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SPECIAL ARTICLE

Ten years of human papillomavirus vaccination. From dermatology to oncology via infectology☆

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Abstract Human papillomavirus (HPV) was first identified in dermatology, and it was subsequently demonstrated that is was required for the development of uterine cervical cancer and other tumours, after a persistent infection by any of its oncogenic genotypes. Ten years ago, the most common infections and cancers associated with HPV could be prevented by immunization with 2 vaccines, one bivalent, and another tetravalent, and having just marketed a nonavalent one. During the period 2007–2008, the HPV vaccine was included in the Autonomous Communities vaccination calendar, and it is the second vaccine, after that of Hepatitis B, that prevents cancer. In these 10 years that these vaccines have been available the knowledge has progressed and there have been significant advances in vaccination strategies, as well as in the indications and recommendations. These include, lowering the age in the vaccination schedule, prescribing of 2 doses at 9 years and at 13–14 years, systematic vaccination of the male in some countries, immunization of the woman after adolescence, implementation of vaccination programmes in developed countries, prevention of other cancers, recommendations for vaccinations for populations at high risk of HPV infection, scientific evidence on the impact and effectiveness of vaccination, and confirmation of the safety of these vaccines, with more than 270 million doses administered, as has already been observed in clinical trials. The role of health professionals is essential to achieve and maintain high vaccine coverage.

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Diez años de vacunación frente al virus del papiloma humano. De la dermatología a la oncología a través de la infectología

Resumen El virus del papiloma humano (VPH) se identifica en primer lugar en dermatología y posteriormente se demuestra que es una causa necesaria para el desarrollo de cáncer de cuello uterino y de otros tumores, tras una infección persistente por alguno de sus genotipos oncogénicos. Desde hace 10 años, las infecciones y neoplasias más frecuentes relacionadas con el VPH pueden prevenirse mediante la inmunización con 2 vacunas, una bivalente y otra tetravalente, y acaba de comercializarse una nonavalente. Durante el periodo 2007-2008 se incluyó la vacuna frente al VPH en el calendario de las comunidades autónomas y es la segunda vacuna, después de la de la hepatitis B, que previene el cáncer. En estos 10 años de disponibilidad de estas vacunas se ha progresado en su conocimiento y se han producido avances importantes en las estrategias de vacunación y en las indicaciones y las recomendaciones: adelanto de la edad de vacunación en el calendario, pautas de 2 dosis desde los 9 hasta los 13-14 años, vacunación sistemática del varón en algunos países, inmunización de la mujer más allá de la adolescencia, implementación de programas de vacunación en países en desarrollo, prevención de otras neoplasias, recomendaciones de vacunación para poblaciones de riesgo elevado de infección por el VPH, evidencia científica del impacto y la efectividad de la vacunación, y confirmación de la seguridad de estas vacunas, con más de 270 millones de dosis administradas, como ya se había observado en los ensayos clínicos. El papel de los profesionales de la salud es fundamental para alcanzar y mantener coberturas vacunales elevadas.

''If men are not vaccinated, the prevalence of HPV will not decrease, as they are transmitters of infection.''

Zur Hausen, *La Vanguardia*, September 18, 2009.

Introduction: a century of human papillomavirus

More than one century ago, in 1907, Ciuffo proved the infectious aetiology of warts and suggested that the cause was a virus, since he was able to transmit the infection through injection of lesion filtrates in human volunteers[1]; later, evidence emerged that genital warts were a manifestation of a sexually transmitted infection. In the 1940s, the advent of electronic microscopy allowed the identification of viral particles in these warts (human papillomavirus [HPV]). In 1953, Bunting was the first to visualize a virus, HPV, within the cells of a wart (papilloma).[2] Thus, dermatology and venereology are found in the origins of the history of the pathology of HPV.

In the 1970s, Orth[3] demonstrated the oncogenic potential of the virus in epidermodysplasia verruciformis, and in the 1980s, Zur Hausen[4] found that HPV DNA is present in most cervical cancers. This author was awarded for his discovery of the role of infection in the pathogenesis of cervical cancer with the Nobel Prize in Physiology or Medicine ten years ago, in 2008, sharing the honour with Barré-Sinoussi and Montaigner, who received the award for their discovery of human immunodeficiency virus. In the 1990s, Bosch et al.[5] and Walboomers et al.[6] confirmed that HPV was present in nearly every case (99.7%) in a series of cervical cancer biopsies from patients in 22 countries; presence of the virus is necessary, although not sufficient, for the development of this cancer along with other cofactors that determine the malignant progression of infection by HPV. Persistent infection by any of the 12–15 oncogenic or high-risk genotypes out of the 150 HPV types that cause cutaneous or genital disease is necessary for the development of cervical cancer preceded by preneoplastic lesions (cervical intraepithelial neoplasia [CIN]: CIN1, CIN2 or CIN3).[7,8]

Thus, infection by HPV plays a role in the pathogenesis of these cervical tumours as well as anogenital and oropharyngeal tumours, and its role in other types of tumours is currently under investigation. The risk of progression from low- to high-grade lesions (from dysplasia to neoplasia) is greater in individuals with persistent infection by any of the oncogenic genotypes, although most HPV infections are silent and temporary and resolve spontaneously within 2 years from transmission. Five percent of all human cancers worldwide are associated with HPV.[9]

Last of all, the most significant breakthrough in regards to HPV has been the development of vaccines in the past 10 years that can prevent the most frequent HPV-related infectious diseases and cancers (primary prevention), conditions that we may be able to treat in the future with therapeutic vaccines that are currently being investigated. The virus-like particles used in preventive vaccines are not infectious or oncogenic, as they contain no viral DNA, but they can induce production of antibodies against the virus. Vaccinology enters the history of HPV one century after it starts and plays a key role in the complex and fascinating chapter that is currently unfolding, in which various medical and surgical specialties are converging, collaborating and participating.

When 2017 ends, it will have been 10 years since the first 2 HPV vaccines were introduced in the Spanish market—first, the quadrivalent one, in October 2007 (HPV 6, 11, 16 and 18), which had already been approved by the Food and Drug Administration (FDA) in 2006, and then the bivalent one (HPV 16 and 18), in January 2008. The results of a clinical trial of an earlier monovalent vaccine (HPV 16) had been published in 2002, showing an efficacy of 100% (95% confidence interval [CI]: 90–100), but this vaccine never reached the market, as a quadrivalent vaccine developed by the same laboratories was in late-stage trials.[10] A fourth vaccine was licensed in May 2017, the nonavalent vaccine, that expands the spectrum of prevention with the inclusion of 5 additional HPV types (31, 33, 45, 52 and 58); the FDA approved it in December 2014.[11]

In October 10, 2007, the Consejo Interterritorial del Sistema Nacional de Salud (Interterritorial Council of the Spanish National Health Service) included vaccination against HPV in its immunization schedule, and recommended routine vaccination of all girls in a single age cohort, to be chosen between 11 and 14 years by each autonomous community based on its needs, priorities and vaccination logistics, calling for introduction of the vaccine in each community by 2010; three autonomous communities introduced vaccination against HPV in late 2007, and the rest during 2008.[12]

The routine immunization schedule of the Asociación Española de Pediatría (Spanish Association of Pediatrics) has included vaccination against HPV since 2008. The current recommendations for HPV vaccination (2017 immunization schedule) are the following: routine vaccination of all girls, preferably at 12 years, or at a later age if vaccination is delayed, and providing information and possibly recommending the quadrivalent vaccine to male patients.[13] The introduction of a nonavalent HPV vaccine is expected to increase prevention of HPV-related cervical cancers from 70% to 90%, and may prevent between 85% and 95% of HPV-related vulvar, vaginal and anal cancers.[13]

The HPV genotypes included in the 3 vaccines cause between 70% and 90% of precancerous and cancerous cervical lesions; the genotypes included in the quadrivalent and nonavalent vaccines cause 90% of anogenital warts and a variable percentage of other lesions in the anogenital and the oropharyngeal regions (13%–72% of oropharyngeal cancers and 90% of cases of anal cancer).[14]

The HPV vaccine is the second vaccine included in the routine immunization schedule to prevent cancer, following the hepatitis B vaccine, and the third one, after the hepatitis B and A vaccines, introduced to prevent a sexually transmitted disease, in this instance, the most prevalent in the world.

Advances in vaccination against human papillomavirus in the first decade of the HPV vaccine

In the 10 years that HPV vaccines have been available, we have furthered our knowledge and made significant progress in vaccination strategies and the indications and recommendations for vaccination against HPV:

- Lowering of the age of vaccination from age 14 years to preadolescence (11–12 years), possibly starting at age 9 years, as specified in the summary of product characteristics, which is currently done in some countries. To achieve the maximum possible protection, it is important to vaccinate before sexual debut so that individuals are immunized prior to potential HPV exposure.[11,14]
- Approval of the use of a 2-dose schedule for all 3 vaccines in children aged 9–14 years (9–13 years for the quadrivalent vaccine), which promotes adherence and improve the acceptability and effectiveness of vaccination.[15] A clinical trial of a single-dose schedule led by Rolando Herrero is going to be carried out in Costa Rica in a sample of 20 000 adolescents aged 12–16 years.[16] This strategy would have a considerable impact by facilitating vaccination against HPV in developing countries.
- Routine vaccination of boys and men is now practised in 13 countries: Austria, Belgium, Croatia, Italy, Sweden, Switzerland, United States, Canada, Argentina, Brazil, Israel, Australia and New Zealand.[13] In men, immunization prevents development of anogenital warts, precancerous anal lesions and anal cancer. We expect that in the future, further research will prove the effectiveness of the vaccine in preventing other HPV-related cancers, such as scrotal, penile or oropharyngeal cancer. But the main justification of universal vaccination is the prevention of the sexual transmission of the virus, as both men and women are involved in the chain of infection and may become asymptomatic carriers, transmit the virus, or develop HPV-related diseases.[17,18] Universal vaccination would reduce the rate of HPV transmission and increase herd immunity.
- Vaccination of women past adolescence: this is a new approach in the primary prevention of cervical cancer and HPV-related diseases. Clinical trials in women aged more than 25 years have shown that HPV vaccines are safe, immunogenic and efficacious. However, the benefits of vaccination are variable, as this subpopulation is heterogeneous in terms of HPV status, with effectiveness decreasing with increasing age. For this reason, recommendations made from a public health perspective do not include women aged more than 25 years, for whom decisions regarding vaccination are made individually based on the judgement of patient and physician. It should be taken into account that the risk of being newly infected by HPV in sexually active women remains significantly high throughout the lifespan, and that persistent infection becomes more frequent with increasing age and immunosenescence.[19,20] In 2012, the Asociación Española de Patología Cervical y Colposcopia (Spanish Association of Cervical Pathology and Colposcopy), supported by several other scientific societies, published a first article establishing recommendations and the indication for vaccination of women outside routine immunization programmes,[21] followed, in 2016, by a clinical practice guideline that made the following recommendation for this age group: ''women aged more than 25 years may benefit from vaccination against HPV, regardless of whether they are already infected by any HPV type (moderate-quality evidence, strong recommendation in favour).''[22]

- Implementation of vaccination programmes in developing countries since 2013 thanks to the collaboration of the Global Alliance for Vaccines and Immunization (Gavi) and the United Nations International Children's Emergency Fund (UNICEF), expected to reach more than 40 million young women in over 40 countries by 2020.[23] The World Health Organization fact sheet on immunization coverage published in July 2017 reported that by the end of 2016, the HPV vaccine had been introduced in 74 countries, including 4 in which the vaccine had only been introduced in some regions.[24]
- Prevention of tumours outside the anogenital region, chief of which are head and neck tumours (mouth and throat). Other HPV-related cancers include tumours of the oesophagus, colon, larynx, lung, prostate and urinary tract.[9,14]
- Publication of the first recommendations for vaccination of populations at high risk of infection by HPV, persistent infection or malignant transformation: individuals with HIV infection, men who have sex with men, women aged more than 25 years with HPV infection or precancerous cervical lesions, and patients with inflammatory bowel disease, congenital bone marrow failure syndromes, primary immunodeficiencies, survivors of childhood cancers, solid organ or haematopoietic stem cell transplant recipients, undergoing treatment with immunosuppressive or biologic agents, or with recurrent respiratory papillomatosis.[22]
- Primary and secondary prevention of cervical cancer: screening for cervical cancer should still be performed in vaccinated women, although with the pertinent modifications to the screening protocol regarding the age at which screening should start, its frequency, and the diagnostic test employed, changes that will reduce screening costs. The awareness of the viral aetiology of cervical cancer has allowed the use of additional methods in screening programmes, such as the HPV test, thus improving them.[7]
- Impact and effectiveness of vaccination against HPV: a large amount of data and scientific evidence has been accumulated in the past 10 years, providing solid evidence of its effectiveness in preventing genital warts in men and women and the development of precancerous lesions in the cervix. A systematic literature review and meta-analysis of 20 articles published between January 2007 and February 2014, all corresponding to studies conducted in 9 high-income countries (United States, Australia, England, Scotland, New Zealand, Sweden, Denmark, Canada and Germany), and representing more than 140 million person-years of followup, analyzed the differences between the pre and post-vaccination periods in the prevalence of HPV infection and the frequency of anogenital warts and high-grade cervical lesions. This study reported that in countries that achieved a vaccination coverage rate of 50% or greater, there was a statistically significant 68% decrease in the prevalence of infection by HPV types 16 and 18 in female adolescents aged 13–19 years (relative risk [RR], 0.32; 95% CI, 0.19–0.52) and a significant 61% decrease in the frequency of anogenital warts (RR, 0.39; 95% CI, 0.22–0.71). Furthermore, in countries with high vaccination coverage rates, there was a significant decrease in the frequency of anogenital warts in women aged 20–39 years (RR, 0.68; 95% CI, 0.51–0.89) and in male adolescents aged 15–19 years (RR, 0.66; 95% CI, 0.47–0.91), which is indicative of herd immunity. There was also a significant decrease in the frequency of high grade precancerous cervical lesions in female adolescents aged 15–19 years (RR, 0.69; 95% CI, 0.66–0.73).[25] Another review of articles published over a 10-year period (2007–2016) found reductions of about 90% in the prevalence of infection by HPV types included in the quadrivalent vaccine and the frequency of anogenital warts, an 85% reduction in the frequency of high-grade cervical lesions, and a 45% reduction in the frequency of low-grade cervical lesions.[14]
- Safety of HPV vaccines. The more than 270 million doses administered worldwide since 2006 and the systematic reviews and meta-analyses published to date provide solid evidence of the high safety of these vaccines, confirming the results of prelicensure trials, although a few isolated and unsubstantiated claims have aroused concerns regarding their safety.[26] In some countries, such as Japan, Colombia and Denmark, these claims have had a significant impact on vaccination coverage, resulting, for instance, in a marked increase in the incidence of cervical cancer in Japan in recent years.[27] Some of the diseases involved in these claims are multiple sclerosis, Guillain-Barré syndrome, complex regional pain syndrome, postural orthostatic tachycardia syndrome, venous thrombosis, coeliac disease, primary ovarian insufficiency, premature ovarian failure and autoimmune diseases, although scientific evidence has ruled out a causal relationship between these diseases and administration of the HPV vaccine. The latest update of the Global Advisory Committee on Vaccine Safety (GACVS) on the safety of HPV vaccines, included in its 2017 report and its seventh statement on the subject since 2007, reasserted the high safety of these vaccines and ruled out the possibility of any association with these diseases. The GACVS reported an overall risk of anaphylaxis of 1.7 cases per million doses of HPV vaccine, similar to that of other vaccines, and that syncope is a common anxiety or stress-related reaction to the injection that also occurs in response to the administration of other vaccines during adolescence.[26,28] Although administration of the vaccine is not recommended in pregnant women, inadvertent administration of HPV vaccine during pregnancy has not been associated with adverse events in the mother, foetus or newborn.[26,29]

Epilogue

Infection by HPV meets the criteria for being considered a pandemic, as it is universal (affecting men and women throughout the lifespan and worldwide), causes a wide range of diseases (with possible manifestations including cancer, warts and transient or persistent infection) and is highly transmissible (increasing frequency in an increasing number of regions).[30]

The history of the pathology of HPV and its prevention provides yet another example of the interconnection of different specialties, which is found in many fields of medicine. Professionals involved in the vaccination of adolescents (paediatricians and paediatric nurses) or adults (family physicians and nurses), vaccinologists, virologists,

epidemiologists, preventive medicine specialists, gynaecologists, infectious disease specialists and dermatologists, among other health professionals, play an essential role in promoting awareness and educating the public on HPV infection, and in the promotion and implementation of vaccination against HPV, and have succeeded in achieving a 77.5% vaccination coverage in Spain in 2016 (somewhat lower compared to the previous year).[31] We must make a concerted effort to increase vaccination coverage and achieve universal immunization through routine vaccination of male individuals if we are to reduce the incidence of HPV-related cancer. School-based vaccination is a key intervention in the pursuit of high vaccination coverage rates, as demonstrated, for example, by the hepatitis B vaccination programme implemented in the adolescent population of Catalonia in the past 25 years.[32] We must not forget the important role of pharmacists in educating the public or the need to provide adequate information to parents and adolescents before vaccination.

Conflict of interest

The author has collaborated in educational activities funded by GSK, Sanofi Pasteur MSD and MSD.

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