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COMBINED VACCINES IN PEDIATRICIAN PRACTICE

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Annotation. Currently, there is a trend towards reducing the use of invasive methods in pediatrics, which also relates to vaccine prevention. The creation of modern multicomponent vaccines contributes to a reduction in the number of painful injections for infants, since most vaccines are administered in the first year of life.

The article presents convincing data on the high effectiveness and safety of combined vaccines. The possibility of their effective combination with other monovaccines, the absence of a sum of adverse reactions, and even their reduction due to a decrease in the frequency of vaccinations (in the case of using monovaccines) has been shown.

Keywords: vaccine prophylaxis, combined vaccines, monovaccines, combination of various vaccines, reactivity, effectiveness, safety, children.

Introduction. The expansion of immunoprophylaxis has led to the emergence of a large number of vaccines with proven effectiveness for infants. As part of the mandatory vaccination calendar, most countries use parenteral vaccines against hepatitis B (HBV), diphtheria, tetanus, whooping cough, type b (Hib) hemophilic infection, poliomyelitis, tuberculosis, measles, rubella, parotitis. Many countries have implemented mass vaccination of children against pneumococcal infection and smallpox; the use of vaccines against meningococcal infection is expanding. It is clear that administering such a large number of monovaccines is inconceivable, and even with long-established trivaccines like ACDS and measles-rubella-parotitis, the number of injections will not significantly decrease.

The natural way out is to create combined vaccines. Currently, vaccines containing 6 components (diphtheria and tetanus toxoids, cellular pertussis, inactivated polio (IPV), hepatitis B, and hemophilic type b vaccines) are widely used in all countries.

Methods. It can be administered alongside the Hiberix vaccine, meaning it is actually a tetravaccine. Now a whole family of 5- and 6-component Infanrix vaccines has been registered. The Infanrix Hex vaccine is 6-component (AaCDS + HBV + IPV + Hib); it is produced as a syringe dose with 5 components and Hib-component lyophilizate in a separate vial, dissolved immediately before vaccine administration. The vaccine syringe dose (0.5 ml) contains:

- Adsorbed diphtheria anatoxin (D), not less than 30 IU;
- adsorbed tetanus toxoid (C), not less than 40 IU;
- Adsorbed acellular pertussis toxoid (AAA), 25 mcg;
- adsorbed filamentous hemagglutinin (FHA), 25 mcg;
- Adsorbed pertactin, 8 µg;
- adsorbed recombinant protein HBsAg, 10 µg;
- type 1 (Mahoney) poliovirus, 40 D-antigen units;
- type 2 (MEF-1) poliovirus, 8 D-antigen units;
- type 3 poliovirus (Saukett), 32 D-antigen units.

Adjuvants: aluminum chloride - 0.5 mg, aluminum.

“The immunogenicity of the Infanrix Hex vaccine was also studied in a group of 186 premature and low-weight infants” [7]. Their response to the 3-fold administration of the vaccine (2-4-6 months) was pronounced, although the titers were somewhat lower than those of full-term infants. After the introduction of the booster dose in the 2nd year of life, the titers practically equalized and persisted for a long time, so that before the second revaccination against whooping

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cough at age 4, they remained at a protective level in the vast majority of premature and full-term infants.

Results and Discussion. Effectiveness. Since the transition to using the hexavaccine occurred under conditions of mass vaccination against diphtheria, tetanus, poliomyelitis, and hepatitis B, its effectiveness can be judged by maintaining practically zero morbidity. Phosphate - 0.2 mg. Auxiliary substances: sodium chloride - 4.5 mg, medium 199 (M199), containing amino acids - 1.15 mg, water for injections - 0.5 ml.

Hib-component (in a separate vial due to possible interaction in solution with other components) contains 10 mcg of lyophilized conjugate of capsular polysaccharide (PRP) *Haemophilus influenzae* type b, 20-40 mcg of adsorbed tetanus toxoid (C), 12.6 mg of lactose; 0.12 mg aluminum phosphate. The vaccine contains no preservatives and meets all the requirements of the World Health Organization (WHO). Infarrix Penta is the indicated syringe dose, but without a Hib component.

As can be seen from the Infarrix Hex composition, it includes conventional doses of components for monovaccines; unlike several other combined vaccines, it contains vaccinated. "Infarrix Hex's protective potential was studied in relation to Hib-infection: it was 68% for children who received 1 or 2 doses, 90.4% for those who received the primary course (3 doses), and 100% for those who received 3 doses and revaccination in their second year of life" [8].

Data on the protective effect of the hexavaccine against whooping cough are taken from a study of the Infarrix vaccine, which has the same composition. The effectiveness was 88.7% in Germany [9] and 83.9% in Italy, with a protective effect lasting up to 6 years [10].

Thus, the effectiveness of Infarrix Hex is quite comparable to the effectiveness of previously used combinations of Infarrix with monovaccines.

Contraindications to Infarrix Hex (and other family vaccines) do not differ from those for the vaccines included in it:

- not 2 but 3 components of the acellular pertussis vaccine, which, according to some data, enhances its immunogenicity.

All Infarrix family vaccines are administered from 6 weeks of age. Their immunogenicity has been studied in several large-scale studies [2, 3]. It has been shown that with different administration regimens (2-3-4, 2-4-6, 3-4-5 months, 6-10-14 weeks), the immune response after the primary series does not differ depending on the administration regimen, with serotoxicity reaching 96-100%; after revaccination, at the 2nd year of life, protective antibody titers against all infections are observed in almost all children, and the average geometric titers of antibodies do not differ significantly from those achieved with the simultaneous administration of Infarrix and the corresponding monovaccine. Moreover, "it has been shown that the seroprotective levels of antibodies to vaccine antigens are determined in most children 4-6 years after revaccination (below the indicators for antibodies to pertussis toxin). The introduction of a booster dose of hepatitis B vaccine after 7-9 years caused a pronounced anamnestic response in 98.9% of children, indicating the formation Immunological memory development" [4].

"Since in many countries, as in Russia, the hepatitis B vaccine is administered during the newborn period, the immune response to subsequent administration of 3 doses of Infarrix Hex has been studied. It has been shown that 3 doses of the vaccine cause seroconversion (with antibody titers of $\ll 10$ mIU/ml) in all cases (regardless of vaccination at birth)" [5]. "When HBV was administered during the newborn period and at 1 month of age, Infarrix Hex's application led to the same concentration of antibodies to HBsAg as after the introduction of HBV-monovaccin" [6].

- increased sensitivity to active substances, including polymyxin and neomycin;
- hypersensitivity after administration of Infarrix Hex vaccines;
- encephalopathy of unknown etiology, developed within 7 days after the previous vaccination with the pertussis vaccine;

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- vaccination is possible in mild forms of acute respiratory viral infections (ARVI), acute intestinal infections (ACI), etc. Reactogenicity. Acellular pertussis vaccines-

These vaccines (including combined ones) differ from the whole cell type of ACDS in their significantly lower reactivity, which has predetermined the preference given to these vaccines in a growing number of countries. This fully applies to the Infanrix vaccine family.

Clinical studies of the vaccine have shown that after infanrix hex administration, pain at the injection site is observed in 15-20% of children, fever - in 20-25%, however, pronounced local and general (fever above 39.5°C) reactions are noted in less than 1% of cases. No significant differences were found in the frequency and severity of adverse reactions to the administration of Infanrix Hex and the simultaneous administration of Infanrix with HPV, HBV, and Hib-vaccine.

Post-licensed data on more than 28 million doses of Infanrix Hex showed a low frequency of spontaneous appeals for adverse events (0.7-5.9 per 100,000 doses), comparable to the frequency of other vaccines containing the pertussis component. Temperature increase (5.9 per 100,000) and erythema in the affected area were most common. Injections (2.1 per 100,000). More severe neurological complications - encephalitis or encephalopathy, Guillain-Barré syndrome - had a frequency of 0.02 and 0.01 per 100,000 doses, respectively, and their connection to vaccination was not proven [2]. In several studies, adverse events within 1 month after vaccination were detected in 0-18% of vaccinated individuals - in response to less than 3% of the doses. Most often, these were common diseases - ARVI, rhinitis, bronchitis, and acute respiratory infections. In one study, these events were noted in 63.3% of children who received Infanrix Hex and 63.8% of those who received Infanrix + IVP + Hib + VGV (vaccination with individual drugs in different body parts on one day), of which only 4.3 and 4.1%, respectively, were associated with vaccination; the most pronounced (3rd degree) can be attributed to no more than 2.5 and 4.5% of the total number of vaccination-related reactions, respectively. The possible connection between the syndrome of sudden infant death and the introduction of Infarix Hex was also studied. "In this case, as a rule, a negative result was obtained. Thus, in Germany, among Infanrix Hex vaccinated children aged 1-2 years, the sudden mortality rate was lower within 14 days after vaccination compared to the general child population" [3]. Infanrix family of vaccines in the immunocorrective calendar. Depending on the possible individual schedule for vaccinating the child against viral hepatitis B, the pediatrician can use various options for administering the Infariks Hex vaccine.

The introduction of the 4th revaccinating dose of the hepatitis B virus vaccine does not pose any danger and only strengthens the immune response to vaccination;

The national calendar contains the norm for 4 doses of hepatitis B vaccination in children from risk groups.

In practice, there is often a situation where the schedule of both ACDS-vaccination and viral hepatitis B is disrupted.

"Immunization tactics when extending intervals between vaccinations against hepatitis B are regulated by the letter of Rosпотребнадзор of the Russian Federation dated May 18, 2007" [11].

In Table. In the 3rd chapter of the dissertation, schemes for administering Infandrix Hex for deviations in the ACDS schedule and vaccination against viral hepatitis in children of the first two years of life are presented.

Combination of Infanrix family vaccines with other vaccines. Analysis of changes in the immunoprophylaxis calendars of industrialized countries showed that the main trend is the introduction of new antigens and optimization of immunization periods, which allows for the use of combined vaccines with an increasing number of components. This approach allows prophylactic medicine of Russia. In Table. 1 is represented using-reduce the injection load on the child and thereby currently implemented vaccination scheme for children up to 20 months of age. Excluding influenza vaccination, the child must receive 18 injections for complete immunization (16 if Bobo-Coke vaccines and the divaccine coronary arthritis are used), with 3 injections per

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visit. If vaccination against pneumococcal infection and smallpox is also carried out, 4-5 more injections should be added to these extreme figures. Using Infarix family vaccines, it is possible to reduce the number of injections in the first 2 years by more than 2 times - up to 7, which not only reduces injuries but also opens up prospects for introducing additional injection vaccines into the Calendar. Improve the perception of both «old» and new vaccines by parents and society as a whole. “This, in turn, can lead to increased coverage of the child population based on voluntary and conscious choice. Both the immunogenicity of all 6 components and the formation of immunological memory, which was evidenced by the growth of antibody titers after the introduction of the booster dose” [12]. “Dutch researchers came to the same conclusion by comparing the immunogenicity of 10-valent, protein-conjugated D H. influenzae (Sinflorix), pneumococcal vaccine when administered with Infarix Hex and corresponding mono-vaccines according to a 2-3-4 month scheme” [13].

No differences were found in the simultaneous administration of the C-type and Infarix Hex conjugated meningococcal vaccine compared to the administration of these vaccines on different days. At the same time, it was noted that there was no increase in reactivity when administered simultaneously [14]. “In another study, it was shown that the administration of the 4th dose of Infanrix Hex together with the 4-valent conjugated meningococcal vaccine of types A, C, W-135, Y causes an immunological response no worse than when these vaccines are administered separately: 1 month after vaccination, "97.3% of children had titers for all meningococcal antigens "1: 8" and "98.2% - protective titers for all Infanrix Hex antigens, while Infanrix Hex's reactivity was not higher than when administered separately” [15].

Finally, it was shown that when Infanrix Hex was administered simultaneously with the 10-valent Sinflorix pneumococcal vaccine and different meningococcal types with conjugated vaccines, the percentage of children with antibody levels above the minimum necessary protective value approached 100%

Conclusion. At the same time, the reactions at the injection sites of the meningococcal vaccine and Infanrix Hex, “as well as the overall reactions, did not differ” [16].

Registration of the Infanrix family of combined vaccines in Russia creates prerequisites not only for reducing the trauma of immunoprophylaxis courses for children of the first 2 years of life, but also for the introduction of new vaccines, primarily pneumococcal ones, into the Calendar. The available data allow us to consider the combined Infanrix Hex and Infanrix Penta vaccines to be highly immunogenic. Their safety and reactivity profile (including when combined with other parenteral and enteral vaccines) allows them to be recommended for mass use within the National Preventive Vaccination Calendar. The introduction of combined vaccines in the Immunoprophylaxis Calendar is a global trend that meets the interests of children, parents, medical workers, healthcare organizers, and society.

“The risk of hospitalization for ARVI, pneumonia, acute respiratory infections, sepsis, bacterial meningitis, and viral lesions of the central nervous system, but also for some of them, reduces this risk” [18].

vaccines will be able to reduce the costs of administration, storage, and circulation of vaccines and immunobiological preparations, while increasing the coverage and vaccination coverage of the population.

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