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Review Article

Preventive vaccination against cervical cancer: Korean Society of Gynecologic Oncology Guideline

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ABSTRACT

After human papillomavirus (HPV) vaccine guidelines published by Korean Society of Gynecologic Oncology (KSGO) in 2011, new studies have been published, leading to additional data regarding efficacy, safety, number of vaccination rounds, and ideal age of vaccine administration. We searched and reviewed the literatures focused on the efficacy of 2-dose schedule vaccination, the efficacy of 3-dose schedule vaccination in middle-aged women, the ideal age of 3-dose schedule vaccination, the safety of HPV preventive vaccine, and the ability of cross-protection of each HPV preventive vaccine. The KSGO has revised the previous guideline based on the results of the above studies.

Keywords: Human Papillomavirus Vaccine; Uterine Cervical Neoplasms

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No potential conflict of interest relevant to this article was reported.

Summary of clinical guideline for cervical cancer preventive vaccination, version 3.0

1. Key question 1: Is the 2-dose schedule of human papillomavirus (HPV) preventive vaccine effective?
   - The 2-dose schedule of the quadrivalent HPV preventive vaccine is considered as effective as the 3-dose schedule when administered to girls aged 9 to 13 years and can be implemented (1B).
   - The 2-dose schedule of the bivalent HPV preventive vaccine is considered as effective as the 3-dose schedule when administered to girls aged 9 to 14 years and can be implemented (1B).
   - Based on immunogenicity and sexual behavior research, we recommend optimal vaccination age as 11 to 12 years old in a 2-dose schedule (1E).

2. Key question 2: Is the 3-dose schedule of HPV preventive vaccine effective in middle-aged women?
   - The 3-dose schedule of the quadrivalent HPV preventive vaccine has a preventive effect in middle-aged women (27 to 45 years); before vaccination, a clinical assessment of individual patient risk and state of inoculation should be performed (2B).
   - The 3-dose schedule of the bivalent HPV preventive vaccine has a preventive effect in middle-aged women (26 to 45 years); before vaccination, a clinical assessment of individual patient risk and state of inoculation should be performed (2B).

3. Key question 3: At what age should the 3-dose schedule of HPV preventive vaccine be administered?
   - The quadrivalent HPV preventive vaccine should be administered to 9- to 26-year-old females (1A).
   - The bivalent HPV preventive vaccine should be administered to 9- to 25-year-old females (1A).
   - Based on studied ages, previous guideline, and ages recommended by the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE), we recommend that the optimal vaccination age range of the 3-dose schedule is 15 to 17 years (1E).

4. Key question 4: Is the HPV preventive vaccine safe?
   - We do not recommend vaccination in pregnant women (1E).
   - The HPV preventive vaccine can be administered to breastfeeding women (1A).
   - The safety of the 2-dose schedule of HPV preventive vaccine does not differ significantly from that of the 3-dose schedule of HPV preventive vaccine (1A).

5. Key question 5: Does the HPV preventive vaccine provide cross-protection against HPV types not included in the vaccine?
   - The quadrivalent HPV preventive vaccine provides cross-protection against HPV type 31, which is not included in the vaccine (A).
   - The bivalent HPV preventive vaccine provides cross-protection against HPV types 31, 33, and 45, which are not included in the vaccine (A).

INTRODUCTION

Human papillomavirus (HPV) is a common infection in sexually active women [1]. Of the approximately 40 types of HPV that infect the female genitalia, 15 are described as oncogenic or high-risk with regard to invasive cervical cancer (ICC) and other cancers of

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the female genitalia [2]. The majority of infections are known to recede within 2 years, but continuous infection for >2 years by oncogenic HPV types is a major cause of ICC and precancerous cervical lesions [2]. HPV 16 and HPV 18 are the most widespread types, causing approximately 70% of cases of ICC worldwide and 50% of cases of cervical intraepithelial neoplasia (CIN) 2/3 [3,4]. Additionally, HPV 16, 18, 45, 31, 33, 52, and 58 account for approximately 90% of all cases of invasive ICC, while HPV 16 and 18 cause 40% to 50% of vulvar cancer and 70% of vaginal cancer cases.

Adenocarcinoma within the cervical canal often goes undiagnosed by screening and has a high relapse rate and poor prognosis. In South Korea, although screening has helped greatly with the early diagnosis of squamous cell carcinoma and resulted in a decreasing incidence of invasive squamous cell carcinoma, the incidence of uterine cervical adenocarcinoma has not declined. Meanwhile, in low-risk HPV, HPV 6 and 11 cause 90% of cases of genital warts, 10% of cases of low-grade CIN, and 100% of cases of recurrent respiratory papillomatosis.

Since the Korean Society of Gynecologic Oncology (KSGO) revised clinical guideline for the HPV vaccine in 2011 [5,6], new studies have been published, leading to additional data regarding efficacy, safety, number of vaccination rounds, and ideal age of vaccine administration. The KSGO has revised the previous guideline accordingly.

MECHANISMS OF ACTION OF THE HPV VACCINE

1. Quadrivalent HPV vaccine (Gardasil)

Gardasil (Merck Sharp & Dohme Co., Kenilworth, NJ, USA) is an inactivated recombinant quadrivalent vaccine made from virus-like particles (VLPs) manufactured using the L1 protein from HPV types 6, 11, 16, and 18 [7]. Because VLPs do not contain viral DNA, they are unable to infect cells or reproduce and thus cannot cause disease. In non-clinical trials, L1 VLP vaccine efficacy resulted from the humoral immune response.

2. Bivalent HPV vaccine (Cervarix)

Cervarix (GlaxoSmithKline Biologicals, Brentford, UK) is a genetic recombinant vaccine made from VLPs manufactured using the L1 major capsid protein from HPV types 16 and 18 [8]. Because VLPs do not contain viral DNA, they cannot infect cells or proliferate. In animal experiments, L1 VLP vaccine efficacy resulted from the humoral immune response and cell-mediated immunity. Exudation of anti-HPV immunoglobulin G (IgG) from the serum to the cervical mucosa seems to be a basic defense mechanism against continual infection by oncogenic HPV, a major cause of ICC [9].

NEW EVIDENCE REGARDING THE HPV VACCINE

1. Key question 1: Is the 2-dose schedule of HPV preventive vaccine effective?

1) Quadrivalent HPV vaccine (Gardasil)

In a randomized clinical trial comparing immunogenicity and antibody response in girls aged 9 to 13 years and young women aged 16 to 26 years [10], girls who received the 2-dose vaccine showed 2.07-fold (95% CI, 1.62 to 2.65) and 1.76-fold (95% CI, 1.41 to 2.19) higher

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geometric mean antibody titer (GMT) for HPV 16 and 18, respectively, compared to young women who received the 3-dose vaccine. The ratios of the GMT for 3-dose vaccination against 2-dose vaccination in the girl group were 0.95 (95% CI, 0.73 to 1.23) and 0.68 (95% CI, 0.54 to 0.85) for HPV 16 and 18, respectively, indicating that the antibody titers of the 2-dose vaccination are not lower than those of the 3-dose vaccination. In addition, an investigation of immunogenicity by Hernandez-Avila et al. [11] found similar efficacy between 2- and 3-dose vaccination in a group of 9- to 10-year-old girls at 21 months after inoculation.

The level of evidence for the efficacy of 2-dose vaccination with the quadrivalent vaccine was deemed MODERATE, because indirectness was considered serious with the use of GMTs to determine efficiency.

2) Bivalent HPV vaccine (Cervarix)

For 2-dose vaccination with the bivalent vaccine, two papers from a randomized clinical trial were used as evidence [12,13]. The trial was a partially blinded but randomized clinical trial in healthy girls and young women 9 to 25 years of age. The subjects were divided into 9- to 14-year-olds, 15- to 19-year-olds, and 20- to 25-year-olds. The 9- to 14-year-olds were given 2-dose vaccination, while the 15- to 25-year-olds were given 3-dose vaccination. Comparative immunogenicity and safety were evaluated with follow-up until 24 and 48 months after vaccination, respectively. HPV 16 and 18 antibody titers in the 9- to 14-year-old group were higher than antibody titers in the 15- to 25-year-old group and remained higher at 24, 36, and 48 months after vaccination. Antibody responses to HPV 16, 18, 31, and 45 were similar in both groups, but titers for HPV 16 and 18 were higher than those in cases of natural infection.

The level of evidence for the efficacy of 2-dose vaccination with the bivalent vaccine is deemed MODERATE, because indirectness was considered serious with the use of GMTs to determine the efficacy of the vaccine.

HPV vaccine administration to 9- to 13-year-olds is safe and effective, the immune response is good, and the preventive efficacy persists long-term. In South Korean girls, the mean age of first sexual activity is 12.8 years [14], and the risk of HPV infection increases immediately thereafter. According to the standard vaccination timetable from the Centers for Disease Control and Prevention, a hospital visit is scheduled at 11 to 12 years of age. Hence, the committee recommends 11 to 12 years as the optimal vaccination age for 2-dose HPV vaccination.

Based on the above results, the recommendations for two-round vaccination are as follows.

- The 2-dose schedule of the quadrivalent HPV preventive vaccine is considered as effective as the 3-dose schedule when administered to girls aged 9 to 13 years and can be implemented (1B).
- The 2-dose schedule of the bivalent HPV preventive vaccine is considered as effective as the 3-dose schedule when administered to girls aged 9 to 14 years and can be implemented (1B).
- Based on immunogenicity and sexual behavior research, we recommend optimal vaccination at 11 to 12 years of age with a 2-dose schedule (1E).

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2. Key question 2: Is the 3-dose schedule of HPV preventive vaccine effective in middle-aged women?

1) Quadrivalent HPV vaccine (Gardasil)

Three studies have investigated the quadrivalent vaccine in middle-aged women [15-17], including a multi-institution, randomized, double-blinded study evaluating safety, immunogenicity, and efficacy in 24- to 45-year-old females and a long-term observational study of the same subjects. Therefore, these studies were considered as a single randomized clinical trial and a single observational study, respectively. Using interim analysis of the mean follow-up period of 2.2 years, the vaccine efficacy for the per-protocol population was 90.5% (95% CI, 73.7 to 97.5) against HPV types 6, 11, 16, and 18 (prevention of infection or disease related to each HPV type) and 83.1% (95% CI, 50.6 to 95.8) for HPV 16 and 18 alone. When the intention-to-treat population was analyzed, vaccine efficacy against the four types of HPV was 30.9% (95% CI, 11.1 to 46.5), while that against HPV 16 and 18 alone was 22.6% (95% CI, –2.9 to 41.9).

When these subjects had completed ≥4 years of follow-up, the disease prevention efficacy against the four types of HPV was 88.7% (95% CI, 78.1 to 94.8). Among women who were vaccinated at least once and were judged not to have been infected by any of the four HPV types, vaccine efficacy was 66.9% (95% CI, 4.3 to 90.6). At 48 months after the first inoculation, the serum antibody positive rates for HPV 6, 11, 16, and 18 were 91.5%, 92.0%, 97.4%, and 47.9%, respectively, and no serious vaccine-related adverse effects were observed.

After 6 years, the per-protocol population of the same women showed no CIN or endocervical glandular lesions related to HPV types 6, 11, 16, or 18, and immunogenicity was maintained for the four HPV types. The level of evidence for the efficacy of 3-dose quadrivalent HPV vaccination in middle-aged women was deemed MODERATE.

2) Bivalent HPV vaccine (Cervarix)

One randomized clinical trial [18] and three observational studies [9,19,20] have examined bivalent vaccine in middle-aged women. The randomized clinical trial aimed to test vaccine efficacy in women aged >25 years in groups of 26- to 35-year-olds, 36- to 45-year-olds, and 46- to 55-year olds. The preventive effect against persistent infection of HPV 16 or 18 for at least 6 months or against CIN 1 was significant at 81.1% (97.7% CI, 52.1 to 94.0) across all age groups, 83.5% (45.0 to 96.8) in the 26- to 35-year-old group, and 77.2% (2.8 to 96.9) in the 36- to 45-year-old group. No related cases were observed in the 46- to 55-year-old group, which included comparatively few participants; therefore, the committee considered these data insufficient to verify the vaccine's efficacy.

The three observational studies evaluated the maintenance of immunogenicity and vaccine safety for up to 10 years after the first inoculation in 15- to 55-year-old female subjects. Blood tests performed in the first month after full inoculation showed a serum antibody response in 100% of cases, and the IgG titers for HPV 16 and 18 in vaginal secretions and serum were highly correlated irrespective of age group. In serum antibody tests conducted 48 months after the inoculation course, antibodies against HPV 16 were detected in 100% of subjects, and antibodies against HPV 18 were detected in 99.4% of subjects. In addition, in all age groups, the antibody titer was highest at the first month after the inoculation course before continually decreasing toward a plateau. However, the antibody titer remained 11 times

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higher for HPV 16 and 5 times higher for HPV 18 than that observed after natural infection in the 46- to 55-year-old group. After continued observation of these patients, all were positive for HPV 16 antibodies 6 years after the first inoculation, and >97% were positive for HPV 18 antibodies. In addition, all age groups showed an antibody titer 9.3 to 45.1 times higher than natural infection for HPV 16 and 4.3 to 19.4 times higher for HPV 18.

The level of evidence for the efficacy of the 3-dose bivalent HPV vaccine in middle-aged women was deemed MODERATE because indirectness was considered serious with the use of GMTs to determine vaccine efficacy in the three observational studies.

Using the above results, the followings are recommended for use of the HPV vaccine in middle-aged women.

- The 3-dose schedule of the quadrivalent HPV preventive vaccine has a preventive effect in middle-aged women (27 to 45 years); before vaccination, a clinical assessment of individual patient risk and state of inoculation should be performed (2B).
- The 3-dose schedule of the bivalent HPV preventive vaccine has a preventive effect in middle-aged women (26 to 45 years); before vaccination, a clinical assessment of individual patient risk and state of inoculation should be performed (2B).

3. Key question 3: At what age should the 3-dose schedule of HPV preventive vaccine be administered?

1) Quadrivalent HPV vaccine (Gardasil)

In terms of studies of the quadrivalent vaccine, a total of 13 randomized, comparative clinical trials conducted in females of 9 to 26 years of age were found and used as evidence [4,21-32]. The efficacy of the quadrivalent vaccine preventing HPV 16-related CIN 2/3 was 100% [21,25,27]. In addition, the antibody ratio against HPV 18 was approximately 60-fold higher than in naturally infected women [22]. Persistent infection or disease related to HPV types 6, 11, 16, and 18, which are included in the quadrivalent vaccine, were reduced by 90% (95% CI, 71 to 97) compared to females who were inoculated with a placebo [23]. Five-year follow-up observations showed a 96% reduction and a vaccine efficacy of 100% [26] with a high efficacy and stable antibody concentration being maintained for at least 5 years [28]. Moreover, an integration of two randomized comparative clinical trials with a mean follow-up of 3.6 years showed that, in female subjects not infected with 14 types of HPV, the quadrivalent vaccine prevented 100% of HPV 16- and 18-related high-grade cervical, vulvar, and vaginal lesions cases as well as 100% of HPV 6- and 11-related genital warts cases [30]. In a study of 9- to 15-year-old girls, the antibody titer was 1.7 to 2.7 times higher than in young women 16 to 23 years of age, and serum tests after 18 months showed an antibody-positive rate of 91.5% [24,29]. According to a randomized comparative clinical trial from Korea, the level of antibodies against viruses included in the vaccine was slightly higher at 7 months in youths 9 to 15 years of age [31]. Another study on subjects of the same age group reported that antibodies against virus types included in the quadrivalent vaccine were maintained up to 96 months; of 429 subjects inoculated with the quadrivalent vaccine at an average age of 12 years, none showed disease or persistent infection for >12 months in relation to the quadrivalent antibodies [32].

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Based on nine papers describing randomized clinical trials in 16- to 26-year-old women and four papers on randomized comparative clinical trials in 9- to 15-year-old girls, the level of evidence for this key question for the quadrivalent vaccine was deemed HIGH. However, it should be noted that the studies of 9- to 15-year-old girls were based on immunogenicity.

2) Bivalent HPV vaccine (Cervarix)

In terms of studies investigating the efficacy of the bivalent vaccine, there have been eight randomized comparative clinical trials and three observational studies [9,19,20,33-40]. The female subjects in these studies were 9 to 25 years old, and the preventive effect against HPV 16- and 18-related CIN 2+ was 100% after a mean follow-up of 9.4 years. Moreover, in all studies, the preventive effect against CIN 3 and HPV infection was higher in women who had not been infected by oncogenic HPV compared to women with a history of sexual contact or who had been infected with oncogenic HPV. These studies demonstrate that the optimal age to implement 3-dose vaccination with the bivalent vaccine is 9 to 25 years, before sexual contact occurs. However, it should be noted that studies of 9- to 14-year-old girls were based on immunogenicity. The quality of evidence was deemed HIGH.

Among studies of 3-dose HPV vaccination, none had performed a comparative analysis between age groups to identify optimal vaccination age. Hence, clinical guideline for cervical cancer preventive vaccination developed by the Korean Society of Gynecological Oncology in 2011 and the recommended age of the World Health Organization (WHO) Strategic Advisory Group of Experts in Immunology (SAGE) were accepted [5,6,41].

Based on the above results, the followings are recommended with regard to targets for HPV vaccination.

- The quadrivalent HPV preventive vaccine should be administered to 9- to 26-year-old females (1A).
- The bivalent HPV preventive vaccine should be administered to 9- to 25-year-old females (1A).
- Based on studied ages, previous guideline, and ages recommended by the WHO SAGE, we recommend that the optimal vaccination age for the 3-dose schedule is 15 to 17 years (1E).

4. Key question 4: Is the HPV preventive vaccine safe?

1) Quadrivalent HPV vaccine (Gardasil)

Safety of the HPV vaccine was determined according to vaccine type and number of doses. First, according to a study by Block et al. [24], when 3-dose vaccination with the quadrivalent HPV vaccine was administered to girls and boys 10 to 15 years of age, the severity of adverse effects at the injection site was moderate or low in 97% of subjects. In addition, 5 days after injection, the proportion of patients with a fever >37.8°C was 13.8% for males and 12.8% for females, which was higher than the 7.3% for 16- to 23-year-old females. However, mild fever <39°C was observed in 96.4% of subjects. The safety of 3-dose vaccination with the quadrivalent vaccine in 24- to 45-year-old women was confirmed from the results of three randomized comparative clinical trials [15-17]. These studies were long-term follow-up observational studies in the same group of women, and a median follow-up period of 6.26 years for severe vaccine-related adverse effects was unprecedented. According to

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a study by Ferris et al. [32], when 3-dose HPV vaccination with the quadrivalent vaccine was implemented in 9- to 15-year-olds with no sexual experience, there were no prior reports of severe adverse effects in boys or girls after 8 years of follow-up. The safety of 3-dose quadrivalent HPV vaccination in 16- to 26-year-old women was confirmed in three randomized comparative clinical trials; although the rate of adverse effects near the vaccine injection site was significantly high, there was no difference in systemic adverse effects [23,27,29]. Since the findings of this key question could be suitably evaluated based on the evidence for Key Question 3, it was not separately recommended.

2) Bivalent HPV vaccine (Cervarix)

For 3-dose vaccination with the bivalent vaccine in females 9 to 25 years of age, safety was confirmed in six randomized comparative clinical trials [33,34,36-39]. After a mean long-term follow-up of 9.4 years, symptoms at the site of the infection were significantly higher than in the placebo group, but there were no differences in other systemic adverse effects, chronic diseases, or autoimmune diseases. For 3-dose bivalent vaccination in female subjects 15 to 55 years of age, vaccine-related adverse effects consisted of only one report of optic neuritis when patients were monitored for up to 6 years after the first inoculation [20]. Three-dose bivalent vaccination for women aged ≥25 years was verified in a single, randomized study [18]. Adverse effects at the site of injection, such as pain and swelling, were significantly higher in the vaccination group. Although adverse effects were reported in 10% of the vaccination group and 9% of the placebo group, <1% of these adverse effects were considered vaccine-related, and all were concluded irrelevant to mortality. Since the findings of this key question can be suitably evaluated based on the evidence for Key Question 3, it was not separately recommended.

3) Special situations

To date, in phase 3 clinical trials, the vaccination group has shown no statistically significant differences from the placebo group in pregnancy/childbirth-related data, such as newborn survival rate, congenital birth defects rate, delivery type (vaginal or cesarean), miscarriage, stillbirth rates, or ectopic pregnancy rates. No intervention is required when the vaccine is administered during pregnancy. However, since studies of the impact of the vaccine on pregnancy are currently limited, HPV vaccination during pregnancy is not recommended.

The effects of the quadrivalent vaccine on breastfeeding were confirmed through the studies of Paavonen et al. [36] and Garland et al. [42]. Compared to the placebo group, the quadrivalent vaccine group showed no differences in survival at birth, congenital defects, cesarean delivery, vaginal delivery, miscarriage, or ectopic pregnancy. There was also no significant difference in newborn health when the quadrivalent vaccine was administered during breastfeeding.

The safety of 2-dose vaccination was confirmed by two randomized comparative clinical trials [13,43]. These two studies compared safety when administering the same vaccine in 2 or 3 doses and concluded that there was no significant difference in safety between the 2- and 3-dose schedules for both the quadrivalent and bivalent vaccines. The quality of this evidence was judged as HIGH.

In an observational study by Scheller et al. [44] investigating 3,983,824 women inoculated with the HPV vaccine, the vaccine did not increase the incidence of multiple sclerosis or

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other demyelinating diseases of the central nervous system. Moreover, according to an observational study by Ojha et al. [45] analyzing data registered with the United States Vaccine Adverse Event Reporting System, 14,822 adverse events were reported, and 4,670 were associated with the quadrivalent vaccine. However, there was no significant difference in the risk of Guillain-Barre syndrome compared with other vaccines [45]. There has been no reported evidence of an association or correlation between HPV vaccination and incidence of neurological or venothrombotic diseases [43,46]. According to a study by Leung et al. [43], in 0.8% of their 2-dose bivalent vaccination and 2-dose quadrivalent groups, immune disease was potentially related to the HPV vaccine. However, the study design included patients who received the HPV vaccine as the control group to verify the incidence of disease rather than patients who had received a different vaccine. In the study of L. Grimaldi-Bensouda et al. [47], although it was a case-control study, there was no evidence of autoimmune diseases following vaccination with Gardasil; therefore, HPV vaccination cannot be concluded to show an association with autoimmune disease compared to other vaccines.

Complex regional pain syndrome has a very low incidence; therefore, there have been no prospective studies to determine a causal relationship with HPV vaccination. Hence, based on a review of previous statements by the WHO Global Advisory Committee on Vaccine Safety [48], recommendations of the European Medicines Agency Pharmacovigilance Risk Assessment Committee [49], and statements by International Federation of Gynecology and Obstetrics [50] and the Australian Therapeutic Goods Administration [51], HPV vaccination has no causal association with complex regional pain syndrome. Complex regional pain syndrome may be induced by pain occurring in the course of the immune response rather than from the vaccine itself.

Through the above results, the followings are recommended with regard to targets for HPV vaccination.

- We do not recommend vaccination in pregnant women (1E).
- The HPV preventive vaccine can be administered to breastfeeding women (1A).
- The safety of the 2-dose schedule of HPV preventive vaccine does not differ significantly from that of the 3-dose schedule (1A).

5. Key question 5: Does the HPV preventive vaccine provide cross-protection against HPV types not included in the vaccine?

Three randomized comparative clinical trials confirmed the cross-protective effects of the quadrivalent vaccine [4,27,30]. The efficacy of reducing cervical lesions was 18% to 20% irrespective of HPV type, and specific analysis found a 19% reduction in high-grade lesions, a 50.7% reduction in vulvar and vaginal lesions, a 62% reduction in genital warts, an 11.3% reduction in cervical epithelial cell abnormalities, and a 23.0% reduction in uterine cervical treatment. The cross-protective effects of the bivalent vaccine were verified using five randomized comparative clinical trials [18,36-38,52]. Irrespective of HPV type, the effectiveness of the vaccine in preventing moderate CIN or more severe lesions was 70.2% in female patients who had not been infected with oncogenic HPV prior to sexual contact and 30.4% in all vaccinated female patients. In another study, the preventive effect of the vaccine was 71.9%, while a long-term follow-up study analyzed female patients without

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sexual contact and found an efficacy of 93.2% for preventing CIN 2+. In addition, the vaccine efficacy against 6-month persistent infection by HPV 31 was 79.1%, while that against HPV 45 was 76.9%, indicating a cross-protective effect against HPV types not included in the bivalent vaccine. The efficacy of preventing CIN 2+ associated with 12 types of HPV not included in the bivalent vaccine was 54.0%.

According to a meta-analysis investigating the cross-protective effects against HPV types 31, 33, 25, 52, and 58, which are not included in the vaccines, the quadrivalent vaccine had a preventive effect against persistent infection by HPV 31, while the bivalent vaccine had a preventive effect against persistent infection by HPV 31, 33, and 45 as well as CIN 2+ [53]. Furthermore, a study of 12- to 15-year-old girls also demonstrated a persistently high concentration of cross-neutralizing antibodies against HPV types not included in the bivalent or quadrivalent vaccines. However, according to the reported results, there are slight differences in HPV types for which a cross-protective effect has been observed, and the effects of the bivalent vaccine against persistent infection by types 31 and 45 decreased over time. Hence, additional results need to be reported to make a clear conclusion about the cross-protective effects of the two vaccines.

Based on the above results, the followings are recommended in relation to the cross-protective effects of the HPV vaccine against HPV types not included in the vaccine.
One of the opinions presented at the public hearing was that this key question and its recommendations were based on those for Key Questions 1 and 2 recommending vaccination with the HPV vaccine. Thus, the recommendation grade was meaningless, and it would be more appropriate to indicate only the evidence grade. This suggestion has been reflected below, with only the evidence grade displayed.

- The quadrivalent HPV vaccine provides cross-protection against HPV type 31, which is not included in the vaccine (A).
- The bivalent HPV vaccine provides cross-protection against HPV types 31, 33, and 45, which are not included in the vaccine (A).

DISCUSSION

When the 2-dose HPV vaccine was administered to girls, immunogenicity testing showed that more than two-fold higher GMT was maintained compared to 3-dose vaccination [10,12,13]. Moreover, when the efficacy of 2-dose vaccination was compared with that of 3-dose vaccination in the same population of girls, statistically similar GMTs were maintained [10,12,13]. Although these was a randomized comparative clinical trial that intended to verify the efficacy of 2-dose vaccination in 9- to 14-year-old girls, the study was based on immunogenicity. Therefore, future prospective studies are needed that confirm the incidence of CIN or ICC after 2-dose vaccination in this age group.

With regard to HPV vaccine safety, observational studies and randomized clinical trials showed no association with incidence of multiple sclerosis or other demyelinating diseases of the central nervous system, Guillain-Barre syndrome, neurological disease, venothrombotic disease, or autoimmune disease [43-46]. Moreover, although there have been no prospective

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studies to identify the causal relationship between complex regional pain syndrome and HPV vaccine, it is believed that cases to date occurred not because of a problem with the vaccine itself, but as the result of pain caused by the immune response.

These guidelines have been reviewed and compiled based on papers published up to early 2015 and will require revision if additional studies of the bivalent or quadrivalent vaccine are published or if the nonavalent HPV vaccine currently used in the United States and other foreign countries is introduced in South Korea.

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