

Efficacy of a prophylactic human papillomavirus vaccine against high-grade vulval and vaginal intraepithelial neoplasia

Jorma Paavonen

Department of Obstetrics and Gynecology, University Hospital Haartmaninkatu 2, 00290 Helsinki, Finland
Tel.: +358 504 272 060
Fax: + 358 947 174 902
jorma.paavonen@hus.fi

Vulval and vaginal high-grade intraepithelial neoplasias (VIN 2–3 and VaIN 2–3, respectively) precede vulval and vaginal cancers. The incidence of VIN and VaIN is increasing, and the mean age of women with these lesions is decreasing. Human papillomavirus (HPV) types 16 and 18 cause the majority of these lesions in young women. The most common HPV type detected is HPV16, followed by HPV18. A combined analysis of three randomized trials among 18,174 women (aged 16–26 years) showed that a quadrivalent HPV vaccine given at day 1, months 2 and 6, was highly effective against these lesions during a mean follow-up of 3 years. The vaccine efficacy in the per-protocol analysis was 100% against VIN 2–3 or VaIN 2–3 associated with HPV16/18. In the intention-to-treat population, the vaccine efficacy was 49%. The vaccine was safe and well tolerated. Thus, prophylactic administration of quadrivalent HPV vaccine is effective in preventing high-grade VIN/VaIN, suggesting that such vaccination could result in reduced rates of HPV-related vulval and vaginal cancers. This is an important ‘bonus’ effect of the vaccine.

Compared with cervical cancer, vulval and vaginal cancers develop less frequently. Vulval cancer is six-times and vaginal cancer 20-times less common than cervical cancer [1]. Nonetheless, vulval and vaginal cancers account for approximately 6% of all gynecological cancers [1]. No screening programs exist for vaginal and vulval malignancies.

As with cervical intraepithelial neoplasia (CIN) grade 2–3, high-grade vulval and vaginal lesions, for example, vulval intraepithelial neoplasia grade 2–3 (VIN 2–3) and vaginal intraepithelial neoplasia grade 2–3 (VaIN 2–3) are precursors to human papillomavirus (HPV)-related invasive cancers [2,3]. Although the true incidence of VaIN is unknown, the incidence of VIN 3 and invasive vulval cancer has increased worldwide since the 1970s [4–8]. Vulval carcinoma is associated with HPV infection, especially HPV16, 18, 33 and 31 [3,9–10].

The annual progression rate of untreated vulval carcinoma *in situ* to invasive cancer is at least 10%; which is higher than that of CIN 3 [10]. Patients with VaIN have a 2% risk of developing invasive cancer [11]. Treatment of VIN and VaIN intraepithelial neoplasia is challenging, can be disfiguring and requires long-term follow-up, since disease recurrence is common [12,13]. Data show that, as with grade 2–3 cervical neoplasia, high-grade vulval and vaginal lesions are surrogate markers for HPV-related vulval or vaginal cancer.

Human papillomavirus vaccines

Prophylactic administration of a quadrivalent HPV 6/11/16/18 or a bivalent HPV 16/18 L1

virus-like-particle (VLP) vaccine has been shown to be 90–100% efficacious against CIN 2/3 or adenocarcinoma *in situ* (AIS) associated with HPV 16 or 18 infection [14–16]. The quadrivalent vaccine was also highly effective against disease caused by infection with HPV 6 and HPV 11, which cause most anogenital warts and a proportion of low-grade intraepithelial neoplasias [17].

Combined analysis of three randomized clinical trials

A combined analysis of three randomized clinical trials of the quadrivalent HPV vaccine was recently reported, regarding its effect on the rates of high-grade VIN and VaIN [18]. A total of 18,174 women aged 16–26 years were enrolled in one of three double-blind, placebo-controlled, randomized trials. Participants were drawn from 157 sites in 24 countries in the Americas, Europe and Asia. The mean age of the women was 20 years, the mean age at first sexual intercourse was 16.7 years, the median lifetime number of sexual partners of nonvirgins was 2, 22% had a history of past pregnancy and 58% were using hormonal contraception.

Individuals were randomly assigned to receive either a quadrivalent HPV 6/11/16/18 L1 VLP vaccine (Gardasil®, Merck and Co., NJ, USA) or placebo. Study vaccine or placebo was administered at day 1, month 2 and month 6. The quadrivalent vaccine contained 20 µg HPV 6 L1 VLP, 40 µg HPV 11 L1 VLP, 40 µg HPV 16 L1 VLP and 20 µg HPV 18 L1 VLP. Individuals

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returned to the study site for genital examination and collection of cervical and anogenital swabs at follow-up visits scheduled 1 and 6 months after dose three, and at 6–12 month intervals thereafter. All external anogenital lesions that were possibly, probably or definitely HPV-related, or whose diagnosis could not be ascertained, were biopsied. If several lesions were present, the investigator was requested to obtain at least one specimen from each affected area (vagina, periurethral area, left labia, right labia, perineum or perianal area). If lesions of more than one morphology were present a representative sample of each morphology was biopsied. Infection with HPV 6/11/16/18 was determined with PCR and serology. A case was defined as a pathology panel consensus diagnosis of VIN 2–3 or VaIN 2–3, with HPV 16 or 18 DNA detected in an adjacent section from the same tissue block, adjacent biopsy tissue or a biopsy swab. For intention-to-treat analyses of all cases of VIN 2–3 and VaIN 2–3, irrespective of causal HPV type or whether or not HPV DNA was detected in the lesion, a case was defined as one of the above end points.

Summary of overall results

In the per-protocol susceptible population, vaccine efficacy was 100% (95% CI: 72–100) (Table 1). The per-protocol population was defined as individuals who were HPV 16/18 DNA negative by PCR and seronegative to HPV 16/18 at enrolment, who remained PCR negative throughout the vaccination period, received all three doses, and did not violate the protocol.

In the intention-to-treat population, the vaccine reduced the incidence of high-grade VIN/VaIN associated with HPV 16/18 by 71% (95% CI: 37–88) (Table 1).

When all cases of high-grade lesion were assessed in the intention-to-treat population, irrespective of whether or not HPV DNA was detected in the lesion and irrespective of causal HPV type, the vaccine efficacy was 49% (95% CI: 18–69) (Table 1). The benefit of vaccination in the intention-to-treat population was initially masked by prevalent infection or disease against which the vaccine has little effect. However, as vaccination prevented new HPV 16/18 infection over the course of follow-up, reductions in the incidence became more apparent (Figure 1).

The most common vaccine-related adverse reactions in vaccine versus placebo recipients were fever (10.3 vs 8.6%), nausea (4.2 vs 4.1%),

dizziness (2.8 vs 2.6%), injection-site pain (83.9 vs 75.4%), swelling (25.4 vs 15.8%), erythema (24.6 vs 18.4%) and pruritus (3.1 vs 2.8%). Less than 1% reported a serious systemic adverse experience, with no difference between the vaccine or placebo groups. Across the studies, 18 deaths were reported, and the most common cause was motor vehicle accident, followed by overdose or suicide (six vaccine vs five placebo).

Implications & significance

This combined analysis of the three different randomized trials provides the first evidence of an important ‘bonus’ effect of the vaccine [18]. The study provides evidence that this prophylactic quadrivalent HPV vaccine, developed to prevent cervical cancer, also prevents HPV-related vulval and vaginal precancers in 16–26-year-old women. The vaccine was 100% effective in preventing VIN 2–3 and VaIN 2–3 associated with HPV 16 or 18 in a population that was naive through completion of the vaccination regimen. Vaccine efficacy against HPV 16/18-related VIN/VaIN 2–3 in the intention-to-treat population, which included women who could have already acquired HPV 16/18 infection and those with vulval or vaginal HPV-related disease before vaccination, was 71%. Additionally, a 49% reduction in all high-grade VIN or VaIN, irrespective of causal HPV type, was seen in the intention-to-treat population, providing an estimate of the potential public-health benefit.

By combining data from three clinical trials that enrolled more than 18,500 women, the study provides the highest possible precision of the estimate of vaccine against VIN 2–3 and VaIN 2–3 associated with HPV 16 and 18 available to date.

The HPV vaccines have already been shown to be 90–100% effective in preventing HPV 16/18-related CIN grade 2–3 and AIS, both of which are obligate precursors of invasive cervical cancer [14–16]. Previous studies have shown that vaccination is well tolerated and safe [15,16].

An increasing incidence of high-grade VIN and vulval cancer has been noted over the past 30 years [5–8]. This trend is worrying, as these cancers are not amenable to a screening program. Whereas, previously, vulval cancer was seen almost exclusively in older women, recent studies have shown that a large proportion of these cancers now occurs in younger women. In older women, vulval cancer may occur in association with non-HPV-related lichen sclerosis.

Table 1. Vaccine efficacy in preventing high-grade vulval and vaginal lesions associated with human papillomavirus 16 and 18, and all high-grade vulval and vaginal lesions (irrespective of cause).

	Vaccine (n = 9087)			Placebo (n = 9087)			Efficacy (95% CI)
	Number in given population	Cases	Rate (cases per 100 person-years at risk)	Number in given population	Cases	Rate (cases per 100 person-years at risk)	
Per-protocol susceptible population HPV 16/18-related VIN 2/3 or VaIN 2/3	7811	0	0.00	7785	15	0.08	100% (72–100)
Intention-to-treat population HPV 16/18-related VIN 2/3 or VaIN 2/3	9087	9	0.03	9087	31	0.12	71% (37–88)
Intention-to-treat population. All VIN 2/3 or VaIN 2/3	9087	27	0.10	9087	53	0.20	49% (18–69)

HPV: Human papillomavirus; VaIN: Vaginal intraepithelial neoplasia; VIN: Vulval intraepithelial neoplasia.

Modified from [18].

However, almost all vulval cancer cases among younger women are HPV-related, with a high proportion attributable to HPV 16. In this study, a total of 64% of all cases of VIN 2–3 seen in the placebo cohort were attributable to HPV 16. Other HPV types can also be involved in VIN and VaIN, although less frequently than HPV 16. The mean duration of follow-up in the combined analysis was

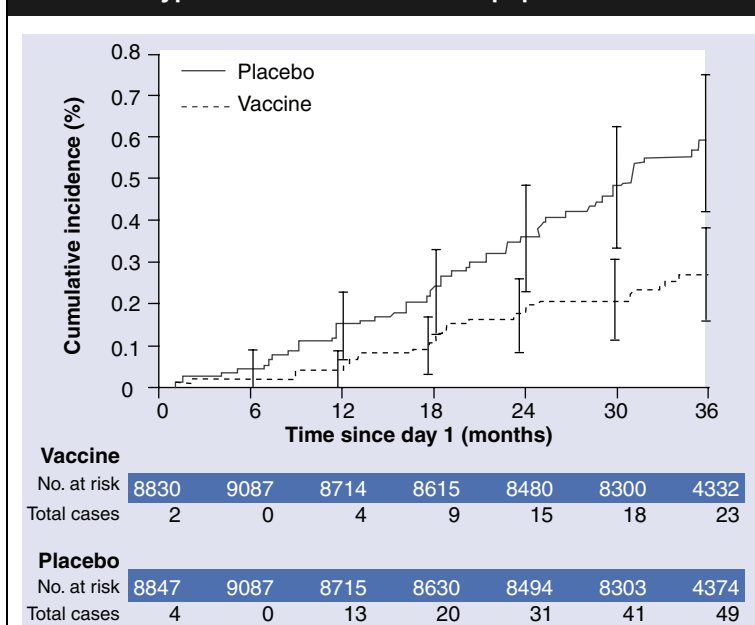
36 months. Even within this relatively short time, surprisingly many young women developed an end point of high-grade VIN/VaIN, corresponding to an incidence of up to 120.

Treatment for VIN and VaIN can cause anxiety, depression, sexual dysfunction and poor self-image. The treatment of choice for VIN is surgery. Since the disease can be multifocal, surgery can be disfiguring and mutilating for these patients and adequate margins are sometimes impossible to achieve. Topical treatments are not very effective and data are limited [19,20]. The recurrence rate of VIN is high [12,13]. Furthermore, women with VIN or VaIN have a substantial risk of developing invasive vulval cancer, even after treatment [10,12].

Precursors of vulval and vaginal cancers are often not recognized. Prevention of these conditions by a vaccine has the potential to lower a woman's risk of developing vulval and vaginal cancer. Furthermore, mutilating surgery and repeated treatments may be avoided in the future. However, the real benefits to individuals and society at large will need to be weighed against the costs of vaccination.

Conclusion & future perspective

In summary, implementation of HPV vaccines is a great opportunity, but many questions remain. For instance, what is the duration of the immune response? How many vaccine doses are needed? Does the vaccine have any therapeutic efficacy among women already exposed to the vaccine HPV types? Does the vaccine have any

Figure 1. Time to any vulval intraepithelial neoplasias, grade 2/3 or vaginal intraepithelial neoplasias, grade 2/3, irrespective of causal HPV type in the intention-to-treat-population.

Reproduced with permission from [18].

cross-protection against other closely related HPV types? Is there a risk for type replacement after widespread vaccination? Finally, what is the long-term safety of the vaccines?

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Executive summary

- Vulval cancer accounts for 3–5% of all gynecologic cancer cases.
- Vaginal cancer accounts for 1–2% of all gynecologic cancer cases.
- Vulval and vaginal high-grade intraepithelial neoplasias (VIN 2–3 and VaIN 2–3) are valid surrogate markers for vulval and vaginal cancer.
- The quadrivalent vaccine was 100% effective in preventing human papillomavirus (HPV) 16/18-related high-grade lesions in young women unexposed to the vaccine HPV types.
- The quadrivalent vaccine was 49% effective against all high-grade VIN/VaIN irrespective of whether or not HPV was detected in the lesions.
- These findings support the prophylactic efficacy of the quadrivalent vaccine in ultimately preventing HPV 16/18-related vulval and vaginal cancer.

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