Review

Review of current knowledge on HPV vaccination: An Appendix to the European Guidelines for Quality Assurance in Cervical Cancer Screening

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Abstract

The recognition of a strong etiological relationship between infection with high-risk human papillomaviruses and cervical cancer has prompted research to develop and evaluate prophylactic and therapeutic vaccines. One prophylactic quadrivalent vaccine using L1 virus-like particles (VLP) of HPV 6, 11, 16 and 18 is available on the European market since the end of 2006 and it is expected that a second bivalent vaccine containing VLPs of HPV16 and HPV18 will become available in 2007. Each year, HPV16 and HPV18 cause approximately 43,000 cases of cervical cancer in the European continent. Results from the phase-IIb and III trials published thus far indicate that the L1 VLP HPV vaccine is safe and well-tolerated. It offers HPV-naive women a very high level of protection against HPV persistent infection and cervical intra-epithelial lesions associated with the types included in the vaccine. HPV vaccination should be offered to girls before onset of sexual activity.

While prophylactic vaccination is likely to provide important future health gains, cervical screening will need to be continued for the whole generation of women that is already infected with the HPV types included in the vaccine. Phase IV studies are needed to demonstrate protection against cervical cancer and to verify duration of protection, occurrence of replacement by non-vaccine types and to define future policies for screening of vaccinated cohorts.

The European Guidelines on Quality Assurance for Cervical Cancer Screening provides guidance for secondary prevention by detection and management of precursors lesions of the cervix. The purpose of the appendix on vaccination is to present current knowledge. Developing guidelines for future use of HPV vaccines in Europe, is the object of a new grant offered by the European Commission.

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1. Introduction

The current review is an appendix to the European Guidelines on Quality Assurance in Cervical Cancer Screening, which will be published early 2007 and where guidance is provided on organised secondary prevention in the member states of the European Union. The European Commission is currently preparing a grant to develop supplementary recommendations on future use of HPV vaccination.

Persistent infection of the uterine cervical epithelium with oncogenic human papillomavirus types is a necessary but insufficient causal factor in the carcinogenesis of cervical cancer (Bosch et al., 2002). The recognition of this strong causal association had led to the development of several prototypes of prophylactic and therapeutic vaccines (Frazer, 2004; Galloway, 2003; Schneider and Gissmann, 2003; Tjalma et al., 2004). Recently, an IARC expert group confirmed that for thirteen HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66) there is sufficient evidence that they can cause cervical cancer (Cogliano et al., 2005; IARC, 2007). Pooled case-control studies indicate possible involvement of five additional types (HPV26, 53, 68, 73 and 82) in cervical carcinogenesis (Munoz et al., 2005; IARC, 2007). Moreover, HPV16 and (to a lesser degree) HPV18 are linked with more rare cancers, namely cancer of the vulva and vagina in women, cancer of the penis in men, and cancer of the anus, oropharynx and larynx in women and men (Parkin and Bray, 2006).

In this review, we briefly address some immunologic aspects of HPV infection and summarize the published results of placebo-controlled phases-II and -III vaccination trials. Some relevant public health questions concerning future prophylactic and therapeutic immunisation are also discussed.

2. Immunity against human papillomaviruses

2.1. Humoral immunity

HPV infection is restricted to epithelial cells; therefore presentation of viral antigens to the host immune system is limited. Natural HPV infection of the genital tract gives rise to a slow and modest but measurable serum antibody response in most but not all infected individuals (Carter et al., 1996, 2000). The intensity of this humoral response depends on viral load and persistence (Ho et al., 2004). The presence of HPV antibodies is long lasting but does not contribute to the clearance of established infections (Shah et al., 1997). HPV serology is an important tool in epidemiological studies to assess past exposure (Dillner, 1999; Dillner et al., 1996, 1997; Lehtinen et al., 2001).

The capsid of papillomaviruses is composed of two viral proteins: the major capsid protein, or L1, and the minor capsid protein, or L2 (Orth and Favre, 1985). Virus-neutralising anti-L1 antibodies are generated against epitopes at the surface of the viral capsid and are essentially type-specific (Carter et al., 2000; Hines et al., 1994; Roden et al., 1996). The L2 protein is situated more internally of the capsid, but a small segment is exposed at the surface, and this segment can induce virus-neutralising anti-bodies as well (Christensen et al., 1991; Kawana et al., 1999; Roden et al., 2000). These anti L2-antibodies are less potent than anti-L1 antibodies (Christensen et al., 1991; Roden et al., 2000; White et al., 1999) but they appear to show some cross-reactivity to heterologous HPV types (Greenstone and Nieland, 1998; Nieland and Da Silva, 1999).

There is a series of methodological issues that make it difficult to unambiguously study whether immunity against type-specific reinfection occurs. Significant, though not complete, protection against reinfection has been found to be associated with the presence of HPV antibodies (Konya and Dillner, 2001). Other studies have shown that antibodies elicited by natural infection with a specific HPV type does not confer protection, since sero-positivity is not significantly associated with reduction in re-infection with homologous types (Viscidi et al., 2004).

The discovery that the L1 capsid protein could be expressed in eukaryotic cells and could self assemble into so-called virus-like particles (VLPs) was a critical step in the development of HPV vaccines (Zhou et al., 1991). HPV
L1 VLPs contain the same conformationally dependent neutralizing epitopes that are present on infectious viruses. The structural integrity of capsid proteins is necessary to elicit protective antibodies (Kirnbauer et al., 1994). Denaturation or improper folding of the L1 protein alters the presentation of epitopes and yield unprotective antibodies. The L2 protein can also be expressed with L1 protein in yeast or insect cells, giving rise to “L1 plus L2”.

2.2. Cellular immunity

Clearance of a naturally acquired HPV infection is triggered by a specific cell-mediated immune (CMI) response. This subject was extensively reviewed by Man (1998). Dendritic cells or Langerhans cells, present in the cervical epithelium, play an important role in recognizing HPV infected cells and stimulating Th1 helper cells, which elicits the production of cytotoxic T-lymphocytes (CTL) (Niedergang et al., 2004). These cytotoxic effector cells attack infected cells, resulting in the resolution of the infection (Stern, 2004). However, little is known about how to modulate these immune responses.

3. HPV vaccination

3.1. Prophylactic vaccination

Vaccination with VLPs gives rise to virus-neutralizing antibodies in serum. Vaccination by intramuscular injection of L1 VLPs has been shown to be highly immunogenic and well tolerated in phase-I trials. Recently, three randomised placebo-controlled phase-II trials with, respectively, a monovalent HPV16 vaccine, a bivalent HV16/18 vaccine and a quadrivalent HPV6/11/16/18 vaccine candidate have consistently demonstrated almost complete protection against persistent infection with the targeted HPV types (Harper et al., 2004, 2006; Koutsy et al., 2002; Mao et al., 2006; Villa et al., 2005). Moreover, these trials confirmed the safety of the vaccines and showed strong immuno-responses that were several orders of magnitude higher than those observed after natural infections. All the trials showed 100% protection against the development of CIN associated with the HPV types included in the vaccines, although the trials were insufficiently powered to prove this hypothesis. The characteristics and main reported results of these studies are summarized in Table 1.

Two pharmaceutical companies (Merck Sharp and Dohme [MSD] and GlaxoSmithKline [GSK]) are currently conducting large multi-centre phase-III vaccine trials in all continents except Africa (Table 2) (Cohen, 2005). In addition, the National Cancer Institute (United States) is conducting a population-based trial in Costa Rica. All these phase-III trials aim to demonstrate that vaccines protect against histologically confirmed high-grade CIN associated with the targeted HPV types. Anticipated results of phase-III trials of the quadrivalent MSD vaccine showed 100% protection against HPV16/18-associated CIN2 and adenocarcinoma in situ in HPV naive women who received the complete vaccine regimen (ATP) (Skjeldestad, 2005).

3.2. Therapeutic HPV vaccines

Development and maintenance of cervical precursors and their progression to invasive cancer requires the continued intra-cellular expression of the viral oncoproteins of E6 and E7 (Steenbergen et al., 2005; Zur Hausen, 2002). Therefore therapeutic vaccines have aimed at stimulating T-cell responses against these viral early oncoproteins. Currently, different methods and formats of therapeutic vaccines such as administration of peptide antigens or recombinant proteins, plasmid DNA vaccines, viral vector vaccines, and administration of E7 pulsed dendritic cells, are being evaluated (Stern, 2005). Trials show that these vaccines are safe and variably immunogenic, although there is often no correlation with clinical outcomes (Stern, 2004).

4. Questions about HPV vaccination

4.1. Endpoints

Although cervical cancer is the most important clinically relevant endpoint, it was agreed that surrogate end-points are needed, for two simple reasons: (1) malignancies develop slowly and cancer as an endpoint requires very large and lengthy studies, and (2) state-of-the-art clinical management requires that premalignant lesions are treated immediately, making such an endpoint unfeasible in a clinical trial setting (Pagliusi and Teresa, 2004). On the other hand, evidence of incident HPV infection with a type-specific vaccine is an endpoint that would seem to be an obvious choice for a clinical trial against an infectious disease. However, a high percentage of sexually active women, are at least transiently infected with one or more genital HPV types. Because HPV-induced clinical disease occurs in only a relatively small proportion of infected individuals, estimates of vaccine efficacy cannot be based on protection against infection.

Recently, a WHO expert group reached a consensus and proposed histologically confirmed high-grade CIN or worse disease (including cervical cancer) associated with one of the target vaccine types as an acceptable surrogate endpoint for phase-III vaccination trials (Pagliusi and Teresa, 2004). Type-specific persistence, defined as presence of the same HPV type at two or more consecutive visits separated by 6–12 months, is another interesting outcome measure (Lowy and Frazer, 2003).

Comparing the incidence of cervical and other HPV-associated cancers in vaccinated and non-vaccinated cohorts, by linkage to cancer registries, will provide the ultimate proof of protection against cancer (Lehtinen, 2004, 2005;
Table 1
Study characteristics and main results reported by three randomised placebo-controlled phase-IIb HPV vaccination trials

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Vaccine</th>
<th>Adjuvant</th>
<th>Dosage of VLPs</th>
<th>Vaccination schedule</th>
<th>Study size</th>
<th>Study sites</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Age range</th>
<th>Duration follow-up</th>
<th>Efficacy: protection against</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koutsy et al. (2002) and Mao et al. (2006)</td>
<td>HPV16 L1 VLP, produced in yeast (Saccharomyces cerevisiae)</td>
<td>225 mg aluminiumhydroxy-phosphate sulphate</td>
<td>IM injections, 0.5 mL, at 0, 2 and 6 months</td>
<td>Randomised: 1194 vaccine/1198 placebo, ATP: ≥7 M</td>
<td>16–23 years</td>
<td>USA</td>
<td>Women, HPV DNA negative at M0 and M7, HPV16 seronegative at M0</td>
<td>Pregnancy, history of abnormal Pap, ≥6 sex partners</td>
<td>48 months</td>
<td>53 months</td>
<td>At 18 M: 91% (CI: 80–97%), at 48 M: not documented</td>
</tr>
<tr>
<td>Harper et al. (2004, 2006)</td>
<td>HPV16 and 18 L1, produced in Spodoptera frugiperda SF-9 and Trichoplusia ni Hi-5 cell substrate, respectively, via a recombinant baculovirus vector</td>
<td>500 mg AlOH and 50 mg 3-deacylated monophosphoryl lipid A</td>
<td>IM injections, 0.5 mL, at 0, 1 and 6 months</td>
<td>Randomised: 560 vaccine/553 placebo, ATP: ≥7 M</td>
<td>15–25 years</td>
<td>Brazil, USA, Canada</td>
<td>Healthy women, cytologically normal, seronegative for HPV16 and 18. HPV DNA negative for 14 types (16, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68)</td>
<td>Healthy women, accepting contraception, virgins only when looking for contraception</td>
<td>≥6 months</td>
<td>53 months</td>
<td>ATP at 53 M: HPV16: 98% (CI: 87–100%), HPV18: 89% (CI: 53–99%), HPV16/18: 95% (CI: 84–99%)</td>
</tr>
<tr>
<td>Villa et al. (2005)</td>
<td>HPV6, 11,16 and 18 L1 VLP, produced in yeast (Saccharomyces cerevisiae)</td>
<td>225 mg aluminiumhydroxy-phosphate sulphate</td>
<td>IM injections, 0.5 mL, at 0, 2 and 6 months</td>
<td>Randomised: 277 vaccine/275 placebo, ATP: 6 M: 256 vaccine/260 placebo, ATP: ≥7 M: 239 vaccine/242 placebo</td>
<td>18–23 years</td>
<td>Brazil, Europe, USA</td>
<td>Healthy women, accepting contraception, virgins only when looking for contraception</td>
<td>Pregnancy, previous abnormal smears, ≥4 sex partners. Women with a previous HPV infection were NOT excluded</td>
<td>36 months</td>
<td>36 months</td>
<td>Not documented</td>
</tr>
</tbody>
</table>

ATP: according-to-protocol analysis; CI: 95% confidence interval; GMT: geometric mean titre of antibodies; ITT: intention-to-treat analysis; VLP: virus like particles. *No cases in vaccinated or placebo group.

Lehtinen et al., 2006a,b). In anticipation of such results, estimations of the impact of HPV vaccination on the burden of cervical cancer incidence and mortality must be based on the observed surrogate endpoints using mathematical modelling (Barnabas et al., 2006; Garnett et al., 2006).

4.2. Duration and consistency of the antibody response to VLPs

The long-term duration of protection against HPV infection, elicited by vaccination is still unknown. Type-specific L1 VLP-antibodies reach maximum titres at month 7, i.e. 1
month after administration of the third dose. Titres decline until month 24 and remain rather stable thereafter (Villa et al., 2005, 2006). Nevertheless, at 3 years, antibody titres remain 2–20-fold higher than in placebo controls (Villa et al., 2006).

Complete protection against HPV16 associated CIN lesions was observed over the whole follow-up duration of two phase-IIb trials: 48 months for the monovalent HPV16 vaccine and 53 months for the bivalent HPV16/18 vaccine (Harper et al., 2006; Mao et al., 2006). The use of ASO4 adjuvant (3-O-desacyl-4′-monophosphoryl lipid A and aluminium salt) triggers higher virus-neutralizing antibody titres and production of memory B cells compared to VLPs adjuvanted with aluminium salt alone (Giannini et al., 2006). Whether this will result in prolonged enhanced protection against cervical lesions is still unknown.

### 4.3. Optimal target age range for vaccination

Epidemiological studies indicate that many women become infected within several months of initiation of sexual activity (Koutsky et al., 1992; Winer et al., 2003; Woodman et al., 2001). Therefore, vaccination at an age of 12–14 years, just before initiation of sexual contacts, or at childhood age, perhaps adding a booster in adolescence or early adulthood, seems like an obvious strategy. The protocols of phase-IIb trials have excluded women who were vaccine-type HPV DNA- or sero-positive at enrolment or who became HPV DNA-positive during the administration period. Nevertheless, a reduced protection was observed in a small cohort of non-HPV naïve women who received the HPV16 VLP (Mao et al., 2006). The preliminary analysis of the large phase-III with the quadrivalent vaccine observed that protection against HPV16- or HPV18-associated CIN2+ or AIS was absent among women who were baseline HPV DNA-positive and sero-positive for HPV16 or 18. Protection was strongly reduced (efficacy of 31.2; 95% CI: <0–54.9%) for women who were HPV DNA-positive but sero-negative at the time of vaccination. These data suggest a potential utility of testing for the HPV status before vaccinating women who have already initiated sexual contacts or when vaccinating older women.

### 4.4. Immunization of males

Genital tract HPV infection is sexually transmitted. Therefore, immunization of men may help prevent transmission to and infection of women. Modelling studies on herd immunity, i.e. indirect protection of those who remain susceptible, owing to a reduced prevalence of infections in the risk group for disease, have been published (Garnett, 2005; Hughes et al., 2002; Taira et al., 2004). Hughes et al. (2002) determined that vaccinating women alone could reduce the prevalence of infection with the specific HPV type in the vaccinated group by 30%, and that vaccinating both males and females could reduce the prevalence by 44%. Taira et al. (2004) estimated that vaccinating boys would affect cervical cancer incidence only marginally and concluded that it was not cost-effective compared with vaccinating only girls.

Currently, few data are available regarding the immune responses to HPV VLPs in men, although studies are being initiated (Cohen, 2005; Geipert, 2005). Immunisation of men with VLPs is expected to elicit a serum immune response similar to that in women. A major obstacle in testing the efficacy of HPV vaccines in men has been the lack of safe, simple and reliable sampling methods.

### 4.5. Inclusion of HPV types

Antibody responses elicited by VLP immunization are quite specific for the individual HPV type, with limited cross-neutralisation even for closely related HPV types. Thirteen (or more) different “high risk” types have been identified as causative agents of cervical cancer (Cogliano et al., 2005; Munoz et al., 2003). These considerations raise an important question: “How many different HPV types can be included in prophylactic vaccines, given that each type requires a certain amount of antigen to be included in the preparation?” (Franco and Harper, 2005; Munoz et al., 2004).

Fig. 1 shows the cumulative proportion of the main HPV types present in cervical cancer, estimated for Europe from surveys and population-based case-control studies conducted by IARC (Munoz et al., 2004). It also illustrates the estimated number of cervical cancer cases that can be attributed to the same ranked combination of HPV types. According to the most recent available estimates published in GLOBOCAN-2002, approximately 60,000 new cases of cancer occur yearly in Europe (Ferlay et al., 2004). If all women at risk were vacci-

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Fig. 1. Cumulative proportion of cervical cancers in Europe that are attributed to a ranked combination of HPV types and the number of cervical cancers occurring each year expected to be caused by these types. In Europe, 60,000 cases of cervical cancer occur yearly. Sixty five percent, or 39,240 cancer cases, are attributed to HPV16. 71.5% (or 6.1% more) can be attributed to HPV16 or HPV18. Almost 88% of cervical cancers are attributed to one of eight HPV types (HPV16, 18, 33, 31, 45, 56, 35 and 52). Adapted from Munoz et al. (2004) and Ferlay et al. (2004).

nated with a 100% effective HPV16 vaccine, 39,000 incident cases of cervical cancer could be avoided. Adding HPV18 type to the vaccine could potentially avoid 43,000 cases per year (71.5%). An octovalent vaccine could potentially reduce the incidence with 88%. This simple extrapolation assumes absence of replacement or cross-protection, which respectively should decrease or increase vaccine efficacy. Replacement means that other HPV types not included in the vaccine cocktail might take over the carcinogenic role of the eliminated types. Follow-up over 5 years of the phase-II trials did not show evidence of such a replacement phenomenon. Moreover, the GSK trial using a bivalent HPV16/18 vaccine with an AS04 adjuvant reported partial cross-protection against infection with HPV types related to HPV16 and 18 was reported (Dubin et al., 2005). Protection was 94.2% (95% CI: 63.3–99.9%) and 54.5% (95% CI: 11.5–77.7%) for incident infection with HPV45 and HPV31, respectively (Harper et al., 2006).

4.6. Combination of screening and HPV vaccination

Current L1 VLP vaccines do not include all oncogenic types. Moreover, since such vaccines are aimed at protecting HPV-naïve individuals, and the effect on women already infected may be low or even absent, screening will continue to be necessary. Setting up vaccination programmes for teenage girls, will have an observable impact on cancer incidence trends only after 2–3 decades.

Nevertheless, vaccination may allow starting screening of vaccinated cohorts at older age, increasing the screening interval and reducing the burden of precursor lesions requiring follow-up and treatment in vaccinated cohorts. Goldie, looking for the most cost-effective strategies, estimated that conventional cytological screening every 5 years starting at 30 years of age could result in 67% reduction in lifetime cancer risk. Adding vaccination against HPV16 and 18, assuming 80% efficacy, could yield a reduction of 89% (Goldie et al., 2004).

Health authorities and care providers should understand that screening and vaccination are complementary strategies (Schiller and Davies, 2004). Neglecting screening because vaccination programmes have begun could paradoxically lead to an increase of the cervical cancer burden.

4.7. Vaccination against non-oncogenic HPV

HPV types 6 and 11 jointly cause more than 90% of genital warts (Lacey et al., 2006). Low-grade and even non-progressive high-grade dysplastic lesions of the cervix may be caused by these and other non-oncogenic types as well. Moreover, HPV types 6 and 11 can cause serious disease in rare circumstances. HPV6 and HPV11 are the major cause of recurrent respiratory papillomatosis, a severe disease that may be fatal. So-called giant condylomas or Buschke-Löwenstein tumors of the vulva, penis and anus are also associated with these HPV types (Cogliano et al., 2005). These tumours are regarded as having a low potential for malignancy, but may also be fatal. The vaccine manufactured by Merck contains L1 VLPs of both HPV 6 and HPV 11. Phase-II trials have shown complete protection against external genital lesions but were underpowered to generate statistically significant results (Villa et al., 2005). High clinical and statistically significant protection was confirmed in phase-III trials.2

4.8. Inclusion of HPV proteins in addition to L1 in vaccines

Addition of other proteins to the L1 VLPs requires increased technological challenges and costs. A combination of L1 and L2 appears promising since anti-L2 could protect against heterologous HPV types. The addition of early antigens (E6 or E7 in particular) is also being investigated to determine if a cell-mediated immune response could be elicited along with the antibody response to the L1 VLP component (Greenstone and Nieland, 1998). If so, this would open the way to development of chimeric vaccines with a therapeutic and prophylactic activity (Schiller and Nardelli-Haefliger, 2006; Stanley, 2003).

5. Licensure of VLP vaccines

On 8 June 2006, the US Food and Drug Administration (FDA) approved Gardasil®, the quadrivalent vaccine, developed by MSD, containing VLP L1 of HPV types 6, 11, 16 and 18, for use in females 9–26 years of age (see footnote 2). The FDA recognised the indication of protection against cervical cancer, genital warts (condyloma acuminata), cervical adenocarcinoma in situ, cervical intraepithelial neoplasia (grades 2, 3 and also 1), vulvar intraepithelial neoplasia (grades 2 and 3) and, vaginal intraepithelial neoplasia (grades 2 and 3) caused by the vaccine types. The FDA press release stated that the vaccine is effective if administered prior to HPV infection.

The Advisory Committee for Immunization Practices (ACIP) of the CDC, recently recommended routine vaccination of girls of 11–12 years old, but also allowed the administration of the vaccine to girls of 9 or 10 years and girls and young women of 13–26 years of age.3

On 27 July 2006, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) adopted a positive opinion, recommending to grant a marketing authorisation of Gardasil for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts.4 On 20 September 2006, EMEA has provided the official authorization for marketing of the vaccine in the European Union, specifying that its use should be in accordance with official recommendations.

An application is also introduced at the EMEA for licensure of Cervarix (the bivalent VLP L1 HPV16/18 vaccine manufactured by GSK).

6. Conclusions and recommendations

Results from the phases-IIb and -III trials published thus far indicate that the L1 VLP HPV vaccine is safe and well tolerated. It offers HPV naïve women a very high level of protection against HPV persistent infection and cervical intra-epithelial lesions associated with the types included in the vaccine.

Currently, only prophylactic HPV vaccines have shown promise. While prophylactic vaccination is likely to provide important future health gains, cervical screening will need to be continued for the whole generation of women that is already infected.

Due to the multiplicity of HPV types and the fact that the coming vaccines are essentially type-specific, the prophylactic vaccines are not likely to eradicate cervical cancer. A reduction in background risk by elimination of the most important HPV types would affect cost-effectiveness and timing/intervals of screening programs, but would not obviate them.

The continuous monitoring of which HPV types are spreading in the population will become necessary, for early monitoring of “fill in” phenomena, inappropriate vaccination strategies or other reasons for vaccination failure.

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References


Skjeldstad FE. Prophylactic quadrivalent human papillomavirus (HPV) (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine (GardasilTM) reduces cervical intraepithelial neoplasia (CIN) 2/3 risk, 43rd Annual Meeting of IDSA, San Francisco; 2005.


