

Clinical Practical Recommendations for Turkish National Vaccination Schedule for Previously Healthy Children (National Vaccination Schedule) and Vaccines not Included in the Schedule - 2015

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Vaccination is the most effective, most reliable and cost-effective approach of protecting children's and adults' health and preventing infectious diseases. It is the right of each and every child to get immunized against the diseases that have an effective and reliable vaccine. The healthy children in our country have been vaccinated on a regular basis for a long time within the framework of continually-expanding national immunization schedule.

This article was written in an attempt to present practical recommendations regarding the available and non-available vaccines in the Turkish National Immunization Calendar (Expanded Immunization Program (GBP), prepare a practical national guideline inclusive of all the vaccines applicable for children and bring the issue out to the open for general debate. A similar recommendation article titled "*Vaccine Calendar Recommendations of Pediatric Diseases Association*" was published in the *Journal of Pediatric Infection (Çocuk Enfeksiyon Dergisi)* in 2009.

There has for a long time had a successful and quickly-strengthening GBP within the framework of Expanded Immunization Programme (EIP). Apart from this vaccine schedule administered to previously-healthy children, there are also vaccination recommendations for children and adults who have a high risk situation (immune deficiency, immunosuppressant treatment, chemotherapy, cancer, organ transplantation, and splenectomy) and travel to risky regions. Immunizing the healthy adults should be considered as the supplementary part of childhood vaccination.

In parallel to the developments in the field of vaccination, it is inevitable to strengthen the national immunization schedules and put the developments into practice. It naturally expected that each and every country will implement a national immunization schedule in accordance with their social conditions, incidence features of diseases and financial conditions. A national immunization schedule fundamentally aims to cover for previously healthy children (those who did not have a health problem previously). The contribution of country-wide vaccination to community health care and the extraordinary benefits it provides makes the financial cost-benefit calculations meaningless. In this connection, our national vaccination schedule is frequently updated- in the light of country's data- it scope is gradually expanded.

In accordance with the decisions of Immunization Advisory Committee of the Ministry of Health of Turkish Republic, adopting the national immunization schedule aimed at healthy children and administered free-of-charge country-wide and taking full part in every effort aimed at its implementation constitute the basis of the national vaccination practices. On the other hand, it will be appropriate that the vaccines not yet available on our national vaccination schedule, but administered to children on a national scale in various developed countries are also added to our national schedule as soon as possible should they be considered to be applicable on the basis of Turkey's data. Furthermore, the children raised healthily, with good education and great care as the adults of the country in the

Received: 06.02.2015
Accepted: 12.03.2015

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Infectious Diseases Society -
Available online at
www.cocukenfeksiyon.org
www.jpeditriinf.org
DOI:10.5152/ced.2015.1516

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future, with the awareness that they will constitute the most important national and international resource and power of the country, it will be beneficial and necessary for those vaccines to be administered to our children within the most appropriate and broad framework. Within this framework, it will be a wise move to recommend the vaccines not yet available on our national vaccination schedule to be added to the schedule in such a way not to hamper the administration of already-available vaccines with appropriate time ranges, and therefore propose an extensive immunization recommendation guideline; this new guideline will need to be updated on a regular basis. It will be recommended to support with such a guideline that the vaccines not yet available on our national vaccination schedule, but are recommended to children are administered to children with the consent of their families and by getting their costs met by their families or private insurances.

Physicians are expected to be equipped with the up-to-date knowledge and information in the relevant field of medical science. It is this equipped knowledge and information of the physician that will define his/her approach towards protection, diagnosis and treatment. A physician is also legally liable to keep track of the medical developments relevant to his/her field of expertise. This particular situation becomes all the more important with the regards to vaccination practices that have changed over the years. For instance, the doctor who fails to inform the family about a vaccine recommended nowadays, approved and brought into use by the Ministry of Health, but not yet available on the national immunization schedule, and who fails to administer the vaccine may be held accountable, based on this failure, for the problems likely to develop in the patient. This particular situation may be interpreted as a malpractice according to the declaration of Malpractices in Medicine in 1992 by the World Medical Association. In this connection, it is crucially important for the doctors to recommend the necessary vaccines within the recom-

mendation framework of modern medical science and get this recommendation written on the patients' documents. It will be a wise approach, for now, to support the move to inform the families about the vaccines in question-within the period for these vaccines to be placed on the national immunization schedule-within the framework of practical recommendations- and get them administered to children.

It is very important to keep the vaccination records systematically and in such manner to protect them for a long time in an attempt to make medical evaluations in the future. For this purpose, it should be emphasized that each and every child has a vaccine and health care card, their vaccinations be recorded on an appropriate section and way on those cards, these cards be closely examine on application to a doctor for a particular complaint-in order to create an opportunity for the vaccination-, the families be informed about an potentially missing vaccine and vaccines be completed as soon as possible.

There is yet no uniform health care or vaccination card in our country. Therefore, it will be crucially important to record children's vaccination and significant health information on a card able to be kept on transparent holder and on data processing so that doctors in the future may be informed about the children, to keep all the information a one card only, to specify the detailed information about vaccination (date of administration, name of the vaccine and its dose) on this card, to bring the card in every visit to the doctor and to consider it as a valuable commodity to be used in case of need.

The significance of national data regarding the relevant diseases is crystal clear in generating and updating national immunization schedule. Therefore, it is crucially important that notifications regarding vaccine-preventable diseases as well as adverse effects of vaccinations are made by the self-sacrificing doctors in our country in terms of the data build-up and the contributions they are going to make to the decisions.

Chart. National Immunization Chart (National Immunization Schedule) Vaccines of the Ministry of Health of Turkey (0-18 age) - 2015*

	Birth	1. month	2. month	4. month	6. month	12. month	18. month	24. month	Elementary 1. grade or age 4-6	Elementary 8. grade or age 10-12
Hepatitis B (BHA)	I	II			III					
BCG			I							
aBDT-IPA-Hib			I	II	III		IV (R)		aBDT-IPA (R)	dT (R)
OPA					I		II (R)			
Pneumococ (KPA)			I	II	III	IV (12-18 months) (R)				
KKK						I			II (R)	
Varicella (SA)						I				
Hepatitis A (AHA)							I	II		

Additional Chart. Additional Vaccines on the National Immunization Schedule Vaccines of the Ministry of Health of Turkey (0-18 year of age)-2015*

	Birth	1. month	2. month	4. month	6. month	9. month	18. month	24. month	Elementary 1. grade or age 4-6	Elementary 8. grade or age 10-12
Rotavirus (RVA)			I	II	(III)					
dapT, dapT-IPV										Preferably instead of DT, one dose
Human Papilloma Virus (HPA)										Used instead of dT, one time Between 9-18 years 3 doses in total
Influenza (IIA)						Every year after the 6 th month (age-appropriate dose and number)				
Meningococcal (KMA4)						Within the framework of practical recommendations, 1 or 2 doses after informing the families				
<p>*: Practical recommendations regarding the main chart or additional chart have been given as foot notes. The months on the main chart and additional chart (1, 2, 4, 6, 9, 12, 18 and 24th months) specify the end of that month; the periods between the vaccines have been specified as months.</p> <p>Abbreviations: BHA, hepatitis B vaccine; BCG, tuberculosis vaccine; aBDT-IPA-Hib, five-valiant combination vaccine inclusive of acellular pertussis, diphtheria, tetanus, inactivated poliovirus and Haemophilus influenzae type b; OPA, oral poliovirus vaccines; KPA, conjugated pneumococcal vaccine; MRM, combination vaccine of measles-rubella- mumps; AHA, hepatitis A vaccine; dT, adolescent/adult type diphtheria, tetanus vaccine; RVA, rotavirus vaccine; SA, varicella vaccine; IIA, inactivated influenza vaccine; IIA-3, 3-valiant inactivated influenza vaccine; KMA4; 4-valiant conjugated meningococcal vaccine, abdT, acellular pertussis- adolescent/adult type diphtheria, tetanus vaccine; Elementary School; I, II, III, 1, 2 and 3rd vaccines; R, booster dose/doses.</p> <p>The months specified (Months 1, 2, 4, 6, 9, 12, 18 and 24) indicate the end of that month.</p>										

Footnotes:**General Information:**

The time ranges (periods) between the vaccines were given as months. Vaccine time ranges can also be calculated by noting that a month is composed of four weeks and by converting the time ranges into weeks; ≥ 4 -month vaccine interval is considered as a month; no need to calculate it by converting into weeks.

In order not to cause missed opportunity in vaccines, the vaccination card of the child taken to the doctor for any complaint should be looked at; if there is no card, a card should be produced for the child, vaccine advice should be given to the child's family in a simple and basic language; and an effort has to be immediately initiated in order to complete the missing vaccines. Every vaccination should be recorded on the card and the family should be informed about the adverse effects of the vaccine. Practice obstacles in unreliable vaccination should be avoided. Every vaccine application should be carefully recorded onto child's card and the family should be informed.

Children with immune deficiency or suppression should be given live vaccine and a pediatric infectious diseases consultant should be consulted.

There is no absolute time interval in the administration of two different inactive vaccines; the vaccine can be administered on the same or another day. The same is true for inactive and live vaccines as well. Two live vaccines can be administered at the same time; however, if not administered at the same time (for MRM and SA), there should be at least one month (28 days) interval between them.

After live vaccines such as measles, MRM and varicella, one month-wait for PPD skin test should be observed; PPD skin test can be performed at the same time with the vaccines.

The Ministry of Health, if needed, organizes additional mass vaccine practices (vaccines campaigns). Children whose vaccine cards are proved to be fully complete may not be vaccinated as part of these mass campaigns. On the other hand, it is not harmful to give an extra vaccine to a child even if the actual vaccine card is not fully complete. Furthermore, the Ministry of Health should support the additional country-wide mass vaccine practices within the framework of national interest that the Ministry considers necessary.

BCG (Tuberculosis) vaccine

- Generally, it may be administered between 0-3 months with each two months apart.
- It is administered intracutaneously by an experienced health personnel onto the left shoulder as 0.05 mL (0.5 diyzem) at age of 1 month and 0.1 mL (1 diyzem) after age of 1 month.
- It is administered in the first three months without the PPD skin test is performed; and then the PPD skin test is performed if it is negative. If PPD skin test is positive (if the induration diameter is ≥ 10 mm in those BCG is not administered), on the basis of the infant, detailed history, family history, physical and laboratory examination findings, it is evaluated in terms of tuberculosis infection and tuberculosis; if there is no symptom or finding of the disease, treat-

ment of the tuberculous infection is initiated with a single drug (isoniazid); if there is symptoms of tuberculosis disease, tuberculosis disease treatment is initiated with more drugs and family screening is performed as well.

- In cases in which PPD solution is not present, BCG may be vaccinated without the PPD skin test so that children do not go without tuberculosis vaccination after the third month.
- In children in whom BCG vaccine is known to be complete (whether the vaccination scar is visible or not) and in whom there is the vaccination scar there is no need to implement PPD skin test in order to research the effectiveness of the BCG vaccine at any age within the first 6 months and administer the BCG vaccine based on the results.
- In a child younger than 6-year old and BCG-unvaccinated, BCG is administered to the child based on the PPD skin test result. In BCG unvaccinated children older than 6, there is no need to administer the BCG vaccine.

Hepatitis B vaccine (BHA)

- *Rekombinan* is a hepatitis B vaccine which is produced with the DNA technology and which only includes hepatitis B surface antigen (HBsAg); it is an inactive vaccine administered intramuscularly.
- It is administered three times with the schedule of "0, 1 and 6th month". The first vaccine should be administered on the day of birth of the infant. The second hepatitis B vaccine should be administered at least one month after the first one; third BHA at least four months after the first one and at least 2 months after the second one. The third (last) hepatitis B vaccine should not be administered before the end of sixth month. The third BHA vaccine can be administered between 6-9 months.
- Immunization with BHA should be initiated within the first 72 hours (in the first 24 hours if possible) in all the newborns. If the mother is HBsAg-negative, BHA in some conditions can be delayed until the end of the second month; however, it is better to administer the vaccine during the birth if possible or right after it.
- In newborns given birth by the HBsAg-positive mothers, the hepatitis B vaccine and hepatitis B immunoglobulin 0.5 mL (BHIG) should be administered within the 12 hours following birth. For infants with a birth weight of <2.000 g and whose mothers' situations are unclear regards to HBsAg, there are recommendations to apply BHIG de (0.5 mL) (4). However, in order to avoid redundant use of the BHIG, which is a man-made product, and as it can be administered within the first seven days, it should be remembered that mother's condition in terms of

HBsAg should be identified quickly and if the mother is found to be HBsAg-positive, the infant should be injected BHIG (0.5 mL) in the shortest time possible (within a week the latest). It should be ensured that the second vaccine in these infants should be given in the first month and third one in the sixth month and between 1st and 3rd month after the third vaccine, serologic evaluation should be made in the infant.

- In infants under the birth weight of 2,000 gr.; a) if the mother is not a carrier of hepatitis B (HBsAg negative), the first hepatitis B vaccine is administered at the end of the first month or when the infant reaches the weight 2,000 gr.; after the first dose, the vaccine is repeated in the first and 6 months with the total of three times. However, in order not to cause missed-opportunities, it should be to administer the vaccine at birth, afterwards, pretend as if the vaccine was inefficient and administer the vaccine again in the first month; in short, it will be more appropriate for our country to administer the BHA with the "0, 1 and 6th month charts", three times more in the 1, 2 and 6-7th months with the total of 4 times. b) If the mother is the carrier of hepatitis B, (HBsAg positive), or her situation is unclear, the first hepatitis B vaccine is administered within the first 12 hours; afterwards, it should be pretended as if the vaccine was not administered or ineffective, with the schedule of "0, 1 and 6th month", the vaccine is repeated three times in the 1, 2 and 6th month; so, the vaccine is given four times in total.
- In newborns where mother's HBsAg is unknown, it is treated as if the mother is HBsAg is positive until the situation is clarified and the first hepatitis B vaccine is administered in the first 12 hours. If the mother is HBsAg-positive, the infant is given HBIG (0.5) as soon as possible before the 7th day. It should be ensured that the second vaccine is given in the first month and third one in the sixth month; then serologic evaluation should be made after 1-3 months.
- A child who is previously not vaccinated with hepatitis B, there is no need for testing before the onset of hepatitis B vaccination.
- In infants whose mothers are HBsAg-negative, there is no need to perform a test to determine the serological transformation after the hepatitis B vaccine series. The cases with a high risk of hepatitis B carriage, serologic evaluation is recommended 1-2 months later following the last vaccine; it should be noted that this identification can be done between 9-18 months.
- In those with high hepatitis B virus carriage (risk clumps), serologic evaluation 1-2 months after the last vaccine is recommended. In this connection, the

infants of HBsAg-positive mothers, hemodialysis patients, those under the risk of perforating injuries due to occupational or work place environment and children living with HBsAg-positive people in the same place or home (domestic) have a greater risk of hepatitis B infection.

- Infants with an HBsAg-positive mother are recommended a serologic evaluation 1-3 months after the last vaccine (sixth month) or in one of the 9-15th follow-up visits. In case of non-response to the vaccine (<10 mU/mL), if the child is not HBsAg positive, immunization is repeated with additional three vaccines. This second vaccine series is implemented with the schedule of "0, 2 and 4th month" (2-month interval) or "0, 1 and 6th month", and a serologic evolution is done one month after the last vaccine. Still, if there is no response after this second 3-vaccine series, there is a high risk that there will be no non-response in later vaccines as well and there is no need for new vaccination series.
- Hepatitis B vaccine in children (<10 years old) is administered as the pediatric dose (0.5 mL, 5 or 10 µg/0.5 mL according to the vaccine producer).
- Hepatitis B vaccine in Turkey can interchangeably be used with each other; the vaccine series under use can be completed by the vaccines of other producers.
- In addition to the single antigen hepatitis B vaccines in Turkey, there are also combination vaccines (for instance, BHA-abDT-IPA-Hib six-valent combination) inclusive of hepatitis B and other vaccines. In the newborn period, only single antigen hepatitis B vaccine is administered. Six-valent combination vaccine inclusive of hepatitis B vaccine can be implemented in week six at the earliest. In infants with an HBsAg-negative mother, after the first hepatitis B vaccine is administered with single antigen in the newborn period, vaccination can be suspended with 3 six-valent combination vaccines in the 2, 4 and 6th months with 2-month intervals. After the six-valent combination vaccine series is implemented, it should be remembered that the total number of hepatitis B vaccines will be 4. As there are vaccines administered free of charge within the framework of Expanded Immunization Program of the Ministry of health, it will most probably not be necessary to administer the six-valent combination. However, the relevant information about this issue may be necessary when the vaccination of the children living abroad is organized or evaluated.
- The six-valent combination vaccine (BHA-aBDT-IPA-Hib) should not be used as the booster dose of the 5-valent combination vaccine after the 18th month; there is still no sufficient data about it regarding efficiency and reliability.

Pertussis, diphtheria, tetanus, poliomyelitis, *Haemophilus influenzae* type b vaccines:

ABDT-IPA-Hib five-valent combination vaccine, dT vaccine, acellular pertussis-adolescent/adult type diphtheria-tetanus (abdT) vaccine

- aBDT vaccine is administered as five-valent combination vaccine together with IPA and Hib vaccines.
- Five-valent combination vaccine is implemented three times (2, 4 and 6th month) with 2-month interval; the primary vaccination series is administered 3 times as the forth (1st booster dose) in 18-24 months. Administration of the primary vaccination series in the 2, 3 and 4th months during epidemics does not make any difference in terms of serologic transformation. The fourth aBDT-IPA-Hib vaccine can be administered in the 12th month if there is an interval of sabin, OPA after the 3rd vaccine.
- Accompanying the 3rd and 4th vaccines of the five-valent combination vaccine series, live poliomyelitis (salk vaccine) vaccine is orally administered two times (OPA) (2 doses in total).
- The obstacles of aBDT vaccine are the same as those in BDT. The adverse effects of acellular pertussis vaccine are less. In order to minimize the adverse effects of the vaccine, starting it before or after the five-valent vaccine, paracetamol (10 mg/kg/dose) can be given 8 times with 6-hour intervals.
- The upper age limit for aBDT-IPA-Hib vaccine is 72 months.
- It is recommended that one dose of adolescent/adult type reduced dose acellular pertussis vaccine, (adolescent/adult type diphtheria-tetanus, abdT) after age 7 or 10 years after aBDT-IPA is employed; afterwards, vaccination continues with dT vaccine every 10 years.
- In the 8th grade of Elementary school, adult-type diphtheria-tetanus (dT) is applied and then a repetition of the vaccine is recommended once in 10 years.
- When dT vaccine is administered instead of tetanus (T), the booster dose of childhood diphtheria vaccine is shot and the immunization of those previously non-immunized diphtheria-sensitive people is ensured. In every situation inclusive of pregnancy where tetanus vaccine is needed, dT vaccine should be applied.

Adolescent/adult type acellular pertussis – diphtheria-Tetanus (abdT) vaccine and Adolescent/adult type acellular pertussis – diphtheria-Tetanus - inactive poliovirus vaccine (abdT-IPA)

- The abdT vaccines of both vaccine producers are in use and approved in our country. Although abdT vaccines are usually recommended for children >10 years of age, practical recommendations can be for children aged >7 (4).

- The abdT-IPA vaccines of both vaccine producers are in use and approved in our country. (In the short product information of the abdT-IPA in our country, approved use is indicated for children aged >3 and >4.
 - abdT and abdT-IPA vaccines can be administered for children aged >7 regardless of the period in which the vaccines "D", "d" or "T" inclusive of toxoids were administered.
 - At the age of >7, for dT vaccination in those who have not been vaccine before, one of the three (first vaccine, if possible) "0, 1, 6-12 month" vaccines is recommended to be abdT.
 - All the adolescents are recommended to be immunized with abdT at the age of 11-12.
 - At the age of 7-10, as the patient is without a vaccine, those who have been shot the abdT within the framework of dT (0, 1, 6-12 month) do not need the booster dose of abdT at the age of 11-12.
 - Those who have not been administered the abdT vaccine at the age of 11-18, abdT can be administered only once.
 - Instead of one of the dt vaccines administered with ten years intervals, addT vaccine is recommended.
 - In every pregnancy, (with the preference of >20 week, at the 27-36th week), regardless of the interval period before the previous dT or after the abdT vaccines, abdT vaccine is recommended (4). For our country, it will be appropriate to replace the abdT vaccine with one of the two tetanus vaccines administered during pregnancy.
 - If the abdT vaccine has not been administered during pregnancy, the mother should be administered the acdT vaccine just after the delivery after considering mother's status of tetanus immunization during pregnancy.
 - The family members at all age such as the parents, baby sitters and other members who have close contact with infants aged under 1 are recommended to be vaccinated with abdT.
 - Healthcare workers are recommended to be vaccinated by abdT.
 - In cases where abdT is recommended, abdT-IPA can be administered as well; there are no clear recommendations regarding their use during pregnancy.
 - The aBDT vaccine or a vaccine inclusive of the aBDT has been inappropriately administered at the age of 7-10, the adolescent period (11-18 years) can be considered for the abdT vaccine or one dose of abdT vaccine can be administered at the age of 11-12; if it has not been administered at the age of 11-18, the adolescent period should be considered as the abdT vaccine.
- In our national immunization schedule, the first 2-dose five-valent combination (aBDT-IPA-Hib), the next 2 doses within the simultaneous five-valiant combination are administered as IPA (aBDT-IPA-Hib) and OPA.
 - Due to the circumstances of our country, OPA still preserves its significance in practice. Therefore, time-time OPA is recommended to all children if there is no contradiction in accordance with our national immunization schedule.
 - Since it is a live virus vaccine, OPA should not be administered to children with immune compromised (immune deficiency or immune suppressed-related cancer patients) and with an immune-compromised family member, and this situation should be questioned prior to OPA administration. In such cases, all the poliomyelitis (Polio) vaccines are given as IPA through five-valent (aBDT-IPA-Hib vaccine) or four-valent (aBDT-IPA) combination vaccine.

H. Influenza type b (Hib) vaccine

- Hib vaccine is administered as a total of four times as the five-valent aBDT-IPA-Hib combination vaccine; 3 times as primary vaccine series, with two-month interval (2, 4 and 6th months) and the 4th vaccine (booster dose) in the 18-24th month.
- After the age of five, there is no need to administer the Hib vaccine to healthy children who are not in the risk group.

Pneumococcal vaccines; Conjugated pneumococcal vaccine (KPA), polysaccharide pneumococcal vaccine (PPA)

- Thirteen-valent conjugated pneumococcal vaccine (KPA-13) is present in our national immunization schedule. Besides, 10-valiant KPA is also approved in our country. All the information related to KPA in this article is given basically for KPA-13 in our national schedule.
- KPA is administered in the 2, 4 and 6th month as the primary vaccination series and a fourth dose in the 12th months as a booster dose.
- In children under one year, there should be at least one month interval between 1st and 2nd KPA doses and 3. And 3th doses; the interval between 3rd KPA vaccine and the last (fourth) vaccine (booster dose) should be at least four months. The booster dose should not be given before the 12th month.
- In cases where KPA has not been previously administered;
- In 2-6 month infants, a total of 4 vaccines with 3-dose primary vaccination and one booster dose,
- In 7-11 month infants, with 2-dose primary vaccination and 1 booster dose, a total of 3 vaccines are applied

Poliomyelitis (Polio) vaccines

- Polio vaccine can be administered inactive poliovirus vaccine (IPA) or oral polio virus vaccine (OPA).

- In 12-23 month children, 2-dose KPA with two-month interval is administered.
- A single shot of KPA is applied to aged 2-5 children who were not vaccinated before or with missing vaccines.
- Single dose of KAP-13 is additionally recommended to children after the 14th month until age five previously vaccinated with 7-valent KPA.
- There is no need for another KPA-13 dose for children who were given KPA-13 vaccine after the age of 1.
- The KPA and PPA vaccines to be applied to high risk groups have been excluded from discussion. However, there is a significant group of people in the community in whom pneumococcal infection increases. The following group of people constitute the risky groups regarding pneumococcal infection; chronic heart disease without primary immune problem, (especially cyanosis congenital heart disease, cardiac insufficiency), chronic lung disease (if the patient takes extended high dose oral corticosteroid including asthma), diabetic mellitus, situations generating BOS leakage, cochlear implant, functional or structural spleen failure (sickle cell anemia, other haemoglobinopathies, congenital or acquired asplenia, spleen function disorder), various immune suppression situations (immune deficiency diseases except chronic granulomatous disease, organ transplantation, cancer, immune suppressive chemotherapy or radiotherapy treatment, chronic renal failure, nephritic syndrome and children with HIV infection. These high risk group children are recommended single dose of KPA-13 between the ages 6-18 (and also PPA-23, two months later). Similarly these high risk children are recommended additional single dose KPA-13 (and PPA-23, two months later) even if they were previously and fully vaccinated KPA-7 series aged between 2 and 6.
- The pneumococcal vaccine for healthy children in our national immunization schedule is KPA-13. The twenty-three-valent polysaccharide pneumococcal vaccine is a recommended vaccine for high risk and ≥ 2 years patients in terms of the development of invasive pneumococcal disease, and it is not recommended instead of KPA in healthy children. If it was or was not previously applied in high risk groups, KPA can be applied instead of PPA or initially KPA and then two months later, PPA as well. The details of pneumococcal vaccines to be applied to high risk group patients have not been discussed in this article.

Measles, rubella, mumps (KKK) vaccine

- KKK vaccine is given as two doses with the first one in the 12th month and the booster dose when the child is aged 4-6 or in the first grade of elementary school.

- Vaccine should be given two times at least with two-month interval. So, every child should be given two KKK vaccines, if there is a delay for routine schedule.

Varicella vaccine (SA):

- Varicella vaccine is recommended two doses with the first dose in the 12th month and 2nd dose as a booster dose when the child is aged 4-6 or in the first grade of elementary school. However, in our national immunization schedule, varicella vaccine is applied only at the end of age 1 and actually there is no booster dose; however, the second dose is expected to be included in the national schedule free of charge in the near future.
- Two vaccines are recommended to children older than 4 years with two-month intervals who have not been vaccinated before.
- The booster vaccine doses are changeable; vaccines of different manufacturers may be given interchangeably as booster doses.

Hepatitis A vaccine (HAV)

- The vaccine is approved for children older than 12 months; however, due to high level of antibody caused by the maternal infection, there are insufficient number of studies regarding the effectivity of early vaccination.
- HAV is recommended as two doses in the 18th and 24th months with six-month interval.
- If possible, the two HAV vaccines should be ones of the same manufacturers; however, vaccines of different manufacturers can be changeable.
- HAV is administered to the 18-year olds as a pediatric dose (0.5 mL, inclusive of 720 ELU, 25 U, and 80 U according to the manufacturer). Adult dose of HAV is different from the pediatric dose and is double of the pediatric dose.
- The vaccine is employed without serological testing to children under 6; in previously non-vaccinated children older than 6, antiHAV- IgG may be tested as a different approach and the vaccine may be given if the result is negative.

Some vaccines (such as rotavirus vaccine, influenza vaccine, *human* papillomavirus vaccine, conjugated meningococcal vaccine) not yet included in our national immunization schedule. They are known to be effective and safe, applied on a nation-wide scale in many countries, also approved for use in our country are recommended provided that the cost of the vaccine is met by the family or private insurance. Recommendations for these vaccines are provided below.

Rotavirus vaccine (RVA)

The epidemiologic studies in our country reveal similar to the data in developed countries that rotavirus

is a significant agent in hospitalized or outpatient cases with acute diarrhea. Even though it does not cause significant level of mortality and long-term sequelae, high level of rotavirus disease burden and health care costs generate the justification for the recommending the use of rotavirus vaccine. Parents should be informed and if the parents agree, the vaccine is given.

RVA can be given after the 6th week. RVA is given 2 or 3 doses depending on the manufacturer with 2-month interval; the last vaccine should be given before the 6-8th months. Recommended rotavirus vaccination should start in the first 6-12 weeks; the first dose should be given before the 15th week. In 2-dose schedule, RVA should be given in the 2 and 4th months (or in the 2. or 3rd months); in 3-dose schedule, it should be given 2, 3 and 4th months (or 2, 3 and 4th months).

Rotavirus vaccines can be given simultaneously with the other pediatric vaccines. There is no reliable data suggesting that vaccination should be completed with different rotavirus vaccines and its administration is not recommended. Since rotavirus vaccines are live virus ones, they should not be applied to those with immune deficiency.

Inactive influenza virus vaccine (IIV; influenza vaccine)

Influenza virus infections tend to progress seriously in infants and provide a basis for serious respiratory system infections. Furthermore, it is commonly known that the epidemics caused by influenza infections especially in childhood spread to adults and generate losses of education as well as great economic losses for health system and working parents.

Even if influenza virus vaccines fail to protect children from all influenza infections, families should be informed and the efforts aimed at encouraging the administration of the vaccine to all healthy children older than 6 should be supported.

There is currently 3-valent inactive influenza vaccine in our country (IIV-3). Four-valent inactive influenza vaccine (IIV-4) and live attenuated influenza vaccine (CZiA-3, CZiA-4) have not yet approved in Turkey.

- IIV-3 is mainly recommended to the children with high influenza risk aged 6-month-18 years and is employed every year.
- IIV-3 is mainly recommended to the children older than 6 with high risk of influenza infection. The high risk chronic metabolic disease; chronic lung diseases such as asthma and cystic fibrosis, diseases suppressing the respiratory system or increasing the aspiration risk, hemodynamic ally significant heart diseases, immunocompromis diseases or treatments, crescent-cell anemia and other haemoglobinopathies, diseases requiring long-term aspirin treatment (such as rheumatoid arthritis and Kawasaki

syndrome), chronic kidney disease, diabetes mellitus.

- 6-23-month healthy children, those with close contact with 0-5-month healthy children, those with close contact with high risk children (including contact), the persons caring the <24-month children and high risk children as well as all health care personnel as they are considered high risk group are especially recommended the vaccine.
- According to the 2008 Health Practice Declaration, those in the risk group due to their diseases, living in nursing homes and those over the age of 65 are reimbursed their influenza vaccine cost once a year.
- Apart from the high risk groups, vaccination of all children aged 6-month-18 years should be encouraged.
- The product information on the vaccine regarding dosage is taken into consideration; the vaccine is usually applied half dose (0.25 mL) in the 6-35th months and complete dose (0,5ml) for those aged 3 and older.
- When the influenza vaccine is given first at ≤8 years, it is given 2 doses with one-month interval; it is given as a one dose after the age of ≥9. If there is a significant antigen change (antigenic shift) or pandemic again, 2-dose vaccine can be given to the children who were regularly given the influenza vaccine.
- Since influenza vaccine is prepared based on the virus types expecting to cause epidemics every year, it should be repeated every year if protection is expected to continue. Influenza vaccine can be given between the months of September and April. However, the vaccine should be applied in children to be shot first time and given 2-doses before the virus infection season commences or at the beginning of the season (September-October).

Human papillomavirus vaccine (HPV)

It was revealed in many studies that HPV vaccines had a protective effect against cervical cancer (2 or 4-valent; HPA-2 and HPA-4) and warts (four-valent, HPA-4). When HPV is given in the adolescence period, it provides a more effective protection in comparison to older age schedule and antibody responses were found to be higher between the ages 9 and 15. The vaccine is not recommended before the age 9. The vaccine is primarily recommended to girls; however, there are countries in the world where 4-valent (HPV-4) vaccine is recommended to men as well. HPV is one of the vaccines present in the national schedule of many developed countries.

TWO HPV vaccines developed by two different manufacturers have been approved in Turkey. HPV is given intramuscularly to girls as 3 doses from the age of 11-12 with (0, 2 and 6th month" schedule (HPA-4) or "0, 1 and 6th month" schedule (HPA-2). The interval between the first and second vaccines of HPV should be at least

1 month and the between second and third months at least 3 months. The vaccination schedule of those unvaccinated is recommended to be completed at 13-18. HPV can be given simultaneously with other adolescent vaccines.

The human papillomavirus epidemiologic data in Turkey are not yet sufficient; however, since the vaccine has been shown to be efficient and reliable in the developed and many other countries, HPV is recommended to girls after the age of 9.

Meningococcal vaccines: Meningococcal polysaccharide vaccine (MPA), Conjugated meningococcal vaccine (KMA), Meningococcal serotype B vaccine

Meningococcal vaccines are inactive vaccine and are applied intramuscularly.

Meningococcal polysaccharide vaccine (MPA)

- 4 meningococcal serotypes (A, C, W135, Y), the most frequent cause of disease include purified capsule polysaccharides.
- It is administered after 2 years of age.
- It is not recommended for healthy individuals.
- Generally, its use should be considered in the absence of 4-valent conjugated meningococcal vaccine (KMA4).
- It is administered in cases of the absence of structural or functional spleen, terminal complement, which generate high risks in terms of meningococcal disease.
- It is administered to those go on a pilgrimage and umrah to mecca and to their military services.
- It recommended to be administered to boarding school students.

Conjugated meningococcal vaccine (KMA):

- Three different A, C, Y, W135 serotype capsule polysaccharides types developed by different companies, different carrier proteins-dependent of 4-valent conjugated meningococcal vaccines (KMA-4) have been approved in Turkey:
- KMA4-CRM: Non-toxic, CRM-197 mutant diphtheria toxin has been used as carrier protein. It has been approved by FDA to be used after two months (2 months - 55 years old) and after two years of age in our country.
- KMA4-D: Diphtheria toxin has been used as carrier protein. It has been approved by FDA to be used after nine months (9 months - 55 years old) and between 9 months-11 years old (between 9-23 months, two times with three-month intervals) in our country; it has not yet been approved by EMA (*European Medicines Agency*).
- KMA4-T: Tetanus toxin has been used as carrier protein. It has been approved in our country and by

EMA to be used (1-55 years old) after one year old; It has not yet been approved by FDA.

- Protection duration of KMA4 vaccines is limited; the differences between them have not been scientifically proven; furthermore, for instance in the USA, except the children under high risk group in terms of meningococcal disease, KMA4 are not recommended for pediatric vaccination of pre-infancy and adolescence (≤ 11 years) (4).
- In cases where pediatric vaccination needs to be administered, KMA-4 should be preferred over MPA4.
- In terms of meningococcal vaccination of healthy children, the following is recommended; in the practice administered in the USA, healthy children who are aged 11-12 and 16 years of age, are administered a total of two times KMA4-CRM or KMA4-D; previously unvaccinated children are administered the vaccine at age 13-18; if the first vaccine is done at age 13-15, second one is administered at age 16-18; if the first vaccine is shot at age ≥ 16 , the second dose (booster) is not to be administered; children with HIV infection aged 11-18 are administered two times with at least eight weeks apart (4).
- The main circumstances constituting high risk in terms of invasive meningococcal disease can be summarized as the absence of structural or functional spleen, sickle cell disease, lack of complement (C5-9, properdin, factor D, factor H), HIV infection, travel to high endemic region, and epidemic cases where risks and intercourse rates are high. Details of meningococcal vaccination practice in high risk cases have not been mentioned in this article.
- It is recommended that children on the way to pilgrimage and umrah regions or to the countries where meningococcal infection is a problem, age-appropriate KMA4 be administered and adults be administered KMA4 once.
- If polysaccharide or protein-driven meningococcal vaccination (MPA4 or KMA4) has already been administered, but if the high risk with regards to meningococcal disease still continues, the following vaccination schedule should be followed;
 - children aged 2-6, three years after the first vaccination
 - children aged 7-18, five years after the first vaccination
 - Those vaccinated twice in the primary vaccination after five years.
 As long as the risk prevails, vaccination should be repeated every five years.
- **Meningococcal serotype B vaccine:** Meningococcal B vaccine having the protected and not specific for the lineage proteins in the surface of meningococcus is used in some countries has not

yet been approved in our country and meningococcal serotype B vaccine in use in some countries has not yet been approved in our country.

- Contagious meningococcal infections that can be epidemic or endemic are usually endemic in our country.
- Prevalence of meningococcal disease usually tends to focus on 3 different age groups; infants and young children below than 5 years of age, (especially <1-2 years), adolescent and young adults and those ≥ 65 years old.
- Prevalence of contagious meningococcal infections may change even in the same country annually depending on the country and regions, and there may be great differences in serogroup distributions. Therefore, countries may include different vaccines inclusive of country-specific serotypes into their national immunization schedule.
- Meningococcal vaccines may be administered as part of (for instance, KMA-4 for adolescent in the USA, KMA-1/A in some African countries, and KMA-1/C in the United Kingdom) national immunization schedule or they may be applied to those under great risks.
- In the studies done in our country, meningococcal carriage rate has been reported to be 1-21%, the annual prevalence of contagious meningococcal disease is line with the criteria set out by the WHO for middle or low-middle level endemic regions. As it is the case in the world, the disease is more prevalent especially in infants (<1-2 years) in our country as well. There is no dominance of a single serogroup in our country; there are differences according to years and regions. Therefore, the conjugated meningococcal vaccines to be administered in our country should be multifactorial (KMA-4). With regards to meningococcal disease, high risk groups must definitely be vaccinated. In high risk group vaccination, it will be wise to prefer KMA4 vaccine instead of MPA4. Patient's family should be informed that protection period of KMA4 vaccines are 3-5 years, the efficiency of serotypes included is 50-80% and vaccination should be done according to the will of the family. In this connection, the families of healthy children visiting the physician for any reason should be informed, taking account of the right to demand information and to be informed of meningococcal disease and vaccines, that healthy children could be vaccinated the KMA4 vaccine, but that they are limited in terms of the protection period, extent (serotypes) and percentages, and of the fact that there is no recommendation by the Immunization Advisory Committee of the Ministry of Health for the administration of KMA4 vaccines to healthy children.

Footnotes:

- In our country, following hepatitis B vaccines by different manufacturers are approved; *Engerix-B Pediatric™* (10 mikrog/0.5 mL), *Engerix-B Adult™* (20 mikrog/mL), *Euvax-B™* (10 mikrog/0.5 mL), *Euvax-B™* (20 mikrog/mL), *H-VAC Pediatric™* (10 mikrog/0.5 mL), *H-VAC Adult™* (20 mikrog/mL), *HB-Vax PRB™* (5 mikrog), *HB-Vax PRO™* (10 mikrog) and *GenHevac B™* (20 mikrog/0.5 mL). In our national vaccine schedule, *Euvax-B™* vaccine is currently in use.
- In our country, following vaccines by different manufacturers are approved; *Infanrix-Hexa™* (BHA-aBDT-İPA-Hib) six valent, *Infanrix-IPV-HIB™* and *Pentaxim™* (aBDT-İPA-Hib) five valent, *Tetraxim™* (aBDT-İPA) four valent, *Td-Vac™* and *Tetadif™* dT and *Tetavax™*. In our national vaccine schedule, *Pentaxim™* five valent and *Tetraxim™* four valent combination vaccines and *Tetadif™* dT vaccines are currently in use. In practice and in our country, the abdT vaccines of two vaccine manufacturers are approved; (*Adace™*, *Boostrix™*).
- In practice and in our country, the abdT-İPA vaccines of two vaccine manufacturers are approved; (*Adacel polio™*, *Boostrix polio™*).
- In our country, vaccines named *Act-HIB™*, *Hiberix™* and *PedvaxHIB™* that are carrier protein- dependent (*conjugated*) *H. influenzae* type b (Hib) are approved.
- Seven valent conjugated pneumococcal vaccine (*Prevenar™*) that was added to the national vaccination schedule in November 2008 was replaced by the 13 valent conjugated pneumococcal vaccine (*Prevenar 13™*) in November 2011. 10 valent KPA (*Synflorix™*) is also approved in our country.
- In our country, measles-mumps-rubella combination vaccines named *MMR II™*, *Priorix™* and *Trimovax™* by different manufacturers are approved. In our national vaccine schedule, *Priorix™* is currently in use.
- In our country, varicella vaccines named *Okavax™*, *Varilrix™* and *Varivax™* by different manufacturers are approved. In our national vaccine schedule *Varivax™* is currently in use.
- In our country, following hepatitis A vaccines by different manufacturers are approved; *Avaxim Pediatric™* (80 iü/0,5 ml), *Avaxim Adult™* (160 iü/0.5 mL), *Epaxal™* (24 iü/0.5 mL), *Havrix Ped 720™* (720 eü/0,5 ml) and *Havrix™* (1.440 eü/mL). In our national vaccine schedule *Havrix Ped 720™* is currently in use.
- In practice and in our country, rotavirus vaccines of three vaccine manufacturers are approved;

Rotarix™, 1 valent human RV vaccine (RV1) and *Rotateq™*, 5 valent cattle-human RV hybrid RV vaccine (RV5).

- In our country, following vaccines by are approved; İİA-3 intramuscular vaccine named *Fluad™*, *Fluarix™* and *Vaxigrip™*, İİA-4 intramuscular vaccine named *Fluarix Tetra™* and İİA-3 percutaneous vaccine named *Intanza™* ($\geq 18-60$ years).
- In our country, following HPV vaccines by different manufacturers have recently been approved; *Cervarix™*, 2 valent HPV vaccine (HPA2) and *Gardasil™*, 4 valent HPV vaccine (HPA4). *Gardasil 9™*, 9 valent HPV vaccine (HPA9).
- In practice, meningococcal polysaccharide vaccines (MPA4) developed by different manufacturers named *Mencevax ACWY™* and *Menomune™* are used.
- In practice and in our country, the following vaccines of three vaccine manufacturers are approved; KMA4 vaccine; *Menactra™*, (KMA4-D, carrier protein diphtheria toxoid), *Menveo™*, (KMA4-CRM, carrier protein CRM-197 mutant diphtheria toxin) and *Nimenrix™*, (KMA4-T, carrier protein tetanus toxoid).

- In our country, application has been made for approval for the meningococcal serotype B vaccines named *Bexsero™*.

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