

Practice Guideline



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Updated clinical practice guidelines for human papillomavirus vaccination: the Korean Society of Gynecologic Oncology recommendations

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ABSTRACT

The Korean Society of Gynecologic Oncology (KSGO) first developed clinical guidelines for the appropriate administration of human papillomavirus (HPV) vaccines tailored to the Korean context in 2016. In 2019, additional guidelines were introduced following the development of the nonavalent HPV vaccine. The 2021 revision included recommendations for vaccination in middle-aged women and men, as well as the potential benefits of vaccination following conization. In this latest revision, the guidelines focus on the necessity of HPV vaccination in middle-aged men, the Society's position on the single-dose schedule recently recommended by the World Health Organization to expand global vaccine coverage, recommendations regarding additional 9-valent vaccination for those previously vaccinated with bivalent or quadrivalent vaccines, and updated scientific evidence supporting the two-dose schedule for adolescents aged 9 to 14 years.

Keywords: Human Papillomavirus; Vaccination; Prevention; Cervical Cancer; Cervical Intraepithelial Neoplasia

INTRODUCTION

Cervical cancer ranks as the fourth most common cancer among women globally. In 2022 alone, 661,021 new cases were diagnosed, and 348,189 women died from the disease [1]. While the widespread implementation of human papillomavirus (HPV) vaccination and cervical cancer screening has led to a decline in incidence over the past 30 years, cervical cancer remains the most prevalent gynecologic malignancy, particularly in developing countries [2].

High-risk human papillomaviruses (HR-HPVs) are the main cause of cervical cancer, with about 90% of cases diagnosed as HPV-related. HPV is the most prevalent sexually transmitted

Conflict of Interest

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

Author Contributions

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infection worldwide, and around 70% of women experience HPV infection more than once in their lifetime. Although most HPV infections resolve spontaneously, persistent infection can lead to the development of cervical precancerous lesions and, eventually, cervical cancer [3]. Moreover, HPV is also associated with other malignancies—including vaginal, vulvar, penile, anal and oropharyngeal cancers—as well as genital warts in both women and men. As a result, the importance of preventive vaccination against HPV is increasingly emphasized for both sexes to reduce the burden of HPV-related disease [4].

The Korean Society of Gynecologic Oncology (KSGO) revised its clinical guidelines for cervical cancer prevention vaccines in 2011, 2016, and 2021 [5-8]. Following the introduction of the nonavalent vaccine in Korea, specific recommendations for its use were issued in 2019 [9]. In 2021, these recommendations were further expanded to include middle-aged women [8]. In line with these academic recommendations, the HPV vaccination rate among the target population has gradually increased. Since 2016, the HPV vaccine has been included in the National Immunization Program (NIP) through the “Healthy Women First Step Clinic” initiative, targeting girls aged 12 to 13. However, despite the increasing vaccination rate, Korea has not yet achieved the World Health Organization (WHO)’s goal for cervical cancer elimination. In contrast, Australia—through active vaccination policies for both males and females and the early implementation of a NIP—is expected to become the first country to eliminate cervical cancer by 2028. In alignment with global strategies for cervical cancer prevention, Korea has recognized the need for more proactive domestic efforts and has revised its guidelines accordingly.

Five key questions (KQs) were summarized (Table 1), and summary of the revisions to the HPV vaccination recommendations since the 2021 version is provided in Data S1.

Table 1. Five key questions and recommendations updated in guidelines for HPV vaccination

#	Item	Detail
KQ1	Key question Recommendation	What are the recommended age and number of doses for the HPV vaccination? - The bivalent HPV vaccine is recommended for females aged 9 to 45 years (IA) and males aged 9 to 25 years (IIC). - The quadrivalent and nonavalent HPV vaccines are recommended for females aged 9 to 45 years and males aged 9 to 26 years (girls and women aged 9–26 years, IA; women aged 27–45 years, IIB; and boys and men aged 9–26 years, IA). However, males aged 27 to 45 years may also receive the vaccine after consulting with a healthcare provider. - The bivalent, quadrivalent, and nonavalent HPV vaccines can be administered in two doses to boys and girls aged 9 to 14 years, with a 6-month interval between the doses (IB).
KQ2	Key question Recommendation	Single-dose HPV vaccination for ages 9 to 14, which has been recommended by WHO, is it feasible? Since there is insufficient evidence on the safety and efficacy to introduce it, the 2-dose vaccination schedule will be maintained until clear evidence on the effectiveness of a single dose is accumulated.
KQ3	Key question Recommendation	Is HPV vaccination effective in individuals who are already infected with HPV? Administration of the bivalent, quadrivalent, or nonavalent HPV vaccines is recommended for women already infected with HPV, as it can reduce the risk of infection with HPV subtypes they have not yet contracted (IIB).
KQ4	Key question Recommendation	Does HPV vaccination influence preventing the recurrence of HPV-related diseases in patients who have undergone conization? Administration of the bivalent, quadrivalent, or nonavalent HPV vaccines is recommended for women who have undergone conization, as it can prevent infection with the relevant HPV subtypes and reduce the risk of recurrence of HPV-related diseases (IB).
KQ5	Key question Recommendation	Is additional vaccination with the nonavalent HPV vaccine beneficial with respect to recurrence of related diseases for women who have already completed vaccination with the bivalent or quadrivalent HPV vaccine? Additional vaccination with the nonavalent human HPV vaccine is recommended, as it can reduce the risk of infection from additional HPV subtypes (IIB).

HPV, human papillomavirus; KQ, key question; WHO, World Health Organization.

MATERIALS AND METHODS

1. Strategy for developing recommendations on HPV preventive vaccination

Following the development of recommendations on HPV in 2021, a new WHO position paper released in December 2022 provided updated guidance on the number of doses required for the bivalent, quadrivalent, and nonavalent HPV vaccines in individuals under 14 years of age, as well as on revaccination with the nonavalent vaccine for those previously immunized with the bivalent or quadrivalent vaccines. In response, the current national recommendations have been revised to incorporate the latest evidence regarding all three HPV vaccines. The scope and KQs guiding the update were established through a series of committee meetings. These questions focused on evaluating the effectiveness of 2-dose vaccination schedules, assessing cross-protection against non-vaccine HPV types, and examining vaccine effectiveness in middle-aged women and men.

2. Strategy for literature search

To search for the most recent updates, search strategies were constructed based on the Patient/Problem, Intervention, Comparison, Outcomes framework for each KQ. Searches were conducted in Ovid-MEDLINE, Ovid-EMBASE, and the Cochrane Library. The retrieved articles were independently screened for inclusion or exclusion by two reviewers per article, according to the selection and exclusion criteria for all KQs. In the first phase, titles and abstracts were reviewed for selection or exclusion, and any article selected by at least 1 reviewer proceeded to full-text review. In the second phase, full texts were reviewed by the committee members for inclusion or exclusion.

3. Quality assessment of literature

For the selected studies, randomized controlled trials were assessed using the Cochrane Risk of Bias tool, while non-randomized clinical trials and observational studies were evaluated using the Newcastle-Ottawa Quality Assessment Scale Cohort Studies. The quality assessment was conducted independently by 2 reviewers, and any discrepancies in the quality ratings were resolved through consensus between the 2 reviewers.

4. Summary of evidence and data extraction

For the final set of selected studies, 2 working-level committee members independently extracted relevant data using a predefined data extraction form. For each KQ, the level of evidence and grade of recommendation were determined according to the criteria outlined in **Table 2**. In situations where the evidence was insufficient or conflicting, all guideline committee members participated in structured discussions followed by voting to reach consensus on the final recommendations. For KQs lacking adequate evidence to establish a definitive recommendation at this stage (KQ2), we did not propose a specific recommendation. Instead, we identified the current knowledge gaps and emphasized the need for further well-designed studies to strengthen the evidence base.

CLINICAL CONSIDERATIONS AND RECOMMENDATIONS

1. KQ1: What are the recommended age and number of doses for the HPV vaccination?

The KSGO recommended in 2016 that the appropriate age for 3 doses of the HPV vaccine is 9–26 years for females receiving the quadrivalent vaccine and 9–25 years for females receiving

Table 2. Level of evidence and grades of recommendation

Variables	Description
Levels of evidence	
I	Evidence from at least one large, randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without a control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages, optional
D	Moderate evidence against efficacy or for adverse outcomes, generally not recommended
E	Strong evidence against efficacy or for adverse outcomes, never recommended

This table adapted from the Infectious Diseases Society of America—United States Public Health Service Grading System (reprinted by permission of Oxford University Press on behalf of the Infectious Diseases Society of America).

the bivalent vaccine [7]. In 2019, it was recommended that the appropriate age for 3 doses of the nonavalent vaccine is 9–26 years for females [9]. In 2021, this recommendation was expanded to include females aged 9–45 years and males aged 9–26 years. This guideline investigates the necessity of vaccination in middle-aged men and the effectiveness of the 2-dose regimen in females and males aged 9–14 years.

Bivalent and quadrivalent vaccines

In a clinical trial published in 2009, the quadrivalent HPV vaccine was administered to women aged 24–45 years. The prevention rate of infections or diseases related to HPV types 6, 11, 16, and 18 was found to be 90.5% (95% confidence interval [CI]=73.7%–97.5%), and the prevention rate specifically for HPV types 16 and 18-related diseases was 83.1% (95% CI=50.6%–95.8%) [10]. Forty-eight months after the first vaccine dose, the seropositivity rates for HPV types 6, 11, 16, and 18 were 91.5%, 92.0%, 97.4%, and 47.9%, respectively, with no serious adverse effects observed [10,11]. A long-term follow-up study of 1,610 participants over approximately 10 years confirmed sustained protective effects against HPV 6, 11, 16, and 18-related diseases in women aged 27–45 years for up to 10 years (median, 8.9 years), with antibody responses also maintained over the 10-year period [12]. In studies on the number of doses, antibody responses in girls aged 9–13 years who received 2 doses of the quadrivalent vaccine were found to be non-inferior to those in women aged 16–26 years who received the proven three-dose regimen [13].

In a serological study conducted 10 years after administration of the quadrivalent HPV vaccine in males aged 9–15, 89.96% were observed to be seropositive for HPV types 6, 11, and 16. Antibody titers were found to be 16%–42% higher in males aged 9–12 compared to those aged 13–15 [14]. In males aged 16–26, the per-protocol analysis showed a reduction in the incidence of anal intraepithelial neoplasia grades 2 and 3, and condyloma acuminata (genital warts) related to HPV types 6, 11, 16, and 18 by 74.9% (95% CI=8.8%–95.4%) and 90.4% (95% CI=69.2%–98.1%), respectively, with no serious adverse effects related to the vaccine [14–16]. Additionally, in males aged 9–45, one month after receiving three doses of the vaccine, 100% showed antibody formation against all four HPV types [17]. Based on these findings, an indication for the prevention of anal cancer was added in 2017.

In women aged 26–55 who received three doses of the bivalent HPV vaccine, the effectiveness of preventing 6-month persistent infection or mild cervical intraepithelial neoplasia

(CIN) associated with HPV types 16 and 18 was analyzed by age group. The results showed significant effectiveness in the 26–35 age group at 83.5% (95% CI=45.0%–96.8%) and in the 36–45 age group at 77.2% (95% CI=2.8%–96.9%). However, no significant effect was observed in the 46–55 age group [18].

In addition, antibody titers and the duration of antibody persistence against HPV types 16 and 18 were found to decrease in women aged 27–35 and 36–45 compared to those aged 18–26 [19]. Multiple studies reported no serious adverse events or safety concerns. In studies on the number of doses, when comparing girls aged 9–14 who received two doses of the bivalent HPV vaccine with individuals aged 15–25 who received three doses, the antibody response in the 9–14 age group was not inferior [20]. Among males aged 10–18 who received the bivalent vaccine, 100% were seropositive for HPV antibodies seven months after vaccination, and no serious adverse effects were reported [21].

Although the roles of the bivalent and quadrivalent HPV vaccines are diminishing globally—including in Korea—due to the development and commercialization of the nonavalent vaccine, maintaining current recommendations remains necessary, as these vaccines are still utilized within the NIP in Korea. The bivalent vaccine has currently been excluded from the NIP, and its continued commercialization will need to be monitored. Any future revisions to the recommendations should take this into account. Based on the above research findings, vaccination with the bivalent and quadrivalent HPV vaccines is recommended as follows.

- The bivalent HPV vaccine is recommended for females aged 9–45 years (IA) and males aged 9–25 years (IIC).
- The quadrivalent HPV vaccine is recommended for females aged 9–45 years and males aged 9–26 years (Females and males aged 9–26 [IA]; females aged 27–45 [IIIB]).
- For both the bivalent and quadrivalent vaccines, two doses are recommended for individuals aged 9–14 years, with a minimum interval of 6 months between doses. For those aged 15 and older, three doses are recommended as before (IB).

Nonavalent vaccine

The immunogenicity and safety of the nonavalent HPV vaccine were evaluated in women aged 16–45. At 7 months after vaccination, antibody titers against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in women aged 27–45 were not inferior to those in women aged 16–26, with ratios ranging from 0.60 to 0.67. Additionally, the seropositivity rate for all HPV types in women aged 27–45 was over 99%, and no serious adverse events related to the vaccine were reported [22].

A study was conducted to demonstrate the immunogenicity and safety of the 9-valent HPV vaccine in young men aged 16–26 by comparing the results with those of young women in the same age group. The study included 1,106 heterosexual men (HM), 313 men who have sex with men (MSM), and 1,101 young women who had not yet received HPV vaccination. The geometric mean antibody titers against the nine HPV types in HM were not inferior to those in women, whereas in MSM, the titers were lower than those in both HM and women [23]. In terms of safety, no serious vaccine-related adverse events were reported in either men or women.

Additionally, a modeling study on the timing of HPV infection in adults showed that 25% of women are infected with HR-HPV types at age 35 or older, and 29% of men are infected

between the ages of 27 and 45 [24,25]. Therefore, to prevent the transmission of HPV-related diseases, active HPV vaccination is strongly recommended for both adult men and women.

However, unlike the safety evidence from Western countries for middle-aged men, the quadrivalent and nonavalent vaccines have not yet been approved domestically. Therefore, vaccination for men aged 27 and older may be considered only after thorough consultation with healthcare professionals regarding future risk of HPV exposure based on sexual activity, potential benefits despite reduced efficacy, the current lack of sufficient evidence in this age group, and cost and safety considerations.

In studies related to the number of vaccine doses, HPV antibody tests conducted 4 weeks after the last dose in girls aged 9–14 who received 2 doses at either 0 and 6 months or 0 and 12 months showed that antibody titers were not inferior to those in the 3-dose group. Notably, the 0 and 12-month 2-dose group exhibited higher antibody titers against eight HPV types—except for HPV type 45—compared to the 0 and 6-month 2-dose group. Therefore, vaccinating before the age of 14 is economically advantageous as it reduces the costs associated with completing the vaccination series and is more effective by providing protection before HPV infection occurs [26].

Based on the above research findings, the recommendations were determined as follows.

- The nonavalent HPV vaccine is recommended for females aged 9–45 years and males aged 9–26 years (females and males aged 9–26 [IA]; females aged 27–45 [IIIB]). However, for males aged 27 and older, vaccination may be considered following thorough consultation with healthcare professionals.
- Two doses are recommended for individuals aged 9–14, with a minimum interval of 6 months between doses. For those aged 15 and older, three doses are recommended as before (IB).

Table 3 summarizes the recommended vaccination schedules for the 3 vaccines.

2. KQ2: Is the single-dose HPV vaccination for ages 9–14, as currently recommended by the WHO, feasible to implement in Korea?

The WHO's Strategic Advisory Group of Experts on Immunization (SAGE) identified low vaccine accessibility, the difficulty of completing a 2-dose schedule, and the relatively high cost as key reasons for the global HPV vaccination rate being only 13%. Therefore, to promote universal immunization and encourage completion of the vaccination schedule, in April 2022, WHO recommended a 1- or 2-dose schedule for females aged 9–20 years, and a 2-dose schedule with a 6-month interval for those aged 21 and older [27].

Table 3. Recommended dosing schedules for each HPV vaccine, stratified by gender and age group

Vaccine type	Age at first vaccination	Number of doses	Vaccination schedule
2-/4-/9-valent	9 to 14 yr	2	0, 6–12 mo
2-valent*	Female: 15 to 45 yr	3	0, 1, 6 mo
	Male: 15 to 25 yr		
4-/9-valent	Female: 15 to 45 yr	3	0, 2, 6 mo
	Male: 15 to 26 yr†		

HPV, human papillomavirus.

*The bivalent vaccine is currently excluded from the National Cancer Vaccination Program.

†Men aged 27–45 may receive vaccination after consultation with healthcare professionals.

The United Kingdom and Australia revised their HPV vaccine recommendations in 2023 to align with the WHO's updated guidance. Both countries were relatively early adopters of the national HPV vaccination program, having implemented it for over 16 years, and they also include male vaccination as part of their programs.

In South Korea, the HPV vaccine has been included in the NIP since 2016, providing free vaccination to female adolescents aged 12–13, with the target age group recently expanded to include those up to 17 years old. While the WHO revised its recommendations with a focus on efficient allocation of vaccine resources, particularly for low-income countries, this approach does not align with the current context in South Korea. Due to the lack of sufficient evidence on the safety and effectiveness of a single-dose HPV vaccination in the Korean population, the committee has decided to maintain the current recommendation until more conclusive evidence supporting the effectiveness of a single-dose schedule becomes available.

3. KQ3: Is HPV vaccination effective in individuals who are already infected with HPV?

According to a phase 3 randomized clinical trial, among women who were already infected with HPV types 16 or 18 at the start of the study, the bivalent vaccine showed 90% efficacy (31.8–99.8) in preventing cervical intraepithelial neoplasia grade 2 or higher (CIN2+) caused by other HPV types to which they were not yet exposed [28]. Additionally, in a study of women aged 27–45 who tested positive for HPV 16, those who received the quadrivalent vaccine (n=5) showed a 24- to 930-fold increase in antibody titers and a 3- to 27-fold increase in memory B cell counts compared to the unvaccinated group (n=5) [29].

For the nonavalent vaccine, among women who were positive for HPV types 6, 11, 16, and 18, but negative for types 31, 33, 45, 52, and 58 at the beginning of the study, the incidence of cervical disease caused by the latter five types significantly decreased (95.1% for all grades, 91.1% for high-grade lesions). Similarly, in women who were positive for HPV types 31, 33, 45, 52, and 58, but negative for types 6, 11, 16, and 18, the incidence of cervical disease caused by these four types also significantly decreased (97.4% for all grades, 95.8% for high-grade lesions) [30].

Based on these results, the recommendation was determined as follows.

- Vaccination with the bivalent, quadrivalent, or nonavalent HPV vaccine is recommended for women who are already infected with HPV, as it can reduce the risk of infection with other HPV subtypes to which they have not yet been exposed (IIB).

4. KQ4: Does HPV vaccination influence preventing the recurrence of HPV-related diseases in patients who have undergone conization?

In a post hoc analysis of a randomized clinical trial on the bivalent HPV vaccine, among women aged 15–25 who underwent surgical removal of cervical lesions after vaccination, the vaccine efficacy against recurrence of CIN2+ was 88.2% (95% CI=14.8–99.7) [31]. However, another study reported no significant vaccine efficacy in a similar context [32]. A meta-analysis that included these two studies on the bivalent vaccine and three additional studies on the quadrivalent vaccine found that HPV vaccination was effective in reducing recurrence of cervical lesions. The odds ratio (OR) for CIN2+ recurrence was 0.4 (95% CI=0.21–0.78) when vaccination was given before treatment (e.g., conization), and 0.28 (95% CI=0.14–0.56)

when given after treatment, indicating that HPV vaccination can help prevent the recurrence of cervical lesions [33].

In a study involving 312 women diagnosed with CIN grades 1 to 3 who underwent treatment such as conization, participants were randomly assigned to receive either the quadrivalent HPV vaccine or a placebo and were followed for 24 months. The vaccine showed a statistically significant efficacy of 58.7% in reducing the recurrence of CIN 1–3 compared to the placebo group [34]. In a prospective case-control study of patients who underwent conization for CIN2, vaccination was associated with an 81.2% reduction in the risk of developing high-grade CIN (95% CI=34.3–95.7) [35]. A retrospective study conducted among Korean women aged 20–45 found that patients who had been diagnosed with high-grade CIN and treated with conization showed reduced recurrence when they received the quadrivalent HPV vaccine (recurrence rate: 2.5% in the vaccinated group vs. 7.2% in the unvaccinated group). The unvaccinated group had a significantly higher risk of high-grade CIN recurrence (hazard ratio=2.84; 95% CI=1.335–6.042) [36].

In a retrospective study that included the nonavalent vaccine, women who received vaccination after undergoing conization (bivalent: 19.6%, quadrivalent: 4.6%, nonavalent: 64.1%) had a lower incidence of persistent or recurrent high-grade intraepithelial neoplasia compared to the unvaccinated group (3.3% vs. 10.7%, $p=0.015$). The risk of lesions was significantly reduced, with an OR of 0.2 (95% CI=0.1–0.7) [37].

A meta-analysis published in August 2023 included 20 studies on the administration of bivalent, quadrivalent, or nonavalent HPV vaccines in women who had undergone conization. The overall vaccine effectiveness against the recurrence of CIN2+, regardless of HPV subtype, was 69.5% (95% CI=54.7–79.5). Notably, the highest vaccine effectiveness was observed in the group that received their first vaccine dose after undergoing conization, with an effectiveness of 78.1% (95% CI=68.7–84.7) [38].

Based on these results, the following recommendation was made.

- Vaccination with the bivalent, quadrivalent, or nonavalent HPV vaccine is recommended for women who have undergone conization, as it can prevent infection with the corresponding HPV subtypes and reduce the risk of recurrence of HPV-related diseases (IB).

5. KQ5: Does additional vaccination with the nonavalent HPV vaccine help prevent the recurrence of HPV-related diseases in women who have already completed vaccination with the bivalent or quadrivalent HPV vaccine?

A study conducted between 2010 and 2011 evaluated the safety and immunogenicity of three doses of the nonavalent HPV vaccine in women aged 12–26 who had previously received the quadrivalent HPV vaccine. The results showed that women who were revaccinated with the nonavalent vaccine exhibited high immunogenicity. In the group that received 3 doses of the nonavalent vaccine following three doses of the quadrivalent vaccine, antibody titers against HPV types 6, 11, 16, and 18 were higher than those in the group that only received the quadrivalent vaccine. However, antibody titers against HPV types 31, 33, 45, 52, and 58 were lower in the group that received the nonavalent vaccine as a revaccination compared to the group that had not received the quadrivalent vaccine but received the nonavalent vaccine alone [39]. Regarding adverse reactions, injection site pain, swelling, and redness were

reported more frequently in the vaccine group than in the placebo group, but there was no significant difference in systemic adverse reactions [40].

Between 2006 and 2011, HPV genotype testing was conducted on 60,775 Korean women aged 18 to 79 (median, 44 years). Among women infected with HR-HPV types, the most observed HPV types were HPV 16, 52, and 58, in that order [41]. This finding is consistent with the 2023 WHO report on HPV and HPV-related cancers in Korea [42]. However, the bivalent vaccine shows limited cross-protection against HPV 31, 35, and 45, and the quadrivalent vaccine provides little to no cross-reaction for the five additional types, whereas the nonavalent vaccine offers broader coverage, enabling prevention of HPV 52, 58, and other high-risk types that currently contribute substantially to the disease burden in Korea [40,43]. Therefore, considering the epidemiology of HPV in Korea, additional vaccination with the nonavalent vaccine for individuals previously vaccinated with the bivalent or quadrivalent vaccines is expected to provide significant clinical benefits by addressing the unmet need for prevention of HPV types 52 and 58.

- In women who have already completed the bivalent or quadrivalent HPV vaccination, an additional dose of the nonavalent vaccine is recommended as it can reduce the risk of infection with additional HPV subtypes (IIB).

DISCUSSION

This recommendation is based on clinical trial results showing that the preventive effect against HPV-related diseases in the 2-dose vaccination group is not inferior to that in the 3-dose group. Therefore, for girls and boys aged 9 to 14, 2 doses of the bivalent, quadrivalent, or nonavalent HPV vaccine are recommended [7,44,45].

In this recommendation, although there was discussion about expanding the age range for male HPV vaccination, the target age for males receiving the quadrivalent or nonavalent vaccine was maintained at 9 to 26 years, consistent with previous guidelines. However, a note was added stating that vaccination may be considered for those aged 27 and older after consulting with a healthcare provider, based on limited research available for this age group. This is because, for the quadrivalent vaccine, there is only one clinical trial targeting men aged 27 to 45, which evaluated immunogenicity and safety in a small sample of just 150 men aged 9 to 45, making the evidence insufficient [17]. Similarly, for the nonavalent vaccine, there are no direct comparative studies on immunogenicity in men aged 27 to 45, and the recommendation considers this age group's vulnerability to HR-HPV infections rather than direct evidence of vaccine efficacy [24,25]. Currently, South Korea's Ministry of Food and Drug Safety has not approved HPV vaccination for middle-aged men, and expansion of indications and vaccination targets will likely be needed based on additional research results in male populations. A phase 3 double-blind, randomized, placebo-controlled trial related to oropharyngeal cancer—an HPV-related male disease—is currently underway, with the first analysis expected in 2026. The recommendations are anticipated to be updated based on the results of this study.

This recommendation suggests that vaccination in patients already infected with HPV may help prevent infection with other HPV subtypes. However, this point could be misunderstood

and requires clear explanation. Multiple clinical studies have shown that vaccination does not help eliminate an existing HPV infection, so patients should be adequately informed of this when being vaccinated [28-30]. Furthermore, a recent meta-analysis convincingly demonstrated that HPV vaccination in patients who have already undergone conization is beneficial in preventing the recurrence of CIN2+. However, it is still uncertain whether starting vaccination before conization leads to better outcomes than beginning vaccination after the procedure [38]. Similarly, even individuals who have completed the bivalent or quadrivalent HPV vaccination series may receive an additional dose of the nonavalent vaccine to prevent infection with other HPV subtypes. However, when the nonavalent vaccine is administered after the quadrivalent vaccine, antibody titers against HPV types 6, 11, 16, and 18 are higher than in individuals who received only the nonavalent vaccine. In contrast, for the other 5 high-risk types (HPV 31, 33, 45, 52, and 58), antibody titers are higher in those who received three doses of the nonavalent vaccine alone compared to those who received the quadrivalent vaccine followed by the nonavalent vaccine. Therefore, this distinction should be clearly explained [39].

Regarding the safety of the HPV vaccine, observational studies and randomized controlled trials have found no association between vaccination and the occurrence of multiple sclerosis and other central nervous system demyelinating diseases, Guillain-Barré syndrome, neurological disorders, venous thromboembolism, or autoimmune diseases [46-49]. Additionally, a recent big data study conducted in Korea involving girls aged 11 to 14 found no link between HPV vaccination and 33 serious complications, including Hashimoto's thyroiditis, rheumatoid arthritis, and severe headaches [50].

If, moving forward, both men and women actively receive vaccination while considering Korea's specific epidemiology and gender-specific disease characteristics, Korea will soon become a country that has effectively eliminated cervical cancer.

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SUPPLEMENTARY MATERIAL

Data S1

Summary of revisions to the HPV vaccination recommendations

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