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Vaccination in Previously-Healthy Children: Practice Recommendations on Vaccines Included and Not Included in the National Immunization Schedule of the Republic of Turkey – 2020

Önceden Sağlıklı Çocuklarda Aşılama: Türkiye Cumhuriyeti Ulusal Bağışıklama Çizelgesinde Yer Alan ve Almayan Aşılara İlişkin Uygulama Önerileri - 2020

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Vaccination is the safest, most efficient, and cost-effective approach in protecting children's and adults' health and preventing infectious diseases. Immunization against all diseases with efficient and safe vaccines is the right of every child. In Turkey, healthy children are regularly vaccinated based on a national immunization schedule, the coverage of which is gradually extending.

This article has been written to present practice recommendations on vaccines included and not included in the National Immunization Schedule, create a national practice guideline covering all vaccines administered to children, and develop the subject matter in light of discussions. Three similar recommendation articles have been published in the Journal of Pediatric Infection (Çocuk Enfeksiyon Dergisi), including "Vaccination Recommendations of Pediatric Infectious Diseases Society" in 2009, "The National Vaccination Schedule in Previously Healthy Children: The Practical Recommendations about Additional Vaccines" in 2014, and "Clinical Practice Recommendations for Turkish National Vaccination Schedule for Previously Healthy Children (National Vaccination Schedule) and Vaccines not Included in the Schedule-2015" in 2015 (1-3). Based on recommendations and discussions on previous articles and developments in the field of vaccination, this article covers up-to-date practice recommendations on vaccines included and not included in the national vaccination schedule of Turkey.

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Turkey successfully implements a National Immunization Schedule that is swiftly updated as a part of the Expanded Immunization Program (EIP). Aside from this vaccine schedule administered to previously-healthy children, there are also vaccination recommendations for children who are at high risk in terms of infections due to immune deficiency, immunosuppressant treatment, congenital or acquired asplenia (splenectomy), cancer, medical treatment (chemotherapy), or radiation treatment (radiotherapy) for cancer, organ transplantation and children and adults traveling to risky regions (4-6). Immunizing healthy adolescents should be considered within the framework of the pediatric vaccination schedule as an integral part of childhood immunization. It is common for every country to implement a vaccination schedule in conformance with its social conditions, incidence features of the diseases, and monetary capabilities. A national immunization schedule, essentially, aims at covering previously healthy children (children with no prior health problems). The contribution of nationwide vaccination in community health and its extraordinary benefits render monetary cost-benefit calculations over vaccines meaningless. Within this context, the national immunization schedule of Turkey is updated accordingly, and its coverage is expanded in light of the country's data.

Following the decisions of the Immunization Advisory Committee of the Ministry of Health of the Republic of Turkey, adopting the National Immunization Schedule implemented free-of-charge nationwide for healthy children and partaking strongly in all efforts for its practice form the basis of the efficacy of national immunization. On the other hand, it would be reasonable that the vaccines administered nationwide to children in various countries but not yet included in the National Immunization Schedule be included in the schedule as soon as possible when deemed appropriate based on the country's data.

Furthermore, it is beneficial and necessary for the healthy, educated, and well-nurtured children who would constitute the country's most significant source and power nationally and internationally to be vaccinated as recommended. Within this framework, it would be a rational approach to recommend the vaccines not yet included in the National Immunization Schedule to be added to the program in a way not hampering the administration of already-available vaccines with appropriate time ranges. Therefore, it is rational to propose an extensive immunization recommendation guideline on behalf of the Turkish Pediatric Infectious Diseases and Immunization Society and update it annually or at more frequent intervals when necessary. It should be recommended, with such a guideline, to administer these vaccines not yet included in the National Immunization Schedule to children with the consent of their families and covering the costs by the family, or private insurances if any.

Physicians are expected to be equipped with up-to-date medical knowledge. This level of knowledge will determine the physicians' approach to prevention, diagnosis, and treatment. Physicians are also legally liable to follow medical advancements relevant to their specialties. This situation is important for vaccine practices that have differed significantly in years. For instance, a physician who does not inform the family of the patient and does not administer the vaccine that is not yet included in the National Immunization Schedule but is recommended at present and approved for practice and use by the Ministry of Health can be held accountable for the problems likely to arise in his/her patient due to this negligence. Within this context and the framework of the recommendations of medical science, physicians must recommend the vaccines that should be administered to children and note her/his recommendation down on patients' files. It would be an appropriate approach to inform the families on the vaccines in question and support their administration to children if the families can afford the costs until these vaccines to be included in the National Immunization Schedule.

Table 1-A. National Immunization Schedule Vaccines of the Ministry of Health of the Republic of Turkey (0-18 years) - 2020.*

Vaccines	Birth	1st month	2nd month	4th month	6th month	12th month	18th month	24th month	1st grade of Elementary School or age 4-6 years	8th grade of Middle School or age 10-12 years
Hepatitis B (HBV)	I	II			III					
BCG			I							
TDaP-IPV-Hib			I	II	III		IV (R)		**TDaP-IPV** (R)	**Td** (R)
OPV					I		II (R)			
Pneumococcal Conjugate Vaccine 13 (PCV13)			I	II		III (12-18 months) (R)				
MMR*						I			II (R)	
Varicella (VV)						I				
Hepatitis A (HAV)							I	II		

Table 1-B. Vaccines not Included in the National Immunization Schedule of the Ministry of Health of the Republic of Turkey (0-18 years) - 2000.*

Vaccines	Birth	1st month	2nd month	4th month	6th month	12th month	18th month	24th month	1st grade of Elementary School or age 4-6 years	8th grade of Middle School or age 10-12 years
Rotavirus (RV)			I	II	(III)					
Tdap, Tdap-IPV									After 4 years of age	
Human Papilloma Virus (HPV)										9-14 years: Total 2 vaccines, ≥15 years: Total 3 vaccines
Inactive Influenza (IIV)					Every year after 6-months of age (at age-appropriate dose and number)					
Meningococcal Conjugate (MCV4)			After 2nd month (according to the approved manufacturer recommendations of the vaccine)							
Meningococcal B Vaccine			After 2nd month (according to the approved manufacturer recommendations of the vaccine)							

* Practice recommendations regarding the vaccines in Table 1-A and Table 1-B are specified in footnotes. Months in Table 1-A and Table 1-B (1, 2, 4, 6, 12, 18, and 24 months) indicate the end of that month; the period between the vaccines are given as months.
Abbreviations: BCG indicates tuberculosis vaccine; HAV, hepatitis A vaccine; HBV, hepatitis B vaccine; HPV, human papillomavirus; IIV, inactive influenza vaccine (3- or 4-valent); MCV4; 4-valent meningococcal conjugate vaccine; MMR, the combination of three vaccines inclusive of measles, mumps, and rubella vaccines; OPV, oral poliovirus vaccines; PCV, pneumococcal conjugate vaccine (13-valent PCV is used in Turkey); RV, rotavirus; Td, tetanus and adolescent/adult type diphtheria vaccines; Tdap tetanus, adolescent/adult diphtheria, and acellular adolescent pertussis vaccines; TDaP, tetanus, diphtheria, and acellular pertussis vaccines; Tdap-IPV, the combination of four vaccines inclusive of tetanus, adolescent/adult diphtheria, acellular adolescent pertussis, and inactive poliovirus vaccines; TDaP-IPV, the combination of four vaccines inclusive of tetanus, diphtheria, acellular pertussis, and inactive poliovirus vaccines; TDaP-IPV-Hib, the combination of five vaccines inclusive of tetanus, diphtheria, acellular pertussis, inactive poliovirus, and *Haemophilus influenzae* type b vaccines; VV, varicella vaccine; I, II, III, 1, 2 and 3rd vaccines; R, rapel/booster dose/doses.

Keeping vaccination records systematically and in a manner that enables their long-time safekeeping is important in terms of health evaluations in ensuing years. Therefore, each child should have a vaccination-and-health card, each vaccine administration should be recorded appropriately on the card and other documents. These cards are evaluated when a physician is consulted for any purpose and to provide an opportunity for vaccinations, families are informed of missing vaccines if any, and missing vaccines be administered and completed at the soonest time possible.

There is no uniform children's vaccination-and-health card at present in Turkey. Thus, the information of every child's vaccination and important health issues needs to be recorded on a card that can be safely kept in a transparent cover, and on a data-automation system so that in the future it could be of guidance to physicians of the child. The quality of the practices on healthcare and vaccination will be increased by keeping all records on one card and a data-automation system, specifying in detail all information related to vaccination (such as date of administration, name of the product, vaccine dosage), bringing the card to all physician visits, and safekeeping it as an important document to be used when necessary.

National data on related diseases is of vital importance for the creation and update of national immunization schedules. Hence, meticulous reporting of vaccine-preventable diseases and adverse effects of the vaccinations by the physicians working selflessly in the field has paramount significance on the contributions it will provide for data accumulation and decision-making process.

General information

Time intervals between the vaccines and the youngest age of administration: Accepted and implemented as 4 weeks = 28 days. Vaccine intervals are counted as months for periods of ≥4 months. Vaccine intervals can be calculated by noting that one month is composed of 4 weeks and by converting the specified time ranges into weeks for periods of <4 months. In practice, it would be easy to adopt that 4 weeks equal to 28 days. It is important to note that the vaccine administered ≤4 days before the youngest age or the shortest period recommended is appropriate and the one administered ≥5 days prior is inappropriate and should not be counted as performed and must be re-administered. For the repetition of the vaccine in question, the shortest period between the two doses of the relevant vaccine must be provided between the inappropriate vaccine and the new one (4).

Apart from particular presentations, serologic investigation for the related infection after or before administering the vaccine is not necessary.

In order not to cause missed opportunities in vaccines, vaccination status of the children brought to the physician for any reason should be evaluated, vaccination card be seen if the child has one and if not, a vaccination card should be produced, the family must be informed about vaccines using simple language, immediate action must be taken to complete the missing vaccines, and the family must be informed of their scheduled visit for the next vaccine. Each vaccination administered must be recorded on the vaccination card, and the family must be informed about the adverse effects of the vaccine. Practice obstacles with no validity should be avoided in vaccinations.

Live vaccines should not be administered in children with immunodeficiency and immune-suppression, and a pediatric infectious diseases specialist must be consulted in this regard if possible (4).

There is no absolute time interval between the administration of two inactive vaccines; vaccine administration can be performed on the same day or at another time interval. The same goes for inactive and live vaccines. Two live virus vaccines administered through the same route, for instance, the MMR and varicella vaccines administered subcutaneously, can be performed at the same visit; however, if these vaccines are not administered simultaneously, at least one-month (28-day) interval should be between the administration of these two live vaccines.

One month has to go by for the tuberculin skin test (TST) to be performed following the administration of live vaccines such as MMR and varicella vaccines.

The Ministry of Health organizes additional mass immunization practices (vaccination campaigns) when deemed necessary. These additional mass vaccinations may not be administered to children with a written document showing that the vaccines in question have been administered fully. However, there is no harm in re-administering the vaccines in children that do not lack the vaccines in question. Moreover, it is necessary to support the additional mass vaccine practices that the Ministry of Health sees fit to be performed nationwide within the framework of national and universal benefit.

BCG (Tuberculosis) Vaccine

- Can be administered between 0-3 months, generally in the 2nd month.
- It is administered by an experienced healthcare professional intradermally to the left shoulder, 0.05 ml (≤1 year of age), or 0.1 ml (>1 year of age).
- It is administered in the first 3 months without TST, and then it is administered by performing TST and if the test is found negative. If the TST is found positive and if TST induration diameter is ≥10 mm in those not having had BCG, the infant is evaluated in terms of tuberculosis infection and tuberculosis disease based on a detailed history, family history, and findings of physical and laboratory evaluations. If there is no symptoms or signs of the disease, latent tuberculosis infection (LTI) treatment is provided with a single anti-tuberculous drug (isoniazid) for 6 months in Turkey (9 months in some other countries) and family screening is performed, and if there is a symptom or finding of the disease, then tuberculosis disease treatment is initiated with multiple anti-tuberculous drugs and family screening is performed, as well.
- After the third month, in cases of absence of the TST solution, BCG vaccination should be postponed until the TST solution has been obtained.
- According to records, in children known to have had BCG (with or without a scar) or in children with the BCG scar, TST does not have to be performed to investigate the efficacy of the BCG vaccination, and BCG administration is not necessary according to the result of the test.
- BCG is administered if the TST is negative (induration diameter <10 mm) in children under the age of 6 who have not received BCG vaccination. BCG administration is not necessary for children over the age of 6 who have not had BCG vaccination.

Hepatitis B Vaccine (HBV)

- Hepatitis B vaccine, an inactive vaccine, composed of HBsAg (hepatitis B surface antigen) as the immunizing antigen is administered intramuscularly.
- Hepatitis B vaccine is administered three times with a schedule of "0, 1st and 6th months" or "0, 1st-2nd and 6th months".
- For the first dose of hepatitis B vaccination in newborns, the mother's HBsAg status and the weight of the newborn are crucial.
- In newborns weighing 2.000 g or over and whose mother is HBsAg negative, the first dose of the hepatitis B vaccine should be administered within the first 24 hours after birth.
- In newborns weighing 2.000 g or under and whose mother is HBsAg negative, the first dose of the hepatitis B vaccine should be administered when the baby reaches 1-month of age (at the end of 1 month).
- In obligatory cases, the first dose of the hepatitis B vaccine can be delayed if the mother is HBsAg-negative, but it should be opted for that the vaccine is administered at the earliest date recommended.
- In newborns whose mother is HBsAg-positive, the first dose of the hepatitis B vaccine must be administered within the first 12 hours following birth and a 0.5 ml hepatitis B immunoglobulin (HBIG) must be administered intramuscularly from another site, no matter the age of pregnancy and birth weight. In newborns weighing 2.000 g or over and whose mother is HBsAg positive, the second dose of the hepatitis vaccine must be ensured to be administered in the 1st month and the third one in the 6th month, and the baby must be evaluated for HBsAg and Anti-HBs 1-2 months after the last vaccine dose.
- In newborns whose mother's HBsAg status is unknown, the mother is acted as HBsAg positive until her status be-

comes clear, and the first dose of the hepatitis B vaccine is administered to the newborn within the first 12 hours after birth no matter the birth weight. In the meantime, the mother is swiftly evaluated in terms of HBsAg within the first 12 hours if possible, and the approach is maintained according to the result of this evaluation.

- In newborns whose, mother's HBsAg status is unknown and who weighs under 2.000 g, a 0.5 ml HBIG must be administered intramuscularly from another site.
- In newborns whose mother's HBsAg status is unknown and who weigh 2.000 g or over, HBIG must be administered as soon as possible if the mother is found HBsAg positive or within 7 days at the latest if the mother's status remains unclear. In newborns weighing 2.000 g or over and who are evaluated as such, the second vaccine dose must be ensured to be administered in the 1st month and the 3rd dose in the 6th month of age, and the infant should be evaluated for HBsAg and Anti-HBs 1-2 months after the last vaccine dose.
- In infants weighing under 2.000 g, a) if the mother is HBsAg-negative, the first vaccine is administered at the end of the 1st month, then after the first dose, the vaccine is repeated in the 1st month and the 5th or 6th month, and thus, the vaccine is administered 3 doses in total. b) if the mother is HBsAg positive or the mother's HBsAg status is unknown, the first dose of the hepatitis B vaccine administered within the first 12 hours after birth is later considered "non-effective" and regarded as "dose 0". Hepatitis B vaccination is repeated in months "1, 2, and 6 or 7" with the schedule of "0, 1st and 5th-6th month", and thus the hepatitis B vaccine is administered 4 doses in total.
- While hepatitis B vaccination is implemented with the "month 0, 1st and 6th -month" schedule, the second dose of hepatitis B vaccine should be administered at least 4 weeks after the first dose and the third dose of hepatitis B vaccine should be administered at least 16 weeks after the first dose and at least 8 weeks after the second dose. The last dose (3rd or 4th) of the hepatitis B vaccine in infants can be administered at the end of the 24th week (164 days) at the earliest.
- The newborns that could not be vaccinated at birth should receive hepatitis B vaccine doses with the "0, 1st and 6th -month" schedule.
- In a child previously known not to have had hepatitis B vaccination, it is unnecessary to perform serologic tests before the start of hepatitis B vaccination if there is no other reason.
- There is no need for any testing to determine serologic status following the hepatitis B vaccination series in infants whose mother is HBsAg-negative.
- A serologic evaluation is made on the 9th-12th month follow-up after the hepatitis B vaccination series in infants whose mother is HBsAg-positive. This evaluation must be made before the age of 9 months to increase the possibility of detecting late-onset hepatitis B virus infections.
- In other clusters under high risk of hepatitis B infection and carriage (those sharing the same household with HBsAg-positive persons, those under risk of sharp object injuries due to their professions or workplace environment, and hemodialysis patients), serologic evaluation is recommended 1-2 months after the last dose of the hepatitis B vaccine.
- In serologic evaluation, HBsAg negativity and a ≥10 mIU/ml anti-HBs concentration prove that the infant did not experience infection and developed appropriate immune protection with vaccination. If HBsAg is negative and anti-HBs concentration is <10 mIU/ml following a 3-dose hepatitis B vaccination, an additional dose of the hepatitis B vaccine must be administered to the infant as the 4th one and a serologic evaluation must be made 1-2 months after the 4th dose. Infants with HBsAg negativity and a ≥10 mIU/ml anti-HBs concentration following the 4th dose of the hepatitis B vaccination are considered as infection-free and sufficiently immune. Infants with HBsAg negativity and a <10 mIU/ml anti-HBs concentration following the 4th dose of the hepatitis B vaccination must be vaccinated twice more with at least a 2-month interval, and a serologic evaluation must be performed 1-2 months after the 6th dose. When Anti-HBs concentration is found again as <10 mIU/ml, continuing hepatitis B vaccination is not recommended.
- In the event of non-responsiveness (anti-HBs <10 mU/ml) to a 3-dose vaccination series in hepatitis B vaccination, the other option is to repeat immunization with additional 3 doses of the hepatitis B vaccine if the child is not HBsAg positive. This second vaccine series is implemented with the "0, 2nd and 4th-month" (at 2-month intervals) or "0, 1st and 6th -month" schedules, and a serologic evaluation is performed again 1-2 months after the last (6th) dose of vaccine. If serologic conversion response is not found following this second 3-vaccine series, non-responsiveness to subsequent vaccines is quite high, and thus a new hepatitis B vaccine or vaccine series is not needed and recommended.
- Hepatitis B vaccine is implemented by the age limit and quantity of antigen set by the manufacturer as a pediatric dose.
- The hepatitis B vaccines containing single-antigen (only HBsAg) should be used in infants younger than six weeks of age. Apart from the single-antigen hepatitis B vaccines

in Turkey, a combination vaccine (6-valent vaccine of HBV-Tdap-IPV-Hib) containing hepatitis B vaccine and other vaccines is also approved. This 6-valent combination vaccine containing hepatitis B vaccine can be administered at the 6th week at the earliest. In infants older than 6-weeks, a combination vaccine containing hepatitis B vaccine can be used. In infants whose mother is HBsAg-negative, following the single-antigen hepatitis B vaccine administered during the newborn period, the vaccination can be continued with the 6-valent combination vaccine with a total of 3 doses administered in the 2nd, 4th, and 6th months with two-month intervals. It does not constitute a problem to have had a total of 4 doses of the hepatitis B vaccines in children in the hepatitis B vaccine is administered at birth and the 6-valent combination vaccine is used afterward at the 2nd, 4th, and 6th months.

- The 6-valent combination vaccine containing the hepatitis B vaccine (HBV-Tdap-IPV-Hib) should not be used as the booster dose of the 5-valent combination vaccine (Tdap-IPV-Hib) administered in the 18th month; there is not sufficient data on efficiency and reliability on this matter.

Pertussis, Diphtheria, Tetanus, Poliomyelitis, and *Haemophilus influenzae* Type B Vaccines:

In this context, the oral poliomyelitis vaccine (OPV) is a live vaccine administered orally, and the others are inactive vaccines administered intramuscularly.

Combination vaccine containing acellular (a) Pertussis (P), Diphtheria (D), Tetanus (T), inactive poliomyelitis (inactive poliovirus), conjugate *Haemophilus influenzae* type b vaccines (five-valent Tdap-IPV-Hib vaccine), adult diphtheria (d)-Tetanus (T) combination vaccine (Td) and Tetanus (T) vaccine

- Tdap vaccine is administered together with IPV and Hib as a combination vaccine (Tdap-IPV-Hib).
- The Tdap-IPV-Hib combination vaccine is administered three times as basic vaccination series at two-month intervals in the 2nd, 4th, and 6th months, and a booster dose is administered in the 18th-24th months (1st booster) and thus is implemented 4 times in total. In terms of serologic transformation, it does not make a difference to perform the basic vaccination series in the 2nd, 3rd, and 4th months during epidemics. The fourth Tdap-IPV-Hib vaccine dose can be administered at the end of the 12th month and at least 6 months after the 3rd dose. If the 3rd and 4th doses are administered with at least 4-month intervals, then the fourth vaccine dose does not need to be repeated. If the fourth vaccine dose is administered at age ≥4 years, a fifth vaccine dose containing Tdap (4-valent; Tdap-IPV combination) may not be administered.
- In company with the 3rd and 4th vaccine doses (6 and 18 months) of the Tdap-IPV-Hib vaccination series, live oral poliomyelitis vaccine (OPV) doses are additionally implemented 2 times in total.
- Conditions preventing the administration of the Tdap vaccine are the same as those of BDT. Adverse effects of acellular pertussis vaccines are fewer.
- The upper age limit for the Tdap-IPV-Hib vaccine is 72 months.
- At the age of middle school 8th grade, adult diphtheria-tetanus combination vaccine (Td) is administered and recommended to be repeated every 10 years.
- When Td is implemented instead of tetanus (T) vaccine, a booster dose of the childhood diphtheria vaccination is administered and previously non-immune persons susceptible to diphtheria are immunized. In every case where tetanus vaccination is needed, including pregnancy, Td should be implemented.

Acellular (a) adolescent/adult pertussis (p)- adolescent/adult diphtheria (d)-Tetanus (Tdap) vaccine and acellular (a) adolescent/adult pertussis (p)- adolescent/adult diphtheria (d)-Tetanus (T)-inactive poliomyelitis (inactive poliovirus, IPV) vaccine (Tdap-IPV)

- In practice, there are two Tdap vaccines of two manufacturers; practice recommendations for Tdap vaccines are for ages >4 years (5). Both vaccines are approved in Turkey.
- In practice, there are two Tdap-IPV vaccines of two manufacturers; practice recommendations for Tdap-IPV vaccines are for ages >4 years.
- Tdap and Tdap-IPV vaccines can be administered after any vaccine covering "D", "d" or "T" toxoids without considering the time elapsed.
- For those without diphtheria and tetanus vaccination at age >7 years, one of the 3 vaccinations of Td in "month 0, 1st and 6th-12th months" is recommended to be Tdap or Tdap-IPV (and if possible, the first vaccine).
- All adolescents are recommended to be immunized with Tdap at age 11-12 years.
- Those having received Tdap vaccination as part of Td vaccination (month 0, 1st and 6th-12th months) at age 7-10 years due to not having had vaccination does not require Tdap again at age 11-12 year.
- One dose of Tdap should be administered to children at the age of 11-18 years and not having had the Tdap vaccine before.
- It is recommended to administer a single dose of Tdap vaccine instead of Td administered at 10-year intervals.

- In every pregnancy (preferably between 27th and 36th weeks), the Tdap vaccine is recommended to be administered no matter the time elapsed between the previous Td or Tdap vaccine (5,6).
- If the Tdap vaccine was not administered during pregnancy, the mother must be vaccinated with Tdap right after delivery.
- All family members, caretakers, and family elders of all ages in close contact with notably the newborn and children under the age of 1 are recommended to be vaccinated with Tdap.
- Healthcare workers must be vaccinated with Tdap.
- In cases where Tdap is recommended, the Tdap-IPV vaccine can also be administered. Even though there is no clear recommendation of Tdap-IPV practice during pregnancy, the Tdap-IPV vaccine is administered to pregnant women in the United Kingdom.
- TDaP vaccine or any vaccine containing TDaP, if administered inappropriately a) at the age of 7-10 years, it can be accepted as the adolescent (11-18 years) dose instead of Tdap vaccine, or a Tdap vaccine can be administered at the age of 11-12 years; b) if administered at the age of 11-18 years, it should be accepted.

Poliomyelitis Vaccines: Inactive Poliovirus Vaccine (IPV) and Live Oral Poliovirus Vaccine (OPV)

- Poliomyelitis vaccine can be administered as an inactive poliovirus vaccine (IPV) and live oral poliovirus vaccine (OPV).
- In the National Immunization Schedule of Turkey, the first two doses of the poliomyelitis vaccine are administered as IPV in the Tdap-IPV-Hib combination vaccine and the next two doses are administered as IPV in the Tdap-IPV-Hib combination vaccine and OPV simultaneously.
- OPV preserves its significance in practice due to the location and circumstances of Turkey. Therefore, the national immunization schedule recommends two doses of OPV to all children who do not have any impeding problems.
- Since it is a live virus vaccine, OPV is not recommended in children with immune disorders (immunosuppressed or immunodeficient, those receiving cancer treatment) and in children who have a family member with immune problems, and this condition should be questioned before OPV practice. In these cases, all poliomyelitis vaccines are administered as IPV through the Tdap-IPV-Hib combination vaccine or Tdap-IPV combination vaccine.
- With the recommendation of the World Health Organization (WHO), instead of the 3-valent OPV containing type 1, 2, and 3 polioviruses, the 2-valent OPV containing type 1 and 3 polioviruses have begun to be administered as of 2016 in Turkey; IPV contains type 1, 2 and 3 polioviruses.

***H. influenzae* type b (Hib) vaccine**

- Hib vaccine is administered four times in total, including three doses of basic vaccination series with two-month intervals (2nd, 4th, and 6th months) within the Tdap-IPV-Hib combination vaccine and within the 4th Tdap-IPV combination vaccine as booster (4th) dose in the 18th (-24th) months. A single dose Hib vaccine or a vaccine containing Hib is sufficient for immunity in non-vaccinated children at the age of ≥15 months - 5 years. Children who have not received the primary series and booster vaccine in 0-15 months, children who have not been previously vaccinated, and those who have not received a single Hib vaccine once in >15 months are considered non-vaccinated.
- After the age of 5 years, healthy children who are not at risk do not require the Hib vaccine.
- In children aged 12-60 months at high risk for Hib disease (splenic function disorder, congenital or acquired asplenia, sickle-cell anemia, HIV infection, immunoglobulin deficiency, early complement deficiency, immunosuppressant drug treatment), it is recommended to administer 2 doses of Hib vaccine with 8-week intervals if Hib vaccine has been administered 0-1 time at the age of 1 and younger and to administer a single dose of Hib vaccine if Hib vaccine has been administered 2-3 times at the age of <12 months.
- In children under the age of 5 years receiving immunosuppressant drugs or radiotherapy, if Hib vaccination is administered during treatment or <14 days prior, it should be repeated at least 3 months after the end of the treatment.
- In stem cell recipients, no matter the vaccination history, the Hib vaccine should be administered 3 times at least 4-week intervals 6-12 months after the successful transplantation.
- It is recommended that non-vaccinated children at the age of 15 months-18 years in whom elective splenectomy is performed should be administered with a single dose Hib vaccine or any vaccine containing Hib at least 14 days before the procedure.
- In children of 5-18 years of age at high risk for Hib disease (splenic function disorder, congenital or acquired asplenia, sickle-cell anemia, HIV infection, immunoglobulin deficiency, early complement deficiency, immunosuppressant drug treatment) without prior vaccination, it is recommended to administer single dose Hib vaccine.
- In Turkey, conjugate *H. influenzae* type b (Hib) vaccines of different manufacturers are approved. However, scarcity

in demand makes it difficult to access these single-valent Hib vaccines in times of need. In these times, combination vaccines containing Hib are used according to the patient's age.

Pneumococcal Vaccines: Conjugate Pneumococcal Vaccine (PCV), Polysaccharide Pneumococcus Vaccine (PPSV)

- Pneumococcal vaccines are inactive and administered intramuscularly.
- In November 2013, the 13-valent pneumococcal conjugate vaccine (PCV-13) replaced the 7-valent pneumococcal conjugate vaccine (PCV-7) which was included in the National Immunization Schedule of Turkey in November 2008. The 10-valent PCV (PCV-10) is also approved in Turkey. Information in this section regarding PCV is given for PCV-13 which is included in the National Immunization Schedule.
- Until February 2019, PCV-13 was administered as three doses within the basic vaccination series in the 2nd, 4th and 6th months and fourth as a booster dose in the 12th month (can be administered between 12 and 15 months). As of February 2019, PCV-13 has started to be administered twice in the 2nd and 4th months as basic vaccination series and third as a booster dose in the 12th month (can be administered between 12 and 15 months).
- PCV-13 can be administered after the first 6 weeks of life.
- In children under the age of 1 year, the time elapsed between the first and second PCV-13 doses should be at least 4 weeks (1 month) and the time elapsed between the second PCV-13 dose and the third (booster) dose should be at least 8 weeks (2 months). The booster dose should not be administered before the 12th month.
- In cases where PCV-13 has not been administered before;
  - In children of 2-6 months of age, a total of 3 vaccines including 2 doses of basic vaccination at the 1-2-month interval and a booster dose after the age of 1 year are recommended.
  - In children aged 7-12 months, two doses of basic vaccination with at least 1-month interval should be administered, and after the age of 1, a booster dose is administered at least 8 weeks after the last dose, making it a total of three doses.
  - In children of 12-24 months of age, two doses of PCV-13 with a 2-month interval are recommended.
  - In children of 24-60 months of age who are not in any risk clusters, and are previously non-vaccinated or inadequately vaccinated, a single dose of PCV-13 is recommended.
- No additional PCV-13 dose is needed in children who have received PCV-13 once after the age of 2 years.
- Pneumococcal polysaccharide vaccine (PPSV-23) contains purified capsular polysaccharides of 23 pneumococci serotypes that most frequently cause the disease and is not recommended to be administered instead of or in addition to PCV-13 in healthy individuals under no risks but is administered after the age of 2 in persons with a high risk of invasive pneumococcal disease.
- In children requiring PPSV-23, PCV-13 vaccination should be completed before PPSV-23 if possible, and at least 8 weeks (2 months) should pass between PCV-13 and PPSV-23 vaccinations.
- In children aged 0-11 months with high-risk diseases in terms of invasive pneumococcal disease, including chronic heart disease (especially cyanosis congenital heart disease and heart failure), chronic lung disease (asthma requiring high-dose oral steroid treatment included), diabetes mellitus, cerebrospinal fluid (CSF) leakage, cochlear implant, sickle cell anemia, other hemoglobin disorders, spleen function disorder, congenital asplenia, HIV infection, chronic kidney failure, nephrotic syndrome, diseases requiring immunosuppressant drugs or radiotherapy (cancer, leukemia, lymphoma, Hodgkin's disease), solid organ transplant or congenital immunodeficiency;
  - Four doses of PCV-13 should be administered in the 2nd, 4th, 6th , and 12th months if not priorly vaccinated (PPSV-23 is not given at age <2 years).
- In children aged 12-23 months with high-risk diseases in terms of invasive pneumococcal disease, including chronic heart disease (especially cyanotic congenital heart disease and heart failure), chronic lung disease (asthma requiring high-dose oral steroid treatment included), diabetes mellitus, cerebrospinal fluid (CSF) leakage, cochlear implant, sickle cell anemia, other hemoglobin disorders, spleen function disorder, congenital asplenia, HIV infection, chronic kidney failure, nephrotic syndrome, diseases requiring immunosuppressant drugs or radiotherapy (cancer, leukemia, lymphoma, Hodgkin's disease), solid organ transplant or congenital immunodeficiency;

  Two doses of PCV-13 with at least an 8-week interval should be administered if not priorly vaccinated (PPSV-23 is not given at age <2 years).
- In children aged 2-5 years with high-risk diseases in terms of invasive pneumococcal disease, including chronic heart disease (especially cyanosis congenital heart disease and heart failure), chronic lung disease (asthma requiring high-dose oral steroid treatment included), diabetes mellitus, cerebrospinal fluid (CSF) leakage, cochlear implant, sickle cell anemia, other hemoglobin disorders, spleen

function disorder, congenital asplenia, HIV infection, chronic kidney failure, nephrotic syndrome, diseases requiring immunosuppressant drugs or radiotherapy (cancer, leukemia, lymphoma, Hodgkin's disease), solid organ transplant or congenital immunodeficiency;

- A single dose of PCV-13 should be administered if three doses of PCV-13 have been administered before.
- Two doses of PCV-13 with at least an 8-week interval should be administered if not priorly vaccinated or vaccinated with PCV-13 one or two times.
- Two doses of PCV-13 with at least an 8-week interval should be administered if not priorly vaccinated or vaccinated with PCV-7 in three doses or less or even if a single dose of PCV-13 has been administered.
- A single dose of PCV-13 should be administered if 4 doses of PCV-7 have been administered or the vaccination series have been completed age appropriately.
- PPSV-23 should be administered at least 8 weeks after the last PCV-13 in children if PPSV-23 has not been administered before.
- In children aged 6-18 years with solid organ transplantation and with high-risk diseases constituting problems in terms of invasive pneumococcal disease, including chronic heart disease (especially cyanotic congenital heart disease and heart failure), chronic lung disease (asthma requiring high-dose oral steroid treatment included), diabetes mellitus, cerebrospinal fluid (CSF) leakage, cochlear implant, sickle cell anemia, other hemoglobin disorders, spleen function disorder, congenital asplenia, congenital or acquired immune deficiency, HIV infection, chronic kidney failure, nephrotic syndrome, diseases requiring immunosuppressant drugs or radiotherapy (cancer, leukemia, lymphoma, Hodgkin's disease);
- A single dose of PCV-13 and a single dose of PPSV-23 at least 8 weeks after PCV-13 should be administered if PCV-13 and PPSV-23 have not been administered before.
- A single dose of PPSV-23 should be administered at least 8 weeks after the last PCV-13 vaccine if PCV-13 has been previously administered but PPSV-23 has not.
- A single dose of PCV-13 should be administered at least 8 weeks after the last PPSV-23 vaccine if PCV-13 has not been previously administered but PPSV-23 has.

- It is recommended for children aged 6-18 years with problems regarding solid organ transplant and with high-risk diseases for invasive pneumococcal disease, including chronic heart disease (especially cyanotic congenital heart disease and heart failure), chronic lung disease (asthma requiring high-dose oral steroid treatment included), diabetes mellitus, cerebrospinal fluid (CSF) leakage, cochlear implant, sickle cell anemia, other hemoglobin disorders, spleen function disorder, congenital asplenia, congenital or acquired immune deficiency, HIV infection, chronic kidney failure, nephrotic syndrome, diseases requiring immunosuppressant drugs or radiotherapy (cancer, leukemia, lymphoma, Hodgkin's disease), to be vaccinated only one more time with PPSV-23 5 years later.
- PPSV-23 vaccination is sufficient in children aged 6-18 years who do not have immunodeficiency but suffer from chronic heart disease, chronic lung disease, diabetes mellitus, and chronic liver disease. However, its efficiency increases if PCV-13 is administered priorly. In this case, PPSV-23 is administered with at least an 8-week interval following PCV-13.

Measles, mumps, rubella (MMR) vaccine

- MMR is a live vaccine containing attenuated measles, mumps, and rubella viruses, recommended to be administered subcutaneously; however, if administered intramuscularly by mistake, a repetition of the vaccine is not required.
- MMR vaccine is administered in a total of two doses, the first being implemented in the 12th month and the second between the ages of 4-6 years or in kindergarten/nursery class of the elementary school as a booster dose.
- The two MMR vaccines can be administered at least 4 weeks (1 month) apart.
- In necessary conditions like a journey to problematic countries in terms of vaccination against measles, mumps, and rubella infection or the possibility of an epidemic, infants older than 6 months can be vaccinated with a single dose of MMR. However, the MMR vaccine administered between 6-12 months should be considered missing, regarded as "vaccine dose zero", and these infants should be vaccinated twice with at least a 4-week (1-month) interval after the age of 1 year.
- If children over the age of 1 year (1-18 years) and adults have not been vaccinated with MMR after the age of 1 year and if they do not have a history or evidence of being infected with one of the three diseases, they should be vaccinated with MMR twice with at least 4-week (1-month) interval, and those who have been vaccinated once should be vaccinated again to have two doses of the MMR vaccine.

Varicella vaccine (VV):

- Varicella vaccine is a live vaccine containing attenuated varicella virus, recommended to be administered subcutaneously; however, if administered intramuscularly by mistake, a repetition of the vaccine is not required.

- Varicella vaccine is administered once in the National Immunization Schedule of Turkey in the 12th month.
- Along with several other countries administering the varicella vaccine once, the recommendation and practice commonly accepted in the world are that the first vaccine is administered in the 12th-15th months (>1 year) and the second at age 4-6 years, as two doses in total. This practice is also adopted by the Turkish Pediatric Infectious Diseases and Immunization Society.
- Varicella vaccine is recommended to be administered twice with 4-8-week (1-2-month) intervals (at least 4-week) to every adult and non-vaccinated child after the age of 1 year without history or evidence of varicella infection.
- In previously non-vaccinated children at the age of ≤13 years, a 3-month interval between 2 varicella vaccines is recommended; however, the second vaccine can be administered at least 4 weeks after the first one.

Hepatitis A vaccine (HAV)

- Hepatitis A vaccine is inactive and administered intramuscularly.
- Hepatitis A vaccine is recommended to be administered twice with at least a 6-month interval in all ages after the first year and in non-vaccinated persons and those not having history or evidence of hepatitis A infection.
- Hepatitis A vaccine is approved to be administered to those older than 12 months in Turkey.
- However, due to the limited number of studies claiming the elevation of antibody levels secondary to infection in mothers in Turkey and the insufficiency of the studies regarding the efficiency of early vaccination, hepatitis A vaccine is administered twice with a 6-month interval on 18th and 24th months of age in Turkey.
- In necessary conditions like a journey to problematic countries in terms of vaccination against hepatitis A infection or the possibility of an epidemic, infants older than 6 months can be vaccinated with a single dose of HAV. However, the HAV vaccine administered between 6-12 months should be considered missing, regarded as "vaccine dose zero", and these infants should be vaccinated twice with at least a 4-week (1-month) interval after the age of 1 year.
- Hepatitis A vaccine is generally implemented as a pediatric dose to those under the age of 18 and as an adult dose to those over the age of 18; the content of HAV administered to adults is usually twofold of that of the pediatric dose.

Certain vaccines (rotavirus vaccine, influenza vaccine, human papillomavirus vaccine, meningococcal ACWY vaccine, and meningococcal B vaccine) not yet included in the National Immunization Schedule of Turkey but are known for their efficiency and safety and implemented in many countries nationwide are recommended to be additionally administered by having families or private insurances cover their expenses. Practice recommendations regarding these vaccines are presented below.

Rotavirus (RV) vaccine (RVV)

Similar to the data of other countries, studies conducted in Turkey show that rotavirus is an important agent in children followed in outpatient clinics and as inpatients for acute diarrhea. Even though rotavirus infection does not cause a significant level of mortality and long-term complications in Turkey, the recommendation of the use of rotavirus vaccine in Turkey is based on the fact that rotavirus disease load is much and leads to significant healthcare expenses.

- Rotavirus vaccine is an orally administered live vaccine containing attenuated pathogens.
  - Two rotavirus vaccines developed by two different manufacturers are in use and approved in Turkey:
  - One-valent human RV (RV1) vaccine (Rotarix™): Implemented twice with at least 4-week (1-month) interval; recommended to be administered in months 2 and 4.
  - Five-valent bovine-human RV breed (RV5) vaccine (Rotateq™): Implemented three times with at least 4-week (1-month) interval; recommended to be administered in months 2, 4, and 6.
- The first RVV dose should be administered between 6-15 weeks; after the end of the 6th week the earliest and before the end of the 15th week (15 weeks and 0 day).
- There should be 4-10 weeks between the rotavirus vaccine doses of the vaccination series, constituting whether two or three doses, should be completed before the end of the 8th month (8 months and 0 day), and no rotavirus vaccine dose should be administered after the 8th month even if vaccination has not been completed.
- Rotavirus vaccines can be implemented simultaneously with the other vaccines administered to children.
- There is no data on the completion of the vaccination with different rotavirus vaccines; however, it is not recommended.
- Rotavirus vaccines should not be administered to those with severe combined immunodeficiency.
- Rotavirus vaccine can be implemented by informing the family and with their written consent considering that its benefit will predominate the risk of the disease in immunodeficient and immunosuppressed persons including HIV infection.

Seasonal inactive influenza vaccines (IIV)

Influenza virus infections tend to progress more severely particularly in infants and provide a basis for other severe respiratory infections. It should be kept in mind that influenza infections cause epidemics especially in school-aged children every year and that these epidemics starting in children spread to adults and lead to losses in education and economic difficulty and loss of working day for working parents and the healthcare system. Seasonal influenza vaccines cannot protect those vaccinated from all flu infections. Therefore, before the influenza epidemic period (season) every year, an influenza vaccine with different coverage developed against the influenza viruses presumably considered to create epidemics is used. All efforts aimed at implementing influenza vaccination to all children older than 6 months by informing families must be supported.

- There are 3-valent and 4-valent inactive influenza vaccines (IIV-3, IIV-4) administered intramuscularly, attenuated live influenza vaccines administered nasally, and inactive influenza vaccines administered intracutaneously. 3-valent and 4-valent, live and attenuated intranasal influenza vaccine that has been adapted to cold (LAIV-3, LAIV-4) and cell culture and recombinant hemagglutinin-based influenza viruses approved for adults in some countries like the USA are not yet approved in Turkey.
- Live and attenuated intranasal influenza vaccine (LAIV) that can be administered every year (>2 - 49 years) is not approved in Turkey. LAIV is recommended not to be administered to persons showing a serious allergic response to any influenza vaccine or their components, having asthma or wheezing (2-4 years), having used drugs against influenza in the last 48 hours, using aspirin or aspirin-containing drugs (2-18 years), immunosuppressed persons, to persons with congenital or acquired asplenia, cochlear implant, cerebrospinal fluid (CSF) leakage, to pregnant women, and to persons in close contact with severely immunosuppressed individuals.
  - The term "influenza period" indicates the period between November 2020 and April 2021 in the northern hemisphere for the 2020-2021 period. Vaccine coverage recommended by the World Health Organization (WHO) for a new influenza period can sometimes be the same as the previous period. IIV-3 is composed of two influenza A and one influenza B (Yamagata or Victoria line) vaccines foreseen to have the highest possibility of generating an epidemic; IIV-4 additionally contains the other B vaccine (Yamagata or Victoria line) that is absent in the 3-valent vaccine.
- In Turkey, different manufacturers have different vaccines approved:
  - 3-valent inactive influenza vaccines (IIV-3) administered intramuscularly for ≥6 months of age
  - 4-valent inactive influenza vaccines (IIV-4) administered intramuscularly for ≥6 months of age
- The approved influenza vaccines are not yet included in The National Immunization Schedule of Turkey.
- Recommendations for influenza immunization should be implemented taking into account ≥6 months of approval in children for IIV-3 and IIV-4.
- Seasonal influenza vaccine is implemented every year (>6 months). Since the vaccine is prepared again every year for the virus types foreseen to cause epidemics, it should be repeated every year to sustain protection. Vaccination can be done between September and April. However, it should be preferred to be administered to children who will receive the vaccine for the first time and be given 2 doses before the start of the influenza virus infection season or at its immediate start (September-October-November).
- Patients with chronic diseases and immune problems in whom influenza infection progresses severely, family members of these patients and those of children under the age of 5 years, and healthcare workers should be primarily vaccinated, and all healthy children, adolescents, and adults should be tried to be vaccinated.
- IIV-3 and IIV-4 are initially recommended to be implemented in children of ≥6 months of age with a high risk of severe influenza. Since children between 6 months and 5 years of age, lung diseases like asthma and cystic fibrosis, diseases suppressing the respiratory system or increasing the risk of aspiration, hemodynamically significant heart diseases, diseases requiring long-term aspirin treatment (rheumatoid arthritis, Kawasaki disease), chronic renal and liver diseases and neuropathy, sickle cell disease and other hemoglobin disorders, presence of chronic metabolic diseases like diabetes mellitus, long-term aspirin treatment, immunosuppressant diseases or treatment, living in nursing homes, obesity, and pregnancy or the possibility of pregnancy constitute a high risk in terms of severe or problematic influenza disease, persons in these conditions should be vaccinated initially. Persons with severe or problematic influenza disease, children younger than 5 years, household contacts and caretakers of infants younger than 6 months, and children in close contact with those under high risk should also be initially vaccinated.
- Persons with asthma or other chronic lung diseases, chronic heart disease, diabetes mellitus, and other chronic metabolic diseases, chronic kidney failure and children and adults with disorders of the hemoglobin structure, immunosuppressed individuals and those receiving dru-

gs suppressing the immune system, children at the age of 6 months-18 years receiving chronic acetylsalicylic acid, individuals older than 65 years and those living in nursing homes constitute the risk clusters of the repayment cover of the seasonal influenza vaccine by the Social Security Institution.

- Efforts should continue to administer the annual influenza vaccine to children between 6 months and 18 years apart from those in high-risk groups.
- Seasonal influenza vaccination is implemented twice with an at least 4-week (1-month) interval in children aged 6 months-8 years that will be vaccinated for the first time and once in the following years. The first practice in persons older than 8 years is done once and continued once annually. In case of significant antigen shift and global pandemics, regularly vaccinated children can be administered with the influenza vaccine twice for that year.
- 3-valent inactive influenza vaccines (IIV-3) are recommended to be administered at pediatric doses for children aged 6 months-3 years (0.25 ml) and at adult doses for children aged 3 and over and adults (0.5 ml). Since there is no pediatric IIV-3 in Turkey, IIV-3 vaccination is carried out at half-adult dose (0.25 ml) in 6-36 months and a full adult dose (0.5 ml) at age 3 and older.
- 4-valent inactive influenza vaccines (IIV-4) are standardized in quantity (0.5 ml), and it is recommended to administer the full dose of IIV-4 in all children older than 6 months and adults.

Human papillomavirus (HPV) vaccine

Many studies have shown protective effects of the human papillomavirus (HPV) vaccine against cervical cancer and warts, developed against the HPV that has a causative place in the formation of cervix, vagina, vulva, anus, and penile cancers and warts in the genitalia. Studies report the high efficiency and safety of HPV vaccines. When the HPV vaccine is administered during puberty, it provides more efficient protection compared to that administered at later ages.

- The HPV vaccine is an inactive vaccine administered intramuscularly.
- There are two HPV vaccines developed by two different manufacturers and implemented in the national immunization schedules of many countries. These vaccines also approved in Turkey are not yet included in the National Immunization Schedule of Turkey:

  Cervarix™

  - 2-valent HPV vaccine (HPV-2) (Cervarix™): Provides immunity against 2 HPV types (16,18) responsible for 70% of cervical cancers.

  Gardasil™ and Gardasil 9™

  - 4-valent HPV vaccine (HPV-4) 4 (Gardasil™): Provides immunity against 4 HPV types responsible for 70% of cervical cancers (16, 18) and 90% of genital warts (6, 11).
  - 9-valent HPV vaccine (HPV-9) (Gardasil 9™): Gardasil 9™, which is a 9-valent vaccine (6, 11, 16, 18, 31, 33, 45, 52, 58) developed with the addition of new component vaccines against 5 other HPV types (31, 33, 45, 52, 58) responsible for cervical cancer at a possible rate of 20%, is implemented on girls, women, and men aged 9-26 years since December 2014. Gardasil 9™ is also approved in Turkey; however, has not been put into practice yet.

- HPV-2 is approved with a lower age limit of 9 years and no upper age limit, while HPV-4 is approved for the ages of 9-26 years.
- HPV-4 and HPV-9 vaccines can be administered at older ages; for instance, the same immunization schedule is recommended for the vaccine practice at ages 27-45 in the United States of America.
- HPV-4 and HPV-9 are also approved for boys and adult men, and HPV-4 or HPV-9 is administered to men in the national immunization schedules of many countries. There is no recommendation as to the practice of HPV-2 in men.
- HPV vaccines can be simultaneously administered with other vaccines of the adolescent period.
- HPV vaccines (HPV-2, HPV-4, HPV-9) are recommended to be administered 2 times with a "month 0 and 6th -month" schedule at ages 9-14 and 3 times with a "month 0, 1st-2nd and 6th months" schedule at age ≥15 years.
- In Turkey, HPV vaccines are approved to be administered twice with the "month 0 and 6th -month" schedule at ages of 9-14 years. The time elapsed between the two doses should not be shorter than 5 months, and if the interval is shorter than 5 months, then the second dose should be repeated.
- For age ≥15 years, HPV vaccines are implemented three times with the "month 0, 1st-2nd, and 6th months" schedule. The second HPV vaccine dose should be administered at least 4 weeks (1 month) after the first dose, the third vaccine dose should be administered at least 12 weeks (3 months and at least 5 months after the second and first doses, respectively. The vaccination series should be completed in a year.
- HPV vaccines are strongly recommended to be administered between ages 9-26 years, and initially, girls between 11-12 years and those between 13-18 years with no prior vaccination are recommended to be vaccinated.

- Together with the discussions as to the most appropriate age of HPV vaccination, HPV immunization implemented between the ages of 9-14, especially between 9-11, with two doses of HPV vaccine seems to be the most reasonable and cost-efficient method for Turkey. However, adopting a flexible time range covering older ages would be appropriate in terms of having any social and cultural obstacles create problems in a practice as such.

Meningococcal Vaccines: 4-Valent (ACWY) Meningococcal Conjugate Vaccines (MCV4), Meningococcal B Serotype Vaccine

Meningococcal vaccines are inactive and administered intramuscularly.

The production of meningococcal polysaccharide vaccine (MPV) has been discontinued.

4-Valent (ACWY) Meningococcal Conjugate Vaccines (MCV4)

MCV4 covers the purified capsular polysaccharides of the four most common meningococcal serogroups (A, C, W, Y) causing the disease.

1-valent (A serogroup), 2-valent (A+C serogroups), or MCVs with another coverage implemented in several countries are not approved in Turkey.

- Three different, 4-valent (A, C, Y, W) serogroup capsule polysaccharides conjugated to different carrier proteins MCV4 vaccines manufactured by different companies are approved in Turkey:
  - MenACWY-CRM (Menveo™): Non-toxic CRM-197 mutant diphtheria toxin has been used as the carrier protein. MenACWY-CRM is approved in Turkey to be used after the 2nd month. It is recommended to be administered at different age groups as follows: a) 3 times with at least 2 months apart in children aged 2-6 month and 4th time after the first year of age; b) two times provided that the second dose is administered at least 2 months after the first dose and after the 1 year of age in children aged 6 months-2 years; c) single dose in children older than 2 years and in adults. The use of MenACWY-CRM is approved until the age of 55 in Turkey. There are limited data on the use of MenACWY-CRM in persons aged 56-65, and there is no data on its use in persons aged 65 and older.
  - MenACWY-DT (Menactra™): Diphtheria toxoid has been used as the carrier protein. It is approved in Turkey to be used in children aged 9 months-11 years (two doses at 3-month intervals in children between 9-23 months; single dose after the age of 2 years).
  - MenACWY-TT (Nimenrix™): Tetanus toxoid has been used as the carrier protein. It is approved in Turkey to be used after 6 weeks of age. Its practice regulation in different ages is as follows: a) two doses with a 2-month interval and a third dose after 1 year of age in children aged 2-6 months; b) two doses provided that the second dose is administered at least 2 months later and after reaching 1 year of age in children aged 6 months to 1-year; c) single dose in children older than 1 year, and adolescents and adults. Despite limited data, there is a report that it has been successfully administered in a 103-year-old person.
- MCV-4 vaccines are included in the national immunization schedules of many countries to be administered to healthy children.
- In healthy children, the recommendations are as follows: In the United Kingdom (UK), MCV-4-CRM or MCV4-T is administered as a single dose to healthy children at age 14 years (5); in the United States of America (USA), a total of two doses of MCV-4-CRM or MCV4-D is administered to healthy children aged at age 11-12 and 16 years; if vaccination has not been done before, those at the age of 13-18 years receive the first dose at 13-15 ages and the second dose at 16-18 ages (there should be at least 8 weeks between the two doses), and if the first dose is administered at age ≥16, the second dose does not need to be administered, and children aged 11-18 years with HIV infection should be vaccinated twice with an at least 8-week interval (6). MCV-4 vaccines are implemented as part of the infancy period national immunization schedules in countries like Argentina, Australia, and Saudi Arabia.
- Primary conditions posing a high risk for invasive meningococcal disease include congenital or acquired asplenia, sickle cell disease, complement deficiencies (C5-9, properdin, factor D, factor H), HIV infection, complement inhibitor (i.e eculizumab, rovelizumab) use, a journey to high endemic regions and where the epidemic risk is high.
- In the USA, the practice of MCV4 in persons carrying high risk;

If chronic complement deficiency or complement inhibitor is present:

- MenACWY-CRM at 2, 4, 6, and 12 months in children aged 2-6 months
- Two doses of MenACWY-CRM with an at least 12-week interval and provided that the second vaccine is administered after 1 year of age in children aged 6-24 months

  or
- Two doses of MenACWY-DT with an at least 12-week interval in children aged 9-23 months

- Two doses of MenACWY-CRM or MenACWY-DT with an at least 8-week interval in children aged >24 months

In the presence of congenital or acquired asplenia, sickle cell disease or HIV infection

- MenACWY-CRM at 2, 4, 6, and 12 months in children aged 2-6 months
- Two doses of MenACWY-CRM with an at least 12-week interval and provided that the second vaccine is administered at >12th month in children aged 6-24 months
- Two doses of MenACWY-CRM or MenACWY-DT with an at least 8-week interval in children aged ≥24 months (5).

Within this scope, MenACWY-DT is not recommended in the 9th-23rd months by waiting the 9th month; MenACWY-DT can be administered twice in these children aged ≥24 months with an at least 8-week interval.

- MenACWY-DT should be administered at least 4 weeks after the PCV-13 vaccination series is completed (6).
- Age-appropriate MCV4 administration in children and a single dose of MCV4 in adults is recommended for those traveling to problematic countries in terms of meningococcal infection or for those traveling for Hajj and Umrah.
- If the high risk for meningococcal disease sustains following MCV4 vaccination:
  - Children aged 2-6 years should be re-vaccinated 3 years after the first vaccination
  - Children aged 7-18 years should be re-vaccinated 5 years after the first vaccination
  - Those having received 2 doses in their primary vaccination should be re-vaccinated 5 years later.

Vaccination should be repeated at 5-year intervals as long as the risk continues.

Meningococcal B Serogroup Vaccine

- There are two different meningococcal B serogroup vaccines of two manufacturers used in various countries (Bexsero™, Trumenba™).
- In Turkey, only one of these vaccines (4CMenB vaccine, Bexsero™) is approved to be used after the 2nd month.
- 4CMenB vaccine has been developed with the "reverse vaccinology" method as a vaccine determining the preserved proteins displayed on the meningococcal surface and covering non-specific antigens to the species (one outer membrane vesicles that contain porin A, factor H-binding protein, recombinant Neisseria adhesin A, and Neisserial heparin binding antigen).
- Recommendation of administering the 4CMenB vaccine is as follows: a) 3 doses with a 2-month interval (at least 1) and after the end of 12th month as 4th dose in children aged 2-6 months; b) 2 doses with an at least 2-month interval and a 3rd dose at least two months after the second dose in the second year of life in children aged 6-11 months; c) 3 doses with an at least 2-month interval in children aged 12-23 months; d) 2 doses with an at least 2-month interval in children aged 2-10 years; d) 2 doses with an at least 1-month interval in children older than 10 years and in adults. Furthermore, in certain countries like the example of the United Kingdom, when meningococcal vaccination with Bexsero™ is started at the age range of 2-6 months, the vaccination series is completed in three doses, the first two administered with a 2-month interval and the 3rd dose administered after the 12th month (5).
- Invasive meningococcal infections that can be either endemic or epidemic is generally endemic in Turkey.
- The incidence of the meningococcal disease usually tends to center on three different age ranges; infants and children aged 5 and younger (particularly <1 year), adolescents and young adults, and those aged >65.
- The incidence of meningococcal infection can differ according to countries and regions and even according to years in a given country, and there may be significant differences in serogroup distributions. Therefore, countries can include different vaccines containing appropriate serogroups into their national immunization schedules.
- Meningococcal vaccines can be implemented as part of a national immunization schedule (i.e., MCV4 in adolescents in the USA, MCV-1/A in certain African countries) or to only high-risk groups.
- In Turkey, studies have reported a meningococcal carriage rate of 1-21%, and annual invasive meningococcal disease incidence corresponds to the WHO criteria for middle or low-middle endemic regions. As in the world, the disease also is more commonly seen in infants (<1 year) in Turkey. There is no serogroup dominance in Turkey, but there are variations as regards years and regions. Therefore, a multi-valent vaccine is appropriate for Turkey.
- It would be appropriate to vaccinate high-risk clusters in terms of meningococcal infection, and inform families of healthy children brought to the physician for any reason, regarding the meningococcal disease, its vaccines, and the fact that healthy children can also be vaccinated with CMV4 (ACWY) and meningococcal B serogroup vaccine, but that their protection can be limited in terms of duration and serogroups, and administer CMV4 and meningococcal B serogroup vaccine in line with the consent and demand of the family.

Footnotes:

- In Turkey, the following Hepatitis B vaccines by different manufacturers are approved: Engerix-B Pediatric™ (10

μg/0.5 ml), Engerix-B Adult™ (20 μg/ml), Euvax-B™ (10 μg/0.5 ml), Euvax-B™ (20 μg/ml), H-VAC Pediatric™ (10 μg/0.5 ml), H-VAC Adult™ (20 μg/ml), HB-Vax PRB™ (5 μg), HB-Vax PRO ™ (10 μg) ve GenHevac B™ (20 μg/0.5 ml).

- In Turkey, the following tetanus vaccines by different manufacturers are approved: 6-valent combination named Infanrix-Hexa™ (HBV-Tdap-IPV-Hib), 5-valent combination named Infanrix-IPV-HIB™ and Pentaxim™ (TDaP-IPV-Hib), 4-valent combination named Tetraxim™ (TDaP-IPV), Td vaccine named Td-Vac™ and Tetadif™, and tetanus vaccine named Tetavax™.
- In practice, there are two Tdap vaccines by two vaccine manufacturers (Adacel™, Boostrix™), both are approved in Turkey.
- In practice, there are two Tdap-IPV vaccines by two vaccine manufacturers (Adacel polio™, Boostrix polio™), both are approved in Turkey.
- In Turkey, the following *H. influenzae* type b (Hib) conjugate vaccines by different manufacturers are approved: Act-HIB™, Hiberix™, and PedvaxHIB™.
- In November 2013, 13-valent pneumococcal conjugate vaccine (Prevenar13™) replaced the 7-valent pneumococcal conjugate vaccine (Prevenar™) that had been included in the National Immunization Schedule of Turkey in November 2008. Moreover, 10-valent PCV (Synflorix™) is approved in Turkey.
- In practice, there are two 23-valent pneumococcal polysaccharide vaccines by two vaccine manufacturers (PPV-23; Pneumo-23™, Pneumo-Vax 23™), both are approved in Turkey.
- The following MMR combination vaccines by different manufacturers are approved in Turkey: MMR II™, Priorix™, and Trimovax™.
- The following varicella vaccines by different manufacturers are approved in Turkey: Okavax™, Varicella Vaccine-GCC™, Varilrix™, and Varivax™.
- The following Hepatitis A vaccines by different manufacturers are approved in Turkey: Avaxim Pediatric™ (80 IU/0.5 ml), Avaxim Adult™ (160 IU/0.5 ml), Epaxal™ (24 IU/0.5 ml), Havrix Ped 720™ (720 IU/0.5 ml) and Havrix™ (1.440 IU/ml).
- The following are the rotavirus vaccines by different manufacturers approved in Turkey: Rotarix™, 1-valent human RV vaccine (RV1), and Rotateq™, 5-valent human-bovine RV breed RV vaccine (RV5).
- The following are the inactive influenza vaccines administered intramuscularly and intracutaneously by different manufacturers approved in Turkey: IIV-3 administered intramuscularly: Fluad ™, Fluarix™, and Vaxigrip™, IIV-4 administered intramuscularly: Fluarix Tetra™ and Vaxigrip Tetra™, and IIV-3 administered intracutaneously: Intanza™ (≥18-60 years).
- In practice, there are two HPV vaccines by two manufacturers: 2-valent HPV vaccine named Cervarix™ (HPV2), 4-valent HPV vaccine named Gardasil™ (HPV4) and 9-valent HPV vaccine named Gardasil 9™ (HPV9), all of which are approved but Gardasil 9™ has not been put in practice in Turkey.
- There are three CMV4 vaccines of three vaccine manufacturers: Menactra™ (MenACWY-DT, diphtheria toxoid is the carrier protein), Menveo™ (MenACWY-CRM, the carrier protein is CRM-197 mutant diphtheria toxin), and Nimenrix™ (MenACWY-TT, the carrier protein is tetanus toxoid), all of which are approved in Turkey.
- There are two meningococcal B serotype vaccines by two manufacturers in practice: Bexsero™ and Trumenba™, and for now, only Bexsero™ is approved in Turkey.

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