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Extending Human Papillomavirus (HPV) vaccination beyond female adolescents and after treatment for high grade CIN: the *Italian HPV Study Group (IHSG)* review and position paper

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Abstract. – OBJECTIVE: Human Papilloma-Virus (HPV) vaccination has been introduced in recent years in clinical practice as the most effective primary prevention strategy for cervical cancer and HPV-induced lesions, either pre-malignant or benign. Since its introduction, HPV vaccination has been progressively demonstrated as extremely effective in preventing extra-genital and male diseases also; furthermore, non only adolescents but adult subjects have been investigated and reported as positively responding to vaccine immunostimulation. More recently, effectiveness of post-treatment vaccine administration has been preliminarily investigated with very promising results in terms of decreased recurrences. On this basis, we report an Italian-focused picture of the state of the art and take a position in favour of the extension of HPV vaccination to male adolescents, to older age groups and to already treated subjects.

Key Words:
HPV vaccine, Universal HPV vaccination, HPV age vaccination, CIN, Vaccination after treament, Adjuvant vaccine.

Introduction

HPV Vaccination in Italy: Where We Are and Where We Want to Go

High-risk HPV strains are believed to be responsible for 100% of carcinomas of the uterine cervix, 88% of anal carcinomas, 70% of vaginal carcinomas, 50% of penile carcinomas and 43% of vulvar carcinomas[1-3]. The identification of HPV as one of the main causes of the development of tumors in the anogenital tract and in the head/neck has allowed the development of an increasingly high-performing and effective vaccine protection pathway[4-7]. In Italy, it is estimated that there are about 2,600 new cases/year of cancer of the cervix and 29,603-55,625/year cervical precancerous lesions; 390 cases/year of vaginal-vulvar tumors; 366 cases/year of anal tumors in men and 426 cases/year in women[5] (Table I). The sentinel surveillance system shows a high incidence of genital warts in young people under the age of 25 with an increased trend in both sexes[8]. Data show that HPV related diseases have a significant impact on Italian public health. The estimated total cost of the HPV diseases is about 528 million Euro, of

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Table I. Estimated cases of HPV related tumors in Italy in 2017[5].

	HPV related tumor (%)	Sex	Estimated cases	Estimated cases HPV related	5 years survival
Oral cavity	< 10	Males	3000	270	57%
		Females	1600	144	61%
		All	**4600**	**414**	**59%**
Oropharynx	31	Males	1500	465	37%
		Females	400	124	47%
		All	**1900**	**589**	**39%**
Larynx	2.4	Males	4000	96	69%
		Females	500	12	70%
		All	**4500**	**108**	**69%**
Anus	88	Males	100	88	53%
		Females	200	176	57%
		All	**300**	**264**	**56%**
Penis	50	Males	500	250	74%
Cervix	100	Females	2300	2300	68%
Vulva	25	Females	1200	300	59%
Vagina	78	Females	200	156	39%

which about 211 million Euro for male diseases[9]. In 2014, a mathematical model was reported to assess the impact of female vaccination in Italy, confirming that the introduction of vaccination will reduce cervical cancer[10]. In 2015, a review of the beneficial costs of male HPV vaccination was published. In the previous literature the extension of vaccination to males was also shown to be cost-effective in 53% of studies. However, the reduction of vaccination costs and the two-dose schedule in the adolescent population have led to the economic sustainability of universal vaccination[11]. The BEST II study has estimated that universal HPV vaccination represents a cost-effective option also in the Italian context with a total savings of about 70 million Euro/year[12].

Vaccine Policy and Coverage in Italy

Since 2007, an active and free vaccination program targeting 12-year old girls has been initiated in Italy. Since 2015, three regions have also introduced vaccination for males (11-12-year-old). In addition, some regions also offer the vaccine to male and female individuals, as well as to those who are HIV positive. In the new National Vaccination Prevention Plan (PNPV) 2017-2019, free vaccination is offered to males starting from the 2006 cohort. The PNPV recommends vaccination to unvaccinated adolescents; to women over the age of 25 starting at the time of their first cervical screening and to male homosexuals (MSM). Most of the Regions offer co-payment for other age groups not subject to an active call. These indications are in accordance with the recommendations of the Advisory Committee on Immunization Practices (ACIP)[13,14].

All HPV vaccines can be administered under the PVPN in the form of two doses of vaccine up to 15 years of age, and three doses in the 15-25 age bracket. The use of the nonavalent vaccine (9vHPV) in the target population (males and females at 11-12 years of age) would result in a widening of protection against pretumoral and tumor lesions[15-17] (Figure 1). In 2017, a better cost effectiveness of the universal 9vHPV vaccination than 4vHPV vaccination has been reported**.** Compared to the vaccination program with the quadrivalent vaccine, the nonavalent vaccine in a universal setting shows further reduction of 17% in the incidence of cervical cancer, and 35% and 14% in anal cancer for both sexes, as well as over a million cases in helping avoid genital warts. In other comparison strategies, the intervention with universal HPV9 vaccination results in a cost-savings compared to 4vHPV and 2vHPV, demonstrating an economical sustainability[18]. A crucial element is obviously represented by vaccination coverage. In December 2017, the Italian Ministry

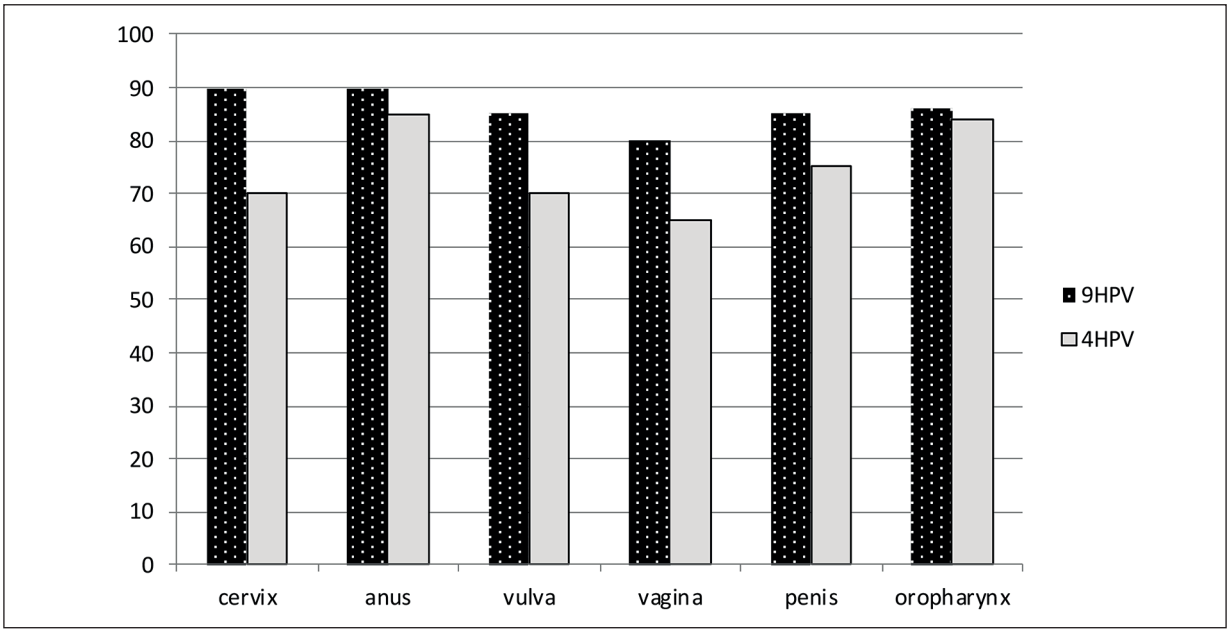

Figure 1. Predicted prevention of HPV related cancers (%) for 4vHPV and 9vHPV vaccine[15].

of Health published data of national and regional coverage for the HPV vaccination: the average coverage in girls is below the optimal threshold set by the PNPV (95%)[13]. The average vaccination coverage in males is quite far from the objectives set by the PNPV 2017-2019, which identifies a gradual increase from the 60% threshold for 2017, up to 95% in 2019 (Figure 2).

Future Perspectives

Data on efficacy, safety and cost-benefit are in favor of universal HPV vaccination in all countries and in the Italian context too[19,20]. Not only, reports on a single dose of HPV vaccine indicate a potentially easier and faster universal vaccination coverage. The Costa Rica Vaccine Trial (CVT), a phase III randomized clinical trial, provided

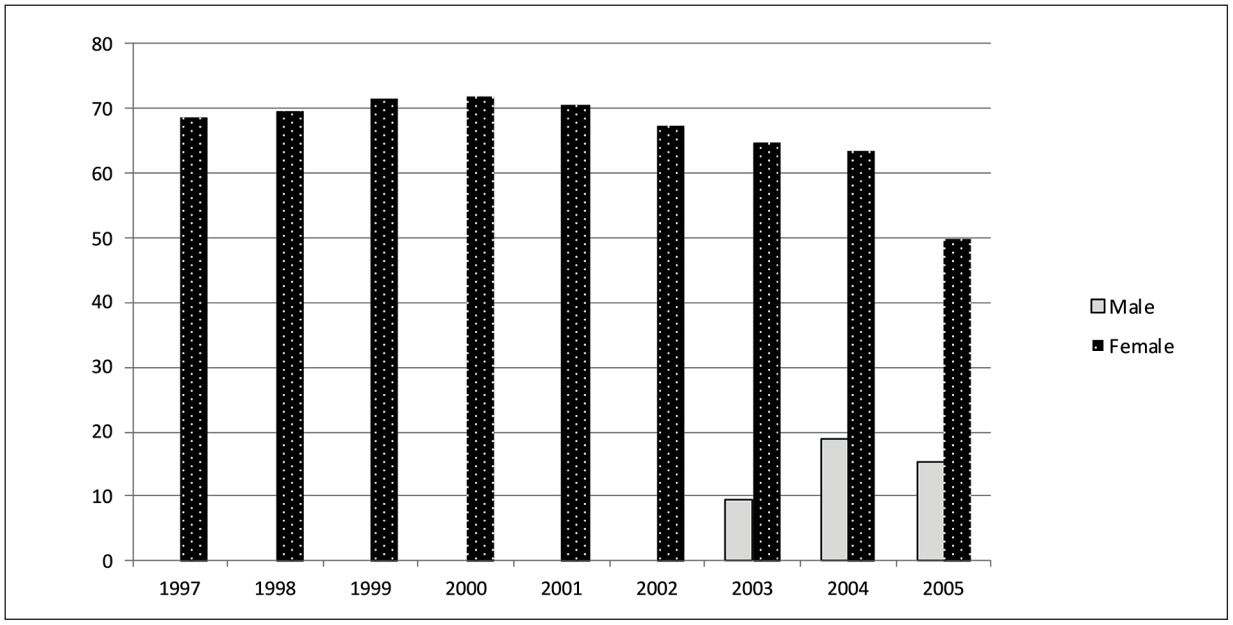

Figure 2. Vaccination coverage for complete cycle (cohorts 1997-2005)[13].

the initial data that one dose of the HPV vaccine could provide durable protection against HPV infection[21,22]. The strongest evidence of efficacy of a single-dose vaccination will eventually come from the ESCUDDO study, a randomized clinical trial comparing a single dose *vs.* two of both the bivalent and nonavalent vaccines. However, the results of this study will not be available until 2023[23]. The success of immunization programs depends upon the understanding of the vaccination benefits. To consolidate the results and allow their improvement, it is essential to actively involve the population and to promote vaccination as an individual right and a matter of responsibility[24]. General practitioners and family pediatricians are firstly involved in the process of health education and health promotion for the primary target population (males and females of 11-12 years of age). School vaccination programs represent the best way for improving the coverage rate, even in the context of health education addressed to teachers, parents and students. Australia was the first country to introduce free HPV vaccination in schools since 2007 for the female population and then subsequently also for males since 2013. From 2018 the program provides for the vaccination of 12-13-year-old males and females with the nonavalent vaccine. Scientific literature has shown a reduction of at least 50% of cervical precancerous lesions in women, and a reduction of 90% of condylomatosis in both sexes[25-27]. In Italy, few surveys evaluated the reasons for limited vaccination coverage. These include fear of adverse events, discordance of information and recommendations among medical professionals, poor knowledge and awareness of HPV-related diseases[28,29]. A recent survey involving 640 pediatricians shows that vaccination is recommended to 77.4% of 11-12-year-old girls, but only to 18% of males[30]. An Italian study[31] evaluated 40 HPV vaccination campaigns in terms of geographical distribution and time, target population, message style, media tools and preventive messages. The campaigns introduced from 2004 onwards are inadequate in terms of communication either regarding timing and geographical distribution; moreover, they are prevalently addressed to adult women, excluding adolescents and males.

The communication tools most frequently used by the Health system are: brochures/leaflets (92%), fliers/posters (72%), television (24%) and radio (15%). When all the communication channels were put together, coverage was around 70%. It will be important to direct resource campaigns that make use of tools suitable for an adolescent population increasingly attracted by new media and social technologies[32]. A recent article[33] evaluated the development of an interactive video game (Land of Secret Gardens) to motivate American pre-teenagers to HPV vaccination, assuming that this tool can be part of a broader communication strategy. A synergy of multiple interventions will be essential to promote culture of vaccination and to obtain an Italian universal HPV vaccination program[34-36].

Long-Term Efficacy and Safety of HPV Vaccination

The first two vaccines were developed against the two high-risk genotypes (hrHPV) HPV16/18 responsible for about 70% of cervical cancers[37]: one is a bivalent vaccine (2vHPV) while the other includes also the low risk genotypes HPV6/11 (4vHPV). Both vaccines provided evidence of very high efficacy against type specific related HPV infection and disease when administered to girls naïve to HPV16/18[38-40]. The titer of antibodies in female children (ages 9-15) who were injected with the vaccine remained elevated after 10 years from vaccination[41], and this suggests a long-term protection. Assessments are still ongoing. Further studies demonstrated that the vaccines can provide some kind of cross-protection against the HPV types 31 (4vHPV), and 31/33/45 (2vHPV)[40]. This is due to the fact that phylogenetically HPV16 is related to HPV31/33 and HPV18 is related to HPV45, and that these types share aminoacid sequences in the L1 protein of the capsid[42]. Because of the high level of antibody titers observed in young vaccinated adolescents, a two-dose schedule was evaluated. Two large-scale double-blind randomized controlled trials[43,44] demonstrated that two doses of vaccine conferred the same protection as the three-dose schedule against infection due to HPV16/18: given the comparability of the two regimens a two-dose schedule was recommended for females in the 9-14 age range[45]. Adolescents (15 years or older) or young adults should continue to receive the three dose schedule. Little data exists on the adequacy of a one-dose schedule; randomized trials assessing the efficacy of one-dose administration of vaccine are ongoing. In 2014 the nonavalent vaccine (9vHPV) was approved by the US Food and Drug Administration, and in 2015 it was also approved by the European Commission. The goal was to maintain the immunogenicity and therefore the protection achieved with the 4vH-

PV, and to extend the protection to other types. A large randomized controlled trial compared the 4vHPV *vs*. the 9vHPV in women, ages 16-26[46]. The 9vHPV vaccine demonstrated a high efficacy (97% for primary endpoint at 54-months follow up) in preventing infection and disease related to HPV 31/33/45/52/58 while generating an antibody response to HPV 6/11/16/18 that was non-inferior to that generated by the 4vHPV vaccine. Subsequent studies demonstrated that the two-dose schedule of 9vHPV in young women was equally immunogenic as the three-dose schedule in older women[47]. Due to the recent development and administration of 9vHPV vaccine, data on the duration of protection are available only for up to 6 years[48,49]. It is important to note that the three vaccines are very effective against HPV16/18, which is the main cause of more than 70% of cervical cancer cases. Focusing specifically on HPV-related cancers, it has been calculated that the increase in prevention achieved by 9vHPV as compared with 4vHPV may range from +2% to +20%, depending on the organ considered[50,51]. HPV vaccines have been administered for more than 10 years and active surveillance and investigation for any adverse event have been in place. Research data indicates that 2vHPV, 4vHPV and 9vHPV vaccines are highly effective and safe. Systemic adverse events (AEs) were similar in vaccinated and placebo groups in both 2vHPV and 4vHPV clinical trials[52-55]. In all the trials injection-site reaction, fever, headache, nausea and dizziness were the most frequently reported AEs. However, no increase in serious AEs has been reported, and rates were quite low, such as for example 2.5 per 100,000 in Australia[56] or 8.4 per 100,000 in Slovenia[57]. Specifically, the rate of death in HPV receiving subjects was significantly lower than expected for paired age groups, and no death was related to the administration[58]. The same profile of safety has been reported for 9vHPV, apart from a slightly more frequent injection site reaction, probably due to the higher concentration of adjuvant[59]. Some AEs have been particularly debated; such as, first of all, syncope occurring on the day of vaccination. The event was associated in fact with HPV vaccine administration; it has been described as relatively benign but underlines the need of having a protocol of observation after the injection. As far as allergy and anaphylactic reaction are concerned, data accumulated in different countries[60,61] showed that the rate of anaphylaxis or anaphylactoid reactions were comparable or even lower than vaccine-related anaphylaxis rates for other vaccines. Moreover, no safety signal was identified for the development of different autoimmune disease, with no difference in the frequency of these disease in vaccinated and control groups[62,63]. Other studies evaluated other potential adverse events. Robust evidence demonstrated the safety of HPV vaccines; thus, the use of these vaccines to prevent cervical cancer has to be a priority as HPV vaccination is highly effective[64].

HPV Vaccination in Women Older than 26 Years of Age

As a prophylactic measure, HPV vaccination is dispensed when the person is not infected before the highest risk of exposure to the viruses[65]. HPV vaccination in older ages underlines the key point of age distribution of HPV infections as causal to cancer development. These persistent infections, when not prevented by vaccination or not interrupted by screening and treatment, are at risk for developing pre-invasive and invasive cancers. Presumably, most of HPV infections in younger women are incident infections, whereas prevalent HPV infections in older women are typically persisting infections[66]. Taking heed of the prophylactic and not therapeutic role of HPV vaccination, the issue of extending HPV vaccination in women older than 26 years of age is of utmost importance both for current public health policy and for long term reduction of HPV related cancers. As serum antibodies detected after natural infection do not confer protection against reinfection with the same genotype, sexually active women are arguably re-infected multiple times in their lifetime[66]. This is the aim of HPV vaccination in older women. Four main studies[67-70] have investigated HPV 16/18 seroconversion in women older than 25 years of age and antibodies' persistence during follow up. A study from Schwarz et al[69] using bivalent vaccine found that one month following the third vaccine dose (month 7) all initially seronegative women were seropositive for anti-HPV16/18 antibodies. At the end of follow up (72 months), all women remained seropositive for anti-HPV16 antibodies and at least 97% were seropositive for anti-HPV18 antibodies. The concentration of antibodies peaked at month 7, followed by a gradual decline until month 18, as reported by other studies[68,70]. Then the antibodies remained steady indicating that they reached a plateau phase. The other study using bivalent vaccine by Skinner et al[67] had a 48-month follow-up and analyzed data in these age brackets:

26-35, 35-45 and over 46 cohorts. All initially seronegative women seroconverted for HPV 16/18 at month 7 and, irrespective of age, all women remained seropositive for HPV 16 up to month 48. All initially seronegative women aged 26-35 remained seropositive for HPV 18 at month 48; 99% of 36-45 year-old women and 97% of 46 years and older women. Einstein et al[70,71] conducted a clinical trial comparing seroconversion in a first cohort with bivalent vaccine and a second cohort with quadrivalent vaccine in a 60-month follow-up, stratifying data in three age groups (18-26, 27-35 and 36-45). At month 7 after vaccination all women who were seronegative/DNA negative before vaccination for the HPV type analyzed had seroconverted for HPV16/18 serum neutralizing antibodies, except for only two women aged 27-35 who did not seroconvert for HPV18 (98%). At month 60, seropositivity rates for the bivalent vaccine remained at 100% in all age groups for HPV16, while for HPV18 rates remained at 100% except for the 27-35 age group (98.1%). Castellsagué et al[68] reported the results of quadrivalent vaccination in women between 24 and 45 with high level of seroconversion at month 7 in previously seronegative women (98.4, 98.1, 98.8 and 97.3% for HPV 6/11/16/18 respectively).

Efficacy

Two phase 3 clinical trials[67,68] have addressed the efficacy of HPV vaccination in preventing persisting HPV16/18 infection in women older than 25 years. Skinner et al[67] examined bivalent vaccine efficacy against 6-month persistent infection or CIN 1 associated with HPV 16/18 as a primary endpoint. It was reported 83.5% efficacy (97.7% CI 45.0-96.8) in women between 26-35 years of age who were seronegative and HPV-DNA negative at baseline and 77.2% efficacy (97.7% CI 2.8-96.9) in the 36-45 age cohort. In the total vaccinated cohort (irrespective of seropositivy and DNA positivity) efficacy was 35.4% (97.7% CI 5.8-56.1) in women between 26-35 yrs. and 53.4% (97.7% CI 15.7-75.2) in the 36-45 age group. No HPV infections were reported in the over 46 cohort. Castellsagué et al[68] evaluated quadrivalent HPV vaccine efficacy against persistent infection, CIN or external genital lesions (EGL) related to HPV 6/11/16/18 infection in a cohort of women between 24-45 yrs. Vaccine efficacy against persistent infection in seronegative and HPV-DNA negative women was 86.2% (95% CI 69.4-94.7) and 92.4% (95% CI 49.1-99.8) against any grade of CIN. Otherwise, vaccine efficacy in the intention-to-treat population (irrespective of seropositivty and DNA positivity) was 42.8% (95% CI 25.5-56.3) and 41.9% (95% CI 5.6-64.9) against any grade of CIN. Interestingly, quadrivalent vaccine offered a significant cross protection against persistent infection of HPV 31 (79.1%, 97.7% CI 27.6-95.9) and HPV 45 (76.9%, 97.7% CI 76.9-95.6). The recent Cochrane review on HPV Vaccination[20] confirms moderate-certainty evidence that HPV vaccines reduce CIN2+ in older women underlining their efficacy in HPV negative women at study enrollment.

Adverse Effects

As reported[72,73], it has been observed that the most common complaint is pain in the injection site, which is self-limiting and spontaneously resolved. These findings support that HPV vaccines are well tolerated in older subjects too.

Cost-Effectiveness

Many studies[74-79] have addressed the cost/effect analysis for an implementation of HPV vaccination in older women. All studies evaluated the bivalent vaccine in a 3-dose vaccination program. Four of them[74,76,78,79] showed the costs for vaccination of women over 26 years of age to be beyond their respective cost-effectiveness thresholds. Thus, they did not recommend HPV vaccination in older women as a cost-effective public health medical intervention. Turner et al[78] reported a marginal cost-effectiveness but only when the vaccine price was below £20/dose and assuming life-long vaccine protection. The only study showing clear cost-effectiveness is from Belgium[77]; the authors reported high cost-effectiveness of the bivalent vaccine for women up to age 33 and a modest cost-effectiveness for women up to age 40. All the researches were based upon mathematical models taking into consideration many variables, such as vaccine price, duration of seroconversion and efficacy, which have not been taken into account in other studies. Thus, they are exposed to wrong assumptions in the mathematical modeling and so further studies are required to evaluate the real cost-effectiveness. The key public health question for vaccinating adult women against HPV is whether the vaccine reduces cancer risk in these women[80]. Even if we have much information from the above exposed phase III clinical trials, we cannot make definitive conclusions on this matter. As detection of HPV-DNA could represent a new infection or a reactivation of a latent HPV virus in basal cells, we are

able to offer protection against new infection of the selected HPV vaccines genotypes, but still not sure if our efforts are countered by viral latency. However, we can conclude that both bivalent and quadrivalent vaccine inducement sustained anticorpal response and vaccination is found to be safe in older women. Further studies are needed to assess the impact of the nonavalent vaccine in older women and compare it to quadrivalent and bivalent vaccines in terms of immunogenity, efficacy, safety and confirming its adjunctive protection. Bosch et al[81] suggested a combined approach to extend HPV vaccination: they propose the vaccine to be offered to women between 9 and 45 years of age, and up to 50, in limited settings. For women younger than 30 an additional screening before vaccination is needed in order to detect HPV positive women and offer the proper follow up. The effect of one round of screening would transform an intention-to-treat cohort into a per-protocol cohort and thus increase vaccine efficacy. Evaluating all these concerns will be useful to public health programs and guarantee every woman an improving standard of care.

Cure and Recurrence Rates After Treatment of HG-SILs

High grade SIL (Hg-SIL) is the current definition proposed by the LAST Project for CIN2 and CIN3 lesions (Cervical Intraepithelial Neoplasia) and represent the true precursor of invasive cervical cancer[82]. The risk of progression to invasive carcinoma actually depends on the severity and size of the lesion, with approximately one third of women with untreated CIN3 eventually developing the invasive disease[83,84]. The factual point of the entire screening process is that the identification end excision of CIN3 lesions avoids the development of cervical cancer. The age of the patient at diagnosis plays a fundamental role in the biologic behavior of the lesion, and most of the current national and international guidelines recommend a more conservative approach in women younger than 25 years of age[85-87]. This is because cervical excision procedures are not exempt from complications. Harm from overscreening and overtreatment include increased reports of preterm birth, premature rupture of membranes, low birth weight and caesarean section. Reproductive-related complication rates appear to be dependent on the length and volume of the specimen and the excised amount of cervical functional stroma[88-92]. The failure rate of excisional treatment – defined as persistent or recurrent CIN2 or worse (CIN2+) is reported as being between 2 and 18%, the majority of which occurring in the first two years following treatment [93,94]. Such a significant variance of reported incidence of failure is evidently related to many counfounding factors, such as age, treatment technique, status of cone margins and of the residual endocervical canal. Moreover, it has been widely recognized that treated women remain at increased risk for subsequent invasive cervical cancer compared to the general population, and this is true for at least the subsequent 10 years. This concept comes from the results of a large multicentric study from the UK, which showed a relative risk five times higher than the general population in the 8 years following treatment[95]. Similar findings came from other studies, including those from the Swedish and Dutch cancer registries, as well as from a large population study based in Canada[96-99]. At the same time, however, other authors did not observe the same trend and actually reported a very low incidence of late occurring invasive carcinomas, not to a mention a very low incidence of re-treatment for CIN2+ recurrences[100,101]. Post treatment follow up schedules and modalities are also of paramount relevance considering their potential impact on female compliance, anxiety and organizational and financial efforts of the provider. Incomplete excision of the lesion (as assessed by the presence of CIN on the margins of the excised specimen or at sampling of the endocervical canal at the end of the procedure) has been shown to be associated with an increased rate of treatment failure. The same has proven true for the persistence of abnormal cells in the cervical canal as evaluated immediately after the surgical procedure. The role of hrHPV-DNA persistence after treatment is extremely important, and hrHPV-DNA testing six months after excision is considered as being the single most indicative prognostic indicator of recurrence. HPV type and viral loading, as well as the role of genotyping and E6/E7 detection in the follow up are currently under investigation[102-104].

Best Performing Strategy of Follow-Up After Treatment of HG-SILs

Currently, despite its low sensitivity, Pap smear is generally used in the follow-up of patients at 6, 12, 18 and 24 months after CIN treatment[105-107]. Although many pathological characteristics such as positive endocervical margin of the cone, lesion size, glandular involvement, histological

grade and age above 35 years have been indicated as significant factors of persistence/recurrence of CIN 2+[108], the risk prediction is suboptimal. In fact, most women with positive resection margins do not develop recurrent disease over time. Conversely women with clear margins could be at risk for disease recurrence (5-7% of the cases) because a multifocal lesion may occur. Moreover colposcopy, usually conducted in the surveillance work-up, has been shown to add little information to the detection rate of residual/recurrent CIN 2+ lesion[109,110]. Therefore, an accurate test able to efficiently predict clinical outcome, reducing the follow-up period, anxiety levels and psychological stress of the women would be particularly helpful. A large amount of published data over recent decades on high risk HPV (hrHPV) DNA testing by means of pooled-based or type-specific methods has definitely demonstrated that persistent positivity of viral infection could predict CIN2+ recurrence more accurately than either cytology, or positive surgical margins[111-114]. Furthermore, it has been documented that in a three-year follow-up period more than 90% of recurrent CIN2-3 cases harbor a persistent hrHPV infection. Conversely no recurrent disease has been found in HPV negative cases[115-117]. Since 20-30% of treated women are still HPV-positive at 6-12 months follow-up, the question is whether this persistence is related to the same original genotype or belongs to a new infection[118-121]. To be classified as "persistent" cervical infection should be related to the same genotype identified before treatment. Prospective studies demonstrated that post-treatment positive hrHPV testing predicts residual/recurrent CIN with a significantly higher sensitivity (SE) and a non-significantly lower specificity (SP) than conventional cytology-based follow-up: 95% *vs.* 74% and 75% *vs.* 78%, respectively. Overall, combined hrHPV and cytology (co-testing) yield the best performance; co-testing demonstrated a 96% SE, 81% SP with 99% of negative predictive value (NPV)[122-124] (Table II). Moreover, hrHPV DNA testing shows a better performance than the margins status, considered the reference for the therapy outcome, with an SE and SP of 1.31 (95% CI 1.11-1.55) and 1.05 (95% CI 0.96-1.15), respectively. Actually, if the risk of persistence/recurrence of HG-SIL considering the margins involved is 25-35%, that is only 0.5-10% in case of margins involved with negative hrHPV testing. On the other hand, the risk of relapse in free-cones varies from 5-7% to 0.5-2.2% if the viral test is negative[114,115,125-127]. Based on these considerations scientific societies recommend the use of HPV testing together with cytology (co-testing) following treatment for HSIL[107,128]. Despite the higher sensitivity, hrHPV testing shows a lower specificity than cytology (ratio 0.96, 95% CI: 0.91-1.01) in identifying persistent disease or relapse, since eradication of the lesion does not necessarily mean eradication of all the infected tissue[122,123]. Hence treated women may remain still positive for the virus as hrHPV testing does not distinguish between a persistent infection and a new transient one. Moreover, it was noted that among women resulting hrHPV-positive during surveillance, certain genotypes confer a higher risk of post-therapy recurrence[113-117,125-128]. In recurrent patients HPV16 tends to clear slowly and less than the other oncogenic types, and residual or recurrent disease in women with persistent HPV16 and/or HPV18 are higher (82%) than in women with a persistence of other hrHPV types such as HPV 31, 33, 35, 45, 52, and 58 (66.7%) or HPV 39, 51, 56, 59, 68, 26, 53, 66, 73, and 82 (14.3%)[115-121]. These observations were confirmed by other reports in which no recurrent or residual disease was found among women with type change or fluctuating HPV positivity, thus emphasizing the importance of type-specific genotyping determination after treatment[122]. In conclusion, the role of hr-HPV-testing has been confirmed as an accurate index of disease clearance and has been adopted along with Pap smear, in the routine post-treatment workup of HG-SIL patients. In cases of microinvasive cervical carcinoma, studies on long term

Table II. Performance of hrHPV-DNA testing, cytology and co-testing in predicting residual/recurrent disease after conization for HG-SIL/CIN 2-3[122-124].

	Sensitivity %	Specificity %	PPV %	NPV %I
Co-testing	96	81	46	99
hrHPV-DNA	95	75	28	99
Pap test	74	78	25	98

follow-up after primary conservative treatment have demonstrated that about 20% of patients experienced early or late diagnosis of recurrent disease. The majority (15%) of cases have an intraepithelial lesion while in 5% an invasive carcinoma may be identified[129,130]. Follow-up protocols have so far consisted of repeat cytology, colposcopy and, eventually, punch biopsy and endocervical curettage. Despite the increasing interest in the clinical uses of HPV testing, few follow-up studies of patients conservatively treated for stage IA cervical cancer have been performed supporting the association between the persistence of high-risk human papillomavirus during surveillance and the detection of recurrent disease[131-133]. Primary results indicate that the median time to viral clearance is relatively longer compared with patients treated for HG-SIL and occurred approximately two years after treatment. By implication, hrHPV positivity within this time interval does not exclude cure. After a median follow-up of 50 months HPV testing had a NPV of 95% for CIN1 and 100% for CIN2+. These findings would indicate that HPV testing is capable to identify patients who have had their lesions fully removed and would make it possible to focus follow-up efforts on a subset of patients at high risk of residual or progressive disease. The associated PPV of 60% for CIN2+ confirms the potential clinical value of these findings and indicates the need for an effort to undertake larger multicentre confirmatory studies. Also, in cases conservatively treated for Adenocarcinoma in Situ (AIS) results from a large population study showed that the positivity of the hrHPV-DNA test represents a more significant predictor than cytology and colposcopy for AIS recurrence (OR 2.95 *vs.* 1.46 and 1.03 respectively) and for disease progression (OR 5.13 *vs.* 1.27 and 1.65 respectively) during follow-up. The predictive power of Pap test and colposcopy did not reach statistical significance in any of the follow-up controls [134,135]. The combination of HPV-DNA testing and cytology reached 90% sensitivity in detecting persistent lesions at the first FU visit and 100% sensitivity at the second FU visit.

The Rationale of Adjuvant HPV Vaccination

Individuals who are sexually active should still be vaccinated consistently with age-specific recommendations; a history of an abnormal Pap test, genital warts, or HPV infection, can reduce vaccine efficacy but it is not a contraindication to HPV immunization[14]. Women already infected with an HPV type included in the vaccine may still benefit from vaccination, thanks to protection against other HPV types. Although licensed vaccines are most effective in subjects never infected with HPV, they also reduce infection and disease among infected subjects, because natural immunity is not entirely protective against HPV re-infection. Some evidences suggest that HPV vaccination increases both the magnitude and quality of natural immunity and demonstrate that sexually active people could also benefit from HPV vaccination. In this regard, several studies described how HPV vaccine improves B-cell memory among previously infected subjects[136-138]. The SICPCV (Italian Society of Colposcopy and Vaginal Cervical Pathology) guidelines updated to 2006, provide for the treatment of all high-grade lesions (H-SIL or CIN2-3 / CIS) due to their progression potential. On the other hand, the spread of precancerous lesions in ever younger women, who have not yet completed their reproductive process, and the tendency to optimize the cost-benefit ratio have led to the implementation of increasingly conservative interventions with excisional techniques, the LEEP technique being the most widely performed[139]. Nevertheless, radical treatment of the cervical lesion does not ensure the elimination of HPV infection, regulated by complex mechanisms involving local and general immunity[140]. In 2014, a review estimated the incidence and described the variability of HPV infection in women following treatment for cervical neoplasia. Eligible articles provided data on (1) baseline HPV infection status within 6 months prior to or at the time of treatment (pre-treatment); and (2) HPV test results for women making their first visit after treatment occurring within 36 months (post-treatment). A total of 25 studies were included reporting post-treatment HPV incidence in nearly 2000 women. Mean patient age ranged from 31 to 43 years. Treatments included LEEP (44%); laser conization (8%); laser ablation, surgical conization, cryotherapy, alphainterferon (4% each); or multiple treatment regimens (32%). Post-treatment follow-up ranged from 1.5 to 36 months. HPV incidence after treatment varied widely, ranging from 0 to 47% in up to 3 years of follow-up. Lower HPV incidence was observed among studies that included relatively younger women and used laser conization[141]. Another review determined HPV persistence in women following treatment of CIN. Follow-up HPV testing ranged from 1.5 to 80

months after baseline. Median HPV persistence tended to decrease with increasing follow-up time, declining from 27% at 3 months after treatment to 21% at 6 months, 15% at 12 months, and 10% at 24 months[142]. Because of this, studies have been carried out in recent years to evaluate the use of the prophylactic vaccine in patients with a history of HPV-related lesions. Kang et al[143] performed a study to determine whether vaccination with the quadrivalent vaccine after loop electrosurgical excision procedure (LEEP) for high-grade cervical intraepithelial neoplasia (CIN2-3) is effective in preventing recurrence of CIN2-3. Over 700 patients aged 20-45 years diagnosed with CIN2-3 and treated by LEEP were enrolled and divided into 2 groups. The first group was vaccinated with the quadrivalent HPV vaccine after LEEP (vaccination group), while the second group was followed without vaccination. Patients were followed for a minimum of 2 years. Thirty-six (4.9%) patients developed recurrences. In the vaccination group (360 patients), 9 patients (2.5%) developed a recurrence, whereas a recurrence was reported in 27 patients (7.2%) in the non-vaccination group (377 patients). In patients infected with HPV 16/18, 5 patients (2.5%) in the vaccination group (197 patients) and 18 patients (8.5%) in the non-vaccination group (211 patients) developed recurrent disease after LEEP ($p<0.01$). Multivariate analysis showed that no vaccination after LEEP was an independent risk factor for recurrent CIN2-3 (HR = 2.840; 95% confidence interval, 1.335-6.042; $p=0.01$). In conclusion, the authors reported that vaccination with the quadrivalent HPV vaccine after treatment may be considered for preventing disease recurrence**.** Joura et al[144] published a retrospective analysis to investigate whether the administration of quadrivalent HPV vaccine compared with placebo, reduced the incidence of subsequent HPV related disease among women who had undergone surgery for cervical disease or were diagnosed vulvar or vaginal disease (genital warts, vulvar intraepithelial neoplasia, or vaginal intraepithelial neoplasia). They measured the vaccine impact for endpoints that were associated with HPV types 6, 11, 16, and 18 and for endpoints associated to other HPV types. The incidence of any subsequent HPV related disease was 6.6 and 12.2 cases/100 person/year among vaccine and placebo recipients respectively (46.2% reduction with vaccination). Vaccination was associated with a reduction of 64.9% in risk subsequent to high grade cervix disease. A total of 229 vaccine recipients and 475 placebo recipients were diagnosed with genital warts, vulvar intraepithelial neoplasia, or vaginal intraepithelial neoplasia, and the incidence of any subsequent HPV related disease was 20.1 and 31.0 cases/100 person/year among vaccine and placebo recipients respectively (35.2% reduction). The authors reported that vaccination with quadrivalent HPV vaccine among women who had surgical treatment for HPV related disease significantly reduced the incidence of subsequent HPV related disease, including high grade disease**.** Garland et al[145] published a post-hoc analysis from a RCT named PApilloma TRIal against Cancer In young Adults (PATRICIA). In particular, they evaluated the efficacy of bivalent (HPV16/18) vaccine in preventing HPV-related disease after surgery for cervical lesions. Healthy women aged 15-25 were randomized (1:1) to receive vaccine or control at months 0, 1 and 6 and followed for 4 years. Women were enrolled regardless of their baseline HPV DNA status, HPV-16/18 serostatus, or cytology. The post-hoc analysis evaluated efficacy in a subset of women who underwent an excisional procedure for cervical lesions after vaccination. The main outcome was the incidence of subsequent HPV-related Hg-CIN (CIN2+) 60 days or more post-surgery. Other outcomes included the incidence of HPV-related CIN1+, and vulvar or vaginal intraepithelial neoplasia (VIN/VaIN). Of the total vaccinated cohort of 18,644 women (vaccine = 9,319; control = 9,325), 454 (vaccine = 190, control = 264) underwent an excisional procedure during the trial. The results demonstrated that women who undergo surgical therapy for cervical lesions after vaccination with the HPV-16/18 vaccine may continue to benefit from vaccination with a reduced risk of developing subsequent CIN2+. However, these results account for the limitations that they come from a post-hoc analysis of the PATRICIA study that was not designed to evaluate the effects of vaccination post-treatment. Furthermore, studies were published reporting the use of quadrivalent human papillomavirus vaccination to treat recurrent respiratory papillomas and high-grade anal intraepithelial neoplasia (HG-AIN). In particular, a case report describes the use of CO_2 laser and quadrivalent human papillomavirus (HPV) vaccination in two patients with nasopharyngeal HPV11-positive recurrent respiratory papillomas (RRP). These patients initially underwent CO_2 laser excision but developed recurrent lesions and underwent HPV vaccination as adjuvant therapy. The recurrent lesions shrank after vaccination

and were again excised with CO_2 laser. Subsequently, these patients had no recurrence of lesions on long term follow-up at 33 months or 6 years after surgery. Thus, in patients with nasopharyngeal RRP, resection with CO_2 laser, and HPV vaccination as adiuvant therapy should be considered in HPV11-associated cases[146]. Recent evidence shows that quadrivalent human papillomavirus vaccination in men who have sex with men (MSM) who have a history of high-grade anal intraepithelial neoplasia (HG-AIN) was associated with a 50% reduction in the risk of recurrent HG-AIN[147]. Therefore, HPV vaccination may represent a viable option after surgical treatment of several HPV-related conditions in an adjuvant fashion. However, even if recent data are encouraging, it must be noted that most of the previous reported results (FUTURE I and II, PATRICIA) present the limitations of study designs not focused on the adjuvant efficacy of HPV vaccines. For this, RCTs are needed to evaluate and possibly confirm the use of HPV vaccination in patients with previous pre-cancerous lesions, especially considering that all the works already published refers to the quadrivalent vaccine, while the nonavalent vaccine has not yet been evaluated in this new and interesting therapeutic perspective.

In 2013, an Italian prospective trial[148] included 4 clinical objectives:

1. Post surgical HPV vaccination of women undergoing surgery for histological diagnosis of cervical high-grade lesions (CIN2+, up to microinvasive cervical cancer - FIGO IA1)
2. Post surgical HPV vaccination of women undergoing surgery for anogenital warts (AGW).
3. HPV prevalence in male partners of women treated for high-grade SIL
4. Impact on cervical screening program of post surgical adjuvant HPV vaccination (analysis of the impact of adjuvant quadrivalent HPV vaccination on post-surgical surveillance).

Patients with cervical diseases were submitted to cervical conization (LEEP), while women with AGW were treated by surgical ablation of the lesions. One month after surgery, all patients were evaluated. Patients satisfying enrollment criteria and desiring to receive the vaccination were included in the project as vaccinated and follow-up arm groups. All "vaccinated" patients received the quadrivalent vaccine, while controls were enrolled in the "follow-up only" arm, as control group. Primary endpoint was the incidence of recurrent CIN2+ post-surgery. Only 2/172 vaccinated women developed a cervical recurrence (1,2%), while 11/172 (6,4%) patients in the control group recurred. The rate of recurrence was significantly higher in the control group, with a p=0.0112 by Pearson's chi-squared test. Clinical effectiveness 4 years after surgery, irrespective of HPV type, was 81.2% (95% CI: 34,3%-95,7%) in reduction of CIN2+ recurrent disease. According to the second clinical objective, 446 women were enrolled in this still ongoing study. All patients were treated by AGW ablation, and 46 presented concomitant CIN2+ diagnosis (10.3%). 63 out of 167 women in the control group developed an AGW recurrence (37.7%), while 38 of the 156 vaccinated women relapsed (24.3%). AGW recurrence rate was significantly higher in the follow up group, with p=0.0116 by Pearson's chi-squared test. Clinical effectiveness 4 years after surgical treatment was 64.4%. The protective role of HPV vaccine in women with a prevalent HPV infection is still not fully understood. To explain the clinical efficay that has been observed, in terms of relapses' reduction in the vaccinated group, two pathways can be hypothesized: "primary" prevention for patients not previously exposed to HPV, vaccine protection against new infection, and "secondary" prevention for patients already exposed to HPV with immunological failure (after initial response of the immune system) or primary failure of immunological response due to viral immune escape mechanism. It must be underlined that those mechanisms are based on a preventive function, inasmuch as HPV-vaccine has no role in prevalent HPV infection or diseases. In other words, the use of the vaccine on prevalent infection without surgical removal of the lesion is useless and irrelevant; however, if combined with surgery (with complete excision of the lesion), it can play a crucial role in reducing disease relapse. Now that the efficacy of adjuvant vaccination has been highlighted by clinical results, vaccination timing is the next step to be evaluated. Vaccine timing is as important as the complete surgical removal as both actions could influence the probability of clinical disease relapse. It can be argued that adjuvant vaccination has a very short "window of time" to be administered to show clinical effectiveness. A possible strategy might be to immunize with the HPV-vaccine immediately before the surgical treatment. Larger randomized

placebo-controlled trials are needed to identify the best vaccination timing linked to surgical approach and to confirm these findings.

Final Considerations and Position Statements

Evidence-sustained data strongly support the fact that universal HPV vaccination (males and females) is the best performing and most cost-effective strategy to reach the goal of total control of HPV related diseases, either benign, premalignant and malignant, occurring in different anatomical areas (genital, anal, oropharyngeal) in both sexes. More recent data and retrospective analysis of large RCT focused the topic of HPV vaccines safety and efficacy in older age groups (up to 45 yrs.); all results consistently demonstrated that HPV vaccines are equally safe, immunogenic and effective in older subjects as in adolescents. The adjuvant role of HPV vaccination after surgical treatment of cervical precancerous lesions (CIN2+) and anogenital warts (AGW) is now beginning to emerge as the "new frontier" and very interesting results are available today. The significant reduction of post-treatment recurrence of the disease, despite preliminary and isolated experiences, must be seen as a crucial step in the identification of the primary and secondary benefits of HPV vaccination. For these considerations, the Italian HPV Study Group (IHSG) takes the position in favour of the universal vaccination of adolescents, of the extension of vaccine offered to older age groups and, as soon as more data will be available to confirm existing preliminary results, of the introduction of adjuvant HPV vaccination in routine clinical practice.

Conflict of Interest

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