European Journal of Cancer 116 (2019) 21–26

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

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

Elmar A. Joura [a,b], Maria Kyrgiou [c,d,*], Francisco X. Bosch [e,f,g], Vesna Kesic [h], Pekka Niemenen [i], Charles WE. Redman [j], Murat Gultekin [k]

[a] *Medical University of Vienna, Department of Gynecology and Gynecologic Oncology, Austria*
[b] *Comprehensive Cancer Center (CCC) Vienna, Austria*
[c] *Department of Surgery and Cancer, Institute of Reproductive and Developmental Biology, Faculty of Medicine, Imperial College London, W12 0NN, UK*
[d] *West London Gynaecological Cancer Centre, Queen Charlotte's and Chelsea – Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, W12 0HS, UK*
[e] *Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO), Barcelona, Spain*
[f] *Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain*
[g] *Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain*
[h] *Clinic of Obstetrics and Gynecology, University of Belgrade, Serbia*
[i] *Department Obstetrics & Gynecology, Helsinki University Hospital and Helsinki University, Finland*
[j] *University Hospitals of North Midlands NHS Trust, Royal Stoke Hospital, Stoke-on-Trent, UK*
[k] *Division of Gynaecological Oncology, Department of Obstetrics and Gynaecology, Hacettepe University Faculty of Medicine, Ankara, Turkey*

Received 3 February 2019; received in revised form 31 March 2019; accepted 10 April 2019
Available online 1 June 2019

KEYWORDS
HPV;
Vaccination;
Cervical cancer;
Immunity;
CIN;
Cervical intraepithelial neoplasia;

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

* *Corresponding author*: Department of Surgery & Cancer, Hammersmith Campus, Imperial College, 3rd Floor, Du Cane Road, W12 0NN, London, UK.
E-mail address: m.kyrgiou@imperial.ac.uk (M. Kyrgiou).

https://doi.org/10.1016/j.ejca.2019.04.032

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.

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.

Funding source

There was no funding.

Conflict of interest

E.A.J. received institutional research and educational support from MSD and personal support from MSD for travelling and speaking at medical symposiums; F.X.B. has received institutional research and educational support from GSK and MSD and personal support from MSD for travelling and speaking at medical symposiums; M.G. has received personal support from MSD for travelling and speaking at medical symposiums; M.K. has received institutional research and educational support from MSD and personal support from MSD for travelling and speaking at medical symposiums; C.W.E.R., P.N. and V.K. report no conflict of interest.

References

[1] Pils S, Joura EA. From the monovalent to the nine-valent HPV vaccine. Clin Microbiol Infect 2015;21:827–33.
[2] de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol 2010;11:1048–56.
[3] Hartwig S, Baldauf JJ, Dominiak-Felden G, et al. Estimation of the epidemiological burden of HPV-related anogenital cancers, precancerous lesions, and genital warts in women and men in Europe: potential additional benefit of a nine-valent second generation HPP vaccine compared to first generation HPV vaccines. Papillomavirus Res 2015;1:90–100.
[4] Joura EA, Ault KA, Bosch FX, Brown D, Cuzick J, Ferris D, et al. Attribution of 12 high-risk human papillomavirus genotypes to infection and cervical disease. Cancer Epidemiol Biomark Prev 2014;23:1997–2008.
[5] Garland SM, Joura EA, Ault KA, Bosch FX, Brown DR, Castellsague X, et al. Human papillomavirus genotypes from vaginal and vulvar intraepithelial neoplasia in females 15-26 Years of age. Obstet Gynecol 2018;132:261–70.
[6] Palefsky JM, Giuliano AR, Goldstone S, Moreira Jr ED, Aranda C, Jessen H, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med 2011; 365:1576–85.
[7] Castellsague X, Munoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Canc 2011;105:28–37.
[8] Schwarz TF, Galaj A, Spaczynski M, Wysocki J, Kaufmann AM, Poncelet S, et al. Ten-year immune persistence and safety of the HPV-16/18 AS04-adjuvanted vaccine in females vaccinated at 15-55 years of age. Canc Med 2017;6:2723–31.
[9] Garland SM, Kjaer SK, Munoz N, Block SL, Brown DR, DiNubile MJ, et al. Impact and effectiveness of the quadrivalent human papillomavirus vaccine: a systematic review of 10 Years of real-world experience. Clin Infect Dis 2016;63:519–27.
[10] Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet 2011;377:2085–92.
[11] Baldur-Felskov B, Dehlendorff C, Munk C, Kjaer SK. Early impact of human papillomavirus vaccination on cervical neoplasia–nationwide follow-up of young Danish women. J Natl Cancer Inst 2014;106:djt460.
[12] Mesher D, Panwar K, Thomas SL, Edmundson C, Choi YH, Beddows S, et al. The impact of the national HPV vaccination program in england using the bivalent HPV vaccine: surveillance of type-specific HPV in young females, 2010-2016. J Infect Dis 2018;218:911–21.
[13] Palmer T, Wallace L, Pollock KG, Cuschieri K, Robertson C, Kavanagh K, Cruickshank M, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. BMJ 2019 Apr 3; 365:l1161. https://doi.org/10.1136/bmj.l1161.
[14] Kavanagh K, Pollock KG, Cuschieri K, Palmer T, Cameron RL, Watt C, et al. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. Lancet Infect Dis 2017;17:1293–302.
[15] Drolet M, Benard E, Boily MC, Ali H, Baandrup L, Bauer H, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2015;15:565–80.
[16] Kyrgiou M, Athanasiou A, Paraskevaidi M, Mitra A, Kalliala I, Martin-Hirsch P, et al. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. BMJ 2016;354:i3633.
[17] Kyrgiou M, Mitra A, Arbyn M, Stasinou SM, Martin-Hirsch P, Bennett P, et al. Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis. BMJ 2014;349:g6192.
[18] Luostarinen T, Apter D, Dillner J, Eriksson T, Harjula K, Natunen K, et al. Vaccination protects against invasive HPV-associated cancers. Int J Cancer 2018;142:2186–7.
[19] Guo F, Cofie LE, Berenson AB. Cervical cancer incidence in young U.S. Females after human papillomavirus vaccine introduction. Am J Prev Med 2018;55:197–204.
[20] Hall MT, Simms KT, Lew JB, Smith MA, Brotherton JM, Saville M, et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study. Lancet Public Health 2019;4:e19–26.
[21] Vichnin M, Bonanni P, Klein NP, Garland SM, Block SL, Kjaer SK, et al. An overview of quadrivalent human papillomavirus vaccine safety: 2006 to 2015. Pediatr Infect Dis J 2015;34: 983–91.
[22] Moreira ED, Block SL, Ferris D, Giiulino AR, Iversen OE, Joura EA, et al. Safety profile of the 9-Valent HPV vaccine: a

combined analysis of 7 Phase III clinical trials. Pediatrics 2016; 138. e20154387.
[23] Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. Lancet Glob Health 2014;2:e406–14.
[24] Westra TA, Rozenbaum MH, Rogoza RM, Nijman HW, Daemen T, Postma MJ, et al. Until which age should women be vaccinated against HPV infection? Recommendation based on cost-effectiveness analyses. J Infect Dis 2011;204:377–84.
[25] Kim JJ, Ortendahl J, Goldie SJ. Cost-effectiveness of human papillomavirus vaccination and cervical cancer screening in women older than 30 years in the United States. Ann Intern Med 2009;151:538–45.
[26] Lehtinen M, Baussano I, Paavonen J, Vänskä S, Dillner J. Eradication of human papillomavirus and elimination of HPV-related diseases - scientific basis for global public health policies. Expert Rev Vaccines 2019;18:153–60.
[27] Elfström KM, Lazzarato F, Franceschi S, Dillner J, Baussano I. Human papillomavirus vaccination of boys and extended catch-up vaccination: effects on the resilience of programs. J Infect Dis 2016;213:199–205.
[28] Damm O, Horn J, Mikolajczyk RT, Kretzschmar MEE, Kaufmann AM, Delere Y, et al. Cost-effectiveness of human papillomavirus vaccination in Germany. Cost Eff Resour Allocation 2017;15:18.
[29] Olsson SE, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. Hum Vaccine 2009;5:696–704.
[30] Joura EA, Garland SM, Paavonen J, Ferris DG, Perez G, Ault KA, et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. BMJ 2012;344:e1401.
[31] Garland SM, Paavonen J, Jaisamrarn U, Naud P, Salmeron J, Chow SN, et al. Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: post-hoc analysis from a randomized controlled trial. Int J Cancer 2016; 139:2812–26.
[32] Kang WD, Choi HS, Kim SM. 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)? Gynecol Oncol 2013;130: 264–8.
[33] Ghelardi A, Parazzini F, Martella F, Pieralli A, Bay P, Tonetti A, et al. SPERANZA project: HPV vaccination after treatment for CIN2. Gynecol Oncol 2018;151:229–34.
[34] Ebisch RMF, Rutten DWE, IntHout J, Melchers WJG, Massuger L, Bulten J, et al. Long-lasting increased risk of human papillomavirus-related carcinomas and premalignancies after cervical intraepithelial neoplasia grade 3: a population-based cohort study. J Clin Oncol 2017;35:2542–50.
[35] Wang J, Ploner A, Sparén P, Lepp T, Roth A, Arnheim-Dahlström L, et al. Mode of HPVvaccination delivery and equity in vaccine uptake: a nationwide cohort study. Prev Med 2019;120: 26–33.
[36] https://www.who.int/immunization/diseases/hpv/en/.
[37] Kjaer SK, Nygard M, Dillner J, Brooke Marshall J, Radley D, Li M, et al. A 12-year follow-up on the long-term effectiveness of the quadrivalent human papillomavirus vaccine in 4 nordic countries. Clin Infect Dis 2018;66:339–45.
[38] Van Damme P, Bonanni P, Bosch FX, Joura E, Kjaer SK, Meijer CJ, et al. Use of the nonavalent HPV vaccine in individuals previously fully or partially vaccinated with bivalent or quadrivalent HPV vaccines. Vaccine 2016;34:757–61.
[39] Bosch FX, Robles C, Diaz M, Arbyn M, Baussano I, Clavel C, et al. HPV-FASTER: broadening the scope for prevention of HPV-related cancer. Nat Rev Clin Oncol 2016;13:119–32.