

## **Related Disease Prevention Strategy with Human Papillomavirus. Foundation of a Programmatic Decision in Chile**

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In relation to the article by Alberto Fica published in this issue of the journal (pages: 196-203), which refers to the incorporation of the vaccine against infection by the human papillomavirus (HPV) to the National Program of Immunizations, as the Ministry of Health (MINSAL) and with the responsibility of leading the Health Planning Division, in which the Department of Immunizations is located, I want to share with the scientific community some of the aspects considered in the incorporation of this vaccine.

This infection is a public health problem in the full spectrum of the effects that it causes, ranging from genital warts, respiratory papillomatosis, cervical cancer and including other types of HPV-associated cancers. That is why the 2014 official immunization schedule indicates "vaccine against human papilloma virus to prevent HPV infection". To support this decision, the available information and international experiences have been extensively analyzed, and different scientific societies and the CAVEI Panel of Experts (Advisory Committee on Vaccines and Immunization Strategies) have been consulted.

With this background, the Immunizations Department proposed to the ministerial authority to introduce the quadrivalent vaccine in 9-year-old girls, applying it in educational establishments to achieve coverage of 95%. This, in the context of a strategy that considers not only the vaccine intervention but also the improvement of surveillance of sexually transmitted infections in sentinel centers, screening coverage with Papanicolaou - Google Search and/or other early diagnosis techniques and, in particular, monitor the immunogenicity of the vaccine applied in our population to assess the evolution of antibody levels over time.

Some relevant aspects of the analyzes indicate that HPV infection has been associated with non-cancerous conditions, both in men and women and, in addition to cervical cancer, with other cancers, most potentially preventable through the use of HPV vaccines. Among the preventable non-cancerous HPV-related conditions, genital warts and respiratory papillomatosis are unequivocally linked to HPV types 6 and 11. In vaginal cancers and their precursor lesions, HPV DNA is detected in most cases; In recent studies, positive HPV DNA has been reported in 64% to 91% of vaginal cancer cases and 82% to 100% of grade 3 vaginal intraepithelial neoplasms (VAIN3). It is estimated that 40 to 50% of vulvar cancers are also associated with HPV. In men, HPV DNA is regularly found in penile cancers (40 - 45%). In both sexes, HPV DNA is detected in most anal cancers (88 - 94%). In head and neck cancers, the prevalence of HPV DNA varies greatly by study and geography. A consistent relationship with HPV has been observed in oropharyngeal cancers, with HPV DNA found in 35 - 50% of cases seen in developed countries. In all non-cervical HPV positive cancers, HPV 16 is the most common type detected, followed by HPV 18, 31, or 33 and 45. Studies on the incidence of cervical cancer have conducted to the idea that this disease is the one that dominates the burden of disease related to HPV. As a consequence, this was the model for vaccine studies, the development of immunization strategies and policies, health economic models, and the development of communication strategies in HPV control. The natural history and epidemiology of other HPV-related cancers have been much less well understood, but in recent years, new information from different sources

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has broadened our understanding of HPV-related diseases, and therefore forces us to rethink the control strategy that until now has been mainly oriented cancer of the cervix. Bosch., *et al.* conducted an analysis of the new information and summarized the main elements that drive the paradigm shift in the prevention of HPV-associated infection (Table 1).

<p>Disease burden in Viral etiology (HPV) has been established for a significant fraction of cancers of the vulva, vagina and anus, in both genders, and penis. A significant fraction of oropharyngeal cancer in both genders is highly associated with HPV infection. Data from industrialized countries with screening programs suggest that the number of anal and oro-pharyngeal cancers is increasing and may have surpassed cancer cervical. There has been an increase in knowledge of the co-morbidity between HPV and human immunodeficiency virus (HIV), the highest mortality rates tend to occur in the same countries (Sub-Saharan Africa). High rates of anal cancer in men who have sex with men and in HIV (+) individuals</p>
<p>Vaccine efficacy Initial data in Australia are showing high efficacy in the prevention of genital warts in cohorts of vaccinated girls, and significant efficacy in men, although lower, in non-immunized men from the same population, a significant example of the impact of the immunity of flock.</p>
<p>Data from studies in men have shown high efficacy against pre-cancerous anal lesions related to HPV and anal cancer and high efficacy in preventing genital warts.</p>
<p>Vaccine accessibility The GAVI Alliance (Global Alliance for Vaccines and Immunization) has included HPV vaccines in the list of vaccines that must be financially supported in eligible countries, opening the possibility of including it in developing countries. The price of the quadrivalent HPV vaccine is being offered at US \$ 5/dose. Many other multinational organizations (PAHO, Revolving Fund) and national offices have negotiated prices that facilitate the development of public vaccination programs.</p>
<p>Economic analyzes have been done to reflect these price levels since developing countries have to pay a fraction of the price.</p>
<p>Clinical Studies In the long term, adding HPV vaccines to infant immunization schedules would lower delivery costs and make outstanding available to 80% of the world's children. Even if reinforcement were necessary in pre-adolescents, the strategy would be highly successful.</p>
<p>Manufacturers would need bridging studies that can be performed in relatively small groups.</p>
<p>Studies with new HPV vaccines are in progress, products that include additional types of HPV. If successful, these vaccines will dramatically change the prevention strategy, target populations, and screening protocols for vaccinated women.</p>
<p>Adapted from ref. 3.s</p>

**Table 1:** Summary elements to consider in the paradigm shift in the prevention of infection associated with human papillomavirus.

When countries evaluate incorporating an HPV vaccine into national programs, an important category in the evaluation is the comparison of the cost-effectiveness of bivalent and quadrivalent vaccines. In general, such a comparison depends on a complex balance between assumptions about the duration of direct protection, the extent and duration of cross protection, and protection against anogenital warts and recurrent respiratory papillomatosis. In this context, an advantage of the quadrivalent vaccine is the additional benefits and cost savings associated with the protection against anogenital warts conferred by the inclusion of HPV types 6 and 11. If the potential differences in cross protection or Vaccine prices are not considered, several studies have found that the cost-effectiveness of vaccination against HPV 16, 18, 6 and 11 is more favorable than for HPV 16 and 18 alone.

In cost-effectiveness analyzes of vaccines, it is generally assumed, in the base case, that both vaccines will have very long duration or lifelong protection for the HPV types included in the vaccines. The clinical results of the phase 3 trials have provided follow-up data close to 10 years, a plateau in the titers of antibodies against HPV 16 after several years of follow-up suggests that the protection is likely to be maintained in the long term; However, in the case of the quadrivalent vaccine it is not clear whether the protection it will be sustained in

the long term for HPV 18. The bivalent vaccine induces high titers of neutralizing antibodies in serum; its long-term clinical implications are unknown, it is possible that it will eventually be associated with a longer duration of protection. The results of trials of both vaccines suggest that the bivalent vaccine may be associated with a higher level of cross-protection against types not included in the vaccine, but the differences in the methods of analysis and the follow-up times make it difficult to compare directly the results. The duration of cross-protection is also an area of uncertainty since neutralizing antibody titers are substantially lower for types not included in the vaccine.

A comparative analysis at an equivalent price in three countries concluded that a bivalent vaccine becomes profitable if it provides 22 to 44% more cross-protection against types not included in the vaccine, than a quadrivalent vaccine. An analysis in Italy concluded that the cost savings from anogenital warts could be offset by the additional savings in treatment costs for pre-cancerous lesions and cervical cancer that derive from increased cross-protection by the bivalent vaccine. However, if quality of life aspects are taken into account, the quadrivalent vaccine could be more attractive due to the gain represented by the prevention of ano-genital warts.

An alternative approach is to calculate the threshold cost at which the two vaccines have equivalent profitability. Jit., *et al.* have carried out an analysis in the United Kingdom, which considers a series of results, the duration of protection and cross protection, and concluded that the bivalent vaccine would have to be £ 19-35 (approximately 22 - 41%) less expensive per dose to be cost-effective equivalent to the quadrivalent vaccine, mainly due to the lack of protection against anogenital warts. This finding is consistent with an analysis for Ireland and Canada that the bivalent vaccine would have to be 22 to 26% less expensive, although these analyzes consider only the results of cervico-uterine cancer and ano-genital warts. This implies that the difference in the profitability of vaccines is mainly given by the burden of disease of ano-genital warts, the relative costs of treating warts, pre-cancerous lesions, and the associated impact on quality of life.

Several countries have incorporated quadrivalent vaccine into their immunization programs with different vaccination coverage. The first study analyzed is the California experience. An estimated 1.4 million Americans have genital warts. The quadrivalent vaccine has been available in the United States of America (USA) since June 2006. The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of girls and boys at 11 to 12 years of age and catch-up vaccination ("Catch up") for girls from 13 years old and boys from 13 to 21 years old. Since 2010, 49% of adolescents between the ages of 13 and 17 in the U.S. has received at least one dose and 32% of them have received the three doses established in the protocol; 21% of women ages 19 to 26 have received at least one dose and in California, 56% received at least one dose of vaccine. Several studies are underway to measure the population-based impact of vaccination. It has been suggested that given the rapid evolution of genital warts after infection, monitoring the trend of these lesions may provide the first evidence of the effectiveness of the vaccine.

Between 2007 and 2010, an average of 1,754,000 women and 258,000 men have been vaccinated annually.

Mind you, figures that increased every year in almost all age groups. Overall, 0.7% of women and 3.3% of men were diagnosed with genital warts. The highest rates were among those 21 to 25 years old, while the lowest were in those over 30 years of age. Between 2007 and 2010, the diagnosis of genital wart decreased by 34.8% (95% CI = -38.2 - 31.5%) among women under 21 years of age, from 0.94% to 0.61% (Ptrend < 0.001).

In 2007, Australia became one of the first countries to implement a national quadrivalent vaccine immunization program for girls 12 - 13 years of age in schools. From 2007 to 2009, two catch-up programs were implemented, one for girls aged 13 to 18 in schools and another for women aged 18 to 26 in the community. In 2010, the school-based program vaccination coverage rates were 83% for the first dose, 80% for the second dose, and 73% for the third dose, with coverage rates that decreased with increasing age. A sentinel surveillance network was established to monitor the effect of the vaccine on genital wart cases across Australia. Initial data showed that two years after the vaccine was introduced, the proportion of genital warts diagnosed fell by 59% in women aged 12 to 26 years eligible to vaccinate in 2007 and by 39% in heterosexual men from the same age. The decrease in genital warts in heterosexual men of younger groups can be attributed to herd immunity, in other words, the indirect protection of unvaccinated people as a result of reduced exposure to infection.

Given this information, we know that there is a short-term impact that we must not avoid and that questions remain about the long-term effects that will be clarified as the countries gain epidemiological evidence that allows us to improve the management of the programs and adapt preventive policies of health [1-9].

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