V.K. Tatochenko

Scientific Center of Children's Health, Moscow, Russian Federation

Vaccination of premature/low-birth-weight children

Author affiliation:
Vladimir Kirillovich Tatochenko, PhD, Professor, chief research fellow of the RAMS SCCH
Address: Moscow, Lomonosovskiy Av. 2/1, 119991, **tel.:** +7 (495) 967-14-21

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The article is dedicated to vaccination of premature/low-birth-weight children. This is an extremely topical issue as these children are the most susceptible to infectious diseases, including controlled diseases; however, specialists are reluctant to vaccinate them due to possible unfavorable responses of premature bodies to the introduction of an immunotropic agent. The authors present peculiarities of immune response of premature infants, of the T-cell level in particular, which are to be taken into account during vaccination. Special attention is given to the safety of vaccines – risk of development of apneic episodes with/without bradycardia, their influence on the frequency of obstructive episodes and effect of simultaneous introduction of several vaccines on body. Moreover, the article sets forward issues of immunogenicity and reactogenicity of various vaccines when administered to low-birth-weight children.
Keywords: *vaccination, immunogenicity, reactogenicity, safety, premature and low-birth-weight children.*

Introduction

Vaccination against many infections conducted in the first months of a child's life is aimed at prevention of the diseases that are severe in this age. This is especially relevant for the children born prematurely (prior to the 37th gestational week) or with low birth weight (less than 2,500g). Thus, among the children developing pertussis in the first months of life, the risk for premature infants is 1.86 [1]; pneumococcal infection comprises up to 10% of the neonatal sepsis, which means that premature infants suffer in the first place [2]. The role of Haemophilus influenzae type b (Hib-infection) is also very significant, as it is the worst causative agent in the first months of life (meningitis, pneumonia, sepsis etc.); relative risk for premature infants is ca. 1.5 [3].

That is why the issue of timely immune prevention of premature and low-birth-weight children, adequacy and safety of the existing and widely used vaccines for this category of children is critical. Convincing data on this topic have been accumulated within the last 15-20 years; in the recent years special attention was given to the vaccination of small premature infants.

Immune response of premature infants

It has been shown on the basis of the existing data that immune system of premature infants is capable of responding to antigenic stimuli and this capability becomes stronger with age, as in term infants. That is why administration of a booster dose of an inactivated vaccine at the age of 1-2 years results in a much stronger response than in case of a vaccination course restricted to the age of 0-1 years.

Due to the reduced gestation duration, premature infants are born with an immune system, which is different from the immune system of term infants. As vaccines were created for children with normal gestation period, their use in premature infants may undergo certain both technical and psychological difficulties concerning not only parents, but also medical personnel. At the same

time, the existing data show that, in general, the immune system of premature infants cannot be deemed completely deficient; "premature" is a better word.

Weakness of the congenital immune system in premature infants manifests itself with the reduction in the ability of dendritic cells and macrophages to capture and represent antibodies. These infants also have a reduced generation of anti-inflammatory cytokines; this may affect the magnitude of immune response, although this capability becomes stronger with age, as in term infants [4].

Adaptive immune reactions associated with functions of T and B lymphocytes are reduced in premature infants, mainly due to the "restricted diversity" of receptors in these cells. In his study, V.M. Studenikin showed that T- and B-cell populations are completely formed in children of 34-36 weeks of gestational age (GA), although co-expression of the early stage markers (CD36+/CD1+, CD38+/CD71+) occurs in 20% of lymphocytes. Normal cell populations circulate in the blood of children of 28-33 GA weeks; however, the share of poorly differentiated subpopulations remains higher throughout the neonatal period. Increased amount of B-cell populations is observed in both groups; expression of the main receptors (CD3+, CD4+, CD8+) normalizes and the amount of poorly differentiated subpopulations decreases within the 1st month of life, especially in children of 28-30 GA weeks [5].

It is known that children of 0-1 years of age respond weakly to the administration of T-dependent antigens (e.g., to polysaccharides); this is especially true for premature infants who respond by generating IgM-antibodies and slow shift to IgG-response more often [6].

T-cell response in premature infants in comparison with term infants is characterized by fewer circulating CD4(+)CD45RO(+) memory cells and CD4(+)CD69(+)IFN-γ(+) cells activated by staphylococcal enterotoxin at the age of both 2 and 7 months. Both groups of children had a similar rate of poliovirus-specific CD4(+)CD45RO(+)CD69(+)IFN-γ(+) memory cells after the immunization against poliomyelitis (scheme – 2-4-6 months) with an inactivated vaccine, although peripheral mononuclear leukocytes of premature infants featured lower poliovirus-specific lymphoproliferative activity. The study showed that the T-cell response of premature infants has certain restrictions in comparison with the T-cell response in term infants, at least within the most part of the 1st year of life [7].

Cellular immunity of neonates, especially of premature infants, is polarized towards the Th2 system due to the relative weakness of Th1 reactions, although the T-cell population in them is higher than in adults. This fact may determine the suboptimal reaction of premature infants to BCG propagating in cellular phagosomes, reduction in the activity of cytotoxic (Tc) cells – to the administration of attenuated viral vaccines [e.g., to the zero dose of oral polio vaccine (OPV)] propagating in cellular cytosol [8].

By the beginning of vaccination (2-3 months), the immune system of premature infants is inferior to the immune system of term infants in terms of such parameters as amount of lymphocytes, T and B cells and CD4/CD8 ratio. Immune response may also be suppressed by steroids taken by many premature infants for chronic pulmonary processes. Although they generate a weaker response to most vaccines, it is enough to protect premature infants [9].

Placental transmission of maternal antibodies (IgG), which protects neonates from several infections, is reduced in premature infants (especially in the infants born before the 32nd gestational week). On the one hand it shows the importance of timely immunization of premature infants, on the other – reduces neutralizing influence of maternal antibodies on several vaccinal antigens [10, 11].

Safety of vaccines

Peculiarities of reaction of premature infants to vaccines. Unexpectedly, safety profile in terms of normal reactions to vaccines administered to premature and low-birth-weight children in comparison with term infants appeared different. The only possible exception is the increase in

the rate of apnea (accompanied or not by bradicardia) and desaturation episodes, which is observed by most authors [12-15].

Observation of 473 premature infants of weight <1,500g (average weight – 910g [375-1,495]), average GA of 27.6 (22.6-34.3) weeks and GA by the moment of vaccination of 37.4 (31.5-48.3) weeks showed that only 2.8% of children had generalized (fever) and local reactions; however, 10% of children had apneic episodes with/without bradicardia [16].

In a different observation of 411 premature infants (average GA – 27 weeks, weight - <1,000g) after vaccination at the age of 2 months, apneic episodes required artificial pulmonary ventilation (APV) in 5.3% of children [17].

As a rule, these episodes develop within 48 hours, rarer – within 72 hours after vaccination; they are more often observed in children with short gestational period who have had similar episodes before vaccination. Risk factors also include apneic episodes 24 hours before immunization, severe postnatal condition, age of less than 70 days or weight less than 1,500g [11, 16, 18].

Absolutely not all registered apneic episodes are directly associated with vaccinal administration, as was shown by the controlled study of 197 children with GA ≤27 weeks and weight ≤1,000g: administration of a vaccine against diphtheria, tetanus and pertussis with acellular pertussis component (DTaP) on the 55^{th}-60^{th} day of life was not accompanied by a higher rate of complications in comparison with the non-vaccinated control group children. Thus, prolonged apneic episodes occurred in 16 and 20.4% of children, accordingly, bradicardia – in 58.1 and 56.1%. Rate of apnea in both groups was 0.5 per child, of bradicardia – 2.6 and 2.7, accordingly [19].

Though apneic episodes are not always associated with vaccination, postvaccinal apnea is an apnea recurrence risk factor at the administration of the next vaccinal dose. Thus, a 3-year-long monitoring of vaccination complications in one of the provinces of Australia showed that 7 out of 58 vaccinated premature infants had recurrent apneic episodes with/without bradicardia. Neither of these 7 children had the 3^{rd} episode at the subsequent immunization. Neither of the 8 term infants with postvaccinal apnea had recurrent episodes [20].

Most authors indicate the benign character of apneic/cardiorespiratory episodes without long-term consequences [21, 22].

Rate of reactions to DTP vaccine administration. Vaccine against diphtheria, tetanus and pertussis with whole-cell pertussis component (DTP) is considered the most reactogenic among the calendar vaccines. Its administration to premature infants used to be considered safe despite the development of unfavorable episodes. Thus, apnea with/without bradicardia developed in 20% out of 98 vaccinated children (GA – 24-31 weeks, average age – 80.6 days); it most often developed without desaturation and ceased spontaneously. 5 children of lesser GA, who were subject to APV longer than other children, required intervention (additional oxygen); in general, the authors indicate clinical insignificance of these episodes [23]. However, in 1999, American Academy of Pediatrics recommended a vaccine with acellular pertussis component – DtaP – to use in premature infants [24].

Rate of reactions to the simultaneous administration of one or several vaccines. Necessity of the simultaneous administration of several vaccines puts a question whether this procedure is traumatic both for term and premature infants; in the latter the schedule of invasive interventions is overloaded besides such vaccination due to additional medical procedures.

Safety issue of the simultaneous administration of several preparations to premature infants was most completely analyzed in the prospective study of 239 children of average GA (28 weeks), 70% of whom received 1 out of 5 vaccines (including DtaP) and 30% - several vaccines simultaneously (ca. half of them received 5 vaccines). 52% of children did not develop apnea, bradicardia or desaturation neither before nor within 72 hours after immunization; in 32% of children, who had had such episodes before vaccination, these episodes did not become more frequent. Postvaccinal episodes developed for the first time in 24 (10%) children and become more frequent in 15 (6%) children. In case of separate administration of vaccines, episodes developed most often after DtaP (22%), PCV7 (12%) and Hib (11%); only 1% of children

developed episodes after administration of IPV, neither – after administration of HBV. The episodes developed in 32% of children in case of simultaneous administration of several vaccines. All the episodes resolved without accidents [25].

Influence of vaccination on the rate of obstructive episodes. Premature infants are especially subject to infections (with obstructive components) caused by respiratory-syncytial and rhinoviruses. They are often associated with vaccination in case of development in the postvaccinal period. This association was analyzed in the 5-year-long study of an insured group of 6,155 premature infants (605 out of them – small premature infants). Administration of inactivated vaccines (DtaP, Hib, PCV7) to children with different pathologies [bronchopulmonary dysplasia (BPD), HIV, mucoviscidosis etc.] resulted in the infection risk reduction [RR (infection development risk in the group of vaccinated children to the control group children, who had not been vaccinated) – 0.83] on the 8^{th}-14^{th} postvaccinal day; the reduction was significantly higher in case of administration of OPV (RR – 0.4). Significant reduction in the rate of obstructive episodes in premature infants without this pathology was observed on the 8^{th}-14^{th} day after administration of live attenuated viral vaccines; RR after MMR – 0.68; after OPV – 0.7; after varicella vaccine – 0.71. Disease risk reduction was observed on the 15^{th}-30^{th} post-MMR day (RR – 83); it was unreliably observed in the subsequent 2 weeks (RR – 0.86) [26].

Vaccine administration technique for premature infants. All researchers deem it acceptable to start vaccination at the age of 2 months (8 weeks). Special attention should be given to vaccinal prevention of hepatitis B (this issue is reviewed in detail below).

Children with signs of a current infection, intense cardiorespiratory instability and no weight gain are the most often preventive vaccination rejected patients. It should be noted at the same time that BPD and oxygen dependency (up to the need in auxiliary ventilation) are not deemed contraindications for vaccination, as BPD may persist in children with this condition for months and years.

Preferable injection site for intramuscular vaccines in premature infants (as in term infants) is the quadriceps muscle of thigh. 16mm-long needles used for vaccination are introduced into the muscle at right angle.

Immunogenicity and reactogenicity in premature infants

Vaccines against diphtheria and tetanus. Administration of toxoids contained in DTP or DtaP vaccines is aimed at the attainment of an antibody level higher than 0.1 IU/ml. Similar and higher levels are usually achieved at the administration of combined vaccines to premature infants. Results of the study by M.C. Aued Perin et al. showed that tetanus antibody levels at the age of 15 months in premature infants (<1,500g) were lower than in term infants; antibody titers equalized after administration of a booster vaccine dose. Interestingly, the cellular immunity analysis (percentage of CD4+ T and CD8+ T cells, which responded to the tetanus toxoid stimulation with IFN γ generation) produced similar results in both groups [27].

Acellular pertussis vaccine. Assessment of response to acellular vaccine components is complex due to the fact that the protective level of antibodies to them has not been determined; antibody level is usually seen only as the "correlate" of protection. Most data indicate that premature infants, even the smallest (GA <32 weeks) respond to the filamentous hemagglutinin and pertactin administration in the same way as term infants. At the same time, pertussis toxin antibody levels after 3 vaccinal doses (at 2, 3 and 4 months of age) were 1.5 times lower. Levels of all 3 types of antibodies equaled the ones in term infants after the booster dose administration at the age of 1 year [28]. That is why, given severity of pertussis infection, it is very important to complete the primary vaccination course and control over the booster dose receipt in premature infants.

Weakness of response to pertussis toxin was not connected with the accelerated primary immunization scheme used in this study. Another study (scheme – 2-4-6 months) obtained the same results: lower pertussis toxin antibody titers after 3 doses and their rise to the post-booster titer level in term infants at 1 year of age [15].

The work of S. Esposito et al., who revealed sufficient levels of specific immune globulins at the age of 5 years in most premature infants who undergone a three-stage vaccination (scheme – 3-5-12 months), indicates the long-term preservation of protective levels [29].

A range of studies claim that premature infants with GA <31 weeks respond to the acellular vaccine administration not only humorally, but also cellularly – with the IFN γ production by peripheral mononuclear leukocytes and the interleukin (IL) 5 and IL 13 secretion in case of exposure to vaccinal antigens [30].

Inactivated poliomyelitis vaccine. Protective antibody levels have been defined in respect of this vaccine – 1:4 or 1:8; this makes it possible to evaluate adequacy of immune response to vaccination. 97% of premature infants with GA <30 weeks had protective titers to 3 poliovirus types [31] after the 3rd vaccine administration dose (scheme – 2-3-4 months).

Along with humoral antibodies, premature infants respond with the secretion IgA-antibody titer increase to the same extent as term infants [32].

The aforementioned study by N.P. Klein et al. [7] showed that poliomyelitis vaccination causes not only adequate humoral response, but also specific T-cell response, although the latter is weaker than in term infants.

Hepatitis B vaccine. Children of birth weight <2,000g may have a reduced response to the hepatitis B vaccine (HBV) administration in terms of both the seroconversion rate and the antibody level. However, HBV causes the same response in premature children as in term infants from 1 month of age regardless of GA and birth weight. Various schemes have been tested in this respect, including scheme 2-4-6 months, which produced the results comparable with the results in term infants [15, 31-34].

The given data served as the basis for formulation of vaccination tactics for premature infants. Children of birth weight ≥2,000g are vaccinated at birth and later – according to the scheme adopted in their country of birth and residence. Children of birth weight <2,000g (in the USA - <1,700g) born to non-HBsAg-carrier mothers are vaccinated from 1 month of age, preferably in compliance with the 4-dose scheme. If a mother is an HBsAg carrier, a premature infant of any weight shall be vaccinated at birth, as it may reduce the hepatitis B infection risk. Besides vaccination, children of weight <2,000g should be additionally protected against infection by administration of 100 IU of specific immune globulin (HBIG). If HBsAg-status of a mother is unknown, children of any weight are vaccinated postnatally, of weight <2,000g – together with HBIG administration. HBIG shall be introduced within 7 postnatal days in children of weight ≥2,000g with HBsAg-carrier mothers.

Response to HBV administered as part of a hexa vaccine to premature infants at the age of 2, 4 and 6 months was comparable to the response in the group of term infants [seroconversion – 93.4 and 95.2%, geometric mean titer (GMT) – 634 and 867 mIU/ml, respectively]. Weaker response was observed in children who had previously received steroids (88.9 and 188.1 mIU/ml, respectively). Booster administration causes the same response in premature and term infants (GMT – 1,771 and 1,965, respectively) [35]. The other study revealed post-booster antibody titers higher than 10 mIU/ml in 96.5% of children of 1,500-2,000g of weight at the age of 18-24 months and in 88.7% of smaller neonates [15].

BCG. According to the international and national standards, this vaccine is not administered at birth to children of less than 2,000g of weight (or GA less than 34 weeks), although we have not found any substantiation of this norm (apart from thin skin observed premature infants and complexity of subcutaneous administration) in medical literature. These children should be vaccinated upon discharge from the 2nd developmental care stage; in the USA it is recommended not to vaccinate such children before 34 weeks of gestational + postnatal age.

Vaccine against the infection caused by Haemophilus influenzae type b (Hib-infection). Results of vaccination of premature infants against this infection showed its absolute protectiveness, although it depended on the GA of children, immunization scheme and the protein conjugate contained in the vaccine. Administration of 2 doses a vaccine conjugated with tetanus toxoid (TT) at 2 and 4 months of age resulted in the appearance of protective antibody levels only in half of children of GA ≤30 weeks; response in the more mature premature infants was much stronger, almost as strong as in term infants. Level of protection equalized in all groups after the administration of booster at the age of 12 months [36].

A vaccine conjugated with tetanus toxoid (TT) causes lower antibody levels and seroconversion rate in children with GA <32 weeks observed until the age of 5 than in premature infants even after 3 administrations (at 3, 4 and 5 months of age). However, the authors emphasize that the vaccination has protective effect for this group, too [37]. It appears that the shortened primary immunization does not produce sufficient results in small premature infants, while almost all children, including premature infants with GA ≤29 weeks, developed protective antibody levels after 3 administrations of a CRM_{197}-conjugate vaccine with at 2, 4 and 6 months of age [33].

Similar results were obtained at administration of a hexa vaccine (scheme 2-4-6, 18-24 months). The percentage of premature infants with protective antibody titers after the primary immunization was slightly lower than in term infants (92.5 and 97.8%, respectively) with lower mean antibody concentration (2.2 and 4.2mcg/ml). 100% of premature infants had protective titers and the mean concentration equal to the mean concentration in term infants after a booster [38].

Modern combined vaccines. We mentioned above the studies of administration safety of modern penta and hexa vaccines to premature infants; this considerably reduces the risk of injury at vaccination. We also mentioned above the data on the response to hepatitis B and Hib components of the hexa vaccine. Study of immunogenicity of other Infanrix Hexa vaccine components shows their efficacy in premature infants. Thus, one of the first publications on this subject demonstrated that the seroconversion rate to 3 pertussis components, 3 poliovirus serotypes, diphtheria and tetanus was almost the same in premature infants after the 3rd dose as in term infants. The same data were obtained for the children of 5 years of age [before and after Infanrix vaccine booster (DTaP)], which is why we may assume that it is possible to use them in premature infants [35, 39].

Pneumococcal vaccine. It is widely known that premature infants are especially susceptible to pneumococcal infection. Appearance of pneumococcal conjugate vaccines (PCV) created the possibility of immune prevention of this infections; it is also important to compare serological response in children of different GA.

The studies of response of premature infants to PCV7 (scheme 2-4-6-16 months) conducted in Poland showed the equally high response of children with GA less than 30 weeks and 30-34 weeks. 1 month later, after the 3rd dose, antibody levels were the same in all groups of children and exceeded 1mcg/ml in most of them; however, there were differences in the levels of certain serotypes; serotype 6B had the lowest levels. Antibody levels were significantly lower prior to the booster dose, though they were ≥0.35mcg/ml, which is considered to be the protective antibody titer, and increased sharply after the booster [40].

Comparative analysis of serological response of term and premature infants vaccinated with PCV7 at the age of 3, 5 and 11 months did not reveal any difference in the levels of anti-pneumococcal titers to all serotypes. Antibody titers reached ≥0.35mcg/ml after the 2nd dose in most children, ≥1mcg/ml – after the 3rd dose. Safety and tolerability were identical in both groups. These data indicated applicability of the immunization scheme 2+1 for premature infants [41].

PCV7 (scheme – 2-4-6 months) in the smallest premature children (birth weight <1,000g) creates a protective antibody level (>0.35mcg/ml) more rarely than in children of 1,000-1,500g of weight only in connection with serotypes 6B (85 to 96%) and 23F (88 to 97%). Antibody level

reaches >0.35mcg/ml in 93.2-99.2% of low-birth-weight children, >1mcg/ml – in 64.4-93.2% of low-birth-weight children [42].
Data on the epidemiologic efficacy of PCV-vaccination of premature infants have also been published.
In the USA, PCV7 efficacy against invasive pneumococcal infection (IPI) in the Kaiser insurance system for children of birth weight <2,500g was 100% (morbidity in the children, who were at the same time vaccinated with a meningococcal vaccine, was 3.4/1,000). Children of low weight and GA had the same rates of fever and local reactions as term infants, excluding cases of reddening and swelling in the injection site [43]. Comparative analysis of prevaccinal (2000) and post-PCV7 (2007) cohorts in Bavaria revealed IPI rate reduction in all children from 0.00015 to 0.000085%, in premature infants – from 0.000261 to 0.000161%. Most infected children appeared to unvaccinated and undervaccinated patients [44].
PCV7 conjugated with nontypeable *H. influenzae* outer membrane's protein D produced excellent results as well. PCV10 was registered in Europe for vaccination of premature infants on the basis of trials 10Pn-PD-DiT-015 and -016 [45]. These open controlled trials were conducted in Spain and Greece and involved children born in the following gestation periods: 27-30 weeks (group I, n=50); 31-36 weeks (group II, n=87) and more than 36 weeks (group III, n=149). All infants received vaccines PCV10 and DTP – HBV – IPV/Hib according to the primary immunization scheme at 2, 4 and 6 months of age and subsequent revaccination within the 2nd year of life. Primary PCV10 vaccination generated immunogenicity towards all vaccinal pneumococcal serotypes both in premature and term infants. 95% of children of GA of 27-30, 31-35 and ≥36 weeks, vaccinated according to the scheme at 2-4-6 and 16-18 months of age, generated post-booster antibody titers >0.35mcg/ml; the vaccine appeared well-tolerable in all children [45]. PCV10 revaccination resulted in a stable increase (5.7-24.3 times) in the concentration of antibodies to all vaccinal pneumococcal serotypes within the period starting from the pre-revaccination time point to the post-revaccination time point both in premature and term infants; this fact indicates formation of the PCV10-induced immunological memory [45].
Meningococcal C vaccine. Separate trials revealed that administration of this vaccine to premature infants (scheme – 3-4-5 months or 3-5-12 months) leads to the formation of neutralizing antibody protective titers comparable with such titers in term infants. No differences have been revealed between vaccines conjugated with TT and CRM_{197} [9, 31].
Influenza vaccination. Influenza vaccination with subunit or split vaccines recommended at the age >6 months is especially indicated for premature infants with the increased risk of infection and severe course of influenza. The available data reveal a rather strong response of these children to 2 administrations 1 month apart at the age of 6-18 months; surprisingly, the response is often stronger than in term infants. Children of GA of 30-32 weeks and most smaller children obtained protective titers already after the 1st dose [46].
Rotavirus vaccination. Oral monovalent (G1P[8]) vaccine administered twice between days 30 and 83 of life to 1,000 premature infants (20% of whom of GA <30 weeks) appeared to be as immunogenic as in term infants. Anti-rotavirus IgA-seroconversion appeared in 85.7% of the vaccinated with GMT – 202.2 IU/ml. These parameters were lower in children of extremely low weight: 75.9 and 110.2 IU/ml, respectively. These data prove rotavirus vaccination of premature infants effective (and safe) [47].
One of the dangers (mostly theoretical) is the risk of live rotavirus release in premature infants with virulence reversion. The 2-week-long study of rotavirus release after administration of 1 dose of a 5-valent reassortant vaccine (RV5) to 15 children with GA of 26-34 weeks disproved this fear. Although trials conducted with EIA and RT-PCR techniques revealed viruses in most children, positive results of a cultural trial were low (8 out of 86 fecal samples; 9.3%). No child out of 53 domestic contacts developed gastroenteritis [48].

Vaccination against measles, rubella, parotitis and chickenpox. As these vaccines are administered in the 2nd year of life, we may expect adequate response of premature infants to

their administration. A small trial (16 premature infants of GA <29 weeks and 16 term infants vaccinated at the age of 15 months) revealed a similarly high seroconversion rate (more than 90% to 3 serotypes of measles, rubella and parotitis) and high GMT. Seroconversion to chickenpox was attained in 69% of premature infants and 60% of term infants [49].

Conclusion

Premature and low-birth-weight children feature immune response peculiarities, such as, in particular, lower antibody titers at administration of certain antigens. However, most "calendar" vaccines and the vaccines, that have not yet been included in the National preventive vaccination calendar (vaccine for prevention of pneumococcal infection, chickenpox, meningococcal C infection and rotavirus infection) can successfully be used both in premature and low-birth-weight infants and even in small premature infants of GA <30 weeks and birth weight <1,000g, who also develop adequate protection against the corresponding infections. Chronological age of vaccination beginning in premature infants is the same as in term infants with the exception of BCG and hepatitis B vaccines in children of weight <2,000g (they require a special vaccination scheme (see above)). Influenza vaccination just before the influenza season is indicated to all premature infants.

Multiple trials showed that administration of both "calendar" and a range of "extra-calendar" pediatric vaccines (e.g., a vaccine for prevention of pneumococcal infection), including vaccines combined with 5-6 components, is safe and is not accompanied by increase in the rate of common generalized and local reactions. As apnea episodes (with/without bradicardia and desaturation) are typical of premature infants, especially of small premature infants, including the period within 48-72 hours prior to the vaccinal administration, immunization of these children should be started in the inpatient hospital on the stage of developmental care while monitoring vital functions. This helps to quickly overcome apnea episodes by increasing oxygen input, more seldom – by the shift to CPAP-therapy (continuous positive pressure therapy) or APV. If a child develops an apnea episode to the administration of the 1st vaccinal dose, the subsequent doses should be administered under monitoring.

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