

Revised Adult Immunization Guideline Recommended by the Korean Society of Infectious Diseases, 2014

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The Korean Society of Infectious Diseases (KSID) published the 1st edition of *Adult Immunization* (Koonja Publishing, Inc., Seoul) in October, 2007. Five years later, in May of 2012, the 2nd edition of the book was published (M.I.P, Seoul). The KSID decided to make small-scale revisions every two years before the publication of the new edition of the adult immunization textbook, due to rapid changes in the environment related to adult immunization. In August, 2012, the KSID set up the Committee on Adult Immunization to develop and revise the guideline, and to conduct research on adult immunization.

This is the revised version of the existing adult immunization recommendations, reflecting the latest research results and trends on each vaccine after the publication of *Adult Immunization 2nd Edition* in 2012. This revision provides information about vaccines against *Streptococcus pneumoniae*; tetanus-diphtheria-pertussis; herpes zoster; human papillomavirus; influenza; meningococcus; Japanese encephalitis;

and yellow fever. Partial revisions have been made to recommendations for vaccines against *S. pneumoniae*, tetanus-diphtheria-pertussis, herpes zoster, and human papillomavirus. For vaccines against influenza, meningococcus, Japanese encephalitis, and yellow fever, the Committee on Adult Immunization has summarized its opinions on recent issues regarding the vaccines. There are no changes from *Adult Immunization 2nd Edition* for vaccines not mentioned in this revised edition.

Pneumococcal vaccine

<Recommendations on Pneumococcal Vaccine for Adults>

A. Healthy adults 65 years of age or older: 13-valent pneumococcal conjugate vaccine (PCV13) or 23-valent

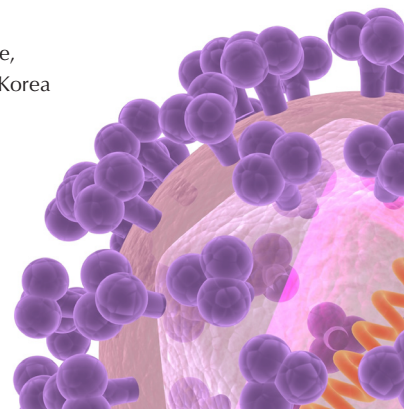
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pneumococcal polysaccharide vaccine (PPV23) should be administered.

B. Persons 65 years of age or older with chronic medical conditions (chronic cardiovascular disease, pulmonary disease, diabetes, alcoholism, or liver disease)

1) Pneumococcal vaccine-naïve persons: PCV13 should be given first, followed by a dose of PPV23 after 6 to 12 months. The two vaccines should not be co-administered, and the minimum acceptable interval between PCV13 and PPV23 is 8 weeks.

2) Persons who previously received PCV13: There is no need for another PCV13 vaccination, but a dose of PPV23 should be given.

3) Persons who previously received PPV23

- Persons who previously received PPV23 before 65 years of age: PCV13 should be given at least 1 year after the last administration of PPV23. Additional dose of PPV23 should be given 6-12 months (a minimum of 8 week) after PCV13 and ≥ 5 years after the most recent dose of PPV23.

- Persons who previously received PPV23 after 65 years of age: PCV13 should be given at least 1 year after the latest dose of PPV23. Additional dose of PPV23 is not recommended.

C. Persons aged between 18 and 64 years with chronic medical conditions (chronic cardiovascular disease, pulmonary disease, diabetes mellitus, alcoholism and liver disease): PCV13 should be given preferentially, and if not available, PPV23 should be given instead.

D. Adults 18 years of age and older with functional or anatomic asplenia, cerebrospinal fluid leak, cochlear implantation, or conditions that result in immunocompromised status (congenital or acquired immunodeficiencies; chronic renal failure or nephrotic syndrome; leukemia; lymphoma; Hodgkin's disease; generalized malignancy; diseases that require treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy; and solid organ transplant)

1) Pneumococcal vaccine-naïve persons: PCV13 should be given first, followed by a dose of PPV23 after at least 8 weeks.

2) Persons who previously received one dose of PPV23: PCV13 should be given at least 1 year after the administration of PPV23. Additional dose of PPV23 should be given at least 8 weeks after the administration of PCV13 and ≥ 5 years after the administration

of PPV23.

3) Persons who previously received two dose of PPV23: PCV13 should be given at least 1 year after the last administration of PPV23.

1. Approval of PCV13 for adults

In October 2013, Korea's Ministry of Food and Drug Safety (MFDS) granted approval for the administration of the 13-valent pneumococcal conjugate vaccine (PCV13) to adults 18 years of age or older.

The 23-valent pneumococcal polysaccharide vaccine (PPV23) has been widely used for a long time. It contains 23 kinds of serotypes and is known to have some preventive effect against invasive pneumococcal disease (IPD) [1, 2]. However, PPV23 has not been proved effective against pneumonia, and it has not been effective enough for patients with underlying diseases who are highly prone to developing pneumococcal disease. Furthermore, PPV23 can stimulate only T-cell independent immune response, which makes the duration of protection short, around 5 years, and it is not able to induce the herd immunity.

In contrast to PPV23, PCV13 induces an anamnestic reaction by stimulating a T-cell dependent immune response. It not only prevents IPD but also clearly decreases the occurrence of pneumonia, otitis media, and nasopharyngeal colonization of vaccine serotypes in children [1]. PCV13 has reduced more than 90% of antibiotic-resistant IPD caused by serotypes, among infants and children. Moreover, it is reported that the vaccine induces the herd immunity, in which adults who have not received it also see a decrease in the number of IPD cases [1]. A double-blind and randomized study (Community-Acquired Pneumonia Immunization Trial in Adults, CAPiTA) conducted on 85,000 adults aged 65 years and older found that vaccination with PCV13 reduced vaccine-type community-acquired pneumococcal pneumonia, vaccine-type nonbacteremic pneumococcal pneumonia, and vaccine-type IPD by 46%, 45%, and 75%, respectively [3]. In a clinical trial on adults over 18 years of age, PCV13 demonstrated superior or similar immunogenicity compared to PPV23, with similar rates of adverse reactions [4-6]. In a study conducted on patients with AIDS, PCV13 showed immunogenicity superior to PPV23 and demonstrated preventive effects against recurrence of IPD [7, 8].

Studies that conducted cost-effectiveness analyses of pneumococcal vaccines agree that the most important elements

affecting the analysis are the level of herd immunity provided by PCV13 administration in children and the efficacy for non-bacteremic pneumococcal pneumonia. This indicates that if PCV13 administration in children does not induce enough herd immunity, but that the vaccine works better among adults in preventing nonbacteremic pneumococcal pneumonia, PCV13 may be more cost-effective than PPV23 for adults aged ≥ 65 years and high-risk groups. In fact, after the U.S. and some European countries introduced the protein-conjugated vaccine into the national immunization program (NIP) for children, IPD in those age groups decreased significantly, as well as among adults due to herd immunity. However, adults 65 years of age and older did not see such an evident decrease as the children did [9, 10]

2. Patterns of diseases caused by *S. Pneumoniae* and serotype distributions

The graph of IPD occurrence by age shows the shape of a U, which is high under the age of 5, then decreases, increasing again after the age of 50. In the U.S., serotypes contained in PCV13 cause one-third of cases of IPD, and serotypes only contained in PPV23 cause 25% of cases of IPD [11]. Among adults 19 years of age or older with immunocompromising conditions, 50% of IPD cases are attributed to PCV13 serotypes, whereas serotypes only contained in PPV23 are responsible for 21% of cases of IPD [12]. In Korea, it was found that 0.36 out of 1,000 inpatients 18 years of age or older had IPD. The fatality rate was reported to be around 30%, and both the number of patients and the fatality rate tended to be higher with older patients. Among IPD patients, 64.9% were found to have underlying disease [13]. According to research on serotype distribution of IPD among adults 19 years of age or older, before the introduction of PCV13, serotypes contained in PCV7, PCV13, and PPV23 accounted for 39.8%, 67.3%, and 73.4% of IPD, respectively [14]. However, after the introduction of PCV13, the serotype coverage rates for IPD decreased in both PCV13 and PPV23, and the difference between the two vaccines as the cause of the disease ranged between 15 and 20% [2]. Also, there was an increase in the proportion of IPD cases caused by serotypes not contained in any vaccine.

3. Recommendations on pneumococcal vaccine for adults by the KSID

In 2014, in its revised guidelines on pneumococcal vaccination, the U.S. Advisory Committee on Immunization Practice (ACIP) advised that all adults 65 years of age and older to receive PCV13, followed by PPV23 [15]. This was the Commit-

tee's conclusion after considering the following factors: the insufficient level of herd immunity among adults aged 65 years and older that is induced from vaccinating children; the proven efficacy of PCV13 in CAPiTA against pneumococcal pneumonia; and cost-effectiveness analysis of the strategy.

Pneumonia is a growing cause of death in Korea, and *S. pneumoniae* is reported as the most common cause of the disease. This necessitates administration of PCV13, which prevents non-invasive pneumococcal disease including pneumonia. PCV13 and PPV23 should be given consecutively because the gap of serotype coverage for pneumococcal disease is widening between PCV13 and PPV23, as in the U.S. and Europe. However, there is insufficient evidence to recommend consecutive administration of PCV13 and PPV23 to all persons 65 years of age and older across the board as there has been no assessment of the cost-effectiveness of PCV13 in this age group.

When administering PCV13 and PPV23, another area that requires consideration is the immune response according to the order in which the vaccines are administered. Booster effect may be induced if PCV13 is administered first, while hypo-responsiveness occurs if PPV23 is given first. Thus, it may be more beneficial to administer PCV13 first [16, 17].

The Committee on Adult Immunization has stated that one of the PCV13 or PPV23 should be given for healthy adults aged 65 years and older. However, the Committee has recommended that adults in the same age group with chronic medical conditions should receive PCV13 first, followed by PPV23 6 to 12 months later, because these individuals have a high risk of severe pneumococcal disease caused by various serotypes. However, PCV13 and PPV23 should not be administered at the same time and there must be an interval of at least 8 weeks between the administrations (Fig. 1).

Tetanus-diphtheria-pertussis vaccine

<Recommendations on Tetanus-Diphtheria-Pertussis (Tdap) Vaccine for Pregnant Women or Women who Plan on Pregnancy>

- A. Women without previous Tdap vaccine are recommended to receive a dose right after pregnancy or before pregnancy. Women between 27 and 36 weeks of pregnancy can be given the vaccine as well.*

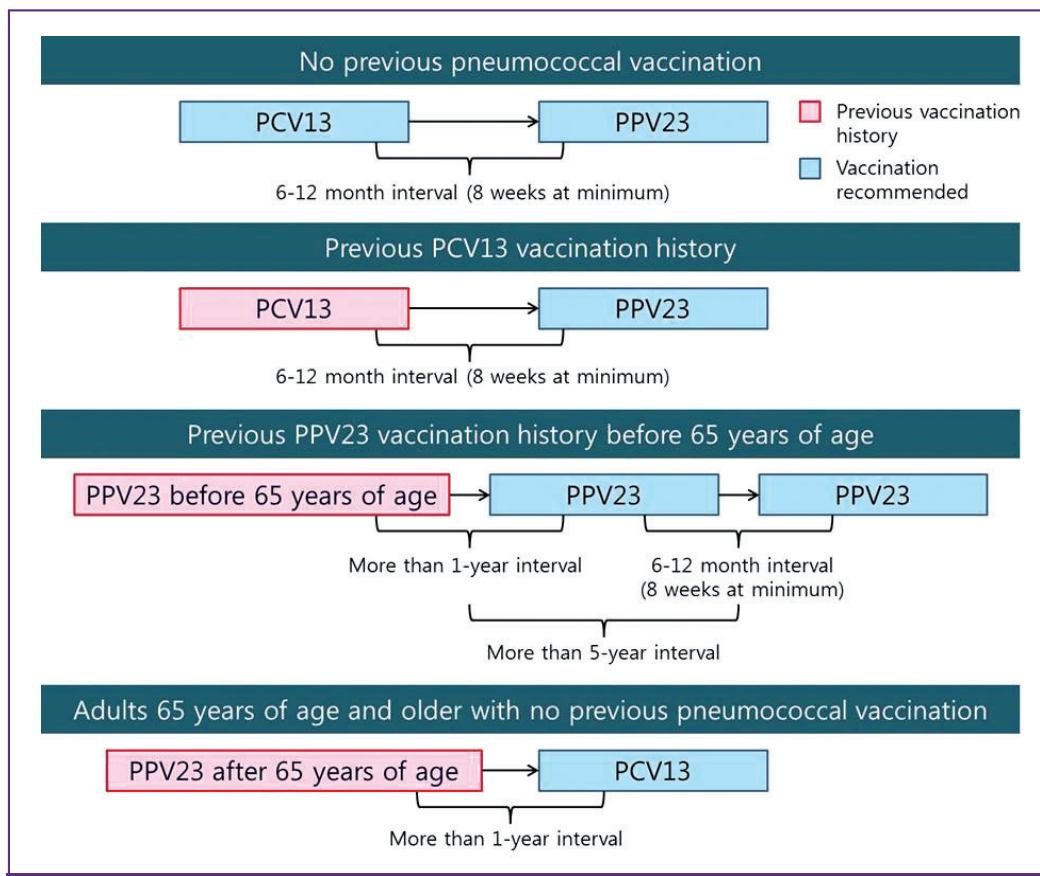


Figure 1. Recommendation on pneumococcal vaccine for Adults 65 years of age or older with chronic medical conditions.

PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine

1. Recommendations on Tdap vaccine for pregnant women in oversea countries

Since 2013, the U.S. ACIP has recommended that women receive a Tdap vaccine during each pregnancy [18]. The U.S. has seen an increasing outbreak of diphtheria nationwide since the early and mid 2000s. Since 2006, the Committee had recommended that pregnant women without previous Tdap vaccine administration receive the vaccine right after pregnancy, as well as any family members or caregivers who would contact the newborn. However such a cocooning strategy did not turn out to be effective, and failed to protect newborns from being exposed to pertussis until the time when they received their first diphtheria-tetanus-acellular pertussis vaccine (DTaP) for infants, two months after birth. In June 2011, the U.S. ACIP sought to provide a remedy for the problem by advising women to receive the Tdap vaccine during pregnancy (after 20 weeks). However, only 2.6% of the advised women took the advice, making it difficult to assess whether the new guideline was effective. The number of pertussis patients jumped to 48,277 in 2012, two to three times higher than the average. Considering the disease burden of pertussis in newborns, the safety of the Tdap vaccine in adults, and the

weakening of immunogenicity acquired from childhood vaccination over time, the ACIP decided to strengthen the guideline to advise women to receive the Tdap vaccine between 27 to 36 weeks of pregnancy regardless of their Td/Tdap vaccination history. The decision was based on the judgment that mothers can acquire antibodies through vaccination that would be passed down to newborns during pregnancy. The grounds for the judgment are as follows: vaccination after giving birth to the first child maintains a sufficient antibody titer not only for the mother but also for the child in the second pregnancy [19]; Tdap vaccination received at any point in pregnancy provides a high antibody titer in the body at the time of childbirth [20]; vaccination during the third trimester provides the highest concentration of vaccine-specific anti-pertussis antibodies transported from mother to infant [21]; and vaccination during pregnancy does not cause a critical adverse reaction in mothers or newborn infants [22]. Vaccination guidelines for family members and caregivers have been strengthened as well. In 2011, vaccination was recommended to adults 64 years of age and younger without previous vaccination history and adults older than 64 years of age if there is a child younger than 12 months in the household [23]. The

guidelines in 2013 recommended vaccination to all adults without previous vaccination [24], and the 2014 edition expanded the range to the population group 11 years of age and older without previous vaccination, directly and indirectly strengthening the cocooning strategy [25].

In the UK, the number of pertussis cases was reported to be 8,819 in 2012, 10 times higher than in 2011, and 13 newborn infants died from the disease. Since 2013, the country has begun advising women to get vaccinated in every pregnancy, while the recommended time of vaccination—between 28 and 38 weeks gestation, ideally before 32 weeks—varies slightly from that in the U.S. [26]. Canada recommends that pregnant women receive a dose of vaccination right after delivery as the best plan or during the third trimester of pregnancy as the second-best plan, if they have had no previous Tdap vaccination in adulthood [27]. In Australia, the best recommendation is vaccination before pregnancy or right after childbirth, and the second-best is vaccination during the third trimester of pregnancy. The country recommends that women get vaccinated again even if they had received a Tdap vaccine before, if more than 5 years have passed since their last vaccination at the time of delivery [28].

2. Recommendations on Tdap vaccine for pregnant women or women who plan on pregnancy by KSID

Women are recommended to receive a dose of Tdap vaccine before pregnancy or right after delivery in the KSID's Tdap vaccine guidelines for pregnant women in its *Adult Immunization 2nd Edition*. The guidelines are similar to those of the U.S. or the UK, as *Adult Immunization 2nd Edition* was published before their guidelines were revised. The number of pertussis cases in Korea has increased in a similar manner to that of the U.S. [29]. The average was 11.4 per year from 1995 to 2008, but increased to 66 in 2009, 27 in 2010, and 97 in 2011. The number hit 230 in 2012 due to a pertussis epidemic in Jeollanam-do [30], but fortunately dropped to 45 in 2013. Currently, there is insufficient evidence to recommend that women receive vaccination in every pregnancy in Korea as in the U.S. and the UK, considering the pertussis dynamics in Korea, while the idea could be reconsidered depending on the pertussis trend and possible future epidemics. Therefore, recommendations regarding the Tdap vaccine for women will remain the same—women without previous Tdap vaccination should receive a single dose before pregnancy or right after delivery. However, pregnant women between 27 and 36 weeks gestation can be vaccinated, because there are solid grounds

that support the benefits and safety of vaccination during pregnancy. Furthermore, as there is clear evidence that pertussis among family members can cause pertussis infection in infants, relevant government agencies should actively promote Tdap vaccination for parents and grandparents who have not received the vaccine previously. Primary healthcare professionals should be encouraged to help further the cause.

Herpes zoster vaccine

<Recommendations on Herpes Zoster Vaccine>

- A. Adults 60 years of age and older should receive shingles vaccination unless a contraindication or precaution exists.
- B. Adults aged between 50 and 59 may be vaccinated depending on individual health conditions.

In July 2011, the MFDS lowered the age limit for herpes zoster vaccine (ZOSTAVAX[®]) usage from over 60 to over 50, expanding the possible subjects of vaccination. However, the KSID held off recommending the vaccine on adults aged between 50 and 59 in the immunization guidelines of the same year. That was because results from the ZOSTAVAX Efficacy and Safety Trial (ZEST), which provided the grounds for the age limit reduction, were not published officially, making verification of the grounds impossible. However the results were officially disclosed in 2012, and verification thus became possible. According to ZEST, herpes zoster vaccination reduced the number of zoster cases in adults aged between 50 and 59 by 69.8% (95% confidence interval [CI], 54.1-80.6) [31]. More than one adverse reaction was observed in 73% of the vaccine group and 42% of the placebo-controlled group, but the difference was largely due to reactions on local parts, as in the previous Shingles Prevention Study (SPS). However, ZEST did not cover many cases in which herpes zoster was followed by postherpetic neuralgia, making it impossible to assess the vaccine's preventive effect against the condition.

The KSID Committee on Adult Immunization officially evaluated the ZEST results and concluded that the study provides grounds that are as sound as the grounds suggested by the previous SPS. However, ZEST did not verify the vaccine's preventive effects against neuralgia following herpes zoster, and there are still controversies regarding long-term immunogenicity and revaccination with zoster vaccine. Therefore, the

Committee advised making the vaccination decision after closely considering the cost and benefit of vaccination according to individual health conditions. The U.S. ACIP did not recommend vaccinating every adult aged between 50 and 59. The organization stated that the vaccination decision should be made considering the health factors of each individual as they may include chronic pain, severe depression, and underlying diseases [32]. Furthermore, there has still been no study performed to conduct a cost-benefit analysis of shingles vaccine in Korea, and there are disagreements over various factors—long-term immunogenicity of the vaccine; need for re-vaccination; how long an adult should wait before a vaccination if he or she has had shingles before; and cost-efficiency of the vaccine for chronic patients—which require further studies.

Human papillomavirus virus vaccine

<Recommendations on Human Papillomavirus Virus (HPV) Vaccine for Men>

- A. Men aged between 9 and 26 can receive HPV4 vaccine to prevent anal cancer, genital warts, and premalignant or dysplastic lesions.

1. HPV vaccination guidelines for men

Males aged 9 through 15 could receive 4-valent HPV vaccine (HPV4) to prevent penis cancer, oral cancer, oropharyngeal cancer and anal cancer related to HPV 16 and 18, and genital warts and recurrent respiratory papillomatosis related to HPV 6 and 11. Theoretically, HPV4 vaccination on boys is expected to have a preventive effect on their future sex partners against cervical cancer. According to a recent phase III clinical trial conducted over more than 4,000 men aged between 16 and 26, HPV4 reduced the cases of anal cancer, genital warts, and premalignant or dysplastic lesions caused by HPV 6, 11, 16, and 18 [33, 34]. The MFDS expanded the age of HPV4 vaccination subjects to men 26 years of age. Therefore, in Korea, males aged between 9 and 26 can receive HPV4 vaccine to prevent anal cancer, genital warts, and premalignant or dysplastic lesions.

In the U.S., boys aged 11 and 12 are all recommended to receive HPV vaccine; men aged between 13 and 21 are advised to have follow-up vaccination; and men aged between 22 and

26 are advised to consider receiving vaccination [35]. Everyone with immunocompromising conditions, including HIV, and homosexuals are advised to receive HPV4 before the age of 26. However, in Korea, it is challenging to customize vaccination recommendation according to age group because there has not been sufficient research conducting cost-benefit analysis on recommending different vaccination for people of different ages. The studies that proved the HPV vaccine's efficacy in preventing the aforementioned diseases were conducted mostly in male homosexuals, who have a higher risk of diseases caused by HPV infection along with HIV patients. Therefore, Korea should give more consideration to vaccinating homosexual men or those with HIV.

2. Safety of HPV vaccine

Recently, there have been concerns regarding the safety of the HPV vaccine. However, the World Health Organization (WHO), through the Global Advisory Committee on Vaccine Safety (GACVS), stated twice, on July 2013 and February 2014, that a worldwide, comprehensive analysis of safety information has revealed that there is no safety risk associated with cervical cancer vaccine or HPV vaccine [36, 37]. Moreover, in March 2014, the MFDS stated that supplements for immune enhancement contained in the HPV vaccine have not shown any safety risk, as a response to concerns raised by some researchers from a Japanese institute [38]. Aluminum hydroxide, the cause for the concerns, is an immune enhancement supplement widely used to improve the effectiveness of vaccines against hepatitis, pneumococcus, and tetanus-diphtheria-pertussis. Its safety has been proved. In fact, the U.S. Food and Drug Administration (FDA) has stated that the maximum amount of aluminum an infant can be exposed to cannot influence his or her health [39]. WHO has also made a statement that aluminum contained in vaccines is harmless [40].

Influenza vaccine

1. Priorities regarding pregnant women

Pregnant women have a higher risk of influenza infection and complications compared to the general population. According to a study conducted in 1918 over 1,350 pregnant women with influenza-like illness (ILI), 43% (585 people) developed pneumonia as a complication, of which 52% (302 people) had a miscarriage [41]. The fatality rate of the subjects was 27%, and it was highest among those in the third trimester of pregnancy. During the 1957 influenza pandemic, influenza

accounted for 20% of deaths related to pregnancy, and half of the infected women of childbearing age were pregnant [42]. During the 2009 influenza pandemic, pregnant patients were estimated to be 4 times more likely to be hospitalized than the non-pregnant patients, and they had higher a higher risk of fatality from critical illness [43]. 20% of pregnant women who were hospitalized in the intensive care unit died [44]. Moreover, influenza was found to increase the risk of preterm delivery, low birth weight, and stillbirth [45]. From these findings, WHO designated pregnant women as the most prioritized subjects of influenza vaccination and advised pregnant women to receive inactivated influenza vaccine regardless of gestation weeks [46]. Research on the disease burden of influenza in Korea is still insufficient. In the 2009 pandemic, out of the 19,727 women of childbearing age who visited 8 hospitals for ILI, 150 pregnant patients were diagnosed with A (H1N1) pdm09, and none of them were critically ill [47]. However, in a study conducted at a teaching hospital, one fatality was reported out of 5 pregnant women hospitalized for A (H1N1)pdm09 [48]. There is no research in Korea that shows whether influenza infection increases the risk of preterm delivery, low birth weight, and infant stillbirth, and more research is needed.

A study was conducted that evaluated the relationship between influenza vaccination and pregnancy in terms of the safety of the fetus. Influenza vaccination of a pregnant woman was safe and did not increase the risk of preterm delivery or low birth weight. The vaccination did not only protect the vaccinated women but also their newborn infants from influenza [49-52]. In fact, indirect immunization from the mother is highly beneficial to infants, because infants under 6 months cannot receive influenza vaccination despite the high disease burden.

Therefore, pregnant women and women of childbearing age must have the highest priority for influenza vaccination during an influenza endemic. Pregnant women are advised to receive the vaccination according to the recommended immunization schedule (from October to December) regardless of gestation weeks. However, the rate of influenza vaccination in pregnancy among Korean pregnant women is only 4 to 20.9%, substantially lower than the vaccination rate among the elderly and people with chronic medical conditions [53-55]. There should be more efforts to raise awareness among pregnant women about the importance of influenza vaccination through public campaigns, education, and free vaccination programs.

2. Quadrivalent influenza vaccinae

The influenza vaccine used in Korea is a trivalent vaccine

that contains antigen representing three influenza viruses - A/H3N2, A/H1N1 and B. However, influenza B viruses can be categorized into two lineages according to the type of antigen (B/Victoria and B/Yamagata), and the cross-reactive immunogenicity between the two lineages is insignificant.

Every year, WHO makes recommendations for vaccine compositions for the Northern and Southern Hemisphere, each according to the lineage that is expected to be epidemic for the year. However, in the last decade, there were lineage-level mismatches between vaccines and circulating strains of influenza B viruses in 50% of the cases. In many cases, influenza B viruses from two different lineages circulated at the same time [56]. In the U.S., five out of 10 seasons from 2001 to 2011 saw lineage-level mismatches between influenza B viruses in vaccines and the circulating B strains. Similarly in Europe, there were mismatches between influenza B vaccines and circulating B viruses in four out of eight seasons from 2003 to 2011. Moreover, 58% of separated viruses belonged to a lineage different from vaccine viruses [56]. According to data provided by the Korea Centers for Disease Control (KCDC), Korea has been seeing influenza B viruses of two different lineages in the same season after the 2009 flu pandemic [57-59]. The lineage-level mismatch and simultaneous circulation of influenza B viruses are considered as one of the most important factors that undermine the effectiveness of influenza vaccines. WHO, starting from the 2013-2014 season, recommends quadrivalent influenza vaccine, which contains influenza B virus strains of two different lineages [60].

According to clinical trials conducted for approval of quadrivalent influenza vaccine, the vaccine has shown non-inferior immunogenicity and no difference in terms of local or systemic adverse reactions compared to trivalent vaccine [61, 62]. Also, in a large-scale clinical trial conducted on 5,168 children aged between 3 and 8 years to test the efficacy of quadrivalent vaccine, it prevented 59.3% of influenza and was highly effective in preventing moderate or severe influenza infection (74.2%) [63].

After 2012, four kinds of egg-based quadrivalent influenza vaccines have been developed and approved by the U.S. FDA [56]. Of the four vaccines, there are three inactivated influenza vaccines: Fluarix[®] Quadrivalent, GlaxoSmithKline; Fluzone[®] Quadrivalent, Sanofi Pasteur; and FluLaval[®] Quadrivalent, ID Biomedical Corporation/GlaxoSmithKline. FluMist[®] Quadrivalent, MedImmune, is a live-attenuated influenza vaccine. Korea is repeatedly experiencing influenza B epidemics in March and April with mismatching lineages of vaccines and circulating virus strains, which calls for the introduction of

quadrivalent vaccines. Quadrivalent influenza vaccines have been developed in Korea and are undergoing clinical trials. Further studies should be conducted to assess the disease burden of the influenza B virus on children and adults and the cost-effectiveness of quadrivalent vaccines.

Meningococcal vaccine

The meningococcal vaccine that is available on the Korean market is MenACWY-CRM (Menveo®). Menveo® is a quadrivalent meningococcal conjugate vaccine approved by the MFDS for people aged between 11 and 55 in May 2012. In Korea, Menveo® has been administered to all new recruits in the military since November 2012. In March 2013, the Ministry approved the vaccine for use for children aged between 2 and 11, and in May 2014, the eligible age was expanded to include infants over 2 months old. Menactra®, another quadrivalent meningococcal conjugate vaccine, is expected to enter the Korean market as well.

After the approval of Menveo® in Korea, more and more children and adolescents have been receiving vaccination. If they have risk factors of meningococcosis such as complement deficiency, history of splenectomy, or hyposplenism, individuals who have received a conjugate vaccine between 2 and 6 years of age need revaccination three years after the first vaccination. If the first vaccination was received after 7 years of age, the person should be revaccinated 5 years later. If the risks continue, revaccination every 5 years is recommended.

While there is limited data on meningococcal outbreaks in Korea, more active meningococcal vaccination seems necessary in some age groups in addition to military recruits. According to age analysis of meningococcosis in Korea, the age groups of 0-2 and 10-16 have high numbers of meningococcosis cases, as in other countries [64, 65]. Meningococcus is hard to culture, and PCR testing is not widely used. Meningococcal infections do not tend to have characteristic symptoms. Because of these traits, it is considered a critical factor of bacterial meningitis in adolescents [66]. The U.S. ACIP recommends that people who have received a conjugate vaccine between the ages of 11 and 15 be given a dose of revaccination 5 years after their first vaccination. That is because after 4 years of age, adolescence is when the risk of bacterial meningitis is the highest, during which time the antibody titer should be maintained. If the first vaccination was between the ages of 16 and 18, the antibody is maintained for 5 years until 21 years of age, so revaccination is not recommended [67]. Korea also needs to ini-

tiate meningococcal vaccination of adolescents aged between 10 and 16, and related research should be conducted.

Japanese encephalitis vaccine

Japanese encephalitis vaccination is scheduled first for infants 12 to 23 months old, followed by the second vaccination 12 months after the first one due to schedule changes for the live-attenuated vaccine [68]. In the previous schedule, infants 12 to 23 months old received their first vaccination, followed by the second vaccination 12 months later and the third vaccination when 6 years old. The schedule of three vaccinations was determined not based on research results but on the inactivated vaccination schedule. China reduced the number of vaccinations from three to two (at 8 months and 2 years old), based on study results. Korea has also changed the schedule from three to two vaccinations, based on the conclusion that the third vaccination at 6 years of age is unnecessary since two vaccinations would provide sufficient antibodies. According to a study, children aged between 5 and 7 were found to have antibodies even before the third vaccination. Moreover, Japanese encephalitis vaccination is included in the NIP of Korea [69]. While there are concerns over the safety of substrates used in producing a live-attenuated vaccine, WHO has concluded that it is safe and effective, and it was able to be included in the NIP.

Inactivated Vero cell-derived vaccines (Beijing-1 strain) were approved in 2013 in Korea and have been used in the country since 2014. Vero cell-derived and genetically recombinant live-attenuated vaccine is produced with chimeric virus (ChimeriVax-JE), which is generated by using YF17D, also used for yellow fever vaccination, as a vector to replace genes that encode prM and E proteins with genes that correspond to SA14-14-2. It was approved in 2013 and is scheduled to be available on the market from 2014.

Yellow fever vaccine

In May 2013, the Strategic Advisory Group of Experts (SAGE) of WHO stated that yellow fever vaccination is effective for the lifetime of an individual, and there is no need for revaccination every 10 years [70]. However, there are quarantine requirements for yellow fever vaccination, and whether revaccination is required or not depends on the requirements of each country. Therefore, revaccination every 10 years is

necessary in order to enter countries that require yellow fever vaccination certification and revaccination.

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Supplementary material

Guideline Korean version.

Supplementary material can be found with this article online <http://www.icjournal.org/src/sm/ic-47-68-s001.pdf>.

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