Anti-HPV vaccination in women treated for HPV-related lesions: effective vaccination strategy for achieving HPV-related diseases control

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ABSTRACT

Human Papillomavirus (HPV) vaccination is able to reduce the risk of relapse in women undergoing surgery for HPV-related lesions. The surgical treatment of these lesions can correlate with a greater risk of preterm parts. The extension of the recommendation of HPV vaccination to patients treated for a previous HPV-related lesion would entail a lower expense for the Health System. Therefore, an increase in the use of HPV vaccination is desirable also in this target population as well as the implementation of a care pathway dedicated to women treated for HPV lesions that includes vaccination in the prevention activities of relapses.

Key words: Human Papillomavirus, Vaccination, HTA.

Human Papilloma virus (HPV) is the most common sexually transmitted infection and it can lead to the development of genital warts, anogenital and oropharyngeal cancers [1]. In Europe, about 90% of HPV-related cancers and 90% of genital warts are estimated to be vaccine preventable every year [2]. In Italy, around 5,000 cases of cancers are due to HPV infections yearly [3]. Therefore, HPV infection control represents a public health priority.

The carcinogenic HPV genotypes 16 and 18 cause about 70% of all cervical cancers worldwide, and types 31, 33, 45, 52 and 58 cause an additional 20%. HPV types 6 and 11 cause approximately 90% of anogenital warts [4].

Among the most frequent malignant lesions associated to HPV infection's progression, there are the precancerous lesions of the uterine cervix (Cervical Intraepithelial Neoplasia - CIN). According to the natural history of CIN, CIN1 regresses in 60% of cases, persists in 30%, progresses to CIN 3 in 10%, and to invasion in 1% [5]. The rate of progression of CIN 2+ to invasive cervical cancer is higher and for this reason the management of CIN1 and CIN 2+ is different [5]. In Italy, an annual number of 21,308 cases of CIN1, 3,218 CIN2 and 3,518 CIN3 is estimated [6, 7]. In 2018, 2,400 new Italian cases of cervical cancer were estimated [3].

HPV infection is more common among adolescent and young adult girls and its prevalence reaches a peak of about 20% in women aged 20 to 24 years and a subsequent decline in women older than 30 years. The average age of women with CIN2+ lesions is approximately 25 to 30 years [5]. Conization using a loop electrosurgical excision procedure (LEEP) is considered appropriate treatment for high-grade cervical intraepithelial lesions. Treatment for CIN2+ is extremely effective and most patients require no further treatment [5]. Nevertheless, the clinical recurrence of cervical Squamous Intraepithelial Lesion (SIL) occurs in 5-35% after conservative treatment, in most cases within first 2 years of follow-up [8]. Risk factors for recurrent or residual disease after conization may include age, HPV genotype, HPV persistence after the treatment and cone margin involvement [5]. However, persistent HPV16 infection is the most important factor for recurrence [5]. Moreover, these patients have a risk of invasive cervical cancer 2 to 4-fold higher than in the general population and a long-lasting increased risk (up to 20 years) for other HPV related disease and cancer [9].

Recent studies [4, 10-14] suggest that HPV vaccination, in women undergoing surgery for HPV linked disease, could impact on disease recurrence. Therefore, it is realistic to discuss the potential benefits of vaccination in this specific target of patients. Table 1 shows the main characteristics of these studies.

In 2006, HPV vaccination was licensed for primary prevention of HPV-related disease in young females [15]. Few years after, immunological and clinical studies offered new important perspectives also for adult women vaccination and RCPs were updated consequently [16-18].

Three different vaccines have been developed [4]: bivalent vaccine (Cervarix) targets HPV types 16/18; quadrivalent HPV vaccine (Gardasil) targets HPV types 6, 11, 16 and 18 and the latest 9-valent vaccine (Gardasil 9) targets the same HPV types as the quadrivalent vaccine as well as types 31, 33, 45, 52, and 58.

HPV vaccines are licensed for safe administration from 9 years of age. The optimal time for HPV immunization is prior to the individual's sexual debut [19] but HPV vaccination is now possible up to 45 years as a personal preventive tool. Indeed, the vaccine is also safe, well-tolerated and is able to determine an antibody response at this age [20, 21]. Therefore, HPV vaccine can also induce protection in older women, and its administration to patients previously treated for HPV-related disease can reduce the disease recurrence rate [4, 10–12].

In 2013, Kang et al. [11] demonstrated a significant disease relapse reduction in women vaccinated after high-grade lesions treatment. Similar impact on clinical recurrence was already found in a post hoc analysis from the Future I and II studies [10]. In 2016, Garland and colleagues [12] re-analysed the data on the bivalent vaccine and found that it can have a role in reducing the risk of CIN2+ occurrence in patients already treated. Hildesheim et al. [13] try to determine whether HPV16/18 vaccination influences the outcome of infections present at vaccination and the rate of infection and disease after treatment of HPV related lesions. The study confirmed no differences in viral clearance or progression rates among infected women with prevalent infection. In addition, an evidence of a reduction in post-LEEP infection rates after vaccination against de novo infections (women exposed to new HPV infections after treatment) was been reported, while the low rate of recurrent high-grade SIL after surgery in this trial prevented a sufficient analysis for clinical recurrences.

A recent Italian study compared two cohorts of women treated for HPV-related lesions (randomised to receive or not HPV vaccination after the surgical treatment), showing that the relapses percentage in the cohort vaccinated with the quadrivalent vaccine was lower and less severe (3 out of 89 women, all low-grade dysplasia) compared to unvaccinated ones (12 out of 89, four cases were high-grade squamous lesions) (3.4% vs 13.5%; $p < 0.05$) [4].

Similar results were shown also by the SPERANZA prospective project [14]. This study demonstrated the clinical effectiveness of HPV vaccination in women treated for CIN2+ and early microinvasive cervical carcinoma. Vaccinated women after the treatment showed a recurrence rate of CIN2+ of 1.2% compared with 6.4% founded in unvaccinated group. The SPERANZA project also described the HPV types related to the clinical recurrences: vaccinated patients were found to be infected by types not present in the quadrivalent vaccine while non-vaccinated were mostly affected by HPV 16 (found in 63.6% of relapses).

As illustrated by the results of the studies listed above,

HPV vaccination in women undergoing surgical therapy for CIN2+ reduces the risk of recurrent disease in the order of 65-88% [10-12, 14]. Therefore, the clinical implications of this strategy can influence the post-treatment management of HPV-related diseases. This does not imply a therapeutic effect of the vaccination but underlines its adjuvant role in surgical treatment [14]. Thus, women should be informed that the vaccination will not treat prevalent HPV infections or disease, nor will it prevent future HPV infections unrelated to the vaccine and therefore adherence to follow-up will remain important. Equally, informing patients of opportunity of adjuvant vaccination is important, as a tool in reducing the probability of clinical relapses.

From a public health point of view, HPV vaccination represents not only a fundamental strategy for primary prevention of cervical cancer but at the same time allows the management of numerous clinical HPV-related conditions. Women treated for previous HPV-related lesions represent a high-risk population justifying the resources destined to achieve a high degree of coverage in this specific cohorts. In fact, this "special" population of women could benefit from an extension of the HPV vaccination recommendation [22].

The economic burden of HPV-related diseases is also significant. Considering only the direct costs, it is estimated that in Italy the total amount spent in 2018 was 542.7 million euros [23]. Furthermore, the HPV-related lesions also correlate with a greater risk of preterm parts, associated with a complex management of the premature new-born that involves serious increases in the absorption of the National Health System (NHS) resources, an important economic commitment for families and a significant loss of productivity for society [24, 25].

Recently, an Italian report of Health Technology Assessment (HTA) on HPV vaccination in women treated for HPV-related lesions was published [6]. From the Budget Impact Analysis (BIA) carried out in this HTA it was possible to calculate the savings obtainable with the extension of the recommendation to the anti-HPV vaccination, with 9-valent vaccine, also to the women treated for HPV-related lesions.

In fact, this extension would entail lower spending on the NHS of € 108,373.62 in the time period considered (5 years) (Figure 1). This saving is due to the reduced incidence of HPV-related lesions following vaccination as well as to the lower onset of preterm parts due to HPV lesions.

Therefore, an increase in the use of HPV vaccination is also essential in this target population as the implementation of a care pathway that includes vaccination as part of relapses prevention activities.

Vaccination is one of the most effective, cost-effective and safe interventions in Public Health. Therefore, the Institutions should plan, organize and manage the vaccination offer, guaranteeing equity and universality in access through, for example, the activation of specific programs for the most vulnerable population groups. The hospital could be an opportune setting for the vaccine proposal and a strict alliance between vaccine experts and gynaecologist is need to achieve high vaccination coverage in the group of treated women.

Promoting HPV vaccination to additional targets represents a good opportunity to increase the HPV immunization level and, subsequently, to reduce HPV-related diseases.

FIGURE 1. Differential results in the Budget Impact analysis of the Italian scenarios with and without vaccination [16].

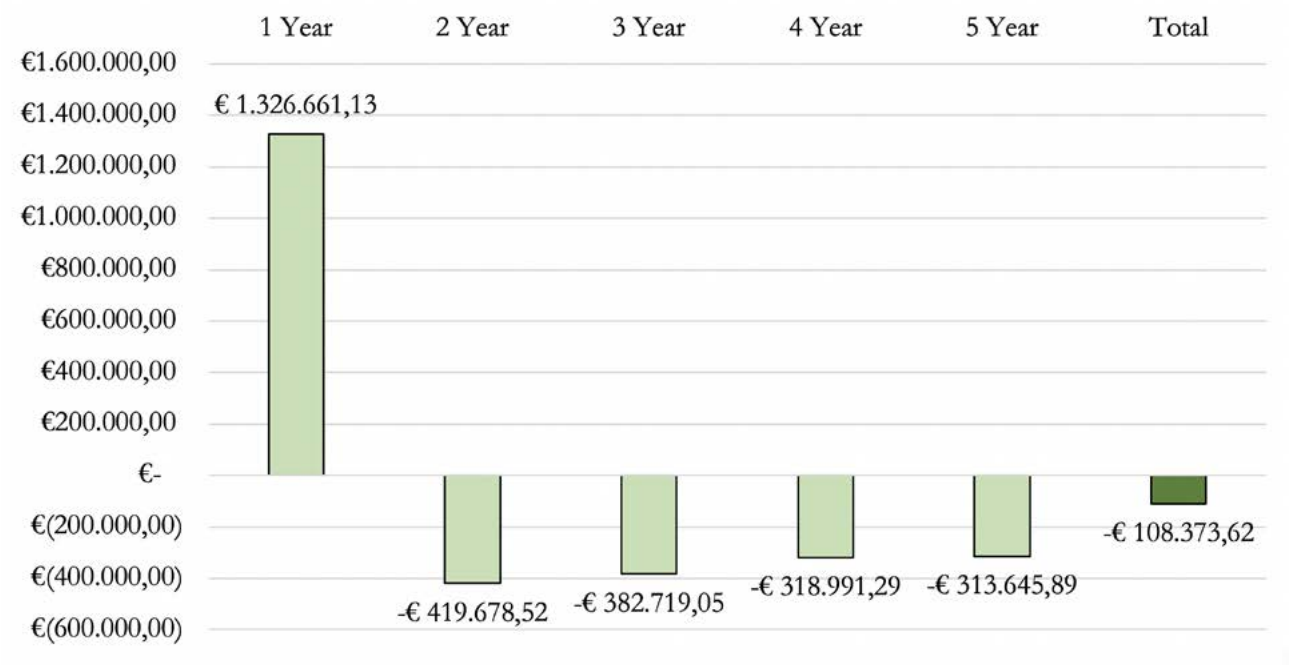

TABLE 1. Main characteristics of the studies supporting the HPV vaccination impact in women undergoing surgery for HPV-related disease on recurrences.

First Author, Year	Title	Type of study	Intervention	Exposed	Unexposed	Outcomes	Results	Conclusions
Joura EA, 2012 [10]	Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data.	Retrospective analysis of data from two international, double blind, placebo controlled, randomised efficacy trials of quadrivalent HPV vaccine(protocol 013(FUTURE I) and protocol 015 (FUTURE II).	Three doses of quadrivalent HPV vaccine or placebo at day 1, month 2, and month 6.	587 women aged 15–26 undergoing cervical surgery (Vaccination group).	763 women aged 15–26 undergoing cervical surgery (Placebo group).	Incidence of HPV related disease from 60 days after treatment or diagnosis.	Vaccination was associated with a significantly reduced risk of any subsequent HPV related disease after cervical surgery, irrespective of causal HPV type, by 46.2% (95% CI 22.5% to 63.2%). Vaccination was associated with a significantly reduced risk of any subsequent cervical disease (by 48.3% (95% CI 19.1% to 67.6%) for CIN grade I or worse) and any subsequent high-grade cervical disease (64.9 % (20.1% to 86.3%) for CIN grade II or worse). 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 in vaccine and placebo recipients respectively (35.2% reduction (13.8% to 51.8%).	Previous 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.
Kang WD, 2013 [11]	Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2-3)?	Retrospective analysis.	Three doses of quadrivalent HPV vaccine: the first dose at 1 week after LEEP and the remaining two doses 2 and 6 months later.	360 patients aged 20-45 years who were diagnosed with CIN2-3 and treated by LEEP (Vaccination group).	377 patients aged 20-45 years who were diagnosed with CIN2-3 and treated by LEEP (Non-Vaccination group).	Number of CIN2-3 recurrences after LEEP.	Irrespective of causal HPV type, 36 (4.9%) patients developed recurrence. In the vaccination group 2.5% (9 patients) developed recurrence, whereas 7.2% (27 patients) in the non-vaccination group developed recurrence. In patients infected with HPV of 16 and/or 18 type, 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 related to vaccine HPV types (HPV 16 or 18 types) 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% CI, 1.335–6.042; $p < 0.01$).	Vaccination with the quadrivalent HPV vaccine after treatment may be considered in preventing recurrence of CIN2–3.
Garland SM, 2016 [12]	Prior human papillomavirus-16/18 AS04 adjuvanted vaccination prevents recurrent high-grade cervical intraepithelial neoplasia after definitive surgical therapy: Posthoc analysis from a randomized controlled trial.	Post-hoc analysis of the PApilloma TRIal against Cancer In young Adults (PATRICIA; NCT00122681).	Human Papillomavirus (HPV)216/18 AS04-adjuvanted vaccine or control (Hepatitis A vaccine) at months 0, 1 and 6 and followed for 4 years.	Healthy women aged 15–25 years. Of the total vaccinated cohort of 9.319 women, 190 underwent an excisional procedure during the trial.	Healthy women aged 15–25 years. Of the total vaccinated cohort (control group) of 9.325 women, 264 underwent an excisional procedure during the trial.	Incidence of subsequent HPV-related CIN grade 2 or greater (CIN2+) 60 days or more post-surgery. Incidence of HPV related CIN1+, and vulvar or vaginal intraepithelial neoplasia (VIN/VaIN) 60 days or more post-surgery.	Efficacy 60 days or more post-surgery for a first lesion, irrespective of HPV DNA results, was 88.2% (95% CI: 14.8, 99.7) against CIN2+ and 42.6% (221.1, 74.1) against CIN1+. No VIN was reported and one woman in each group had VaIN2+ 60 days or more post-surgery.	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+.

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Hildesheim A, 2016 [13]	Impact of human papillomavirus (HPV) 16 and 18 vaccination on prevalent infections and rates of cervical lesions after excisional treatment.	Phase III RCT.	Vaccination (3 doses offered over 6 months) with AS04-adjuvanted HPV-16/18 virus-like particle vaccine or Hepatitis A vaccine (control group).	852 women (18–25 years) with carcinogenic human papillomavirus infection and 142 women of similar age who underwent treatment for cervical precancer.	859 women (18–25 years) with carcinogenic human papillomavirus infection and 169 women of similar age who underwent treatment for cervical precancer.	For the evaluation of infections and lesions that occurred among infected women at the time of enrollment: type-specific HPV viral clearance; development of CIN1 + and CIN2 + cervical lesions. For the evaluation of women treated with LEEP: HPV infection, persistent infection with HPV, new squamous intraepithelial lesion (SIL) and CIN2 +.	There was no evidence of vaccine efficacy to increase clearance of human papillomavirus infections or decrease incidence of cytologic/histologic abnormalities associated with human papillomavirus types present at enrollment. Vaccine efficacy for human papillomavirus 16/18 clearance and against human papillomavirus 16/18 progression from infection to cervical intraepithelial neoplasia 2+ were −5.4% (95% confidence interval −19,10) and 0.3% (95% confidence interval −69,41), respectively. Among treated women, 34.1% had oncogenic infection and 1.6% had cervical intraepithelial neoplasia 2+ detected after treatment, respectively, and of these 69.8% and 20.0% were the result of new infections. No significant effects of vaccination on rates of infection / lesions after treatment were observed Vaccine efficacy estimates for human papillomavirus 16/18 associated persistent infection and cervical intraepithelial neoplasia 2+ after treatment were 34.7% (95% confidence interval −131, 82) and −211% (95% confidence interval −2901, 68), respectively. Evidence for a partial and nonsignificant protective effect of vaccination against new infections absent before treatment was observed. For incident human papillomavirus 16/18, human papillomavirus 31/33/45, and oncogenic human papillomavirus infections post-treatment, vaccine efficacy estimates were 57.9% (95% confidence interval −44, 88), 72.9% (95% confidence interval 29, 90), and 36.7% (95% confidence interval 1.5, 59), respectively.	No evidence for a vaccine effect on the fate of detectable human papillomavirus infections. Vaccination does not protect against infections/lesions after treatment. Evaluation of vaccine protection against new infections and resultant lesions warrants further consideration in future studies.

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Ghelardi A, 2018 [14]	SPERANZA project: HPV vaccination after treatment for CIN2+.	Prospective case-control study.	Quadrivalent HPV vaccine with the first dose injected immediately after counselling (30 days after conization) and the remaining two doses 2 and 6 months later.	248 women aged 18–45 years treated with LEEP for CIN2+ (Vaccinated-group).	276 women aged 18–45 years treated with LEEP for CIN2+.	Number of Clinical disease recurrence (CDR) after HPV vaccination post-LEEP surgery, in women with high-grade CIN and microinvasive cervical carcinoma.	CDR was observed in 11 cases (6,4%) of the NV-group while in the V-group only 2 recurrent cases (1,2%) were recorded. Vaccination was associated with a significantly reduced risk of subsequent HPV related high-grade CIN after cervical surgery by 81.2% (95% CI, 34,3–95,7). In the NV-group, HPV types were HPV 11,16,18,31,33,45,53,82. The most frequent HPV type observed in the NV-group was HPV 16, which was identified in the 63,6% of the CDR. In the NV-group 6 out of 11 patients showed HPV co-infection with one or more HPV types at the time of the recurrence. In the V-group only 2 CDR were detected and they were associated, respectively, to HPV 33 and 82. None of the HPV type contained in the quadrivalent vaccine was detected in the clinical relapses of the V-group. No case of any subsequent high grade CIN related to vaccine HPV types (6, 11, 16, or 18) after cervical surgery was observed, this translates into an efficacy of 100%.	Quadrivalent HPV vaccination in women who undergo surgical therapy for CIN2+ cervical lesion and FIGO stage IA1 cervical cancer reduce the risk of recurrent disease in the order of 80%. Data from the SPERANZA study sustained the clinical effectiveness of HPV vaccination after LEEP treatment in high grade cervical lesions and initially invasive cervical cancer. The clinical implications of this strategy may influence the post treatment management of HPV diseases. This does not imply a therapeutic effect of the vaccines but underlines its role as an adjuvant to surgical treatment.

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First Author, Year	Title	Type of study	Intervention	Exposed	Unexposed	Outcomes	Results	Conclusions
Pieralli A, 2018 [4]	Indication of prophylactic vaccines as a tool for secondary prevention in HPV-linked disease.	Prospective randomized controlled trial.	HPV quadrivalent vaccine at 0, 2 and 6 months post treatment (Vaccination group).	89 women under 45 years of age treated for HPV-linked disease and with negative HPV test, cytology and colposcopy 3 months after treatment.	89 women under 45 years of age treated for HPV-linked disease and with negative HPV test, cytology and colposcopy 3 months after treatment (group that was only submitted to follow-up).	Number of HPV-related recurrent disease after treatment. Rate of abnormal cytology and persistent abnormal cytology during the follow-up period.	In the vaccination group 3.4% (3 women) developed recurrence during the follow-up period. All recurrences were low-grade cervical squamous intraepithelial lesions. In the non-vaccination group, 13.5% (12 women) developed recurrence: 8 low-grade SIL, 3 affecting vulva and vagina and 5 affecting cervix, and 4 developed high-grade cervical SIL. The mean time between the date of enrollment and the date of relapse was 14.5 months (range 6–24) in the non vaccination group and 18 months (range 12–24) in the vaccination group. The difference between two groups, analyzed with t test, did not show a statistical significance ($p = 0.29$). HPV genotyping performed in case of recurrence in the vaccination group highlighted the high-risk (HR) HPV types in all cases: one positive to HPV type 16, one positive to HPV types 18 and 33 and one positive to HPV type 31. In the non-vaccination group, of the three cases of vulva and vaginal recurrences, two were related to low-risk (LR) (HPV 6 -53) and one to HR HPV type 52 and LR-LSIL HPV type 55. During the follow-up period, 25.8% (23 patients) had an abnormal Pap test in the non-vaccination group and 7,9% (7 patients) had an abnormal Pap test in the vaccination group. Of the abnormal Pap tests in the vaccination group, 5 were LSIL related to HR HPV and 2 were ASCUS, 2 were related to HR HPV and two to LR HPV. Of the 23 abnormal Pap tests in the non-vaccination group, 1 was ASCH, 1 was AGC, 8 were LSIL and 13 were ASCUS. 18 (1 ASCH, 1 AGC, 6 LSIL and 10 ASCUS) of the abnormal cytologies were related to HR HPV, 4 (2 ASCUS and 2 ASCUS) to LR HPV and 1 (ASCUS) to a negative HPV test. The mean time during which the Pap tests resulted abnormal in the follow-up period was 11.20 months (range 6–24) in the non-vaccination group and 16.29 months (range 12–24) in the vaccination group, not showing a statistical significance difference with t tests between the two study groups ($p = 0.07$). In the vaccination group, the abnormality of the seven Pap tests was not confirmed in any case at the following 6 months follow-up visit. While in the non-vaccination group, the abnormality of the Pap smear was confirmed in 9 cases (39.1%) in the 6-month follow-up visit. The vaccination was able to reduce both the rate of abnormality to Pap test and the rate of persistent abnormal cervical cytology ($p < 0.05$).	The vaccination with quadrivalent HPV vaccine was a tool to reduce the incidence of recurrence of HPV related disease in women previously treated for cervical squamous intraepithelial lesion. The HPV vaccine can be recommended in women already treated for HPV-related disease given the significant reduction in the incidence of recurrence of HPV diseases and abnormality of the Pap test in the vaccination group. The introduction of HPV vaccination during the follow-up post treatment for HPV-linked disease is recommended to reduce the risk of recurrence.

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