ОЦЕНКА ГУМОРАЛЬНОГО ИММУННОГО ОТВЕТА У ДЕТЕЙ ПРИ ИММУНИЗАЦИИ РАЗНЫМИ ТИПАМИ ИНАКТИВИРОВАННЫХ ГРИППОЗНЫХ ВАКЦИН В СЕЗОН 2019-2020 ГОДА

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Резюме. Грипп является одной из наиболее распространенных респираторных инфекций, вызывающей миллионы случаев заболевания во всем мире. Эффективность вакцинации против гриппа и характер иммунного ответа на препарат могут варьировать в разных возрастных группах и в зависимости от состава вакцины. Поскольку дети подвержены наиболее высокому риску заболевания и являются основными распространителями гриппозной инфекции, исследования иммунологической эффективности вакцин у детей имеют большое значение для контроля эпидемического процесса в целом. Целью данного исследования стала оценка особенностей формирования гуморального иммунного ответа у детей после иммунизации различными типами инактивированных гриппозных вакцин.

Наблюдательное исследование было проведено в сезоне 2019-2020 г. и включало 230 детей в возрасте до 18 лет, а также 87 участников в возрасте от 18 до 60 лет в качестве группы сравнения. Добровольцы, давшие информированное согласие на участие, были привиты одним из трех препаратов: «Гриппол Плюс», «Совигрипп» или «Ультрикс», в открытом режиме. Оценку гуморального иммунного ответа проводили по титру антигемагглютинирующих антител в парных сыворотках добровольцев, взятых до и через три недели после вакцинации.

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Иммуногенность вакцин, проанализированная суммарно по всем препаратам в возрастной группе до 18 лет, удовлетворяла критериям CPMP для оценки инактивированных гриппозных вакцин по показателям кратности прироста антител и доле лиц с сероконверсией в отношении всех трех компонентов (A/H1N1pdm09, A/H3N2 и B/Victoria). У детей в возрасте от 6 до 18 лет наблюдали более активный ответ к компоненту B/Victoria по сравнению со взрослыми участниками (от 18 до 60 лет), которого тем не менее было недостаточно для обеспечения 70%-ной иммунной прослойки лиц с условно защитным титром антител.

Сравнительный анализ иммуногенности препаратов, проведенный для подгруппы детей в возрасте от 6 до 18 лет с исходно низким уровнем антител на момент вакцинации, показал, что сплит-вакцина «Ультрикс» имела преимущество по сравнению с адъювантной вакциной «Гриппол плюс» в формировании антительного ответа в отношении компонента B/Victoria и не отличалась в отношении компонентов A/H1N1pdm09 и A/H3N2. У детей младше 6 лет наблюдалась тенденция к менее выраженному гуморальному иммунному ответу на вакцинацию по сравнению со старшей возрастной группой, что может быть связано с возрастными особенностями иммунной системы у детей младшего дошкольного возраста.

Ключевые слова: инактивированная гриппозная вакцина, дети, подростки, антитела, реакция торможения гемагглютинации, критерии иммуногенности

ASSESSMENT OF THE HUMORAL IMMUNE RESPONSE IN CHILDREN AFTER IMMUNIZATION WITH DIFFERENT TYPES OF INACTIVATED INFLUENZA VACCINES IN THE 2019-2020 SEASON

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Abstract. Causing millions of cases worldwide every year, influenza is one of the most common respiratory infections. The effectiveness of influenza vaccination and the nature of the resulting immune response may vary depending on the vaccine composition and age group. Since children are at the highest risk of disease and act as the main carriers of influenza, the assessment of the immunological efficacy of vaccines in this group is crucial for controlling the epidemic. Therefore, this study aimed to evaluate the characteristics of the humoral immune response in children after immunization with various types of inactivated influenza vaccines.

An observational study was conducted in the 2019-2020 season and involved 230 children (< 18 years old) and a comparison group of 87 adults aged 18 to 60 years. The subjects, who provided informed consent to participate, were vaccinated with one of three vaccines (Grippol Plus, Sovigripp, or Ultrix) in an open-label fashion. The humoral immune response was assessed by measuring the hemagglutination inhibition (HI) titer in the paired sera taken before and three weeks after vaccination.

The immunogenicity of the vaccines in the age group under 18, met the CPMP criteria for the assessment of inactivated influenza vaccines in terms of the fold increase in antibody titers and the proportion of individuals with seroconversion to all three components (A/H1N1pdm09, A/H3N2, and B/Victoria). Although 6 to 18-year-old participants showed a more robust immune response to the B/Victoria component compared to the adult participants (aged 18 to 60), it was insufficient to ensure that 70% of the participants have a protective antibody titer.

A comparative analysis of the vaccines' immunogenicity was carried out for a subgroup of children aged 6-18 who had initially low antibody levels at the time of vaccination. The analysis showed that the split vaccine Ultrix outperformed the adjuvanted vaccine Grippol Plus in generating an antibody response to the component

B/Victoria; however, the antibody responses to the A/H1N1pdm09 and A/H3N2 components did not differ between the two vaccines. The children under 6 years of age demonstrated a less pronounced humoral immune response to vaccination compared with the other age groups, which may be due to the age-related characteristics of the immune system in children of preschool age.

Keywords: inactivated influenza vaccine, children, adolescents, antibodies, hemagglutination inhibition reaction, immunogenicity criteria

The study was carried out within the government contract of the Ministry of Health of the Russian Federation "Assessment of the Intensity of Collective Immunity and Epidemiological Effectiveness of Influenza Vaccines in the Russian Federation (2019-2021)".

List of abbreviations: AB, antibodies; 95% CI, 95% confidence interval; IIV, inactivated influenza vaccine; IQR, interquartile range; HI test, hemagglutination inhibition test; GMT, geometric mean titer.

Introduction

Influenza is one of the most common respiratory infections, causing millions of cases worldwide. Vaccination remains to be the most effective way to prevent influenza-related morbidity and mortality. Children are at higher risk of influenza infection than other age groups [14]. Being the main carriers, children of preschool age are a 'reservoir' for viruses that cause flu and other seasonal acute respiratory viral infections. Influenza causes children to seek outpatient and inpatient treatment and their parents to take sick leave more frequently. The clinical course of influenza infection may vary depending on the age of the child, comorbidities, and the type of virus [for review see 7, 10, 11].

The effectiveness of influenza vaccination and the nature of the resulting immune response may vary depending on the age group and the vaccine composition [5, 6, 9]. In adults, the response to vaccination is often modulated by pre-existing immunity that is formed as a result of multiple vaccinations and past infections [9]. Studying the antibody response in children with a well-documented prior exposure helps identify the factors that influence vaccine efficacy [3]. Although many countries now recommend seasonal vaccination of children, the data on the effectiveness of inactivated influenza vaccines (IIV) in this age group are limited. Therefore, the studies of the immunological efficacy of vaccines in this group are of great importance to control the epidemic.

Antibodies (AB) targeting the hemagglutinin protein of the influenza virus are widely recognized as a crucial component of protection against influenza infection. The antibody titers that inhibit hemagglutination are considered as correlates of protection following the administration of IIV in adults and children [1]. Classic studies conducted by Hobson et al. in 1972, as well as more recent research, established that a titer of 1:40 correlates with 50% protection against influenza infection [4, 12]. This protective titer is a key element in the CPMP criteria for IIV evaluation in adults, proposed by the European Medicines Agency (EMA) (CPMP/BWP/214/96) [2].

The same criteria are typically used for children and adolescents but the question concerning the level of the protective antibody titer in this age group remains unresolved. Children have a reduced ability to develop a cellular immune response and might not have experienced influenza infection or vaccination, so protective titers may differ in children compared to adults. Ng et al. demonstrated that the titers of 1:40 and above corresponded to approximately 50% protection against infection with the A(H1N1)pdm09 and B/Victoria strains in children and adolescents aged 6 to 17 years [8]. However, for children under 6 years of age, a greater titer threshold value of 1:110 may be required to predict 50% protection against clinically confirmed infection [1].

This study, therefore, **aimed** to evaluate the characteristics of the humoral immune response in children from the two age groups after immunization with various types of inactivated influenza vaccines.

Materials and methods

The observational study was conducted during the 2019-2020 epidemic season. The study included 230 participants in total from two age groups: children under 6 years old and those aged 6 to 18. The children were vaccinated with one of the three influenza vaccines (Grippol Plus, Sovigripp, or Ultrix) at two outpatient clinics in St. Petersburg (St. Petersburg State Budgetary Healthcare Institution Municipal Polyclinics N3 and N4). The participants were allowed to choose the preferable vaccine. The comparison group included 87 adults aged 18 to 60 who were vaccinated with the vaccines at the same clinics or at the Smorodintsev Research Institute of Influenza of the Ministry of Health of the Russian Federation. All adult participants signed the informed consent form. For underaged participants, informed consent was obtained from their parents/guardians. The study protocol was approved by the Local Ethics Committee of the Smorodintsev Research Institute of Influenza (protocol No. 145 of 10/4/2019).

There were two types of trivalent inactivated vaccines used for immunization: split or adjuvanted subunit vaccines. Grippol Plus, manufactured by NPO Petrovax, is an inactivated subunit vaccine that contains 5 μg of hemagglutinin of each of the epidemic virus strain subtypes A/H1N1pdm09, A/H3N2, and B and 500 μg of the Polyoxidonium® adjuvant in a 0.5 mL dose. Sovigripp, manufactured by NPO Microgen, is an inactivated subunit vaccine that contains 5 μg of hemagglutinin of each of the epidemic virus strain subtypes A/H1N1pdm09 and A/H3N2, 11 μg of the influenza virus type B, and 500 μg of Sovidon adjuvant in a 0.5 mL dose. Ultrix, manufactured by FORT LLC, is an inactivated split vaccine containing 15 μg of hemagglutinin of each of the virus strain subtypes A/H1N1pdm09, A/H3N2, and B in a 0.5 mL dose. The vaccines' strain compositions were in accordance with the WHO guidelines for the 2019-2020 northern hemisphere influenza season.

The blood sera from children and adults were obtained twice during the study: before vaccination (D0) and on the 21st day after vaccination (D21). The hemagglutination inhibition (HI) test was used to examine the sera as described in the guidelines MU 3.1.3490-17 [13]. To remove nonspecific inhibitors, the serum was treated with a receptor-destroying enzyme (RDE; Denka Seiken, Japan) following the manufacturer's protocol. The antigens used were Dry Influenza Diagnostic Agents for HI (LLC "PPDP", St. Petersburg, Russia; TU 938824-004-4429427-2008) of the three strains corresponding to the vaccine strains. The sera were titrated starting at a dilution of 1:10. A titer < 1:10 was considered equal to 1:5, and a titer > 1:1280 – to 1:1280.

The immunological efficacy of the vaccines in children and adults was assessed following the EMA Note for Guidance on Harmonisation for Requirements for Influenza Vaccines (CPMP/BWP/214/96) for individuals aged 18 to 60 [2]. Seroprotection was defined as the antibody titer of 1:40 or more. Seroconversion was defined as at least a 4-fold increase in titer from pre-vaccination (D0) to post-vaccination (D21). The statistical analysis of the results was carried out using MS Excel 2016, GraphPad Prizm 6.07, and RStudio 2022.12.0. The 95% confidence intervals (CI) for the geometric means were determined using the logarithmic transformation of the data, followed by the calculation of CI for normally distributed data and inverse logarithmic transformation of the values. CI for seroconversion and seroprotection rates were calculated according to the Wald method. For multiple pairwise comparisons between independent samples, the Mann–Whitney test was used without adjustment for multiple comparisons. To compare the sample rates, Fisher's exact test was used without adjustment for multiple comparisons. Differences were considered statistically significant at $p < 0.05$.

Results and discussion

The study of the immune response included 230 children under the age of 18 who were vaccinated with inactivated influenza vaccines during the 2019-2020 epidemic season. The comparison group was randomly selected from 18-60-year-old adults who

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION

	Age (years)			
	Under 6	**6-18**	**Under 18 (in total)**	**18-60 (comparison group)**
Total number of participants, n	21	209	230	87
Vaccine, n				
– Ultrix	2	109	111	42
– Grippol Plus	19	92	111	42
– Sovigripp	0	8	8	3
Mean age (IQR*)	4 (3.6-4.7)	15 (13.0-17.3)	14 (10.9-17.3)	28 (18.3-36.8)
Sex, n				
– Female	9 (43%)	85 (41%)	94 (41%)	21 (24%)
– Male	12 (57%)	124 (59%)	136 (59%)	66 (76%)
Seropositive, n**				
– A/H1N1pdm09	16 (76%)	125 (60%)	141 (61%)	76 (87%)
– A/H3N2	11 (52%)	92 (44%)	103 (45%)	65 (75%)
– B/Vic	10 (48%)	58 (28%)	68 (30%)	38 (44%)

Note. *, IQR, interquartile range; **, the antibody titer ≥ 1:10 at the time of vaccination.

were vaccinated against influenza in the same season. When selecting the comparison group, the balance between the proportions of those vaccinated with each vaccine type and the corresponding indicators of the combined group of participants under 18 was taken into account (Table 1). This study adopted the CPMP criteria (CPMP/BWP/214/96) used for the assessment of inactivated influenza vaccines in adults since there are currently no standardized criteria for the assessment of influenza vaccine immunogenicity in children [2].

First, the total immunogenicity of the trivalent IIVs was assessed in the combined group of children under 18 years of age. The immunogenicity parameters in children were contrasted with those in the comparison group – adults aged 18 to 60 (Table 2, the first and second rows from the top). The humoral response in children met the CPMP criteria for the antibody titer fold increase and seroconversion rates. The fold increase in antibody titers and the number of seroconversions to the B/Victoria component were statistically significantly higher in children compared to the adult group, even though the groups had been initially comparable in terms of the proportion of the participants with low and high levels of antibodies at the time of vaccination. As for the other two vaccine components, A/H1N1pdm09 and A/H3N2, seroprotection rates at the time of vaccination were statistically significantly lower in the children group, which could contribute to the observed difference in the immunogenicity of these components.

One of the criteria for IIV immunogenicity is that at least 70% of the vaccinated develop a protective antibody titer (seroprotection) after vaccination. Seroprotection rates to the A/H1N1pdm09 and A/H3N2 components were lower in children compared to the adult group both before and after vaccination, although it reached the CPMP threshold value at the latter time point. As for the B/Victoria component, the seroprotection rates after vaccination did not reach the threshold value of 70% in both groups. The obtained data aligns with previous studies on the immunogenicity of trivalent IIV during the 2019-2020 season which demonstrated that children, adolescents, and adults exhibited a less significant response to the influenza B component compared to both influenza A components. Particularly low rates were seen in the adult participants and 14-17-year-old adolescents [5].

TABLE 2. IMMUNOGENICITY OF THE TRIVALENT INACTIVATED INFLUENZA VACCINES IN CHILDREN IN DIFFERENT AGE GROUPS AND ADULTS IN THE 2019-2020 SEASON, BASED ON HEMAGGLUTINATION INHIBITION (HI) TEST

Age (years)	Vaccine	Seroprotection rate, % before vaccination (D0)			Seroprotection rate, % after vaccination (D21)			Antibody fold increase			Seroconversion rate, %		
		A/H1N1 pdm	A/H3N2	B/Vic	A/H1N1 pdm	A/H3N2	B/Vic	A/H1N1 pdm	A/H3N2	B/Vic	A/H1N1 pdm	A/H3N2	B/Vic
under 18 in total[&]	all vaccines[‡]	39°°°°	20°°	7	76°°°	73°°	43	4.2	5.5	3.1[‡‡]	58°	66°	53°°°°
18-60[&]	all vaccines [‡]	76°°°°	37°°	13	93°°°	88°°	34	3.6	7	2.1[‡‡]	42°	79°	26°°°°
under 6	Grippol Plus	32	42	16	63	47	42	2.4	2.1	1.7	47	42	42
6-18	Grippol Plus	5***	24*	10	75	70	30***	2.6***	4.2*	2.7*	50**	58**	49
	Ultrix	28***	11*	5	76	79	55***	7.1***	7.9*	4.1*	69**	77**	61
CPMP threshold value					> 70%			> 2.5			> 40%		

Note: [‡], in total for all three vaccines Grippol Plus, Sovigripp, and Ultrix; [‡‡] $p < 0.01$, the statistically significant difference between the underage group (under 18) and the adult group (aged 18-60), the Mann–Whitney test without adjustment for multiple comparisons; [&], the groups are balanced for the proportion of the participants vaccinated with each type of vaccine; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, the statistically significant difference between the Ultrix and Grippol Plus vaccines in the 6 to 18-year-old age group, Fisher's exact test without adjustment for multiple comparisons; ° $p < 0.05$, °° $p < 0.01$, °°° $p < 0.001$, °°°° $p < 0.0001$, the statistically significant difference between the underage group (under 18) and the adult group (aged 18-60), Fisher's exact test without adjustment for multiple comparisons.

Next, we assessed the immunogenicity of the Grippol Plus and Ultrix vaccines in the participants under 6 years of age and those aged 6 to 18 (Table 2, rows 3, 4, and 5 from above). Young children are known to be more susceptible to influenza [14]. According to the published research, the threshold value for the protective antibody titer in this group is higher than the standard, measuring at 1:110 [1]. In our study, the vast majority of children under the age of 6 (19 out of 21) were vaccinated with the Grippol Plus vaccine, which motivated further analysis of the results obtained for this vaccine. The geometric mean titers (GMT) in this group after vaccination were as follows: to A/H1N1pdm09 – 50 (95% CI: 25-99); to A/H3N2 – 33 (95% CI: 16-68); to B/Victoria – 17 (95% CI: 9-29). Before vaccination, the antibody titers above the threshold value of 1:110 were only identified in isolated cases: in one child (5%) – to the A/H1N1pdm09 component and in another child (5%) – to the A/H3N2 component. After vaccination, the antibody titers above 1:110 were observed in 42% of the children for the A/H1N1pdm09 component, in 26% of the children for the A/H3N2 component, and only in one child (5%) for the B/Victoria component.

At the time of vaccination, the age subgroups (under 6 and 6 to 18 years of age) did not differ in the seroprotection rates. Nonetheless, following vaccination with Grippol Plus, all parameters studied suggested a less pronounced immune response in the younger children compared to the group aged between 6 to 18 years. The differences did not achieve statistical significance, which, however, can be attributed to the insufficient sample size of the younger age group.

The fold increase in antibody titer and seroconversion rates for the A/H1N1pdm09 and A/H3N2 components were higher in the participants aged 6 to 18 who were vaccinated with Ultrix, than in children of the same age who received Grippol Plus. Notably, these subgroups were not comparable in terms of the proportion of the seropositive participants at the time of vaccination, as suggested by the corresponding seroprotection rates. The humoral immune response to vaccination is known to be less pronounced in individuals with high pre-existing antibody titers [3, 9]. Nevertheless, vaccination with Ultrix and Grippol Plus led to similar seroprotection rates for the A/H1N1pdm09 and A/H3N2 components, which met the required seroprotection criterion (more than 70%). The seroprotection rate for B/Victoria after vaccination was statistically significantly higher in the subgroup vaccinated with Ultrix compared to Grippol Plus, despite the absence of differences in the number of seropositive individuals on day 0 between the two groups. This difference may indicate better immunogenicity of the Ultrix vaccine to the influenza B component in comparison with the Grippol Plus vaccine.

A key objective of the study was a comparative assessment of the immunogenicity of the Ultrix and Grippol Plus vaccines in children aged 6 to 18 years who had initially low antibody titers (Table 3). No differences in the immunogenicity of these two vaccines were found regarding the A/H1N1pdm09 and A/H3N2 components. However, the data analysis confirmed that the split vaccine Ultrix exhibited a higher immunogenicity to the B/Victoria component

TABLE 3. CHARACTERISTICS OF THE HUMORAL IMMUNE RESPONSE TO VACCINATION IN CHILDREN WITH INITIALLY LOW TITERS DEPENDING OF THE VACCINE TYPE IN THE 2019-2020 SEASON (HI TEST DATA)

Age (years)	Vaccine	Seroprotection rate, % (95%CI)			Antibody fold increase (95%CI)			Seroconversion rate, % (95%CI)		
		H1N1	H3N2	B/Vic	H1N1	H3N2	B/Vic	H1N1	H3N2	B/Vic
6-18	Grippol Plus	62 (47-78)	66 (54-78)	30** (19-40)	8.3 (5.2-13.0)	8.7 (6.0-12.4)	3.8‡ (2.8-5.2)	76 (62-90)	76 (65-86)	55* (44-67)
	Ultrix	70 (59-80)	81 (73-90)	54** (44-65)	13.6 (9.5-20.0)	11 (8.3-15.0)	5.4‡ (4.3-6.8)	84 (75-93)	88 (80-95)	71* (62-80)
6-21&	Flucelvax&	70.6	73.3	64.0	11.1 (4.7-26.0)	7.3 (3.5-15.2)	6.6 (4.0-10.9)	N/D	N/D	N/D
CPMP threshold value		> 70%			> 2.5			> 40%		

Note. * $p < 0.05$, ** $p < 0.01$, the statistically significant difference between Ultrix and Grippol Plus in the 6 to 18-year-old age group, Fisher's exact test without adjustment for multiple comparisons; ‡ $p < 0.05$, the statistically significant difference between Ultrix and Grippol Plus in the 6 to 18-year-old age group, the Mann–Whitney test without adjustment for multiple comparisons; &, comparative data from a similar study of a subunit inactivated vaccine [15]; N/D, no data.

compared to the adjuvanted vaccine Grippol Plus. Importantly, the influenza B virus infection poses the greatest threat to children and is often accompanied by serious complications. Children with influenza B infection require hospitalization in the intensive care unit more often and have a higher mortality rate compared to those with influenza A infection [10, 11].

Furthermore, we compared our data with the results of a similar study that was conducted in the United States on subjects aged 6 to 21 years who had initially low antibody titers in the 2019-2020 season [15]. The analysis showed that Ultrix and Grippol Plus are comparable to the Flucelvax vaccine (Seqirus, USA) in terms of the fold increase of antibody titers against A/H1N1pdm09 and A/H3N2. Moreover, the split vaccine Ultrix showed higher immunogenicity to the influenza A viruses compared to Flucelvax. Both vaccines, however, exhibited a lower fold increase in titer against the B/Victoria component compared to the vaccine produced in the USA. Therefore, it can be advisable to use a vaccine from a foreign manufacturer as a comparator when conducting similar studies. Our data indicate that the vaccine type may impact the antibody response to specific components of the vaccine.

Conclusion

The immunogenicity rates of the studied trivalent inactivated influenza vaccines in children under 18 years of age in the 2019-2020 season met two out of the three CPMP criteria for influenza vaccines: the number of seroconversions > 40% and a significant (at least fourfold) increase in antibody titer. Children (< 18 years old) showed a better antibody response to the B/Victoria component than the adult group (18 to 60 years old) according to the three parameters studied. Yet, this response was not sufficient to ensure 70% persons with HI titer ≥ 40 after vaccination. In the group of participants aged 6 to 18 years, the Ultrix and Grippol Plus vaccines demonstrated similar immunogenicity levels to A/H1N1pdm09 and A/H3N2. The split vaccine Ultrix elicited a better antibody response to the B/Victoria component. The children under 6 years of age tended to have a less pronounced humoral immune response to vaccination, which might be associated with the specifics of the immune system in children of preschool age.

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