue or complete the vaccination schedule, aiming to expand the coverage of additional vaccine types. Moreover, for those who completed the vaccination with the lesser-valent vaccines, further vaccination with the 9-valent vaccine can be determined clinically, considering the circumstances of each case.

Globally, the acceptance of the life-saving vaccine intended to lead to the worldwide elimination of cervical cancer has been slow, and coverage in the countries that need it the most is well below the 90% target. In fact, in 2020 the global coverage with two doses was only 13%. Several factors have influenced the slow acceptance and low coverage of HPV vaccines, including supply challenges, as well as programmatic challenges and costs related to delivering two regimens to older girls, who are typically not part of childhood immunization programs. Added to that is the relatively high cost of HPV vaccines, especially for middle-income countries.[22]

On August 3, 2020, during the WHO assembly, the following term was signed: "Global strategy to accelerate the elimination of cervical cancer as a public health problem and its associated goals and targets for the period of 2020–2030", as a global action and commitment. The institution of a single dose of vaccination against HPV could support this desired, but distant goal.[23] It is also necessary to consider the cost issues for the implementation and maintenance of the vaccination programs against HPV, which for many countries is of considerable difficulty, depending on the scaling of priorities and the complex and not always objective political decisions.

Finally, the lack of knowledge about the risk of diseases caused by HPV continues to be a major obstacle to achieving high population coverage, both in relation to primary and secondary interventions in the control of these tumors. Therefore, any educational actions involving the most different levels of the lay population and health professionals become an essential tool to control the dissemination of erroneous information and to neutralize actions by anti-vaccination groups. The committed effort will be greatly rewarded with a reduction in the rates of cervical cancer and other tumors caused by HPV, which is already being observed in several countries worldwide.

Conflicts of interest

Luisa Lina Villa: has been a clinical trial investigator on Gardasil® for Merck, Sharp & Dohme, and is an occasional speaker on HPV vaccines.

Rosana Richtmann: Occasional speaker on HPV vaccines.

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