

# **Special Article**

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# Recommendations for Adult Immunization by the Korean Society of Infectious Diseases, 2023: Minor Revisions to the 3rd Edition

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### ABSTRACT

The Korean Society of Infectious Diseases has been regularly developing guidelines for adult immunization since 2007. In 2023, the guidelines for the following seven vaccines were revised: influenza, herpes zoster, pneumococcal, tetanus-diphtheria-pertussis (Tdap), human papillomavirus (HPV), meningococcal, and rabies vaccines. For the influenza vaccine, a recommendation for enhanced vaccines for the elderly was added. For the herpes zoster vaccine, a recommendation for the recombinant zoster vaccine was added. For the pneumococcal vaccine, the current status of the 15-valent pneumococcal conjugate vaccine and 20-valent PCV was described. For the Tdap vaccine, the possibility of using Tdap instead of tetanus-diphtheria vaccine was described. For the HPV vaccine, the expansion of the eligible age for vaccination was described. For the meningococcal vaccine, a recommendation for the rabies vaccine, the number of pre-exposure prophylaxis doses was changed. This manuscript documents the summary and rationale of the revisions for the seven vaccines. For the vaccines not mentioned in this manuscript, the recommendations in the 3rd edition of the *Vaccinations for Adults* textbook shall remain in effect.

Keywords: Adult; Vaccination; Immunization; Guideline; Korea

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### BACKGROUND

Since the 1st edition of *Vaccinations for Adults* was published in 2007, the Korean Society of Infectious Diseases (KSID) has published it three times. By the time the 2nd edition was published in 2012, the Committee on Adult Immunization was officially established. The Committee set the amendment cycle to every 5 years for major revisions and every 2-3 years for minor revisions. Minor revisions entail revisions to some vaccines only, based on the latest issues of the guidelines within the past 2-3 years. In 2014, 2 years after the publication of the 2nd edition, the minor revisions made was published [1].

In 2022, 3 years after the publication of the 3rd edition of the Vaccinations for Adults, the task of minor revisions was commenced. After two rounds of meetings in June and July 2022, the decision was to revise the guidelines for seven vaccines: influenza, herpes zoster, pneumococcal, tetanus-diphtheria-pertussis (Tdap), human papillomavirus (HPV), meningococcal, and rabies vaccines. The coronavirus disease 2019 (COVID-19) vaccine was not yet available until the 3rd edition and had to be added; therefore, its guidelines were developed separately. Two authors were assigned for each vaccine and most of them was selected from the authors of the 3rd edition. The authors were asked to draft the guidelines by reviewing the recent data and reaching an agreement on the supporting documents. Drafting of the recommendations took approximately 4 months. The draft version of the recommendations was reviewed and revised twice by the Committee for Adult Immunization, in January and February 2023, respectively. The final draft was released during a hearing in May 2023, and the final version was selected based on the consensus of KSID members.

This manuscript documents the summary and rationale of the revisions for the seven vaccines. For the vaccines not mentioned in this manuscript, the recommendations in the 3rd edition of the *Vaccinations for Adults* textbook shall remain in effect. © 2024 by The Korean Society of Infectious Diseases, Korean Society for Antimicrobial Therapy, The Korean Society for AIDS, and Korean Society of Pediatric Infectious Diseases

Infection &

chemotherapy

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### 1. Influenza vaccine

# <Recommendation for influenza vaccination for older adults aged $\geq$ 65 years>

A highly immunogenic influenza vaccine (high-dose, MF59-adjuvanted or recombinant influenza vaccine) is recommended for the older adults aged ≥65 years to prevent influenza-related hospitalizations and complications. Unadjuvanted standard-dose influenza vaccines can be administered instead of highly immunogenic vaccines.

The Committee for Adult Immunization of KSID has recommended influenza vaccination for all children and adults over 6 months of age. However, among older adults, the titer of the antibody developed after influenza vaccination is only 40-80% of that for healthy adults, and the prevention effect is relatively lower compared to that in healthy adults (31-58%) [2, 3]. Furthermore, the vaccine efficacy decreases significantly particularly with antigenic mismatch; thus, the need to introduce a highly immunogenic vaccine for the older adults has been mentioned continuously. To compensate for the low vaccine efficacy in the older adults, highly immunogenic influenza vaccines were developed including high dose guadrivalent influenza vaccine (Fluzone high-dose guadrivalent; 60 µg HA/strain, 0.7 mL), MF59-adjuvanted quadrivalent vaccine (Fluad guadrivalent), and recombinant influenza guadrivalent vaccine (Flublok) (Table 1). Although the effectiveness/ efficacy data of highly immunogenic quadrivalent influenza vaccines are limited, the immunogenicity of highly immunogenic quadrivalent vaccines is non-inferior to that of highly immunogenic trivalent vaccines in comparative clinical trials. Thus, the effectiveness/efficacy of highly immunogenic quadrivalent influenza vaccines can be presumed based on the clinical data for highly immunogenic trivalent vaccines [4, 5].

Fluzone high-dose trivalent demonstrated a superior



#### Table 1. Highly immunogenic influenza vaccine

Product name	Manufacturer	Targeted age group	Adjuvant	Dosage form	Antigen content/dose	Manufacturing method
Fluzone high-dose quadrivalent	Sanofi Pasteur	≥65 years	None	0.7 mL PFS	60 µg HA/strain	Egg-based
Fluad quadrivalent	Seqirus	≥65 years	MF59	0.5 mL PFS	15 μg HA/strain	Egg-based
Flublok quadrivalent	Sanofi Pasteur	≥18 years	None	0.5 mL PFS	45 μg HA/strain	Genetic recombinant

PFS, prefilled syringe; HA, hemagglutinin.

relative effectiveness (24.2%, 95% confidence interval [CI], 9.7-36.5) against influenza-like illness (ILI) compared to standard-dose trivalent vaccines (15 µg HA/strain, 0.5 mL) in a randomized phase 3 clinical trial [6]. Similarly, in a meta-analysis of many retrospective studies, Fluzone high-dose trivalent demonstrated a significant relative effectiveness (19.5%, 95% CI, 8.6-29.0) against ILI compared to the standard-dose trivalent vaccine [7]. In addition, Fluzone high-dose trivalent demonstrated a significantly higher effectiveness for influenzarelated hospitalizations (17.8%), pneumonia (24.3%), and cardiovascular/respiratory complications (18.2%) compared to the standard-dose trivalent vaccine [7]. When compared with the standard-dose quadrivalent vaccine in older adults aged  $\geq$ 65 years, Fluzone highdose trivalent showed a relatively higher effectiveness (4.9-6.8%) for influenza-related hospitalizations [8, 9]. Fluzone high-dose trivalent had a significantly higher incidence of localized adverse events in the injection site compared to standard-dose trivalent vaccine, but with no increase in the incidence of serious adverse events [10].

Fluad trivalent has shown a superior vaccine effectiveness compared to the standard-dose trivalent vaccine in many observational studies. In a prospective casecontrol study conducted among old adults aged  $\geq 65$ years, the standard-dose trivalent vaccine did not show a significant effectiveness whereas the Fluad trivalent showed a statistically significant effectiveness against influenza (relative vaccine effectiveness, 63%) [11]. In another prospective observational study, Fluad trivalent showed a higher effectiveness (25%) for influenza- or pneumonia-related hospitalizations compared to the standard-dose trivalent vaccine [12]. When compared with the standard-dose quadrivalent vaccine in older adults aged  $\geq$ 65 years, Fluad trivalent showed a relatively higher vaccine effectiveness (3.9-8.2%) against influenza-related hospitalizations [8, 9]. In a meta-analysis of studies that directly compared the effectiveness of Fluzone high-dose trivalent and Fluad trivalent (excluding those sponsored by pharmaceutical companies), there was no significant difference in preventing influenza-related emergency room visits, hospitalizations, and pneumonia between

the two vaccines [2]. Fluad trivalent has been verified for safety in numerous clinical trials and observational studies for its use in the clinical setting for >25 years. Compared with the standard-dose trivalent vaccine, it did not show a difference in the risk for localized/systemic solicited or serious adverse events [13].

Flublok quadrivalent was developed for adults aged  $\geq 18$ years and showed a relatively high efficacy compared to the standard-dose vaccine. It can be administered with caution under the supervision of medical staff as an alternative vaccine in case of a history of severe allergies such as anaphylaxis after vaccination with egg-based or cell-based vaccines [14]. In a randomized phase 3/4 clinical trial that compared the vaccine effectiveness of Flublok guadrivalent and standard-dose guadrivalent vaccine against ILI in adults aged  $\geq$ 50 years, Flublok quadrivalent was 30% (95% CI, 10-47) more effective in terms of polymerase chain reaction (PCR)-positive influenza and 43% (95% CI, 21-59) more effective in terms of culture-positive influenza [15]. When the age groups were stratified to 50-64 and  $\geq$ 65 years, a significant effectiveness of 44% (95% CI, 10-65) and 42% (95% CI, 9-65) were shown in terms of virus culture positivity, respectively. Regarding safety, localized and systemic adverse events were mostly transient and mild without significant difference compared to the inactivated influenza vaccine [16].

Cost-effectiveness analysis has shown that highly immunogenic vaccines would be either cost-effective or cost-saving when compared with standard-dose vaccines [17, 18].

### 2. Herpes zoster vaccine

### <Recommended target and time for vaccination>

- Vaccination with recombinant zoster vaccine (RZV) is recommended for adults ≥aged 50 years. Zoster vaccine live (ZVL) may be administered instead of RZV.
- RZV vaccination is recommended for severely immunocompromised adults aged ≥18 years.

#### <Frequency and method of vaccination>

- 1. RZV is administered as a twice intramuscular vaccinations in the deltoid, 2 to 6 months apart. The minimum interval for vaccination is 4 weeks.
- 2. ZVL is administered as a subcutaneous vaccination on the outside of the upper arm.

Herpes zoster is caused by varicella zoster virus (VZV). After a person recovers from varicella, the virus stays latent in their body. The virus can reactivate years or decades later, causing herpes zoster. Therefore, the herpes zoster vaccine is necessary for people who have been previously infected with VZV although an antibody test for VZV is not mandatory before receiving the vaccine.

ZVL was first approved by the US Food and Drug Administration (FDA) in 2006 and introduced in Korea in 2012. Since then, a live vaccine developed in Korea has been added and two types of ZVL vaccines are in use as of 2022 (**Table 2**). The result of a phase 3 clinical trial for RZV was first published in 2015 [19], and RZV was approved for use in adults aged ≥50 years in 2017 by the US FDA. In Korea, its use was approved in September 2021, and vaccination began in December 2022. Therefore, general population guidelines for herpes zoster vaccine are needed. The Committee for Adult Immunization of KSID has been recommending ZVL vaccination for adults aged  $\geq$ 60 and 50 to 59 years at the discretion of the clinician depending on the condition of the individual. This judgment was based on the epidemiology of herpes zoster in Korea, the effects of ZVL, and duration of the effects. Particularly, the estimated efficacy of ZVL vaccination reaches a statistically non-significant level 9 to 11 years after vaccination [20] and ZVL recommendation was aimed to target the period of the most benefit. However, the disease burden for herpes zoster in Korea is increasing every year, with a rapidly increasing prevalence from the age of 50 years, peaking at 60 to 75 years [21]. In addition, the results of a general population study indicated severity changes when herpes zoster occurs at age  $\geq$ 50 years [22]. Therefore, the need to prevent herpes zoster is important for those in their  $\geq$ 50s. The results of two clinical trials on RZV (ZOE-50, ZOE-70) showed that the occurrence of herpes zoster could be prevented in 96.6%, 97.4%, and 91.3% of those aged 50 to 59, 60 to 69, and ≥70, respectively [19, 23]. These numbers are guite high compared to the numbers shown in the ZVL clinical trial (Shingles prevention study, Zoster efficacy and safety trial), with efficacy in 69.8%, 64%, and 38% among those aged 50 to 59, 60 to 69, and  $\geq$ 70, respectively. In addition, as a result of a 10-year follow-

Table 2. Helpes Zoster Vaccine companson						
Characteristics	Recombinant zoster vaccine (RZV)	Zoster vaccine live (ZVL)				
Vaccine type	Inactivated vaccine	Live vaccine				
Active ingredient	Recombinant varicella zoster virus glycoprotein E immune booster (ASO1B)	Attenuated varicella virus (virus strains: Zostavax- Oka/Merck strain, Sky Zoster-Oka/SK strain)				
Frequency of vaccination	Two times	Once				
Method of vaccination	Intramuscular	Subcutaneous				
Prevention effect for herpes zoster <sup>a</sup>	Ages 50 to 59: 96.6% Ages 60 to 69: 97.4% Ages 70 to 79: 91.3% Ages ≥80: 91.4%	Ages 50 to 59: 69.8% Ages 60 to 69: 64% Ages 70 to 79: 41% Ages ≥80: 18%				
Prevention effect for neuralgia after herpes zoster <sup>a</sup>	Ages 50 to 69: 100% Ages ≥70: 88.8%	Ages 60 to 69: 66% Ages ≥70: 67%				
Duration of prevention effect <sup>b</sup>	≥10 years	8 years				
Risk of reactogenicity <sup>c</sup>	High	Low				
Domestic approval	<ul> <li>Prevention of herpes zoster <ul> <li>adults aged ≥50 years</li> <li>Those aged ≥18 years who are expected to have high risk of herpes zoster infection due to suppressed immunity because of disease, treatment, or immunosuppressants (e.g., autologous hematopoietic stem cell transplant recipients, those with solid cancer, blood cancer, or solid organ transplant recipients)</li> </ul> </li> </ul>	Prevention of herpes zoster in adults aged ≥50 years				
Domestically approved vaccines	Shingrix Inj. (GlaxoSmithKline)	Zostavax Inj. (MSD Korea) Skyzoster Inj. (SK BioSciences)				

 Table 2. Herpes zoster vaccine comparison

<sup>a</sup>Based on the results of clinical trials: ZOE-50 & ZOE-70 for RZV, and Shingles prevention study & Zoster efficacy and safety trial for ZVL. <sup>b</sup>For the RZV, 10-year follow-up results have been reported.

Reactogenicity refers to pain at the vaccination site, redness, edema, systemic fever, myalgia, and headache.

up after the 2nd RZV vaccination, the efficacy did not show a significant reduction, as the number remained at 89% over the 10-year period, from 1 month after the 2nd vaccination [24]. Considering that the long-term efficacy is relatively good for RZV, it seems that RZV vaccination can be recommended for ages 50 to 59. Also, considering the higher and more long-lasting efficacy, RZV is preferred over ZVL. However, ZVL has the advantage of being a single vaccination, cheaper than RZV, and with fewer adverse events due to its lower reactogenicity such as pain at the vaccination site, redness, edema, systemic fever, myalgia, or headache. Thus, ZVL is still regarded as a useful vaccine and its recommendation remains in effect in that it guarantees a choice of vaccine within the general population.

For patients who are severely immunocompromised due to hematopoietic stem cell transplantation, solid cancer, hematologic malignancy, organ transplant, or the use of immunosuppressive agents, the risk of herpes zoster outbreak markedly increases with increased severity and disease burden [25, 26]. Thus, immunocompromised individuals have a great need for herpes zoster prevention, but ZVL could not be recommended as it is a live vaccine. In contrast, RZV is an inactivated vaccine that can be used in immunocompromised individuals, and its immunogenicity and efficacy have been demonstrated in clinical trials that included patients with various diseases suggesting compromised immunity. RZV has demonstrated 68.2%, 87.2%, and 90.5% prevention effects in patients with hematopoietic stem cell transplantation, hematologic malignancy, and potential immune-mediated disease, respectively [27-29]. Therefore, RZV vaccination is recommended for severely immunocompromised patients aged  $\geq$ 18 years in whom the risk for herpes zoster increases.

People who have been vaccinated with ZVL can receive RZV vaccination. This is based on the immunogenicity and safety research results of RZV in individuals who received ZVL, the limited prevention effect of ZVL, and epidemiological characteristic of increased risk of herpes zoster with increasing age [30]. When immunogenicity and safety of RZV were evaluated in adults aged  $\geq$ 65 who had received ZVL vaccination >5 years ago, RZV immune response was found to be similar regardless of prior history of ZVL vaccination, and no significant difference occurred in the incidence of serious adverse events, which was assessed to have a causal relationship with the vaccine [31]. The immunogenicity and safety data for RZV

in those vaccinated with ZVL are from the population aged  $\geq$ 65 years who were vaccinated with ZVL at least 5 years ago; thus, the vaccination interval can be 5 years unless the risk of herpes zoster rapidly increased. However, RZV vaccination can be considered even within 5 years for those aged  $\geq$ 70 years and patients with a disease or condition that greatly increases the risk of herpes zoster. Also, if the recipient of the vaccine can accept two doses of RZV and the cost of the vaccine, RZV vaccination can be administered even within 5 years of ZVL vaccination. However, it is not recommended by experts to administer RZV vaccination within 2 months of ZVL vaccination.

Patients with a history of herpes zoster can receive the herpes zoster vaccine. When ZVL or RZV was administered in patients with a history of herpes zoster, sufficient immune response was induced, and the prevention effect was verified while an increase in adverse events was not significant [32, 33]. For patients who experienced herpes zoster, if the acute phase has subsided and the patient can be vaccinated, the herpes zoster vaccine can be administered. However, a study reported that the effectiveness of ZVL was not significant in the short term if the vaccine was administered within 2 years of onset of herpes zoster [34], and in some countries, herpes zoster vaccination is recommended at one year interval in patients with herpes zoster. Thus, it is preferable to administer herpes zoster vaccine at least, at one- or two-years interval rather than immediately after the onset of herpes zoster.

As the adverse events caused by reactogenicity after RZV vaccination are relatively frequent compared to those for ZVL, RZV vaccination must be accompanied by an explanation and with caution. Reactogenicity refers to pain at the vaccination site, redness, edema, systemic fever, myalgia, and headache. According to the results of the ZOE-50 and ZOE-70 studies, grade 3 adverse events were reported in 16.5% and 3.1% of those vaccinated with RZV and placebo, respectively [22, 23]. Regarding local reactions (pain, redness, and edema), 9.4% of those who received RZV vaccine and 0.3% of those who received the placebo reported grade 3 adverse events. Regarding the solicited systemic reactions (myalgia, fatigue, headache, chills, fever, and gastrointestinal symptoms), 10.8% of those vaccinated with RZV and 2.4% of those vaccinated with the placebo reported at least grade 3 adverse events. However, it is desirable to complete the 2nd vaccination as planned because the symptoms that occur after the 1st vaccination, such as redness, pain, systemic fever, and

myalgia, do not significantly increase the rate of adverse events in the 2nd vaccination.

### 3. Pneumococcal vaccine

The US FDA has approved the 15-valent pneumococcal conjugate vaccine (PCV15) and 20-valent PCV (PCV20) in 2021 for adults aged  $\geq$ 18 years. Furthermore, the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC) has published the vaccination recommendations for PCV15 and PCV20 in adults [35]. The recommendation is to administer PCV20 once, or sequential use of PCV15 and 23-valent pneumococcal polysaccharide vaccine (PPSV23) once in adults who have not received PCV before, all adults aged  $\geq$ 65 years whose vaccination history is unknown, and adults aged 19 to 64 with certain underlying diseases that increase pneumococcal disease or other risk factors. Adults who have not received PCV previously but received PPSV23 are recommended to receive PCV20 or PCV15 vaccination once, at least 1 year after. For those who have received PPSV23 previously, there is no need to additionally administer PPSV23 after PCV15 vaccination. Those who previously received the 13-valent PCV (PCV13) are recommended to receive PCV20 at least 1 year after or additional PPSV23 vaccination according to previous guidelines [36, 37].

PCV15 includes PCV13, 22F, and 33F serotypes (Table 3). In a phase 2 trial, three randomized comparative clinical trials were conducted to assess the immunogenicity and safety of PCV15 in comparison to PCV13 in healthy adults aged  $\geq$ 50 years, American natives aged 18 to 49, adults with at least 1 high-risk factor, and in people living with HIV (PLWH) aged  $\geq$ 18 years [38-41]. Regarding 13 serotypes shared with PCV13, PCV15 satisfied the noninferiority criterion, and showed superior immunogenicity for 22F and 33F included only in PCV15 and serotype 3. In a clinical trial that sequentially administered PPSV23 at 2 to 12 month intervals, PCV15 showed similar or superior immunogenicity to PCV13 [42]. The safety of PCV15 was assessed in seven randomized comparative clinical trials involving 5,630 adults aged  $\geq$ 18 years, including 302 PLWH [35]. The trials included cases with sequentially administered of PPSV23, 1 year after PCV15 vaccination and those with concomitant influenza vaccination. Most adverse events included pain in the vaccination site. fatigue, and myalgia; there was no difference in serious adverse events within 6 months (with 2.5% for PCV15 and 2.4% for PCV13); and no serious adverse events or health issues related to the vaccine occurred [35].

35B 33 24F 23B 23A 16F 15C I5A 20 I7F 17F 15B 15B 12F 12F 12F 11A 11A 11A 10A **P** 10A N N 9N ထထ  $\sim$ 33F 33F 33F 33F 22F 22F 22F 22F 19A 19A 19A 19A 19A 7F 7F 7F 7F 7F 7F 6A 6A 6A 6A വവ ß ß ß c <u>ന</u> ന c 23F 23F 23F 23F 23F 23F 19F 19F 19F 19F 19F 19F 18C 18C 18C 18C 18C 180 4 4 4 4 4 4 98 98 9 9 9 6B 6B <u>6</u>B 6B 6B 6B 4 4 4 4 4 4 PPSV23 PCV20 PCV13 PCV21 PCV15 PCV10 PCV7

Serotype composition of pneumococcal vaccine

able 3.

pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal 20-valent pneumococcal conjugate vaccine; PCV21, 21-valent pneumococcal conjugate vaccine; PPSV23, pneumococcal polysaccharide vaccine. **I3-valent** PCV13, vaccine; conjugate pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV20, PCV7, 7-valent

PCV20 includes the PCV13 serotype and 8, 10A, 11A, 12F, 15B, 22F, and 33F. Phases 2 and 3 clinical trials for assessing the immunogenicity and safety by comparing PCV20 versus PCV13 or PPSV23 in adults aged 60 to 64 and  $\geq$ 18 years (including those with stable disease, excluding immunocompromised patients), have been conducted [43-45]. For the PCV13 serotype, the noninferiority criterion was met but the immunogenicity was low. PCV20 showed superior immunogenicity compared with PPSV23 for six of the seven serotypes not included in the PCV13. The safety of the vaccine was assessed in 4,552 adults aged  $\geq$ 18 years with normal immunity who were vaccinated with PCV20. The most common adverse events were vaccination site pain, myalgia, fatigue, headache, and arthralgia, and the frequency of serious adverse events within 6 months of vaccination was 1.5% for PCV20, and 1.8% for the control group, with no difference. There were no serious adverse events or deaths related to the vaccine.

PPSV23 was introduced in the early 1990s in Korea, and PCV7 was approved in 2003. In 2010, PCV10 and PCV13 were approved [46]. The approval for PCV13 was expanded in October 2014 to include adults ≥aged 18. Since 2013, PPSV23 was introduced in the national vaccination program for the older adults aged  $\geq$ 65 years, and since 2014, the program has included PCV10/PCV13 for children aged <5 years. The national vaccination program also supports PCV10/PCV13 and PPSV23 vaccination for children aged  $\geq$ 12 years if they have risk factors for invasive pneumococcal disease (IPD). According to the 2015 survey conducted in Korea, the PCV10/PCV13 vaccination rate in children aged <24 months reached 98%, while the cumulative vaccination rate for PPSV23 in those aged  $\geq$ 65 years reached 60% [47, 48]. In most countries with mandatory PCV vaccination for children, infection by IPD due to the PCV13 serotype tends to decrease while infection by non-vaccine serotypes tends to increase, and the same trend is observed in Korea. In a recent prospective observational study on IPD conducted nationwide at multiple sites in Korean adults aged  $\geq$ 19 years, the proportion of PCV13 and PPSV23 serotypes were 32.8% and 56.0%, respectively, and the most common serotype was 3 (13.8%) and 19A (9.5%) [49]. In Korea, PCV15 and PCV20 have not yet been introduced. Considering that the percentage of PCV13 serotype is very low at 32.8% and the frequency of serotype 3 is the highest in IPD, it is necessary to introduce PCV15, which has excellent immunogenicity against serotype 3 and additional two

serotypes, and PCV20 which has wider serotype coverage in Korea. In addition, the proportion of non-vaccine serotypes was very high at 41.4%, and if PCV21 shows excellent results in future clinical trials, it may need to be introduced in Korea.

## 4. Tdap vaccine

### <Recommended target and time for vaccination>

- 1. Adults aged  $\geq$ 18 years
- Those who received diphtheria-tetanus-acellular pertussis (DTaP) vaccine in childhood: Tdap or tetanus-diphtheria (Td) vaccination every 10 years
- If the records are unclear or if DTaP vaccination was not administered in childhood (ex. for those born before 1958): three doses of vaccinations [Tdap-Td (or Tdap)-Td (or Tdap)], thereafter Tdap, or Td vaccination every 10 years
- 2. Pregnant women: Tdap vaccination at during gestational weeks 27~36 during every pregnancy
- 3. Adults who anticipate having close contact with an infant aged <12 months (e.g., parents, grandparents, child-care providers, and health-care personnel): Tdap vaccination recommended 2 weeks prior to the close contact, if there is no history of Tdap vaccination
- 4. Wound management after trauma: patients who have never received Tdap vaccination are recommended to receive Tdap. Patients with a history of Tdap vaccination can receive Tdap or Td.

### <Vaccination dose and method>

- 1. 0.5 mL (Tdap, Td) intramuscular injection
- For the schedule of a series of three vaccinations, the preferred schedule is a single dose of Tdap at first, followed by a dose of Td or Tdap 4 to 8 weeks after Tdap, then another dose of Td or Tdap 6 to 12 months later (vaccinate with Tdap at least once during the three vaccinations).

Tdap or Td booster doses are recommended at an interval of 10 years. At least one Tdap vaccination are recommended to prevent pertussis, in ages 11 to 12 years, if possible. As current guidelines, it is recommended that adults receive a single Tdap vaccination, with the exclusion of pregnant women.

When Tdap was administered twice at a 10-yearly interval in adults, the study results indicated both excellent



Table 4.	Summary of	changes to	tetanus-diphtheria-pertuss	is vaccine guidelines
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Situation	Previous recommendation	Revised recommendations
Adults aged ≥18 years	A booster Td vaccination is required every 10 years, and if Tdap has never been administered before, one of these doses should be Tdap instead of Td.	Every 10 years, either Tdap or Td booster vaccination is recommended. If Tdap has never been administered before, the initial vaccination should be Tdap instead of Td.
When three doses of vaccinations are required	The vaccination schedule involves initial administration of Tdap, followed by Td 4 to 8 weeks later, and subsequently, another Td vaccination 6 to 12 months later. If Td was administered initially, then either the second or third vaccination should be given as Tdap.	Three doses of vaccinations [Tdap-Td (or Tdap)-Td (or Tdap)], thereafter Tdap, or Td vaccination every 10 year
Wound management after trauma	If there is no prior history of Tdap vaccination, Tdap should be administered instead of Td.	Patients who have never received Tdap vaccination are recommended to receive Tdap. Patients with a history of Tdap vaccination can receive Tdap or Td.
Pregnant women	Tdap vaccination at during gestational weeks 27-36 during every pregnancy	Consistent with the previous guidelines

Td, tetanus-diphtheria vaccine; Tdap, tetanus-diphtheria-pertussis vaccine.

immunogenicity and safety [50-52]. According to studies published in 2018 and 2019, there was no difference in the rate of adverse events between the Td and Tdap groups 10 years after a previous Tdap dose, and the antibody titer, indicating immunogenicity, also showed similar levels [53, 54]. This research demonstrates that repeated administration of Tdap is safe and suggests the potential for additional preventive effects against pertussis. In January 2019, the US FDA approved booster Tdap vaccination if administered  $\geq 8$  years after previous Tdap dose and for use for tetanus prophylaxis when indicated for wound management if  $\geq 5$  years have passed since the last tetanus vaccination. In October 2019, the Advisory Committee on Immunization Practices recommended that either Tdap or Td vaccines could be used for the decennial Td booster, tetanus prophylaxis when indicated for wound management, and catch-up vaccination for persons aged  $\geq$  7 years with incomplete vaccination history [55]. In Korea, 980 cases of pertussis were reported in 2018, 496 cases in 2019, 123 cases in 2020, and 21 cases in 2021. This trend appears to be a consequence of the ongoing COVID-19 pandemic, and it is anticipated that the incidence of pertussis will rise once again following the end of the COVID-19 pandemic. Consequently, there is a pressing need to revise the current guidelines, which recommend a single dose of the Tdap vaccine for adults and Td as booster doses, to permit the use of both Td and Tdap vaccines. Individuals who have not previously received the Tdap vaccine should ensure to receive it, preferably as their initial vaccination. Vaccination with Td or Tdap is recommended every 10 years thereafter.

The current guidelines specify a minimum interval of 5 years between booster doses of the Td or Tdap vaccine. However, several studies have shown safety even when

Tdap was vaccinated within 5 years of Td vaccination [56, 57]. In addition, a study reported that it was safe to administer two Tdap vaccinations at a 5-yearly interval [58]. There is not enough research on booster vaccination with Tdap in people with incomplete vaccination history during childhood. However, a study showed that there was no difference in safety and immunogenicity between primary vaccination of adults with Tdap and primary vaccination with Td [59]. Also, a study reported that there were no significant adverse events in the mother and fetus when pregnant women were repeatedly vaccinated with Tdap [60, 61]. Based on these research findings, it can be considered safe to administer repeated Tdap vaccinations within a 5-year interval.

Based on the aforementioned studies, we intend to revise the recommendations for tetanus-diphtheria-pertussis vaccination, and these modifications are outlined in **Table 4**.

### 5. HPV vaccine

### <Recommended target and time for vaccination> 1. Women

- 1) Girls aged 11 to 12 years
- 2) Females aged 13 to 26 years: If previously unvaccinated or vaccination was not completed
- 3) Females aged 27 to 45 years: Will be considered in consultation with an expert in case there are advantages
- 2. Men: Ages 9 to 26 years can be vaccinated

The currently available HPV vaccines include the bivalent (Cervarix<sup>®</sup>, GlaxoSmithKline Biologicals, Rixensart, Belgium), and quadrivalent (Gardasil<sup>®</sup>, Merck, Whitehouse Station, NJ, USA) and 9-valent vaccines (Gardasil9<sup>®</sup>,

Merck, Rahway, NJ, USA). The Ministry of Food and Drug Safety expanded the age range for 9-valent vaccine in 2020 to include women aged 45 years.

The expansion of the age range for the 9-valent vaccine was based on a clinical study that compared immune response by age group [62]. By comparing the immune response between women aged 27 to 45 and 16 to 26 years who received the 9-valent vaccine, a non-inferiority between the two groups was demonstrated. In an openlabel clinical trial, the immunogenicity of 9-valent vaccine (geometric mean antibody for HPV types 16, 18, 31, 33, 45, 52, and 58 after 7 months) in women aged 27 to 45 compared to 16 to 26 years did not show a difference. Also, in a safety assessment of women aged 27 to 45 who received the vaccine, safety was similar to that in women aged 16 to 26 years. In 11 clinical studies conducted among women aged 27 to 45 years, the efficacy and safety of the vaccine were demonstrated based on the immunological bridging study data on the bivalent, guadrivalent, and 9-valent vaccines. In three clinical studies that conducted per-protocol analysis on the bivalent and guadrivalent vaccines, efficacy was demonstrated in persistent HPV infections due to the vaccine type, anal genital warts, and cervical intraepithelial neoplasia. In nine studies, the antibody conversion rate for vaccine type HPV was 93.6% to 100% 7 months after the first vaccination, after three vaccinations with the three types of vaccines.

HPV vaccine must be administered during adolescence since it is most effective prior to exposure to HPV. Ages 27 to 45 years are likely to have been exposed to the HPV type included in the vaccine, which reduces the benefit and cost-effectiveness [63]. However, in cases of insufficient vaccine doses, because of the risk of a new HPV infection, it would be beneficial to be vaccinated; thus, vaccination is recommended when it is considered beneficial after expert consultation.

An observational study verified the efficacy of the 9-valent vaccine in 1,100 men who have heterosexual relations, women of the same ages (16 to 26 years), and 300 men who have sex with other men (MSM). For of the nine HPV types tested 7 months after the first vaccination, the antibody titer was non-inferior in men who have heterosexual relationships compared to that of young women and lower compared to that of MSM. When the 9-valent vaccine was compared with a quadrivalent vaccine to assess immunogenicity and antibody positivity rate, antibody titer was similar for HPV 6, 11, 16, and 18 at 7 months after the first vaccination while those for HPV 31, 33, 45, 52, 58 types were higher. The antibody positivity rate was 100% for the nine HPV types when the 9-valent vaccine was received [64].

The protective effects of the HPV vaccine are maintained for a long time. It has protective effects against highgrade cancers of the cervix, vagina, and vulva for at least 10 years in women. Even in men, a high-level of antibody was maintained over 9.5 years of follow-up, with protective effects against anogenital diseases [65].

In Korea, the ages approved for HPV vaccination are 9 to 45 for women and 9 to 26 for men. Girls and boys aged 9 to 14 years are recommended to receive two vaccinations at month 0 and month 6-12 (at least 5 months interval). Including PLWH, children with compromised immunity require three vaccinations. Females aged 15 to 45 and males 15 to 26 years require three vaccinations according to the month O (first vaccination), month 1 to 2 (minimum interval of 4 weeks between 1st and 2nd vaccination), and month 6 (minimum interval of 12 weeks between 2nd and 3rd vaccination, minimum interval of 5 months between 1st and 3rd vaccination) schedules. In Korea, the National Immunization Program (NIP) has been implemented since 2016 using the bivalent or guadrivalent vaccine for adolescent females aged 12 years. As a catch-up vaccination, those between the ages of 13 and 26 who have not been vaccinated or not completed three vaccinations should be vaccinated. Vaccination is effective in mid-age women between ages 27 and 45 years but vaccination should be done based on clinical judgment according to individuals' risks and in consideration of the circumstances of the recipient. Vaccination for boys between ages 11 and 12 years is recommended to prevent penile, oral, oropharyngeal, and anal cancers associated with HPV 16 and 18, as well as genital warts and recurrent respiratory papilloma associated with HPV 6 and 11. For hospital employees with a risk of occupational exposure, vaccination is recommended because HPV infection of the upper respiratory tract (nasal cavity, oropharynx) can be transmitted during surgical incisions or laser procedures although the risk is unknown [66]. Although PLWH are in an immunosuppressed state, high vaccination effects are expected since HPV prevalence is higher among them than that in healthy individuals.

Regarding single vaccination, studies reporting the effects of single compared to two or three vaccinations exist. Thus, considering the cost-effectiveness, the World Health

Organization (WHO) Strategic Advisory Group of Experts on Immunization recently held a discussion on single vaccination [67]. In Korea, thanks to NIP, the vaccination rate was 81.7% in 2019 in 12-year-olds and recently, vaccination has been expanded to include 17-yearolds. The WHO emphasized an efficient distribution of vaccine resources and if more data are accumulated on the effects of single vaccination, the discussion may be initiated in Korea as well.

### 6. Meningococcal vaccine

# <Vaccination recommendation for B serogroup protein conjugate vaccine>

The B serogroup protein conjugate vaccine is recommended along with the existing quadrivalent protein conjugate vaccine for those to receive the meningococcal vaccine\*. Those recommended for vaccination may receive both simultaneously.

\*Persons who have anatomic or functional asplenia; persons who have complement component deficiencies; persons receiving a complement inhibitor; military recruits; laboratory workers occupationally exposed to meningococcus; persons who travel to or live in areas in which meningococcal disease is hyperendemic or epidemic; first-year students living in dormitories, and PLWH.

In May 2022, the B serogroup vaccine (4CMenB, Bexsero®, GlaxoSmithKline Biologicals SA, Rixensart, Belgium) was approved in Korea. Bexsero® is the recombinant protein conjugate vaccine for B serogroup meningococcus and was approved for the prevention of B serogroup invasive protein conjugate vaccine disease in infants aged  $\geq 2$  months. Depending on the time of the first vaccination, two or three basic vaccinations are administered, and one additional is administered in case the first vaccination was administered 2 to 23 months after birth. In children aged  $\geq$ 2 years and in adults, two basic vaccinations are administered (0.5 mL per vaccination) with a minimum of 1-month interval. The timing or need for additional vaccination has not been determined. In those aged  $\geq 6$  months, 63% to 100% produce antibodies 1 month after the two basic vaccinations, and in a study conducted among children in Portugal for severe meningococcal infections due to the B serogroup, a 79% prevention effect was reported [68, 69].

The incidence of meningococcal infections in Korea is very low compared to expectations in consideration of

the incidence (0.5 to 4 cases per 100,000 population) in developed countries. This can be presumed to be underestimated compared to the expected number, due to the effects of antibacterial agents and diagnostic methods [70]. The number of patients with meningococcal meningitis reported to the Korea Disease Control and Prevention Agency (KDCA) is <20 every year but was 40 per year when a high number was being reported [71]. As such, data on the serogroup of meningococcal infections are insufficient: the percentage of B serogroup is increasing continually, as a recent patient data showed. Among the 11 types of patient-isolated strains collected between 2002 and 2003 by the KDCA, only 1 strain of B serogroup (9.1%) was found, whereas among the 19 samples collected from 2010 to 2016, the most, at 7 strains (36.8%), was B serogroup [72, 73]. Among 35 meningococcal strains isolated by the KDCA between 2016 and 2020, the B serogroup accounted for 27 (77.1%) strains [74]. In a Korean meningococcal carrier study, an increase in the B serogroup was identified. In a study conducted in 2005, the Y serogroup was predominant while the C serogroup was predominant in 2009, but from 2010, the B serogroup was the predominant strain in all studies [75-77]. In a carrier study from 2015 and 2021: the B serogroup was identified in 12/49 strains (24.5%) and 14/58 strains (24.1%), respectively [78, 79].

Overseas, two types of B serogroup protein conjugate vaccines, Bexsero<sup>®</sup> and Trumenba<sup>®</sup> (Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA), were approved for use, in 2013 and 2014, respectively. Although individuals recommended to receive the B serogroup vaccination vary by country, most include those with anatomical or functional asplenia, complement deficiency, or complement hypofunction due to treatment, as well as laboratory workers who are occupationally exposed to meningococcus. In addition, vaccination is recommended for patients who have undergone hematopoietic stem cell transplantation, military recruits, dormitory residents, and men who have sex with men in some countries [80]. Many countries recommend vaccination by age group in addition to the situational high-risk groups or those with underlying diseases, mostly in the infancy stage. In some countries, the national vaccination program subsidizes B serogroup vaccination for infants. Some countries include children or adolescents as recommended targets for vaccination while others only include adolescents in the B serogroup vaccination target group [81]. In addition to the high-risk group or by-age vaccination recommendations, some countries are recommending vaccination to control B serogroup outbreak.

Vaccine	Manufacturer (importer)	Product name	Serogroup	Appearance	Dosage form
Quadrivalent vaccine	GlaxoSmithKline (finished	Menveo <sup>®</sup> (MenACWY-CRM)	A, C, Y,	Liquid: C, Y, W-135	0.5 mL/vial
protein conjugate vaccine	product imported)		W-135	Freeze-dried: A	
Quadrivalent vaccine	Sanofi-Pasteur (finished	Menactra® (MenACWY-D)	A, C, Y,	Liquid: A, C, Y,	0.5 mL/vial
protein conjugate vaccine	product imported)		W-135	W-135	
Monovalent protein conjugate vaccine	GlaxoSmithKline (finished product imported)	Bexsero <sup>®a</sup> (4CMenB)	В	Liquid	0.5 mL/prefilled syringe

#### Table 5. Meningococcal vaccines approved in Korea

<sup>a</sup>Bexsero<sup>®</sup> is scheduled to be released within 2024.

Although the causative pathogen for most of the recent invasive meningococcal infections in Korea is the B serogroup, there is a marked lack of supporting data from the general population for selecting targets for vaccination recommendation, separate from the recommendation for quadrivalent protein conjugate vaccine. Therefore, the B serogroup protein conjugate vaccination is recommended for those who are recommended to receive existing general population quadrivalent protein conjugate vaccine, considering the epidemiology of the general population along with overseas recommendations. Those recommended for vaccination can receive both simultaneously. The meningococcal vaccines approved in Korea as of April 2023 are shown in **Table 5**.

### 7. Rabies vaccine

### <Pre-exposure prophylaxis (PrEP)>

Pre-exposure prophylaxis requires intramuscular injection twice on Days 0 and 7 on the deltoid muscle. However, 3-dose primary series are administered on Days 0, 7, and either Day 28 or Day 21, if there is a risk of a very high exposure such as among employees in rabies research laboratories, or if exposure risk period is longer than 3 years such as contacting occupationally wild/stray animals, or traveling to areas with a high risk of rabies; the need for additional vaccination should be determined according to the assessment of ongoing risk including antibody titer test.

Vaccination for rabies PrEP is recommended for people at high-risk of contacting rabies, and a total of three basic vaccinations have been recommended on Days 0, 7, and 28 (or 21). In the product summary of the Purified Vero Cell Rabies Vaccine (PVRV, Verorab®, Aventis Pasteur, Lyon, France) used in Korea, additional vaccination is recommended 1 year after the basic vaccination and additional vaccinations every 5 years thereafter. However, the WHO and CDC only recommend additional vaccination after antibody titer measurement if exposure risk is continued occupationally, such as laboratory employees or animal handlers. In 2018, the WHO recommended 2-dose primary series on Days 0 and 7 for PrEP basic vaccination based on accumulated data [82]. The CDC also revised the basic vaccination for PrEP to two times, on Days 0 and 7, in 2022 [83], considering the barriers affecting adherence to the 3-dose primary series including out-of-pocket costs of rabies biologics (3-dose PrEP vaccination series is currently estimated at  $\geq$ 1,100 USD), confusion about which activities fall within different risk categories, and noncompliance with recommendations for repeated titer checks. In addition, travel medicine providers have indicated that the largest group for which PrEP is recommended (travelers to regions with endemic rabies) might often be unable to complete the 3-dose series.

The US ACIP conducted a systematic review on 12 studies regarding intramuscular/transdermal vaccination for PrEP, including 1,401 individuals, to assess the immunogenicity of the 2-dose primary series. The conclusion, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, is that the immunogenicity of the 2-dose primary series on Days 0 and 7 was comparable to that of 3-dose primary series on Days 0, 7, and 28 (or 21) with a certainty of severity level 2 (risk ratio, 1.00; 95% CI, 0.99-1.01]) [84]. For persons with sustained risks, such as contact with wild/stray animals or travel to areas where rabies is prevalent, checking serial antibody titers was determined unnecessary. Instead, an one-time check of the rabies antibody titer between 1-3 years after the 2-dose primary series was deemed a sufficient assurance of long-term immunogenicity for such persons. The rationale for this conclusion is the data indicating that an antibody titer  $\geq 0.5$  IU/mL 1 year after a rabies PrEP is a marker for long-term immunogenicity [85, 86], and the 2-dose series is known to be protective for at least 3 years [87]. However, it is recommended that antibody titer test be performed after 2-dose primary series, every 6 months in very high-risk groups including employees of laboratories handling rabies virus and every



2 years in case of exposure to risks that are difficult to perceive such as those handling bats.

In Korea, it is difficult to apply the US CDC's recommendations considering that the cost of the three vaccinations is relatively cheaper (approximately 160 USD) compared to that in the US and the antibody titer test is not readily available. Still, since 2014, rabies has not been identified even in wild animal surveillance projects in Korea [88] and the reduction in demand has resulted in instability in the rabies vaccine supply. As such, by principle, it would be desirable to administer 2-dose primary series on Days 0 and 7 for PrEP, whereas, performing a 3-dose primary series for those with a very high-risk of exposure including those working in rabies research laboratories and whose exposure risk period is longer than 3 years such as contacting occupationally wild/stray animals, or traveling to areas with a high risk of rabies. The need for additional vaccination should be determined according to the subsequent risk assessment including antibody titer test.

## SUPPLEMENTARY MATERIAL

### **Supplementary Materials**

Guideline Korean version.

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#### **Author Contributions**

Conceptualization: WSC, HJC. Data curation: WSC, JYS, KTK, HJL, EJC, JYB, BSC. Formal analysis: WSC, JYS, KTK, HJL, EJC, JYB, BSC. Methodology: WSC, JYS, KTK, WBP, SHH, JYC, JSY, JSL, HJC, YHC, DGL, JHC, HJC. Project administration: WSC, JYS, KTK, WBP, SHH, JYC, JSY, JSL, HJC, YHC, DGL, JHC, HJC. Supervision: WSC, JYS, KTK, WBP, SHH, JYC, JSY, JSL, HJC, YHC, DGL, JHC, HJC. Validation: WSC, JYS, WJK, MSL, JSL, YHC, JHC. Writing - original draft: WSC, JYS, KTK, HJL, EJC, JYB, BSC. Writing - review & editing: WSC, JYS, WJK, MSL, JSL, YHC, JHC.

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