Serotype diversity of *Streptococcus pneumoniae* in children with chronic bronchopulmonary pathology in the pre-vaccination and post-vaccination periods

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Серотиповой состав *Streptococcus pneumoniae* у детей с хронической бронхолегочной патологией в довакцинный и поствакцинный периоды

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INTRODUCTION. *Streptococcus pneumoniae* plays an important role in the development of respiratory bacterial infections among children in their early years, people with chronic diseases and elderly people. *Streptococcus pneumoniae* (*S. pneumoniae, pneumococcus*) is the main etiological factor of severe invasive infections (bacteremia, meningitis) and the most common causative agent of acute otitis media, sinusitis as well as community-acquired pneumonia [1]. Nasopharynx epithelium is considered the initial colonization place of *S. pneumoniae* in young children, where it may be detected as a part of the commensal flora [2]. Despite the fact that nasopharyngeal colonization by pneumococcus does not often precede the development of the infectious process, carriage creates source of infection and may be the initial stage of the disease [3].

The main method of fighting pneumococcal infection is vaccinal prevention, which started in the Russian Federation in 2014 using 13-valent pneumococcal conjugate vaccine (PCV13).

It includes serotypes, important for pediatric practice (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18, 19A, 19F, 23F); it is characterized by high immunogenicity and also provides long-lasting immunity and immunological memory [4]. Vaccination causes elimination of vaccine serotypes and an increase in prevalence of non-vaccine, previously rare serotypes among pathogens of invasive infections as well as with carriage of *S. pneumoniae* [5,6].

The problem of pneumococcal infection in children with cystic fibrosis (CF) and congenital bronchial and pulmonary malfunctions (CM) has not been studied enough as *S. pneumoniae* is secreted together with other bacterial pathogens in more than 80 % of cases. However, bacterial infections are generally the leading cause of death just in patients with cystic fibrosis, and bacterial agents might be associated with morbidity and mortality in children with CM [7]. So, understanding the serotype structure of pneumococci and its changes as well as the vaccination effect on serotype strain composition of *S. pneumoniae* with these pathologies is essential determine treatment tactics of these children.

OBJECTIVE of our study: to determine the serotype composition of *Streptococcus pneumoniae* isolates in children with chronic bronchopulmonary pathology prior to mass vaccination against pneumococcal infection and in post-vaccination periods.

MATERIALS AND METHODS.

Over the period of 2011-2021 there was the study of 140 isolates of *S. pneumoniae*, obtained from respiratory specimens (aspirates, bronchial lavage water, sputum) of 86 children (61,4 %) with congenital bronchial and pulmonary malfunctions and 54 children (38,6 %) with cystic fibrosis, observed in FSAI "NMRC for Children's Health" of the Ministry of Health of the Russian Federation. The age of children varied from 0,3 to 17,8 years (the median of 6,5 years). The informed consent of the parents and legal representative was obtained. Demographic and clinical characteristics were examined according to the medical records of patients. Despite the lack of data on the vaccination status of the children screened, official sources for 2015–2018 reports on PCV13 vaccine coverage from 20,9 to 55,3 % of children, born in Moscow [8, 9].

All the isolates were identified using traditional bacteriological methods (colony morphology, α-hemolysis on blood agar, optochin test (Bio-Rad, France) and latex agglutination technique (express test Remel Europe Ltd, UK)).

Pure culture of pneumococci was serotyped in latex agglutination or quelling reactions by Neufeld using specific pool, group and factor serums (Statens Serum Institut, Danmark), and also through molecular typing by multiplex polymerase chain reaction method [10]. Pneumococci were considered untypable if they gave no reaction with any pool serum. *S. Pneumoniae* serotypes, which polysaccharides were included in PCV13, were regarded as "vaccine", all other serotypes were seen as "non-vaccine" (non-PCV13). Statistical data processing was performed using IBM SPSS Statistics 25 software package.

RESULTS AND DISCUSSION. During isolate typing we identified 29 different *S. Pneumoniae* serotypes, two isolates (1,4 %) were assigned to untypable. Most pneumococci (65, %; 91/140) were related to 11 various vaccine serotypes (1, 3, 4, 6A, 6B, 9V, 14, 18C, 19A, 19F, 23F) in the ten-year study period. The proportion of non-vaccine strains was 35% (49/100) and it was presented by 18 serotypes (6C, 6D, 8, 9N, 10A, 11A, 15B/C, 16F, 20, 22F, 23A, 23B, 28A, 28F, 31, 34, 35C, 35F) as well as two untypable isolates. 19F (22,1 %; 31/140); 3 (11,4%; 16/140); 14 (7,9 %; 11/140) and 23F (7,9 %; 11/140) were leading among vaccine serotypes. 11A serotype (6,4 %; 9/140) prevailed over non-vaccine strains. When considering pre-vaccination (pre-PCV13) and post-vaccination (post-PCV13) periods separately, we revealed the change in the incidence of vaccine and non-vaccine serotypes in time. PCV13 serotypes peaked in 2012, entering pre-vaccination period (2011–2014). This year 27,5 % of specimens have had vaccine serotypes (25/91). It is noteworthy that most of these isolates were obtained from children with CM (68 %; 17/25). 14,19F and 23F (46,9 %; 31/66) were the predominant vaccine serotypes in pre-PCV13-period. These findings are consistent with the results, previously observed in our center for children with the nasopharyngeal carriage of *S. pneumoniae* [6]. Among non-vaccine serotypes 11A (9,1 %; 6/66) occurred more often in children with chronic bronchopulmonary pathology in pre-PCV13-period. However, non-vaccine serotype 15 B/C was most commonly detected in children with the nasopharyngeal carriage [6].

We observed a growing trend in non-vaccine serotypes among children with chronic bronchopulmonary pathology in post-PCV13-period. Their number increased by 4,8 %, and most of the specimens (36,7 %; 18/49) with non-PCV13-serotypes fell on 2016–2017, i.e. right after implementing the vaccine in a wide clinical practice that is consistent with the results of previous studies [6]. It was observed, mainly, in the group of children with CM, who had an increase in the number of strains with non-vaccine serotypes from 32,5 % to 45,7 % after 2014. In addition to increasing number of non-vaccine strains, there was a growth in their serotype variety in the postPCV13-period.

Apart from the identified in the pre-vaccination period (11A, 16F, 6C, 15B/C, 10A, 28A, 35C), 23B, 34, 31, 22F, 28F, 20, 6D, 35F serotypes appeared. Two specimens, related to untypable, were also detected in the post-vaccination period.

CONCLUSIONS. The obtained data prove the impact of PCV on the circulation of vaccine and non-vaccine *S. pneumoniae* strains. An increase in the number and serotype variety of non-vaccine strains after implementing PCV13 in the Russian national immunization programme requires continuous monitoring of *Streptococcus pneumoniae* population. The emergence of strains with new non-vaccine serotypes in children with chronic bronchopulmonary pathology shows the need for further study of pneumococcal population, including their serotype variety and sensitivity to antimicrobial drugs.

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