Review article

Vaccination against HPV: indications for women and the impact on the cervical screening programme

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A novel approach for primary prevention of cervical cancer has become available by the discovery of efficient prophylactic human papillomavirus (HPV) vaccines based on virus-like particles. This review elaborates on the progress in the field of prophylactic HPV vaccination achieved in the past decade, provides indications for prophylactic HPV vaccination, and discusses the impact on public health and the current secondary prevention system. In summary, with current vaccines, effective prevention and control of cervical cancer within the next decades requires an integrated vaccination-screening approach, including routine prophylactic vaccination to young women and adapted cervical screening for older women (≥30 years).

Keywords Guidelines, human papillomavirus, primary prevention, public health, secondary prevention.

Introduction

Persistent infection with high-risk human papillomavirus (hrHPV) has been recognised as the necessary cause of cervical cancer and its precursor lesions (i.e. cervical intraepithelial neoplasia [CIN] or squamous intraepithelial lesion for squamous cell carcinoma and adenocarcinoma *in situ* [AIS] for adenocarcinoma).[1–3] Consequently, primary prevention becomes a realistic opportunity to prevent (pre)malignant disease of the uterine cervix. Worldwide, researchers have focused on the development of prophylactic vaccines that generate neutralising antibodies protecting against de novo human papillomavirus (HPV) infections, and accordingly hrHPV-associated diseases. The discovery that the HPV L1 protein, with or without L2 protein, could self-assemble into virus-like particles (VLPs) when expressed from a suitable expression system (e.g. yeast and baculovirus) was a major drive towards the development and clinical application of prophylactic HPV vaccines. The first results of clinical trials on current HPV-VLP-based vaccines raise excitement and prospect for primary prevention of the globally prevalent cancer of the uterine cervix as well as other HPV-associated malignancies. At the same time, discussions on how widespread prophylactic vaccination should be applied and its impact on cervical screening programmes appear. This review will elaborate on the progress in the field of primary cervical cancer prevention achieved in the past decade and will discuss the indications for prophylactic HPV vaccination and the impact on public health.

Mechanism of action of prophylactic HPV vaccines

The currently available prophylactic HPV vaccines are based on VLPs composed of HPV L1 proteins. A VLP is geometrically and antigenically almost identical to the native virion. Thus, VLPs resemble the actual virus morphologically but cannot induce infection as these do not contain viral DNA. Once introduced intramuscularly, VLP vaccines generate high levels of systemic anti-HPV L1 immunoglobulin G (IgG) antibodies.[4] It is assumed that the serum-neutralising IgG antibodies induced by these HPV-VLP vaccines reach the anogenital epithelial surface through diffusion or microtrauma to provide protection against infection of epithelial cells with HPV types represented in the vaccine. Protection is in principle type specific, but cross-reactivity may occur

because phylogenetically related HPV types do share cross-neutralisation epitopes.[5] There is no indication that induction of IgA antibodies at the epithelial surface would be involved in protection by current HPV vaccines. The HPV vaccines induce immune memory,[6,7] likely providing long-term immunity even when initially induced high IgG antibody titres drop in time.

Clinical effects of prophylactic HPV vaccines observed so far

Three prophylactic HPV-VLP vaccines have been clinically evaluated to date, including a monovalent HPV16 L1 VLP vaccine (Merck Research Laboratories, West Point, PA, USA),[8,9] a bivalent HPV16/18 L1 VLP vaccine (Cervarix™; GlaxoSmithKline Biologicals, Rixensart, Belgium),[10–12] and a quadrivalent HPV6/11/16/18 L1 VLP vaccine (GARDASIL®; Merck, Whitehouse Station, NJ, USA, and marketed in Europe by Sanofi Pasteur MSD).[13–17] Both the bivalent and the quadrivalent vaccine have been granted a license by the European Medicines and Evaluation Agency (EMEA, http://www.emea.europe.eu). The quadrivalent vaccine has also been licensed by the Federal Drug Administration of the USA (http://www.fda.gov). The vaccines are administered by intramuscular injection at a dose of 20–40 micrograms of each VLP at three time points over a 6-month period (0, 1 or 2, and 6 months).[18] Both the bivalent and the quadrivalent vaccine have undergone randomised, double-blind, placebo-controlled phase III clinical trials in North America, Latin America, Europe and the Asian Pacific region. The clinical effects reported so far can be divided into generation of HPV immunity, prevention of HPV infections, and prevention of clinical lesions. The trial findings mainly apply to prophylactic vaccination of women; vaccine efficacy in men is currently under evaluation and results from trials on men are expected to be reported in the near future (end 2008). In addition, the feasibility of applying prophylactic HPV vaccination to immunocompromised people awaits efficacy and safety data of trials.

Generation of high antibody titres

The VLP-based vaccines have shown to be highly immunogenic. Virtually, all vaccinated individuals (9–55 years of age) seroconvert and generate high titres of neutralising IgG antibody against the vaccine type(s). The neutralising antibodies have shown to persist for at least 5 years after vaccination at measurable levels higher than those found in natural infections. Antibody responses have shown to be highest in younger (9–15 years) recipients.[12,14,19–21] These findings suggest that an optimal immune response to HPV-VLPs occurs at or around puberty, indicating this age category to be a potential target population. Immune memory is also generated by the HPV-VLP vaccines,[6,7] thereby long-term pro-

phylaxis may be expected, as this is dependent on the persistence of B-cell immune memory.

The primary antibody response to prophylactic vaccination may well be influenced by the vaccine antigen dose, the expression system used for production of VLPs, and the type of adjuvant, which differ between the VLP vaccines. However, immune correlates of protection have not been established, and the minimum protective antibody threshold for disease protection is not yet known.[22] In addition, the duration of protection and the necessity of booster immunisation need to be addressed in long-term follow up of vaccine recipients.

Prevention of HPV infection

Efficacy data of currently available HPV vaccines demonstrate protection against persistent HPV16 and/or HPV18 infections (lasting 6 months or more) of more than 90% up to at least 5 years after vaccination.[8–13,16–18] In addition, cross-protection was demonstrated for the bivalent vaccine reflected by a reduction of 6-month persistent infections with HPV31 (HPV16 related) by 36% (95% CI 0.5–60), HPV45 (HPV18 related) by 60% (95% CI 3–85), and HPV52 (HPV16 related) by 32% (95% CI 4–52).[11] In a combining analysis cross-protection against persistent infection with HPV31/33/35/39/45/51/52/56/58/59, mainly owing to HPV 31/45 [i.e. 45% protection (95% CI 18–63)], was observed for the quadrivalent vaccine.[23] The effect was most pronounced for HPV 31/45, i.e. 45% protection (95% CI 18–63).[23] As the confidence intervals of the efficacy estimates are wide, the extent of cross-protection is not yet well demarcated and will await evaluation of large clinical databases, with more disease included within the non-HPV16/18 categories.

Prevention of anogenital lesions

For both the bivalent and the quadrivalent vaccines, a variety of clinical trials report on efficacy data in preventing HPV16/18-related disease.[10–21,24] In these trials, the efficacy against CIN2/3 and AIS is documented as intermediate endpoint because these lesions are the obligate and immediate precursors to invasive cancer.[25] Estimation of the efficacy against cancer necessitates, yet unavailable, long-term follow up of current clinical trails. The clinical efficacy of current HPV vaccines has been demonstrated to be correlated with the cervical HPV DNA status of the women at enrolment and will accordingly be described below.

HPV16/18-DNA-negative women
Vaccines have particularly been evaluated in cervical HPV16/18-DNA-negative women. These include both HPV-naïve women (i.e. who have never been infected with HPV16/18, as reflected by the absence of HPV16 and/or HPV18 L1 antibodies) and women who have no current infection, but who have been previously exposed to one or more vaccine HPV types (characterised by the presence of

HPV16 and/or HPV18 L1 antibodies). HPV-VLP vaccines demonstrated similarly high clinical efficacy in both groups of women. Protection of more than 95% against cytological abnormalities associated with the targeted HPV types has been documented for HPV16/18 DNA-negative women. In addition, a protective effect of 90–100% against CIN and AIS lesions associated with vaccine-related HPV types has been reported.[8–13,16–18,26] In combining analysis, cross-protection against persistent infection with HPV31/33/35/39/45/51/52/56/58/59, which reduced incidence of precursor lesions CIN2/3 and AIS by 39% (95% CI 6–60), was observed for the quadrivalent vaccine. The percentage of protection was most pronounced for HPV 31/45 (i.e. 62% [95% CI 10–85).[23] Thus, current prophylactic HPV vaccines demonstrate valuable preventive efficacy against the early clinical complications of HPV16 and HPV18 infections and to a certain extent to those associated with some related HPV types and raise prospects for primary prevention of cervical cancer. It will take another 10–20 years of follow up before current clinical trials will be conclusive about duration of protection and efficacy of prophylactic vaccination in reduction of cervical carcinoma incidence. Follow up of vaccinated women is recommended to answer remaining questions regarding the most optimal vaccination schedule and potential need for boosters.[4]

Recent studies indicate efficacy of the quadrivalent vaccine against anogenital warts and vulval and vaginal intraepithelial neoplasia associated with the vaccine-covered HPV types as well, with efficacy rates similar to those for cervical precancer, i.e. more than 95% in HPV-DNA-negative women.[27,28] These findings suggest a broader population benefit from prophylactic HPV vaccination, preventing not only cervical (pre)cancer but also HPV16/18-associated cancers at other anogenital sites in women as well as HPV6/11-associated anogenital warts (in case of quadrivalent vaccine). As a spin off, it may be assumed that men will benefit from the prophylactic HPV vaccines as well in terms of prevention of HPV6/11-associated anogenital warts (for the quadrivalent vaccine) and HPV16/18-associated (pre)cancers of the anus and penis.[29] Additionally, prophylactic HPV vaccination may be effective against HPV16/18-associated head-and-neck (pre)cancers in both men and women.[30] However, this still requires empirical evidence.

HPV16/18-DNA-positive women
Protection against disease caused by HPV16/18 for women who were cervical smear positive for HPV16/18 DNA, as determined by highly sensitive type-specific or consensus (i.e. SPF10-LiPA) polymerase chain reaction (PCR) assays, is marginally or even nonexistent.[12,16,27] Only among HPV16/18-DNA-positive but seronegative women, a minor reduction (observed efficacy of 31.2%; 95% CI <0–54.9)[26] in incident CIN lesions caused by the respective vaccine HPV type was observed, while no effect in double HPV16/18-DNA-/positive seropositive women was found.[9,26] Thus, current HPV-VLP vaccines cannot be used to treat existing HPV infections and associated lesions. Some concerns were raised about potentially aggravated disease course for women persistently infected with HPV16/18 for the quadrivalent vaccine.[26] This finding was, however, not confirmed in subsequent trials,[16,17] and any reasons for first observations are currently unknown. From the established phase III trials performed so far, it may be concluded that no contraindications for prophylactic vaccination are applicable.[11,17] Follow up of vaccinated women who were HPV16/18-DNA-positive at time of vaccination is recommended, on the one hand to monitor their infection and potential emergence of CIN lesions and on the other hand to evaluate potential long-term (positive or negative) effects of prophylactic vaccination on an existing HPV infection. Although nontherapeutic, prophylactic vaccination could theoretically be beneficial to HPV16- or HPV18-DNA-positive women by preventing infection with other type(s) represented in the vaccine for which the woman is negative at baseline (e.g. HPV18 in case of HPV16-DNA-positive women). It may also potentially prevent successive rounds of autoinoculation or recurrent infection by sexual partner(s), which may decrease the extent and duration of viral infection and consequently reduce progression risk. Further evaluation of large clinical databases that have more women included in the HPV16/18-DNA-positive category is crucial.

Who should be vaccinated?

Based on above mentioned vaccine efficacy data, the following indications for prophylactic vaccination may be proposed:

Prepubertal women (just) before sexarche
The optimal target age for prophylactic vaccination is (just) before sexarche (i.e. at 9–14 years).[31] This is based on the fact that women may become infected within several months following initiation of sexual activity,[32–34] and the vaccines are hardly or even noneffective in HPV16/18-DNA-positive women.[9,26,35] Vaccination of girls at even younger ages may, in the absence of boosting doses, increase the risk of waning of vaccine-induced immunity before the phase of high exposure to HPV infections is entered and thereby reduce the expected benefits of prophylactic vaccination.

In many European countries, programmes exist for effective delivery of vaccines to children and these may be supplemented with the HPV vaccine. Otherwise, children may be approached during the last years of junior school or the first year of senior school. The best approach for HPV vaccination, e.g. school based, clinic based, or existing immunisation programme based, will depend on country-specific factors. Research questions regarding the effect on prophylactic HPV vaccine efficacy and safety when applied in combination

with other vaccines, the need for a booster dose to ensure lifelong vaccine efficacy or natural HPV exposure acting as a natural booster, and acceptability of a prophylactic vaccine against a sexually transmitted infection (STI) before sexarche require further attention. Simultaneous administration of HPV vaccine with hepatitis B vaccine (Merck, unpubl data) suggests no impact on antibody response levels, indicating the suitability of implementing prophylactic HPV vaccination in current immunisation programmes. Studies examining the likelihood of population acceptance of prophylactic HPV vaccination to young women (9–14 years of age) demonstrate a general high acceptance,[36–45] even in countries where premarital sexual intercourse is associated with negative repercussions.[46] This suggests that a high compliance rate may be achieved. Modelling and cost-effectiveness studies are continuing to conclude on inclusion of prophylactic HPV vaccination in the national immunisation programme.[47–51]

Catch-up vaccination of 15- to 18-year-old women

Catch-up vaccination involves vaccination of individuals who would have been vaccinated routinely if the vaccination programme had been introduced some years earlier. Catch-up vaccination of women slightly older than the optimal target age, i.e. those of 15–18 years, at start of a routine vaccination programme for 9- to 14-year-old girls, could accelerate the impact of the vaccination programme and increase vaccination benefits at short term. However, it will clearly increase the costs of the vaccination programme and will likely only be cost-effective if vaccination will be given in the far majority of women before the peak risk of HPV infection and as such will be dependent on country-specific factors.

Women aged over 18 years

Within the setting of organised cervical screening programmes, the decision to prophylactically vaccinate older, sexually active women is likely to remain an individual choice. To conclude on the benefits of vaccination for women after sexarche, more clinical trial data on the efficacy and (cost-) effectiveness are required. In studies of women aged 26–55 years, antibody levels induced by the prophylactic vaccine were much higher than after natural infection, although lower than in young women.[52] The level of protection afforded by prophylactic HPV vaccination in this older age group is still unknown. A proportion of women after sexarche, i.e. up to 25% of women aged 18–25 years versus 5–10% of women older than 26 years, depending on geographic region and HPV detection assay used, is HPV DNA positive. Approximately 50% of these cases involve HPV16 and/or HPV18 in the respective age categories.[53–56] Thus, a potential benefit of prophylactic vaccination exists for more than 90–95% of women older than 18 years, depending on geographic region. Nevertheless, prophylactic vaccination so far has shown

a rather low real life efficacy. In an intention-to-treat analysis in the Future II study, vaccination reduced the incidence of HPV16/18-related CIN2/3 or AIS by 44% (95% CI 31–55) and that of CIN2/3 or AIS overall, irrespective of HPV type, by only 18% (95% CI 7–29).[16,17] Because currently, no contra-indications for prophylactic HPV vaccination have been recognised, prophylactic vaccination for any woman after sexarche could be applied, taken into consideration the possibility of pre-existing precancer lesions that should be diagnosed and treated according to standard regimen(s). Continued active follow up of women who are infected with HPV at time of vaccination or who were previously exposed to HPV is necessary to elucidate potential benefits prophylactic vaccination may confer to them. More research data need to be collected to allow determining correlates of vaccine efficacy in these women, which may include the viral load at time of vaccination.

Male vaccination

Evidence to date suggests safety and immunogenicity of HPV vaccines in men (10–15 years of age) as well.[20] The EMEA license for the quadrivalent vaccine includes both sexes. However, formal proof for efficacy of male prophylactic HPV vaccination awaits results from continuing trials in men. Theoretically, benefit of male vaccination includes a decrease in HPV infections and HPV16/18-associated (pre)malignant lesions and HPV6/11-associated anogenital warts (for the quadrivalent vaccine) in men. Additionally, male vaccination could be important for the development of HPV immunity in the population and the reduction of HPV transmission to women. The potential effects require confirmation by pending large phase IV trials. Nonetheless, routine prophylactic vaccination of men is rather unlikely to be cost-effective as the burden of HPV-associated disease, except for anogenital warts, in men is rather small. Models have shown that once vaccine coverage in both women and men exceeds 50%, the benefit of vaccination of men in addition to women is marginal and decreases further with increase in coverage.[57] Selective vaccination of 'high-risk' populations, e.g. men having sex with men, seems more likely to be (cost-)effective, thought rather impracticable.

The effects of prophylactic HPV vaccination on public health

To reach a maximum preventive effect at the population level, prophylactic HPV vaccination should be delivered before the first exposure to the virus, thus in prepubertal women before the sexual debut, and coverage should be high (preferably >90%). Health authorities in several European Union countries have decided to include prophylactic HPV vaccination in the routine schedules. The exact cohort (age category) selected for prophylactic vaccination in each country

varies marginally depending on the logistics, organisation of education, and health service structure available for vaccine delivery as well as cost-benefit analyses adapted to the national situation. Yet, the primary target group in all countries are girls of an age before sexual activity becomes common, i.e. aiming more than 95% of the target group to be sexual naïve.

The impact of catch-up vaccination on public health is hard to predict and will highly depend on coverage as well as target age. It is expected that catch-up vaccination will accelerate the vaccination programme's impact in reduction of disease burden, while not changing the efficacy of the vaccination programme on the long term (i.e. when all birth cohorts have experienced routine prepubertal prophylactic vaccination).

In the scenario of nationwide prepubertal prophylactic vaccination with complete coverage using currently available HPV vaccines (i.e. vaccine efficacy against HPV16/18 of >90% and cross-protection against related types of at maximum approximately 60%) and assuming a protective effect of at least 15–20 years, the following public health effects may be envisioned:

Expected clinical effects of nationwide prepubertal prophylactic HPV vaccination

A reduction of premalignant cervical lesions induced by HPV16/18 (and related types) could be envisaged within 5–7 years following prophylactic vaccination, i.e. ≤40% of LSIL/CIN1, 50–60% of HSIL/CIN2/3, and ≥90% of AIS. So far, efficacy of prophylactic vaccination has been reported for the intermediate end-points of cervical cancer, i.e. CIN2/3 and AIS, because cancer development as end-point takes more than 10–20 years.[25] It may be expected that the maximum effect of current HPV vaccines on the long term (15–20 years) would be a reduction of 75–80% of cervical cancers (approximately 76% of squamous cell carcinomas, approximately 90% of adenocarcinomas).[2,58–61] The highest impact of prophylactic vaccination will be encountered on prevention of cervical high-grade cervical lesions and cancer in younger women (<25–35 years of age), who are either not yet targeted by current screening programmes or within the first screening rounds. Of note, prophylactic HPV vaccination might be particularly effective in preventing adenocarcinomas,[61] as these are often missed by current cervical screening. Additionally, HPV-VLP vaccines may reduce the incidence of other anogenital intraepithelial neoplasia as well as genital warts (those induced by HPV6 and HPV11, and only in case of the quadrivalent vaccine). Furthermore, a decrease in the incidence of other malignancies associated with the HPV types targeted by the vaccines might be envisaged. Finally, it should be realised that by preventing persistent HPV infection and disease, it is likely that prophylactic vaccination will reduce the transmission of vaccine-covered HPV types ('herd-immunity'), although this still requires empirical evidence. If HPV transmission is reduced by prophylactic vaccination, the benefit of vaccination would go beyond vaccine recipients, providing indirect protection to unvaccinated persons as well.

Expected effects of nationwide prepubertal prophylactic HPV vaccination on the medical system

With respect to cervical lesions, the effects of prophylactic vaccination (just) before sexarche on the medical system will be a marked decrease in cytological follow-up examinations, gynaecological referrals for colposcopy, cervical biopsies, and surgical procedures. Due to prophylactic vaccination, women will also encounter less anxiety and less short-term and long-term complications due to treatment. Moreover, vaccines will reduce morbidity due to other HPV-associated disease, such as genital warts in case of vaccination with the quadrivalent vaccine.

Importantly, vaccine effects will also be noticed in women who are not vaccinated due to 'herd-immunity' as well as in those who are not willing to attend the cervical screening programme, under the assumption that they agreed to and received prophylactic vaccination at young age. These so-called nonresponders currently comprise up to 50% of the screening population in Europe,[62–66] and in this population, more than 50% of cervical cancer cases are detected.[66–70] It will be crucial to target these nonresponders and other subgroups within the population that are less likely to access medical services to maximise the public heath benefit of prophylactic vaccination in European countries.

Expected impact of nationwide prepubertal prophylactic HPV vaccination on cervical screening

Screening at older age (≥30 years) will still remain important to protect vaccinated women against cervical cancer caused by non-HPV16/18 high-risk HPV types and to ensure protection of nonvaccinated women. With respect to maximal public health effect of prophylactic vaccination, it is important that vaccinated women understand their need to comply with screening after prophylactic vaccination and to continue protecting themselves against STIs. National authorities should continue their efforts to provide a well-organised and a high-quality population-based screening programme with a high coverage as well as an adequate treatment of precancerous lesions detected. The ultimate goal is to achieve synergy between prophylactic vaccination and screening in a cost-effective manner with maximum benefit for the women. An important question is how prophylactic HPV vaccination could complement existing screening strategies while remaining cost-effective overall. It should be realised that to date high-quality cervical screening yields around 80% protection

against ≥CIN3 lesions, suggesting screening at older age to be preferred over prophylactic vaccination since the latter only reached protection levels of about 18% (95% CI 7–29) in these older women.[16,17,71,72] In countries with limited or no cervical screening, the benefits of prophylactic vaccination for older, sexually active women may be more prominent.

In countries with cervical screening, the screening algorithm will be subject to alterations as a consequence of the implementation of prophylactic HPV vaccination.[73] Prophylactic HPV16/18 vaccination will lower the probability of high-grade lesions after a positive screening result, which argues for modification of the screening system including an increased screening interval. HPV testing by use of clinically validated assays has proven to increase the effectiveness of cervical screening.[54,74–77] Recent follow-up data on longitudinal population-based randomised controlled trials have indicated that HPV testing using hybrid capture 2 or GP5 + 6+- PCR assays in comparison with cytology leads to earlier detection of high-grade CIN lesions or cervical cancer, thereby permitting longer screening intervals.[78–80] Based on these findings, strategies for implementation of HPV testing in cervical screening programmes (e.g. in conjunction with cytology or as primary screening tool with or without cytology as follow-up test) and their consequences for the medical system [among others (a.o.) colposcopy referral rate] are further evaluated in cost-effectiveness studies.

To become cost-effective, it is likely that the combination of prophylactic HPV vaccination at young age (9–14 years) and screening at older age necessitates both prolonged screening intervals and low-cost, high compliance screening protocols (e.g. self-sampling of cervicovaginal specimens), both of which can be accomplished effectively by means of primary HPV testing using clinically validated assays. Assuming a protective effect of prophylactic HPV vaccination of at least 15–20 years, nationwide prepubertal vaccination may allow an onset of the cervical screening programme at the age of 30 years, which has proven effective practice in the Netherlands.[78] Constraint of cervical screening below the age of 30 years is of advantage with respect to most optimal specificity of HPV testing over the age of 30 years.[81]

HPV type replacement and/or escape mutants due to nationwide prepubertal prophylactic HPV vaccination

Despite the fact that phenomena like type replacement (i.e. replacement in the population of vaccine types by existing types not targeted by the vaccines) and emergence of escape mutants (i.e. vaccine-resistant mutant variants/subtypes) following prophylactic HPV16/18 vaccination seem highly unlikely for HPV based on current virological knowledge (e.g. low mutation rate),[82] post-vaccination type-specific surveillance of the vaccinated and nonvaccinated populations by HPV genotyping assays is relevant to fully exclude this pos-

sibility. It should be realised that when type replacement and/or emergence of escape mutants would occur, the full potential of prophylactic HPV vaccination to protect against cervical cancer will never be realised by targeting only a part of all hrHPV types.

Conclusions and recommendations

In view of optimal prevention and control of cervical cancer within the next decades, an integrated vaccination-screening approach is recommended, aiming to protect both vaccinated and nonvaccinated women. Such a comprehensive programme of cervical cancer control should include prophylactic vaccination of HPV naïves at young age (9–14 years), and cervical screening of older, vaccinated and nonvaccinated women (≥30 years). Catch-up vaccination (15- to 18-year-old women) might be applied initially after introduction of routine vaccination for 9- to 14-year-old girls, aiming to accelerate short-term efficacy of the vaccination programme. Prophylactic HPV vaccination of older women after sexarche (older than 18–26 years) will remain an individual decision.[72] Currently, there is no evidence to extend HPV vaccination to men. These recommendations are in agreement with position statement on HPV vaccination of worldwide gynaecology societies and immunisation advisory boards (a.o. organisations such as the European Society of Gynaecological Oncology, UK Joint Committee of Vaccination and Immunisation, UK Royal College of Obstetricians and Gynaecologists, US Advisory Committee on Immunization Practices, the Society of Gynaecologic Oncologists, the American College of Obstetricians and Gynecologists, the Canadian National Advisory Committee on Immunization, the Royal Australian and New Zealand College of Obstetricians and Gynecologists).

With respect to cost-effectiveness of the integrated approach, modifications of the screening system are required, including the use of a clinically validated HPV detection assay as primary screening tool with potential of cytology as triage test, omission of screening for women younger than 30 years of age, an increase of the screening interval, and low-cost, high-compliance screening protocols like self-sampling of cervicovaginal specimens. Only when after several decades prophylactic HPV vaccination has proven long-term efficacy in women, and broader vaccine efficacy (i.e. vaccines that cover the complete range of oncogenic HPV types) has been generated, changes in practice standard and guidelines towards 'vaccination only' may be considered for effective prevention of cervical cancer.

Contribution to authorship

All authors meet the criteria to qualify for authorship, including substantial contribution to conception and design,

interpretation of data, drafting and revision of the manuscript, and approved the final version of the manuscript. ∎

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