D.A. Novikova, N.E. Tkachenko
Scientific Center of Children's Health, Moscow, Russian Federation

Combined vaccine is an effective and safe protection from five controllable infections

Author affiliation:
Novikova Dar'ya Andreevna, MD, head of the vaccinal prevention department for children with health deviations (division "Science") at the Scientific Center of Children's Health (Federal State Budgetary Institution)
Address: 2/1 Lomonosovskiy Av., 119991; **tel.:** +7 (499) 134-20-92

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The article is dedicated to prevention of controllable infections in infants. This is an urgent issue, as up to 40 mln. infectious diseases are registered in Russia every year; infections are particularly prevalent in children. Infectious pathologies may take up to 70% of all health conditions in children. Vaccination is the only effective method of preventing infectious diseases. The authors present international experience of using a pentavalent vaccine, which contains diphtherial and tetanus toxoids, acellular pertussis component, inactivated poliovirus and type b Haemophilus influenzae polysaccharide. This vaccine is included into immune prevention schedules for children of 0-1 (primary vaccination) and 1-2 (revaccination) years of age in many countries. The article presents results of major clinical studies, which confirm low reactogenicity and high effectiveness of the mentioned vaccine.
Keywords: *infectious diseases, prevention, vaccination, pentavalent combined vaccine, effectiveness, safety, children.*

Just like decades ago, it is commonly accepted that infants must be vaccinated against pertussis, diphtheria, tetanus and poliomyelitis. We are finally able to more or less successfully control the primary infectious diseases, life-threatening for infants, only thanks to the vaccination programs. According to the Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, diphtheria and tetanus morbidity has diminished down to singular cases; no cases of poliomyelitis were registered in 2011-2013. Unfortunately, pertussis morbidity remains rather high – 1.44 cases per 100,000 people, although the fact that pertussis morbidity diminished in January-May 2014 by 8% in comparison with the same period of 2013 is rather pleasant [1]. The fact that this category of patients is especially susceptible to such severe complications of pertussis as convulsions, encephalopathies and pneumonias, which are often accompanied by atelectases and apnea must not be ignored [2, 3]. Vaccinal prevention – control of the morbidity level using modern immunobiological agents – remains the primary means of fighting these infections.
Along with the aforementioned infections, such an adverse disease as poliomyelitis must not be ignored as well: infants are particularly susceptible to severe paralytic forms thereof. According to the World Health Organization (WHO) program, the humankind must have gotten rid of this disease (induced by wild virus strain) by 2000. It never happened, though: wild virus continues to circulate in a range of endemic regions (Afghanistan, Nigeria, Pakistan); breakouts of paralytic forms of this disease are still being registered there. That is why the possibility of importation of poliovirus from troubled regions cannot be ruled out. The last breakout of the disease induced by wild poliovirus strain took place in 2010.
However, singular cases of paralytic forms of the disease are registered among children – recipients of live vaccines [1]. The observed situation indicates that the infant immunization program in Russia must be thoroughly revised, i.e. vaccination with a live oral vaccine must take place only after establishment of strong humoral immunity against this infection in infants after the primary vaccination.
A combined pentavalent vaccines, which contains acellular pertussis component, diphtherial and tetanus toxoids, inactivated type 1, 2 and 3 poliovirus strains and the fifth important component – type b Haemophilus influenzae, meets the aforementioned requirements.
Type b Haemophilus influenzae (Hib infection) is an acute bacterial disease characterized by affection of the nervous system (up to 40% of all meningites) and respiratory organs (pneumonia, epiglottis) and sepsis. Under-5 children are the most susceptible to this infection; severe invasive forms occur in under-2 children particularly often. Vaccination against Haemophilus influenzae takes place in 160 countries. Ca. 80% of the WHO member states almost completely liquidated Hib meningitis, epiglottis and bacteremia

thanks to the introduction of vaccination against Haemophilus influenzae; severe pneumonia morbidity diminished by 20% [2].
Vaccination against Hib infection is especially relevant due to an increasing antibiotic resistance of the causative agent. Recent data demonstrate that Hib vaccine introduction resulted in an almost 45% decrease in mortality due to invasive forms of this infection among under-5 children [4].
The WHO recommends introducing conjugate Hib vaccines into all infant immunization programs. Use of this vaccines is a part of the complex WHO strategy of controlling pneumonia, along with breast feeding support, water supply and sanitation improvement etc. [5].
Pentavalent vaccine Pentaxim (Sanofi Pasteur, France), which contains diphtherial and tetanus toxoids, acellular pertussis component (DTaP), inactivated poliovirus (IPV) and type b Haemophilus influenzae (Hib), was licensed in 1997 in Sweden [2, 6]. It is the first pentavalent vaccine with acellular pertussis component used all over the world; it is introduced into vaccination schedules both for primary vaccination (0-1 years of age) and for revaccination (1-2 years of age). Clinical trials of effectiveness and tolerance of this vaccine have started all over the world soon after the drug's registration. Terms of primary vaccination and revaccination may not correlate in different countries (tb. 1); however, tolerance to the drug and vaccination with separate monocomponent vaccines depending on frequency of administration thereof (tb. 2) and generation of specific antibodies has been compared [6-9].
General safety of the pentavalent vaccine with acellular pertussis component has been evaluated in comparison with whole cell vaccine. Decreased rate of postvaccinal reactions has been observed; moreover, febrile convulsions were registered 79% less frequently in Canada in the process of primary vaccination and after revaccination, intracranial pressure increase – 60-67% less frequently [6].
14 clinical trials have been conducted in 9 countries; they demonstrated high tolerance to the vaccine; focal reactions (reddening, edema, injection site thickening, tenderness) were rare. Pentaxim booster dose tolerance was evaluated in France, South Africa, India, China, Vietnam and Thailand; according to this evaluation, revaccination is generally tolerated well, although focal reactions are observed slightly more often than at primary vaccination (see tb. 2).
Tolerance to 3,211 pentavalent vaccine doses in comparison with quadruple vaccine (Tetraxim, Sanofi Pasteur), which contains acellular pertussis component, diphtherial-tetanus toxoid and inactivated poliovirus, together with a Hib vaccine (different parts of the body) was analyzed in France. The rate of adverse reactions, both focal and total, was similar. Comparative studies of tolerance to the pentavalent vaccine in combination with a recombinant hepatitis B vaccine and to vaccination with inactivated poliovirus, acellular pertussis-diphtheria-tetanus vaccine and conjugate Hib vaccine (Hib) demonstrated equivalent tolerance to the immunization.
Several studies [6, 7, 9] demonstrated immunogenicity of the pentavalent vaccine: protective antibody titer against diphtheria and tetanus (more than 0.01 IU/ml) developed in 92.2-100% of children after the primary vaccination, against type 1, 2 and 3 poliomyelitis – in 99.6-100% of children. Type b Haemophilus influenzae antibodies could be observed 1 month after the third administration of the vaccine in 92-100% of cases (according to different authors) [6-9]. Studies of seroconversion to filamentous hemagglutinin and pertactin in Sweden demonstrated that the protective antibody titer against pertactin developed in 97% of the children, who had been administered 3 vaccinal doses, to filamentous hemagglutinin – in 89.1%. Similar data were obtained in the studies conducted in South Korea, Philippines and India. Regardless of the study population and the primary vaccination scheme, in all studies after primary vaccination course, which include 3 doses, high levels of seroconversion in relation to CT and PHA (82.9 and 83.9 -100 -95.9%, respectively) were detected [6]. It is also known that administration of the booster dose at the age of 1-2 years stimulates immune response and protective antibody titer in this case persists until the age of 5-7 and even 7-8 years (according to several authors) [10, 11].
Thanks to low reactogenicity and high effectiveness confirmed by a major clinical trial, pentavalent vaccine Pentaxim, which contains the components necessary to protect infant against the primary dangerous infections, has been introduced to various immunization programs all over the world. Pursuant to the global immunization strategy, the WHO recommends to introduce complex vaccines into the expanded immunization programs with particular care [6]. Due to the low reactogenicity and high efficiency, proven in large-scale clinical study, five component vaccine Pentaxim, containing the components essential for the protection of infants and children from the main dangerous infections, is included in the various immunization programs worldwide. Following the global immunization strategy, WHO recommends including comprehensive vaccine in the expanded programs of immunization intensively [6, 12]. According to the WHO, it is these live-preserving disease-preventing vaccines that

constitute the insurance of economic effectiveness of the whole vaccination program. Another indisputable advantage of the pentavalent vaccine is reduced injection stress for our small patients.
Thus, use of a combined pentavalent vaccine, which contains acellular pertussis antigen, diphtherial and tetanus toxoids, inactivated poliovirus and type b Haemophilus influenzae, serves the interests of children, parents, medical personnel, healthcare officers and society in whole, given its high safety and immunogenicity profiles. Introduction of combined pediatric vaccines will decrease costs of administration, storage and turnover of vaccines, increasing immunization coverage of the population.

REFERENCES

1. Available at: http://www.rospotrebnadzor.ru
2. Tatochenko V.K., Ozeretskovskii N.A., Fedorov A.M. *Immunoprofilaktika-2014* [Immunoprophylaxis-2014]. Moscow, Pediatr"", 2014. 198 p.
3. Uchaikin V. F. *Infektsionnye bolezni u detei* [Infectious Diseases in Children]. Moscow, GEOTAR-Media, 2011.
4. WHO. Available at: http://www.who.int/immunization_monitoring/burden/Pneumo_hib_estimates/en/
5. WHO/UNICEF Ending Preventable Child Deaths From Pneumonia and Diarrhoea by 2025: The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD). *Geneva*. 2013. Available at: http://www.who.int/maternal_child_adolescent/news_events/news/2013/gappd_launch/en/
6. Plotkin S. A., Liese J., Madhi S. A. et al. A DTaP-IPV//PRP~T vaccine (Pentaxim): a review of 16 years' clinical experience. *Expert Rev Vaccines*. 2011 Jul; 10 (7): 981–1005.
7. Nelson J. C., Onchee Yu., Clara P. Dominguez-Islas Adapting Group Sequential Methods to Observational Postlicensure Vaccine Safety Surveillance: Results of a Pentavalent Combination DTaP-IPVHib Vaccine Safety Study. *American Jornal of Epidemiology*. 2013;177 (Issue 2): 131–141.
8. Capeding M. R., Cadorna-Carlos J. et al. Immunogencity and safety of DTaP-IPV. PRP-T combination vaccine given with hepatitis B vaccine: A randomized open lable trial. Bull. *World Health Organ*. 2008; 86 (6): 443–451.
9. Madhi S. A., Cutland C. et al. Immunogenicity and safety of acellular pertussis, diphtheria, tetanus, inactivated poliovirus, Hib-conjugate combined vaccine (Pentaxim) and monovalent hepatitis B vaccine at 6, 10 and 14 month of age in infants of South Africa. *S Afr Med J*. 2011; 101: 126–131.
10. Gustavsson L., Hessel L. et al. Long-term follow-up of Swedish children vaccinated with acellular pertussis vaccines at 3, 5 and 12 months of age indicates the need for a booster dose at 5 to 7 years of age. *Pediatr*. 2006; 118 (930): 978–984.
11. Thierry-Carstensen B., Dalby T. et al. Expirience of monocomponent acellular pertussis combination vaccines for infant, children, adolescents and adults. A review of safety, immunogenicity, efficacy and effectiveness studies and 15 years of field experience. *Vaccine*. 2013; 31: 5178–5191.
12. Baranov A.A., Namazova-Baranova L.S., Galitskaya M.G. *Immunoprofilaktika u detei. Chast' I. Vaktsinoprofilaktika u detei* [Immunoprophylaxis in Children. Volume 1. Preventive Vaccination in Children]. Moscow, Pediatr"", 2012. 82 p.

Table 1. Terms of vaccination and revaccination in different countries

Country	**Term of primary vaccination** (months)	**Term of revaccination** (months)
France	3-4-5 / 2-3-4 / 2-4-6	15/17/20
Chile	2-4-6	*
Sweden	2-4-6 / 3-5	13/12
Turkey	2-3-4	*
Philippines	6-10-14 weeks	18/19
South Africa	6-10-14 weeks	18/19
India	6-10-14 weeks	18/19
Thailand	2-4-6	18/19
China	2-3-4 / 3-3-5	18/20
Vietnam	*	16-19
South Korea	2-4-6	*

Note. * - no tolerance trials.

Table 2. Rate of focal reactions after the primary vaccination of DTaP + IPV + Hib and revaccination (booster dose)

Symptom	Dose 1	Dose 2	Dose 3	Booster dose
Focal reactions (%)				
Reddening ≥ 2 cm	15.2	16.7	12.8	18.7
Thickening ≥ 2 cm	12.8	13.1	15.4	17.1
Pain	11	13	12.5	21.7
Systemic reactions (%)				
Prolonged crying	0.21	0	0.14	0.12
Body temperature rise up to 38-39 ^{o}C	6.1	10.3	9.7	8.7
Body temperature rise up to > 39 ^{o}C	0.2	1.0	1.1	0.7
Anorexia	0.5	0	0.1	2.4
Annoyance	0.5	0.1	1.1	1.1