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Original Research

Human papillomavirus vaccination: The ESGO–EFC position paper of the European society of Gynaecologic Oncology and the European Federation for colposcopy

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Abstract Vaccines against human papillomavirus (HPV) are available in Europe since 2006. They have been highly effective in preventing infection and disease caused by the vaccine types. Clinical efficacy data are available for cervical, vulvovaginal and anal precancer and invasive cervical cancer. Disease reduction is best with early vaccination and a coverage of more than 70%. Gender-neutral vaccination provides direct protection for all men and improves the coverage. A good coverage is followed by herd protection of the unvaccinated men and women. School-based programs appear to be most effective; under the age of 15 years, two doses with an interval of 6–12 months are sufficient. From the age of 15 years, the standard regimen with three doses is recommended. A broad catch-up program for young

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Prevention

adult women and men improves the effectiveness. The vaccines are also effective in sexually active women and men with previous but cleared infections. Vaccination in addition to local treatment of HPV-related disease appears to reduce recurrent or subsequent HPV-related disease. Combination of HPV vaccination and screening with HPV testing is the most effective approach to prevention of cervical cancer. The screening intervals may increase in the vaccinated cohorts. The upper age limit for vaccination remains to be evaluated, is country specific and depends on cost-effectiveness. The European Society of Gynaecologic Oncology and the European Federation for Colposcopy strongly support gender-neutral vaccination programs for children and young adolescents, with a catch-up program for young adults.
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1. Introduction

Since the licensure of the first-generation human papillomavirus (HPV) vaccines in 2006, primary prevention of the majority of cervical cancer cases is possible. Meanwhile, we are aware that a substantial fraction of vulvar and vaginal cancers, most anal cancers and possibly other neoplasms affecting women and men such as oral cancers can be prevented. The first generation of HPV vaccines included the quadrivalent HPV 6/11/16/18 vaccine (Gardasil, MSD) and the bivalent HPV 16/18 vaccine (Cervarix, GSK). From 2015, the second-generation vaccine, the ninevalent HPV 6/11/16/18/31/33/45/52/58 vaccine (Gardasil 9, MSD) was licensed in Europe [1].

More than 50,000 new cases of HPV-related cancers including 35,000 cervical cancers and 10,000 vulvar and vaginal cancers are caused by HPV in Europe. In Europe, HPV 16 causes 66% of invasive cervical cancer and more than 70% of other HPV-related cancers, followed by HPV 18 and 33 [2]. With the second-generation vaccines, almost 90% of these cases are potentially preventable. In addition, there is an estimate of 280,000–540,000 precancerous genital lesions; more than 80% of these are preventable with the HPV vaccines [3–5].

2. Trial results

For all three available vaccines, extensive phase III trials have been performed, including more than 70.000 study participants across all trials. All three vaccines demonstrated a robust clinical efficacy that exceeded 95% against disease related to the vaccine types in subjects not infected with the analysed vaccine type at the time of vaccination [1]. This has been demonstrated for the cervical and vulvovaginal disease in phase III efficacy studies conducted in young women aged 15 to 26 years. In a substudy of young men aged 16 to 26 years, the observed efficacy against anal disease was 75% for the vaccine types [6]. The clinical efficacy was demonstrated also in women aged from 15 to 45 years [7]; immunogenicity was evaluated in girls and boys from the age of 9 years and for adult women up to the age of 55 years [8]. Based on these data, all three vaccines are licensed by European Medicines Agency (EMA) for girls and boys from the age of 9 years without any upper age limit.

3. Real-world experience

From the first-generation HPV vaccines, extensive data on the population-based effect are available for various countries. Some of the countries with good coverage are Australia and, in Europe, Denmark, Portugal and the United Kingdom (UK), whereas coverage remains unacceptably low in some European countries and low-resource settings [9]. Within only three years after the implementation of the vaccination program with the quadrivalent vaccine, Australian data reported a reduction in cervical high-grade squamous intraepithelial lesions (HSILs) by half in young women [10], whereas in Denmark, a reduction of up to 81% was observed in young women with the same vaccine [11]. Vaccination with the bivalent vaccine in the UK reduced HPV 16/18 prevalence by 82%, and for non-vaccine types, HPV 31/33/45 prevalence was reduced by 49% [12]. Cervical HSIL was reduced by 88% [13] in Scotland with the bivalent vaccine;the HPV 16/18 prevalence was reduced by 89%, and for non-vaccine types, HPV 31/33/45 prevalence was reduced by 85% in those girls vaccinated at the age of 12–13 years [14]. The data on the reduction of infection and disease caused by the HPV vaccine types are robust and consistent, although the effect on non-vaccine types appears to be less durable and data far less consistent [15]. The prevention of preinvasive lesions has additional benefits as it minimises the reproductive morbidity caused by local treatment for HSIL [16,17]. A combined analysis of clinical studies in Finland in a total of 190,000 follow-up years is reported on the impact of vaccination on invasive cancer [18]. Data reported diagnosis of 10 HPV-related cancers, including eight cases of invasive cervical cancer, all

observed in the unvaccinated cohorts, not a single case in those being HPV vaccinated during one of these trials. In the US (quadrivalent vaccine), a significant decrease in the incidence of cervical cancer among young women after the introduction of HPV vaccine was observed [19]. Australia projected that cervical cancer may be eliminated as a public health problem within the next 20 years [20].

The side-effects of the licensed HPV vaccines are comparable with those of others. These include predominantly local reactions, which depend on the quantity of antigen and adjuvants, and some, mostly mild or moderate, systemic effects [21,22]. The Global Advisory Committee on Vaccine Safety GACVS of the World Health Organisation (WHO) classified these vaccines as 'extremely safe', this is seconded by the statements of many national agencies such as the EMA and Centers for Disease Control and Prevention (CDC).

Advanced economic modelling from 17 studies across 26 countries reported large between-country disparities, while the vaccine is highly cost-effective in almost all countries and particularly low-resource settings [23]. Countries likely to benefit the most because of lack of organised screening and high disease burden are those that have yet to introduce nationwide vaccination programmes.

4. Who should be vaccinated?

Current national vaccination programs aim girls, and in a growing number of countries (Austria, Croatia, Czech Republic, Denmark, Finland, Germany, Italy, Norway, Slovakia, Switzerland, and UK in Europe; the US, Canada, New Zealand and Australia outside Europe) also boys, before the onset of puberty. A few more countries have a recommendation but no funding for boys. The vaccine is licensed from the age of 9 years. On a population level, HPV vaccination is most effective when vaccination is administered early in life and should be given as early as possible in agreement with national guidelines and programs. This gives the optimal immunologic response and decreases the likelihood of HPV positivity at the time of vaccination.

Vaccination in older age groups can also offer some protection against HPV-related disease. The vaccines have been demonstrated to prevent new infections and disease up to the age of 45 years [7]. In Australia, it has been demonstrated that a catch-up program up to the age of 26 years makes the effects of a vaccination program visible earlier than a program just aiming at the primary target population of prepubertal girls aged 11–13 years. Studies have also shown that this is cost-effective, although this rapidly declines beyond the age of 25 years [24]. The use of the vaccine in older women can also be beneficial at an individual level, but a catch-up program for older women when compared with HPV-based primary screening does not appear to have favourable cost-effectiveness profile for population-based vaccination in developed countries [25].

5. Universal HPV vaccination and herd protection

Although cervical cancer is the most important HPV-related neoplasm globally, other malignancies have been causally associated with HPV. HPV-related oropharyngeal and anal cancer is on the rise, predominately in men. For vaccination programs aiming solely at girls, the protection of men is dependent on the vaccination status of their female partners, and they leave men who have sex with men unprotected. For this reason, Austria, the US, Australia, recently Germany, the UK and other countries have implemented gender-neutral vaccination. Vaccination of men not only protects them directly from HPV-related cancers but also reduces circulation of the virus from unvaccinated cohorts and therefore expedites benefits to women, through a process known as herd protection. Furthermore, in countries with a suboptimal coverage in women that does not exceed 70%, the impact from vaccination with lower coverage can be improved by gender-neutral vaccination immediately, as shown by Lehtinen *et al.* [26] in a community-based randomised controlled trial (RCT) from Finland. In addition, the resilience of a vaccination program is improved by a gender-neutral approach [27]. An important role of the current prevention campaigns is to educate and counsel mothers to give the next generation a better protection, regardless of the sex.

The feasibility of a gender-neutral vaccination program depends on the local resources but should be the preferred concept. The cost-effectiveness of vaccination of prepubertal boys appears to be dependent on the coverage of girls in individual countries and settings [28].

6. Women with HPV-related disease and prior local treatment

The vaccines are also effective in sexually active women and men with previous but cleared infections. The analysis of data from a subset of 2617 women from 3 clinical studies who were HPV seropositive but DNA negative found that no subject receiving HPV 6/11/16/18 vaccine developed disease to a type included in the vaccine to which they were seropositive and DNA negative at enrolment as opposed to 7 cases of cervical disease and 8 cases of external genital disease related to a vaccine HPV type they had previously encountered in the placebo group [29]. These data suggested that although the vaccine confers protection from reinfection or reactivation, natural immunity from induced antibodies does not protect over time.

The efficacy and cost-effectiveness of vaccination after local conservative treatment for cervical

intra-epithelial neoplasia: a randomised controlled trial; the NOVEL trial will start recruitment in 2019. Women after local treatment remain a high-risk group who are in need of risk-reducing adjuvant treatments as the recurrence rate for high-grade preinvasive disease can be as high as 5–10%, while the risk of invasive cervical cancer in these women remains two- to four-fold higher than that in the general population. These women who develop CIN in the first place constitute a subgroup of the infected women who are particularly sensitive to the infection and as a result rapidly acquire reinfections after treatment. Secondary analyses of the phase III RCTs and retrospective studies provide indirect evidence that after treatment for HPV-related disease, and mainly after treatment for cervical HSIL, the onset of new cervical or other HPV-related disease can be substantially reduced by HPV vaccination [30–33]. Because these patients have an increased risk for other HPV-related disease and cancer [34], vaccination can be offered on an individual basis.

7. Setting

It appears that school-based programs or other well-organised public health structures are most effective and ensure equity and hence far superior to opportunistic vaccination [35]. As school-based vaccination may not be feasible in every country, the decision on the setting that could optimise coverage should be in line with the local infrastructure and resources. Funding is crucial to implement nationwide vaccination.

8. Dosage

Early vaccination provides a superior immune response, and it has been shown that 2 doses in 9- to 13-year-old children elicited even higher antibody levels than 3 doses in young adults [36]. The WHO recommends this practice for those younger than 15 years. It is important that the interval between the 2 doses must be 6–12 months. If the second dose is given within 4 months or less from the first dose, there is no difference in the antibody response to that of a single dose. One-dose regimes are under investigation but cannot be recommended at present.

Long-term follow-up data from the randomised trials report high antibody titres and clinical efficacy 12 years after vaccination [37]. To date, there is no evidence to support the need for a booster, although protection may be lifelong.

The protection against HPV 16/18–related disease is crucial as these two subtypes cause the highest burden of the disease. For those already vaccinated with a first-generation HPV vaccine, routine 'revaccination' with the ninevalent HPV vaccine is possible. To achieve the full protection against the five (or seven) new HPV types, a full course of 3 doses (2 doses for those younger than 15 years) has to be applied [38]. Although such a practice on an individual basis is possible, the balance of cost and effectiveness does not permit recommendation of vaccination in population-based programs.

9. HPV-FASTER: combined strategies of HPV vaccination and HPV screening

HPV screening and vaccination are complementary preventive options often implemented as separate and non-coordinated programs. The HPV-FASTER protocol aims to address this disconnect by combining both strategies with the ultimate purpose of accelerating the reduction of cervical cancer incidence and mortality [39].

Vaccination can offer protection to women without a current infection or disease, irrespective of previous viral exposure, and among those currently infected, vaccination can protect against further infections and reinfection with the same HPV type. Importantly, no safety concerns were reported for women who were HPV positive and received three doses of HPV vaccine. In accordance with these findings, the proposal of the HPV-FASTER protocol is to offer HPV vaccination to women in a broad age range of 9–45 years, irrespective of HPV infection status. Women older than 25/30 years would, in addition to the vaccination, be screened using a validated HPV test as part of their initial visit. Indeed, with adequate follow-up of women who test positive for HPV at presentation for vaccination, subsequent lifetime risk of cervical cancer should be very low, tending to zero. A major benefit from the HPV-FASTER protocols is that the predicted subsequent needs for screening may be dramatically reduced to one/two per lifetime, thus increasing sustainability and compliance as well as alleviation of the burden and workload at the health centres, typically overloaded already with patient care.

10. Conclusion

With the introduction of HPV vaccination and the increased accuracy of HPV testing in primary screening, there is the potential to almost eliminate cervical cancer. Furthermore, the vaccines can further substantially reduce the burden of preinvasive disease and other HPV-related cancers, such as anal, oropharyngeal, vulvar and vaginal cancer, with further benefits. In contrast to the cervix, no screening is available for these sites. The infrastructure required for national vaccination is far more easily implemented than national call and recall screening programs, with high coverage making prevention more accessible in low-income settings. The available vaccines have excellent safety profiles, while population-based data from vaccinated cohorts in the real world outside clinical trials have proven that the vaccines are highly effective in the real

world, especially in those countries with a good coverage.

The European Society of Gynecologic Oncology (ESGO) supports vaccination programs for children and young adolescents, with a catch-up program for young adults, if feasible, and also vaccination on an individual basis. Gender-neutral vaccination improves the protection of women and men, while it maximises benefits from vaccination at lower coverage. Individuals with a history of infection or previous treatment of HPV-related disease may also get a benefit from vaccination. The ESGO and the European Federation for Colposcopy are committed to provide appropriate information and education for women, not only in their role as patients but also even more importantly in their role as mothers of the next generation.

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Conflict of interest

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