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ORIGINAL ARTICLE

Immunogenicity of Heptavalent Conjugate Vaccine Against *Streptococcus pneumoniae* in Premature Babies with Low Birth Weight

Ewa Szynczewska*, Danuta Chlebna-Sokół

Department of Paediatric Propaedeutics and Metabolic Bone Diseases of Medical University of Lodz, Poland

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Key Words
adverse events;
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low birth weight;
pneumococcal-CRM197 conjugate vaccine;
prematurity;
Streptococcus pneumoniae

Background: There are few studies about immunogenicity and safety of heptavalent pneumococcal-CRM197 conjugate vaccine (PCV7) in low birth weight infants.
Objective: Assessment of immunogenicity following administration of PCV7 in low birth weight children.
Methods: The PCV7 vaccine was administered to 60 infants divided into two groups: 23 children with birth weight <1000 g (Group I); and 37 children with birth weight ≥1000 g (Group II). Serum was collected four times.
Results: Birth weight of children included in the study ranged from 480 g to 2450 g. The primary immunization caused an increase in the average concentration of antibodies for all serotypes in most of the participants, with no significant differences between the groups. However, there were some differences between various serotypes. Group serotypes 6B and 23F were the least immunogenic (≥0.35 μg/mL, Group I vs. Group II — 6B: 78.3% vs. 67,6% $p = 0.371$ and 23F: 87% vs. 83.8% $p = 0.738$). Prior to the administration of a booster dose, a significant decrease in antibody titer was observed in all children. The last vaccination resulted in an increased concentration of antibodies in all children in both groups, and the results were significantly higher compared to those measured following administration of three doses of the vaccine.
Conclusion: PCV7 is immunogenic in children with low, very low, and extremely low birth weight. Serotypes 6B and 23F were the least immunogenic, and serotype 14 proved to be the most immunogenic.

* Corresponding author. Public Clinic Hospital Number 4 of Medical University of Lodz, Sporna 36/50, 91-738 Łódź, Poland.
E-mail address: eszynczewska@gmail.com (E. Szynczewska).

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1. Introduction

Biological and immunological immaturity of prematurely born children promotes infections, which are the most common cause of hospitalization during the first 2 years of life. *Streptococcus pneumoniae*, one of the most common bacterial pathogens in the world, is one of the most serious hazards. The microorganism often causes otitis media, sinusitis, and pneumonia. In addition, following a successful introduction of mass vaccination against *Haemophilus influenzae* type b, it is responsible for the majority of invasive infections in Poland: sepsis and meningitis.[1] More than 90 serotypes of the bacteria have been identified so far, based on differences in the properties of bacterial capsular polysaccharide antigen. All serotypes may be pathogenic, but seven of them are responsible for about 83% of invasive infections in children younger than 5 years in the USA and 80% in Europe.[2,3] In Poland the rate is 68.7%[4] and overall incidence of invasive pneumococcal disease (IPD) in children aged 0—59 months is 17.6/100,000/year.[5]

Experiences of recent decades indicate that preterms and children born with low weight, like other individuals with immunological deficiencies, should be vaccinated according to their chronological age.[6,7] However, those children may demonstrate an inferior response to vaccine antigens; hence an assessment of their immune response seems important.[8] Moreover, despite the fact that 10- and 13-valent vaccines are currently available, a high ratio of children vaccinated with pneumococcal-CRM197 conjugate vaccine (PCV7) is hampering the assessment of clinical efficacy of the new, conjugated vaccine in the prevention of IPD (especially when compared to placebo). The World Health Organization (WHO) adopted criteria of immunogenicity, compared to PCV7 (immunological response not inferior to PCV7), as a basis for assessment and registration of new vaccines.[9—11]

Most published papers discuss children born at term and with normal weight.[12—14] Only a few of them contain data on immunogenicity of that vaccine in children born prematurely and with low birth weight.[15—19]

Because it is known that the distribution of serotypes and incidence depend on the region and population,[12,20,21] we decided to carry out an assessment of the immune response among Polish children.

2. Materials and Methods

The study was conducted in a group of 60 children born with low birth weight (initially a group of 40, with a further 20 the following year), hospitalized in the Neonate Pathology Ward of the Department of Pediatric Propedeutics and Metabolic Bone Diseases of the Medical University of Lodz, and managed by two outpatient clinics: Prematurity Complications and Neonate Pathology. The University Ethics Committee approved the research. Evaluation of immunogenicity in the same children is planned for the future.

Infants in a stable state of health were administered the conjugate vaccine against *S. pneumoniae*, Prevenar (Wyeth, currently Pfizer, New York, NY, USA), at a dose of 0.5 mL as an intramuscular injection in the lateral thigh. Children with known immunodeficiencies and diagnosed with severe chronic or progressive diseases were excluded from the analysis. Responders were classified into two groups, depending on birth weight: Group I included 23 children with birth weight $<$1000 g; and Group II included 37 children with birth weight $\geq$1000 g (21 of whom were born with weight 1000—1500 g). Vaccinations were planned in accordance to the Polish Expanded Program of Immunization: a basic immunization at ages 2 months, 4 months, and 6 months, and a booster dose at age 16 months, combined with the vaccine against diphtheria, tetanus, pertussis, polio, and *H. influenzae* type b. The dose administered at age 2 months was combined with the vaccine against hepatitis B.

Blood (3 mL) was collected from each patient four times: (1) prior to the first dose of the vaccine (Measurement I); (2) 4 weeks after the primary vaccination (Measurement II); (3) prior to the booster dose administration (Measurement III); and (4) 4 weeks later (Measurement IV). Centrifuged serum was stored at −22 °C. Determination of concentration of specific immunoglobulin G antibodies against all seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) included in the PCV7 vaccine was performed in Statens Serum Institute, Copenhagen, Denmark, using the enzyme-linked immunosorbent assay method. The level of antibodies $\geq$0.35 μg/mL is considered to be protective against IPD.[22]

Nonparametric tests were used for statistical analysis, because distribution of analyzed traits was significantly different from the normal distribution. The Mann—Whitney *U* test was used for a comparison of the results obtained from the two groups. Wilcoxon test was used for the evaluation of changes in antibody levels during the study. The Chi-square test for independence was used, including Yates' amendments, and in some cases Fisher exact test was used for comparison of ratios of children who achieved protective levels of antibodies and to demonstrate the relationship between birth weight and the concentration of antibodies. A null hypothesis was considered rejected when the computer-calculated level of significance met the assumption of $p < 0.05$.

3. Results

Vaccinations were performed in a total of 60 infants (29 boys, 31 girls). All children were born with a birth weight of 480—2450 g (mean 1284 g), at 24—34 weeks of pregnancy (mean 30 weeks). The characteristics of patients are shown in Table 1.

Table 2 summarizes geometric mean antibody concentrations against all seven serotypes included in the vaccine for all children, divided into groups. Concentration of antibodies, first measured prior to the administration of PCV7, was low for all serotypes. After primary immunization, an increase in the average concentration of antibodies for all serotypes was observed in most children, with no significant differences between groups. However, there were differences between various serotypes. For both groups the highest concentration of antibodies was observed for the serotype 14, and the lowest for serotypes 9V and 4 in Group I and for serotype 18C in Group II. Prior to the