REVIEW

HPV-vaccine and screening programs: the new era of global prevention

L. MARIANI
Dept. Gynecologic Oncology, Regina Elena National Cancer Institute, Rome, Italy

Key words

HPV vaccine • Primary and secondary prevention • Screening programs

Background

A vast body of evidence has emerged, in the recent decades, indicating the persistence of high-risk Human Papillomavirus (HPV) infection as the necessary cause, although not sufficient, for the development of cancer of the uterine cervix [1-3]. The biological details that explained the role of HPVs in cervical cancer etiology described some steps (HPV infection and persistence over time, integration into the host genoma and overexpression of E6-E7 oncoproteins, growth of precancer lesions, progression to invasion) that can be distinguished and which provide a background for the secondary prevention of such carcinoma [4].

Cervical cancer is the second most common cancer in women, accounting for at least 250,000 deaths per year worldwide, and overall the disease burden attributable to HPV is significant, with more than 5% of all cancers worldwide attributed to such infections [5]. Indeed, it is currently well documented that a significant proportion of vulvo-vaginal, anal and oro-pharyngeal cancers among women (as well as anal, oro-pharyngeal, and penile cancers among men) are etiologically related to the same high-risk HPV types.

In terms of prevention the burden of scientific knowledge regarding Papillomavirus infection has translated in two main applications that will provide important health benefits: HPV-DNA testing and HPV-vaccine. In the last years molecular testing for high-risk HPV types become available for clinical use, thus changing the strategy of secondary prevention [6] and management of intraepithelial cervical lesions [7]. Furthermore, an effective screening program will be a prerequisite for the evaluation of vaccines effectiveness, and thus vaccination and cytologic screening will be complementary strategies. Although HPV-immunization programs still reveal a number of unanswered questions and some author stressed the necessity of prudence [8, 9], they represents an extraordinary opportunity for primary prevention against cervical cancer and other HPV-related pre-neoplastic/neoplastic diseases.

Thus a global prevention program (through HPV immunization integrated into cytological screening) is viewed as an important breakthrough in public health.

Nevertheless, how to most efficiently carry out such global prevention of cervical cancer is still unclear. This issue will necessitate collaboration among gynecologists, oncologists and experts in preventive medicine, in immunization programs and in sexually transmitted diseases as well.

The HPV vaccines

Two HPV-vaccines, made both by DNA recombinant techniques, are commercially available so far. The quadrivalent vaccine (GARDASIL™, Sanofi Pasteur MSD) and the bivalent vaccine (CERVARIX™, GSK) use an expression systems based on Yeast and Baculovirus, respectively, and are constituted of subunits of the L1 viral protein, assembled into DNA-free structures called *virus-like particles* (VLPs) which are not infectious, nor oncogenic.

Both vaccines protect against HPV types 16 and 18, that are responsible for over 70% of the squamous and glandular cervical cancers [10, 11], as well as other genital pre-neoplastic/neoplastic diseases (vulvo-vaginal). Moreover, oro-pharynx neoplasias have also been linked to HPV infections [12, 13]. Additionally, the quadrivalent vaccine protects also against HPV 6 and HPV 11 infections that are associated to over 90% of anogenital warts and juvenile respiratory papillomatosis [14, 15].

The current indications are: prevention of premalignant cervical lesions and cervical cancer for both vaccine and, actually limited to quadrivalent vaccine, also prevention of high-grade premalignant vulvo-vaginal lesions (VIN2/3 and VaIN 2/3) and external genital warts (condyloma acuminata) related to vaccine types.

The goal of both prophylactic vaccines is to reduce and contain the incidence of HPV related disease by means of a potent (above the level of natural infection) and long-lasting humoral immune response. High level of type-specific IgG, elicit by the vaccines, will prevent viral entry into the cells, thus protecting against the infection.

The high immunogenicity generated by the vaccines depend on the itself nature of VLP (which display many

neutralising epitopes, induce good T cell helper responses for B cells, important for robust antibody and B cell memory responses), and is also related to the adjuvant employed: AAHS in quadrivalent vaccine (Amorphous Aluminum HydroxyPhosphate Sulphate) and ASO4 in bivalent vaccine (a combination of aluminium hydroxide and monophosphoryl lipid A [MPL]).
In order to value the efficacy and clinical benefit, the female populations of the clinical trials have be divided into three categories:

I. **per-protocol population (PP)** included randomised women:
   1. naïve to relevant vaccine HPV type through all vaccination protocol;
   2. received all three vaccinations;
   3. no protocol deviation;
   4. efficacy evaluated after dose 3;
II. **modified intention-to-treat (mITT)** included randomised women:
   1. naïve to relevant vaccine HPV type at inclusion;
   2. received at least 1 vaccination;
   3. efficacy evaluated after dose 1;
III. **intention-to-treat population (ITT)** included all randomised women:
   1. all randomised women regardeless of baseline status;
   2. received at least 1 vaccination;
   3. efficacy evaluated after dose 1.

As demonstrated in phase III randomized trials [16-19] the clinical efficacy of vaccines against high grade cervical intraepithelial neoplasias (CIN2+) is close to 100% in HPV-naïve women *(per-protocol analysis)*, and remains high also in the *modified intention to treat population,* but it is much lower in women previously exposed to vaccine-targeted HPV types at the time of vaccination (*intention-to-treat*). Nevertheless, the protection in ''intention-to-treat'' vaccinated population would be expected to increase over time as women in the placebo group continue to become infected with vaccine-targeted types of HPV. Furthermore, this data also highlights the prophylactic nature of the vaccines, that do not accelerate clearance of viral infections [20], nor prevent the development of CIN in already infected women.
Quadrivalent vaccine has been approved by the FDA (US Food and Drug Administration) and the EMEA (European Medical Evaluation Agency) in 2006, and since then has received approval by other regulatory authorities in over 100 countries. The bivalent vaccine was approved in Australia and by the EMEA in 2007, and in over 60 countries. The US-Advisory Committee on Immunization Practices (ACIP) and many scientific societies (American College of Obstetricians and Gynecologists, American Cancer Society, Society of Gynecologic Oncologists) recommended that the organized HPV vaccination programs target females 11 to 12 years of age, when the immunological response to vaccine is most effective and the HPV-seroprevalence is very low (i.e. ≤ 3% for HPV-16) [21]. Moreover, catch-up programs are also recommended up to 26 years old women irrespective of HPV status [22].
Ongoing studies are evaluating HPV vaccines in women over the age of 26. The rationale for vaccination of adult women is that, even though HPV peak incidence rate occur between the ages of 15 and 25, the majority of adult women have not been previously infected with HPV-16 and/or HPV-18 [23]. Moreover, it should emphasize that low antibody levels after natural infection do not guarantee protection against re-infection of the same genotype or HPV-reactivation [24, 25], thus suggesting that the vast majority of women (even over 25 yrs old) could have benefit from vaccination. We also should take into account that a second peak of HPV infection has been reported after the menopause [26]. What is the significance of such peak remains to be solved: 1- reactivation of latent infection; 2- acquisition of a new infection; 3- a reduced capacity to respond to infectious agents as a result of decline in immune function [27].
It has been established in the FUTURE studies [28] that some women in the placebo-group developed disease despite having antibodies to the offending HPV types at enrollment, thus confirming that natural infection-elicited antibodies may not provide complete protection to HPV over time. Furthermore, the conserved high local and systemic antibody responses in adult women (from 26 to 55 years old) has been assessed up to 2 years after the administration of the first dose of bivalent vaccine [29], thus predicting that women above 26 years of age are likely to benefit from HPV vaccination if further exposed to HPV 16 or 18. Moreover, *ad-interim* results for quadrivalent vaccine shown high profilactic efficacy against disease related to HPV 6,11,16,18 in women up to 45 years naïve to vaccine types [30].
Cross-protection on HPV-genotypes not included into vaccine is strictly related to the polyclonal nature of the immune response to vaccination. Preventing infection and diseases associated with additional oncogenic genotypes immunologically related to HPV 16 and 18 (particularly HPV 31 and 45) may provide an extra measure of protection. A statistically significant protective effect against virological and clinical end-point regarding HPV 31 (persistent infection and CIN2-3/AIS related diseases) has been reported after quadrivalent vaccine in naïve population [31] and in ITT population [32]. Also for bivalent vaccine has been reported a cross-protection against incident infection (with a 66 months of follow-up) and persistent infection (in a short-term 6-months analysis) of HPV 31, HPV 52 and HPV-45 [19, 33]. Indeed, the recently up-dated results from bivalent trials confirm the significant cross-protective efficacy against CIN2+ associated with non-vaccine oncogenic HPV types such as 31 and 33 [34].
Although the clinical benefit for non-vaccine HPVs is not expected to be fully complete as observed for the vaccine relevant genotypes, such additional protection could increase the expected reduction in cervical cancer.

The vaccination programs

In most European countries the national public health authorities, through their government advisory panels, recommended the use of HPV-vaccines in national vaccination programs in order to maximize the public health benefit. In December 2007 the Italian Health Ministry and the Italian Regions stated to offer free vaccine to all Italian girls at 12 years old. Vaccination programs started over the year 2008 with the exception of one region (Basilicata) where vaccination was implemented in 2007.
In this context, vaccination should preferentially occur through organized programs in (multi)cohorts prior to sexual debut (pre HPV-exposition) or close to it.
This setting represents the primary target population for HPV vaccination in Italy, and allows for better standardization, a more rigorous monitoring of vaccination, and is likely to benefit the community nation-wide. This is particularly true when organized vaccination is compared with the vaccination on an individual basis. Opportunistic vaccination is based on a different set of considerations than those used in nation-wide programs, and the ultimate goal is primarily to protect and provide benefit to an individual woman, sometimes irrespective of age. Moreover, vaccines should also be offered in catch-up programs considering the actual official indication of the products at least to girls up to 16 years of age, which corresponds to the upper limit of the Italian obligatory school and will facilitate for high coverage. As a matter of fact, some Regions provide free access to vaccination not only to 12 but also to 13 years old girls and to women older than 13, at a discounted price.
Some issues remain unsolved as we enter the era of vaccination against cervical cancer and other HPV-related diseases. Although vaccination has been the single most effective public health intervention to protect people against infectious diseases, it demands a capillary spread, a high acceptance among the population, an elevated coverage of the target population and the certainty of sustainable economic resources over time. Although religious or ethic reactions against vaccination in adolescents may be take into account (due to the fear that vaccine will promote early sexual activity or might encourage risky sexual behavior), data concerning the parents acceptance are reassuring [35] and mothers are more pragmatic than we might credit them for [36].
Moreover the first data regarding vaccination coverage one year after the start of vaccination programs in different Italian Regions show high acceptance of vaccination in both 12 and 13 years old age groups. Despite that, as for many other western countries, also in Italy women's knowledge about HPV infection and cervical cancer was remarkably poor, as only 23.3% ever heard of them [37].

The screening system

It is critical that women (whether vaccinated or not) continue cytological screening. The need for continue screening program also for vaccinated women is related to the following factors:

- all genital preinvasive/invasive lesions are not exclusively generated by HPV 16 or 18;
- the rate of cross-protective benefit is still to be definitively proven;
- the duration of both HPV vaccines has to be evaluated and monitored during the vaccination programs;
- the optimal vaccine benefit is demonstrated in naïve adolescents/young women, i.e. before they have naturally encountered papillomavirus.

Although disparities exist in access to nationwide cytological programs and although the lack of randomized trials, screening with Pap-test has showed to be highly effective as secondary prevention in most of Western countries. In North America, as well as in Europe, the introduction of cervical screening programs has been associated with reductions in cervical cancer mortality up to 60% [38]. Also in Italy due to organized, as well as opportunistic, screening programs, cervical cancer mortality significantly dropped from 8.6/100,000 in 1980 to 3.7/100,000 in 2002.
Indeed, we cannot forget that even if the vaccine will become more and more widespread, several generations of women worldwide would still need secondary prevention methods because, as quoted by Bosch [39], "*…for most living women today, screening remains their primary option for cervical cancer prevention*".
Nevertheless, we can anticipate that screening cytological protocols will change in the next future, (for both vaccinated and non-vaccinated female populations), so that effective introduction of HPV-vaccines will require an understanding of such new paradigms of cervical cancer prevention.
Indeed, due to the low sensitivity and low reproducibility of cervical cytology, screening strategies are already changing beyond the innovative wave of HPV-vaccination. In this way we are moving from a prevention model based on cytology-colposcopy-histology to a biomolecular model based on virologic detection of HPV and its molecular interactions with the human host [40-43]. The rationale is to use the most *sensitive test* to detect life threatening HPV-infections as up-front tool to identify all women at risk for HSIL, followed by a more *specific test* (Pap-test) as triage to avoid unnecessary referral to colposcopy.
An increasing number of trials have been published that support the high sensitivity of HPV DNA testing, relative to cytologic evaluation for detecting high-grade cervical intraepithelial neoplasia. Up-to-now clinical applications of HPV testing are: 1-triage of women with equivocal cytology results (atypical squamous cells of undetermined significance, ASC-US); 2-surveillance after therapy for cervical intraepithelial lesions; 3- as in addition to cervical cytology screening over 30 years). Incidence rate of CIN3+ among HPV-DNA negative women suggests that preventive strategies in which women are screened every six years, are safe and effective [44].

Moreover, HPV-testing (contrarily to conventional cytology) will maintain its performance also in populations with low-HPV prevalence, as a result of vaccination.

The need for a global prevention strategy

At this moment the main challenges are how to properly combine the two such preventive tools (primary and secondary prevention) and how to optimize overall costs of this new global strategy.
Within the setting of an organized cervical screening program, many mathematical predictive models demonstrated that prophylactic HPV vaccination can reduce cervical cancer, CIN lesions and other genital HPV-related diseases [45, 46]. The costs of HPV-vaccination will be balanced by the savings of reduction in disease incidence, less diagnostic and therapeutic procedures. From such models (assumed 90% vaccine efficacy for at least 10 years and vaccine coverage in 100% of 12-year-old girls) vaccination at 12 years of age with biennial screening beginning at age 24 results the most appealing cost-effective strategy [44, 47].
The rationalization of new screening strategies in low HPV-prevalence settings following HPV vaccination may allow to reduce costly screening programs: deferring the age of starting screening, lengthening the time-interval between screening rounds or modulating the proper timing between vaccination and screening. All these modulations will translate in new screening algorithms for immunized women and could provide evidence of cost-effectiveness of papillomavirus vaccine.
In Italy, having started mass-vaccination of the 12-yrs-old girls during 2008, we have time enough to monitor such variables that may occur over time and that may properly modify the future preventive guidelines (i.e. when the vaccinated cohort will be called by the screening system). Specific public programs have been set-up in different Italian Regions to monitor long-term effectiveness, possible adverse events and increased prevalence of other genotypes as result of a replacement phenomenon.
As for all new vaccinations some key-points need to be clarified because of the limitations of currently available data. The American Cancer Society [48] pointed out that the clinical impact of vaccination on cervical cancer will depend upon several unknown factors: 1-the degree of vaccination coverage; 2- the durability of protection, and thus the need for further boosts; 3- acceptability of community; 4- additive role of cross-protection. These issues still represents an obstacle to forecast the future most effective prevention strategy, although the characteristics and experience of the Italian public health system can provide monitoring of all them and properly modify the future guidelines and adequate adjustments to the ongoing vaccination programs.
Any changes in cervical cancer prevention policies (with or without vaccination) have to be addressed regarding all women at risk and, if not broadly accepted, could translate into higher disparities among the various socio-cultural layers of the female population. We should rather avoid increasing disparities among socio-economic groups, limiting the benefits of vaccine only to the higher-income subset of societies. Indeed, the high price of both vaccines means that they are more available to a small proportion of the population that can afford to pay for them.
This could be the scenario if vaccine uptake would be low in pre-teens, with a high-rate of opportunistic vaccine uptake among older girls (24-26 yrs old) already adhering to national screening recommendations. In this hypothetical scenario, despite high costs, we would not expect a significant decrease in cervical cancer mortality and morbidity.
Another contemplated scenario concerns the false sense of safety produced by the vaccination. Some vaccinated women may perceive to be fully protected from cervical cancer and may be less likely to participate in screening programs. In the United States it has been hypothesized that if 50% fewer vaccinated women participate in screening over a 5 year period following HPV vaccination [49] there would be 4 missed CIN2–3 among 1000 women. Moreover, vaccinated women may also perceive to be totally protected from sexually transmitted diseases other than papillomavirus, potentially leading to changes in their sexual behaviour and increasing the frequency of other sexually transmitted infections. Again, the Italian public system through the organized active and free call for screening can circumvent this risk.

Conclusions

A long-term and accurate monitoring system is needed:
- to fully ascertain the population-based impact and public health significance of vaccination;
- to verify the economic impact for each country, concerning the local issues regarding the dynamic process of vaccination (prevalence, sexually active population, access to health care, ecc.). It is reasonable [50] that the initial positive public health benefit (short-term analysis) will be most apparent for anogenital warts, targeted by low-risk HPV 6 and 11 [51], followed by an increasing benefit over time for all the other HPV-related diseases.

It is important to consider that all of the above mentioned benefits will emerge only when harmonizing the prevention strategies and assuring over time a clear and complete information to the community [52].
Considering that full impact on cervical cancer will take many decades to be revealed, our final recommendations about HPV-vaccination are concerning practical issues surrounding implementation of these vaccines in this moment:
1. Set-up cost-effective preventive programs combining vaccination and screening, based on the specific HPV-prevalence in the corresponding geographical area.

2. Intensify efforts to implement organized vaccination programs with high-coverage among HPV-naive girls, possibly through multicohort programs.
3. Provide adequate HPV type specific surveillance to monitor any changes in HPV type distribution among the general population, to assess the impact of vaccination.
4. Evaluate cross-protection and HPV type-replacement.
5. Ensure adequate access to, and links between, vaccination-registries and screening-registries.
6. Verify the vaccine efficacy in men and in high-risk subsets of patients (HIV, immunosupressed).

Although the proper way to combine primary and secondary prevention into a integrated program remains to define, the potential of this global strategy is to complete the goal of cervical cancer eradication in the next decades.

References

[1] zur Hausen H, de Villiers EM, Gissmann L. *Papillomavirus infections and human genital cancer*. Gynecol Oncol 1981;12: S124-8.

[2] Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. *Human papillomavirus is a necessary cause of invasive cervical cancer worldwide*. J Pathol 1999;189:12-9.

[3] Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV. *The causal relation between human papillomavirus and cervical cancer.* J Clin Pathol 2002;55:244-65.

[4] Schiffman M, Castle P, Jeronimo J, Rodriguez A, Wacholder S. *Human papillomavirus and cervical cancer*. Lancet 2007;370:890-907.

[5] Frazer I. *HPV immunisation. A significant advance in cancer control*. Gynecol Oncol 2007;107:S1.

[6] *The 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests*. Am J Obstet Gynecol 2007;197:346-55.

[7] *The 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in-situ*. Am J Obstet Gynecol 2007;197:340-5.

[8] Lippman A, Melnychuk R, Shimmin C, Boscoe M. *Human papillomavirus, vaccines and women's health: questions and cautions*. CMAJ 2007;177:484-7.

[9] Gostin LO and De Angelis CD. *Mandatory HPV Vaccination. Public Health vs Private Wealth*. JAMA 2007;297:1921-3.

[10] Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. *Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis*. Br J Cancer 2003;88:63-73.

[11] Munoz N, Bosch FX, Castellsague X, Dıaz M, de Sanjose S, Hammouda D, et al. *Against which human papillomavirus types shall we vaccinate and screen? The international perspective*. Int J Cancer 2004;111:278-85.

[12] Preuss SF, Klussmann JP, Jungehulsing M, Eckel HE, Guntinas-Lichius O, Damm M. *Long-term results of surgical treatment for recurrent respiratory papillomatosis*. Acta Otolaryngol 2007; 127:1196-201.

[13] Gerein V, Schmandt S, Babkina N, Barysik N, Coerdt W, Pfister H. *Human papillomavirus (HPV)-associated gynecological alteration in mothers of children with recurrent respiratory papillomatosis during long-term observation*. Cancer Detect Prev 2007;31:276-81.

[14] Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. International Agency for Research on Cancer Multicenter Cervical Cancer Study Group: *Epidemiologic classification of human papillomavirus types associated with cervical cancer*. N Engl J Med 2003;348:518-27.

[15] Clifford G, Franceschi S, Diaz M, Muñoz N, Villa LL. *HPV type-distribution in women with and without cervical neoplastic diseases*. Vaccine 2006;24(Suppl 3):S26-34.

[16] Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, M.D., Harper DM, Leodolter S et al. for the FUTURE I Investigators. *Quadrivalent Vaccine against Human. Papillomavirus to Prevent Anogenital Diseases*. N Engl J Med 2007;356:1928-43.

[17] FUTURE II Study Group. *Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions*. N Engl J Med 2007;356:1915-27.

[18] The Future II Study Group. *Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials*. Lancet 2007;369:1861-8.

[19] Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, Wheeler CM et al. for the HPV PATRICIA study group. *Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial*. Lancet 2007;369:2161-70.

[20] Hildesheim A, Herrero R, Wacholder S, Rodriguez A, Solomon D, Bratti C et al. for the Costa Rican HPV Vaccine Trial Group. *Effect of Human Papillomavirus 16/18 L1 Viruslike Particle Vaccine Among Young Women With Preexisting Infection A Randomized Trial*. JAMA 2007;298:743-53.

[21] Dunne EF, Karem KL, Sternberg MR, Stone R, Unger E, Reeves WC, et al. *Seroprevalence of Human Papillomavirus type 16 in children*. JID 2005;191:1817-9.

[22] Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER for the Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices (ACIP). *Quadrivalent human papillomavirus vaccine: recommendations of the advisory committee on immunization practices (ACIP)*.MMWR Recomm 2007;56:1-24.

[23] Department of health and human services centers for disease control and prevention. Advisory Committee on Immunization Practices. Summary report, February 27-28, 2008 [http://www.cdc.gov/vaccines/recs/acip/downloads/min-feb08.pdf].

[24] Carter JJ, Koutsky LA, Hughes JP, Lee SK, Kuypers J, Kiviat N, et al. *Comparison of human papillomavirus types 16, 18, and 6 capsid antibody responses following incident infection*. J Infect Dis 2000;181:1911-9.

[25] Viscidi R, Schiffman M, Hildesheim A, Herrero R, Castle P, Bratti M, et al. *Seroreactivity to human papillomavirus (HPV) types 16, 18, or 31 and risk of subsequent HPV infection: results from a population-based study in Costa Rica*.Cancer Epidemiol Biomarkers Prev 2004;13:324-7.

[26] de Sanjosé S, Diaz M, Castellsagué X, Clifford G, Bruni L, Muñoz N, et al. *Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis*. Lancet Infect Dis 2007;7:453-9.

[27] Skinner RS, Garland S, Stanley M, Pitts M and Quinn M. *Human papillomavirus vaccination for the prevention of cervical neoplasia: is it appropriate to vaccinate women older than 26?* MJA 2008;188:238-42.

[28] Ferris D and Garland S for the Quadrivalent HPV Vaccine Investigators. *Evaluation of quadrivalent hpv 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with prior vaccine hpv type infection*. The 13th International Congress on Infectious Diseases Kuala Lumpur, Malaysia, June 19-22, 2008.

[29] Schwarz T, Spaczynski M, Schneider A, Wysocki J, Galaj A,

Perona P et al. on behalf of the HPV Study Group for Adult Women. *Immunogenicity and tolerability of an HPV-16/18 AS04-adjuvanted prophylactic cervical cancer vaccine in women aged 15-55 years*. Vaccine 2009;27:581-7.

[30] Luna J, Saah A, Hood S, Barr E. *Safety, efficacy, immunogenicity of quadrivalent HPV vaccine (Gardasil) in women aged 24-4.5* 24th International Papillomavirus Congress, November 3-9, 2007 Beijing, (Presentation #PA1-04).

[31] Brown D, Kjaer S, Sigurdsson K, Iversen O-E, Hernandez-Avila M, Wheeler C, et al. *The Impact of quadrivalent Human Papillomavirus (HPV; Types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic non-vaccine HPV types in generally HPV-naive women aged 16–26 years*. JID 2009;199:926-35.

[32] Wheeler C, Kjaer S, Sigurdsson K, Iversen O-E, Hernandez-Avila M, Perez G, et al. *The impact of quadrivalent Human Papillomavirus (HPV; Types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic non-vaccine HPV types in sexually active women aged 16–26 years*. JID 2009;199:936-44.

[33] Jenkins D. *A review of cross-protection against oncogenic HPV by an HPV-16/18 AS04-adjuvanted cervical cancer vaccine: Importance of virological and clinical endpoints and implications for mass vaccination in cervical cancer prevention*. Gynecol Oncol 2008;110:S18-25.

[34] Skinner R, Apter D, Chow SN, Wheeler C, Dubin G for the HPV PATRICIA Study Group. *Cross-protective efficacy of Cervarix™ against oncogenic HPV types beyond HPV-16/18*. 25th International Papillomavirus Conference, May 8-14 2009, Malmö.

[35] Zimet GD, Liddon N, Rosenthal SL, Lazcano-Ponce E, Allen B. *Psychosocial aspects of vaccine acceptability*. Vaccine 2006;24(S3):201-9.

[36] Garland S, Park S, Ngan HYS, Frazer I, Tay EH, Chen CJ, Bhatla N, et al. *The need for public education on HPV and cervical cancer prevention in Asia. Opinions of experts at the AOGIN Conference*. Vaccine 2008; 26:5435-40.

[37] Di Giuseppe G, Abbate R, Liguori G, Albano L, Angelillo I. *Human papillomavirus and vaccination: knowledge, attitudes, and behavioural intention in adolescents and young women in Italy*. Br J Cancer 2008;99:225-9.

[38] Berg A, Atkins D. *Screening for cervical cancer. Recommendations and rationale. Guide to Clinical Preventive Services*. (2nd ed). US Preventive Services Task Force. Rockville, MD: Agency to Health Care Research and Quality, 2004.

[39] Bosch FX, Castellsague´X and de Sanjosé S. *HPV and cervical cancer: screening or vaccination?* Br J Cancer 2008;98:15-21.

[40] Franco EL, Cuzick J *Cervical cancer screening following prophylactic human papillomavirus vaccination*. Vaccine 2008;26(Suppl 1):A16-23.

[41] Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al. for New Technologies for Cervical Cancer Screening Working Group. *Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test*. J Natl Cancer Inst 2008;100:492-501.

[42] Nieminen P and Anttila A *Introducing HPV screening: challenges and fallacies*. Acta Obstet Gynecol Scand. 2007;86:1416-8.

[43] Wentzensen N, von Knebel Doeberitz M. *Biomarkers in cervical cancer screening*. Dis Markers. 2007;23:315-30.

[44] Dillner J, Birembaut P, Petry K-U, Szarewski A, Munk C, de Sanjose S, et al. *Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study*. BMJ 2008;337:a1754.

[45] Elbasha EH, Dasbach EJ, Insinga RP. *Model for assessing human papillomavirus vaccination strategies*. Emerg Infect Dis 2007;13:28-41.

[46] Goldie S. *A public health approach to cervical cancer control: considerations of screening and vaccination strategies*. Int J Gynecol Obst 2006;94(Suppl 1):95-105.

[47] Kulasingam SL, Myers ER. *Potential health and economic impact of adding a human papillomavirus vaccine to screening programs*. JAMA 2003;290:781-9.

[48] American Cancer Society. *Guideline for Human Papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors*. CA Cancer J Clin 2007;57:7-28.

[49] Kulasingam SL, Pagliusi P, Myers E. *Potential effects of decreased cervical cancer screening participation after HPV vaccination: an example from the U.S*. Vaccine 2007;25:8110-3.

[50] Insinga R, Dasbach E, Allen S, Carides C, Myers E. *Reductions in Human Papillomavirus-Disease Resource Use and Costs with Quadrivalent Human Papillomavirus (Types 6, 11, 16, and 18) Recombinant Vaccination: The FUTURE Study Economic Evaluation*. Value Health 2008;16:1-11.

[51] Fairley C, Hocking J, Chen M, Donovan B, Bradshaw C. *Rapid decline in warts after national quadrivalent HPV vaccine program*. 25th International Papillomavirus Conference, May 8-14 2009, Malmö.

[52] Pagliusi S, Lawson H, Singer A, Monsonego J. *EUROGIN 2007 Patient Education Conference: Sharing experiences and action in cervical cancer prevention — an overview of 2007*. Vaccine 2008;26S:A33-36.

■ Received on March 30, 2009. Accepted on May 21, 2009.

■ Correspondence: Luciano Mariani, Dept. Gynecologic Oncology, Regina Elena National Cancer Institute, via Elio Chianesi 53, Rome, Italy - Tel. +39 06 52665985 - E-mail: luciorm@libero.it