MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 5110-5117
DOI: 10.12659/MSM.908834

Received: 2018.01.05
Accepted: 2018.03.01
Published: 2018.07.23

Persistence of Vaccine-Induced Immunity in Preschool Children: Effect of Gestational Age

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Statistical Analysis C
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Source of support: The study was financially supported by the Medical University of Lublin, Poland with DS 514/2012-2015 grant

Background: A program of immunization that ensures optimal development of acquired immunity should be carried out in all healthy newborns. The aim of the present study was to verify, at 2.5–3 years after the last dose of basic vaccination, if preschool children who have been delivered preterm and at term differ in their levels of post-vaccination protective antibodies.

Material/Methods: Humoral response was assessed in 352 children (mean age: 5.22±0.34 years) who received a series of obligatory vaccinations in the period from birth to 2.5–3 years of age. Antibodies (in IgG class) against vaccine antigens – diphtheria (D), tetanus (T), pertussis (P), *Haemophilus influenzae* type b (Hib), *poliomyelitis* (IPV), measles, mumps, and rubella (MMR) – were measured using ELISA. The level of antibodies against hepatitis B (HBV) was assessed by chemiluminescence.

Results: All children had been immunized according to the Polish National Vaccination Program. The group of 352 children eligible for the study included 46 (13.1%) preschoolers delivered preterm (32–36 weeks of gestation), and 306 (86.9%) born at term (37–42 weeks of gestation). All children maintained seroprotective antibody levels against polioviruses type 1, 2, and 3 (>12 mIU/mL), and against measles antigens (>300 U/mL). No statistically significant differences were found in the proportions of preschoolers born preterm and at term who were seroprotected against other vaccine antigens.

Conclusions: Among preschool children who were immunized according to chronological age, those we were born late preterm do not seem to differ in vaccine-induced immunity from those who were born full-term.

MeSH Keywords: Child, Preschool • Gestational Age • Immunity • Vaccination

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/908834

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Background

Neonates are more prone to infections because their immune systems are not fully developed. The risk of infection is particularly high in preterm infants. Therefore, active immunization by means of vaccination is the principal infection control measure [1–3].

Regulation of immune response in children is a complex process that is modulated by age, genetic factors, and interactions with environmental factors. Optimal development of the immune system in newborns is determined primarily by passive transfer of maternal antibodies during pregnancy and breastfeeding, as well as by exposure to infectious agents. Mechanisms that regulate immune processes in preterm infants manifest a range of deficits and contribute to risks for infections in newborns. Moreover, it is unknown how to safely modulate the immune system of preterm infants in order to avoid potentially harmful and excessive activation prior to the occurrence of adaptive immunity. Protection against pathogens results from the coordination of innate and adaptive immunity mechanisms. Newborns rely on their innate immunity to a great extent since adaptive immunity only develops in the early years of life. During the first months of life, premature infants do not have sufficient maternal antibodies because transplacental transfer mainly takes place in the third trimester of pregnancy [4–6].

Published evidence suggests that vaccination rates in preterm neonates are lower than in full-term newborns. The proportion of premature infants that have been vaccinated during the first 6 months of life may be up to 3–15% lower than the analogous percentage of children born at term [7–9]. Moreover, evidence from clinical studies suggests that synthesis and persistence of post-vaccination antibodies are to a large extent modulated by gestational age at birth. Following vaccination, children who have been delivered at term have higher protective levels of antibodies than those born preterm; also, low birth weight may have an unfavorable effect on post-vaccination immune response [4–6]. However, despite impaired immune response, preterm infants, as well as neonates with low birth weight, were shown to synthesize protective antibodies after stimulation with vaccine antigens [10–12].

In line with the recommendations of the Advisory Committee on Immunization Practices (ACIP), all clinically stable newborns and those delivered preterm, should be vaccinated according to the National Vaccination Program, unless they have signs of infection, metabolic disease, or acute renal, cardiovascular, or respiratory failure [13]. According to general consensus, active immunization of preterm newborns should follow the same schedule as in neonates delivered at term [14,15].

The aim of the study was to assess vaccine-induced humoral immunity in preschool children and to evaluate the relationship between gestational age (GA) and levels of protective antibodies at 2.5–3 years after the last dose of the basic vaccination. This work is an attempt to determine whether prematurity affects acquired immunity.

Material and Methods

Participants

The study included all consecutive preschool children hospitalized at the Orthopedic Surgery Department and the Pulmonology Department, University Children's Hospital in Lublin (Poland) between 1 October 2014 and 31 March 2015 and who satisfied the enrollment criteria. Inclusion criteria were: white ethnicity (since 99.5% of Polish residents are white) with Polish nationality, aged 4.5–5.9 years (preschoolers), born at ≥32 weeks of gestation with birthweight of ≥2200 g, received all obligatory vaccinations between birth and 2.5–3 years of age according to the Polish National Vaccination Program for 2008–2009, and the reason for hospitalization was a non-infectious condition. Their gestational age, birthweight, and type of inoculation (monovalent or polyvalent) differed. Their medical history did not confirm the presence of significant factors impairing functions and development of the immune system. Thus, our study was focused on the assessment of vaccine-induced immunity at about 3 years of age after the administration of basic and obligatory vaccines indicated in the Polish Vaccination Schedule, as well as the determination of the importance of booster doses and factors affecting it.

Exclusion criteria were: recent clinical evidence of immunodeficiency, current or past history of immunocompromise, history of infectious disease caused by a vaccine, history of other infections within 2 months preceding testing for serum antibodies, history of immunosuppressive treatment (other than inhaled or topical corticosteroids), and incomplete vaccination history or medical documentation. The children were admitted to hospital solely on an elective basis. Most of them had had laboratory tests performed along with infectious diseases testing that had been ordered by their general practitioners. The analyses did not reveal any infectious diseases in these patients.

Immunization history

A total of 176 children had been immunized with monovalent vaccines against HBV (3 primary doses 24 h after birth and at 2 and 6 months of age), poliomyelitis (inactivated vaccine, IPV, 2 primary doses of inactivated vaccine at 4 and 6 months of age, followed by a single booster dose at 16–18 months), Hib

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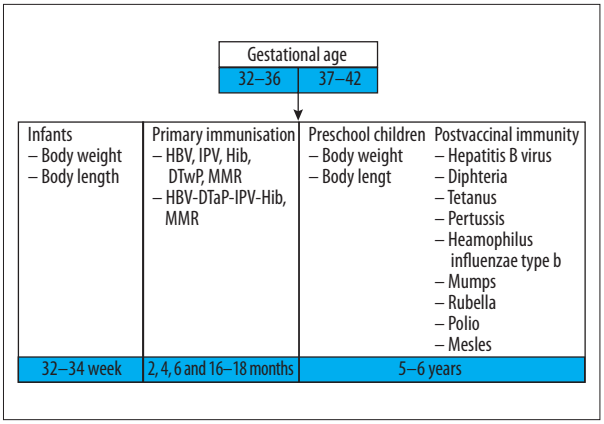

Figure 1. Algorithm for the study.

(3 primary doses at 2, 4, and 6 months, and a single booster dose at 16–18 months), as well as with a tetravalent whole-cell vaccine against diphtheria, tetanus, and pertussis (DTwP, 3 primary doses at 2, 4 and 6 months, followed by a single booster dose at 16 months). Another 176 children had received a hexavalent combined bacterial and viral vaccine with acellular component of pertussis (HBV-DTaP-IPV-Hib, 3 primary doses at 2, 4 and 6 months, and a single booster dose at 16–18 months). Moreover, at 13–15 months of age, all children had been immunized with a single dose of a vaccine against measles, mumps, and rubella (MMR) (Figure 1).

Ethics

The protocol of the study was approved by the Bioethics Committee of the Medical University of Lublin, Poland (decision no. KE-0254/176/2011). Since most preschool children participating in the study were illiterate, their consent to participate in the study was obtained verbally, as certified by their parents/legal guardians and investigator on a separate informed consent form. Furthermore, written informed consent was sought from children's parents or other legal guardians prior to any procedure. This procedure of obtaining informed consent was approved by the Bioethics Committee of the Medical University of Lublin, Poland.

Medical history

Vaccination histories were extracted from patients' immunization cards. A structured interview was conducted with children's parents or guardians. Other medical data were extracted from current hospital documentation.

Serological analysis

Blood samples for serological studies were collected on the second day after admission; 4.7 mL of venous blood was collected using the S-Monovette® 4.9 ml collection system with clotting activator (catalogue no. 04.1934; Sarstedt, Nümbrecht, Germany). Following 10-min centrifugation at 300×g (4°C), the sera were collected to 1.5-ml polyethylene Eppendorf test tubes and stored frozen at –20°C until analysis. None of the samples showed a trace of hemolysis.

Serum levels IgG against diphtheria, pertussis, *Haemophilus influenzae* type b (Hib), poliomyelitis, mumps, measles, and rubella were determined by enzyme-linked immunosorbent assays (ELISA) with kits from IBL International GmbH (Hamburg, Germany), while serum IgG against tetanus were measured with ELISA kits from Diagnostic Automation/Cortez Diagnostics, Inc. (Calabasas, CA, United States). ELISA microplates were read with a VICTOR X3 multilabel plate reader with WorkOut 2.0 data analysis software (PerkinElmer, Waltham, MA, United States). Serum level of post-vaccination IgG against hepatitis B virus (HBV) was determined by means of a chemiluminescent assay, using the ADVIA Centaur XP Immunoassay System from Siemens Healthineers (Erlangen, Germany).

The level of post-vaccination IgG was considered seroprotective whenever it exceeded the cut-off value specified by the manufacturer of a given test: 1.0 IU/mL for anti-diphtheria and anti-tetanus IgG, 10 IU/mL for anti-pertussis IgG against pertussis toxin (PT) and filamentous hemagglutinin (FHA) of *Bordetella pertussis*, 12.5 mIU/mL for anti-HBV IgG, 12 mIU/mL for anti-polio virus type 1, 2, and 3 IgG, 12 U/mL for anti-mumps IgG, 12 IU/mL for anti-rubella IgG, 1.0 µg/mL for anti-Hib IgG, and 300 mIU/mL for anti-measles IgG.

Statistical analysis

Statistical characteristics of continuous variables are shown as arithmetic means and their standard deviations (SDs), medians, and ranges. Normal distribution of continuous variables was verified with the Shapiro-Wilk W test. Depending on the distribution type, statistical significance of intergroup differences was verified with the *t* test or Mann-Whitney U test. Distributions of discrete variables are presented as numbers and percentages; their intergroup comparisons were based on chi-squared test and Fisher exact test. Furthermore, logistic regression analysis was conducted to determine odds ratios (ORs) for coexistence of prematurity with non-seroprotective post-vaccination IgG levels, along with their 95% confidence intervals (CIs). All calculations were carried out using the Statistica 10 software package (StatSoft, Tulsa, OK, United States). Statistical significance threshold for all tests was set at $p<0.05$.

Results

A total of 352 out of 360 preschool children hospitalized during the study period satisfied the enrollment criteria. The reasons

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Table 1. Detailed characteristics of study subjects.

Variable	Preterm infants (n=46)	Full-term infants (n=306)	p
Sex; n (%):			
Female	19 (41.3%)	134 (43.8%)	0.751
Male	27 (58.7%)	172 (56.2%)	
Age (years); mean ±SD	5.25±0.35	5.21±0.34	0.457
Age ≤5.2 years*; n (%)	15 (32.61%)	135 (44.12%)	0.141
Age >5.2 years*; n (%)	31 (67.39%)	171 (55.88%)	
Gestational age (weeks); mean (range)	35.5 (32–36)	39.7 (37–42)	
Moderately premature (32–33 weeks); n (%)	6 (13.0%)	0 (0.0%)	
Late premature (34–36 weeks); n (%)	40 (87.0%)	0 (0.0%)	
Birth weight (g); mean ±SD	3043.07±525.47	3472.60±426.75	<0.001
Birth body length (cm); mean ±SD	52.57±3.49	55.44±3.74	<0.001
Current body weight (kg); mean ±SD	18.65±3.29	21.03±3.60	<0.001
Current body height (cm); mean ±SD	115.93±4.37	118.23±4.60	<0.001
Place of residence; n (%):			
Urban areas	29 (63.04%)	219 (71.57%)	0.237
Rural areas	17 (36.96%)	87 (28.43%)	
Feeding in the first 0-6 months; n (%):			
Exclusively breast milk	27 (58.70%)	201 (65.69%)	
Breast milk + formula	4 (8.70%)	34 (11.11%)	0.393
Only formula	15 (32.61%)	71 (23.20%)	
Type of vaccination; n (%):			
DTwP, HBV, IPV, Hib, MMR	17 (36.96%)	159 (51.96%)	0.058
DTaP-HBV- IPV-Hib, MMR	29 (63.04%)	147 (48.04%)	
Vaccination on time; n (%)	31 (67.39%)	228 (74.51%)	0.307
Vaccination delay (months); median (range)	4.5 (2–9)	3 (1–9)	0.683

* Median value for the whole study group.

for hospitalization were non-inflammatory orthopedic conditions (n=176) and obstructive respiratory diseases (n=176). Another 8 children were excluded from the analysis due to deviations from the National Vaccination Program (n=2), incompleteness of serological documentation (n=2), or withdrawal of parental consent (n=4). The study group included 46 (13.1%) children delivered preterm at between 32 and 36 weeks of gestation, and 306 (86.9%) preschoolers who were born at term between 37 to 42 weeks of gestation. Detailed characteristics of the children born preterm and full-term are presented in Table 1. Preschoolers born at term were characterized by significantly higher body weight and body height, both at birth and at the time of the study.

Serum levels of post-vaccination IgG

All children, both those born preterm and born full-term, maintained seroprotective antibody levels against polioviruses type 1, 2, and 3 (>12 mIU/mL), and against measles antigens (>300 U/mL). Proportions of children born preterm who were seroprotected against other vaccine antigens ranged from 52.1% (anti-diphtheria IgG) to 89.1% (anti-pertussis IgG) when the manufacturers' cut-off values were applied. In the case of children delivered at term, the proportion of seroprotected individuals ranged from 42.2% (anti-diphtheria IgG) to 90.2% (anti-Hib IgG) when the manufacturers' cut-off values were met.

Logistic regression analysis demonstrated that prematurity was not associated with lesser odds for attaining seroprotective antibody level against any of the analyzed vaccine antigens (Table 2).

Discussion

Immune response of premature infants to vaccination can be weaker due to impairment of cell-mediated immunity and reduced synthesis of antibodies [4]. However, it has been also

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Table 2. Specific IgG against vaccine antigens and proportions of children born preterm and full-term, who presented with seroprotective levels of these antibodies at the time of the study.

Variable	Preterm infants (n=46)	Full-term infants (n=306)	p	OR	95% CI
Diphtheria ≥1 IU/mL; n (%)	24 (52.1%)	129 (42.2%)	0.201	1.50	0.80–2.79
Tetanus ≥1 IU/mL; n (%)	33 (71.7%)	211 (69.0%)	0.703	1.14	0.58–2.27
Pertussis >10 U/mL; n (%)	41 (89.1%)	270 (88.2%)	0.547	0.91	0.34–2.47
HBV >12.5 mlU/mL; n (%)	38 (82.6%)	241 (78.8%)	0.352	1.28	0.57–2.88
IPV 12 mlU/mL; n (%)	46 (100.0%)	306 (100.0%)			
Hib >1 µg/mL; n (%)	39 (84.8%)	276 (90.2%)	0.191	0.61	0.25–1.47
Measles >300 U/mL; n (%)	46 (100.0%)	306 (100.0%)			
Mumps >12 U/mL; n (%)	35 (76.1%)	249 (81.4%)	0.397	0.73	0.35–1.52
Rubella >12 lU/mL; n (%)	37 (80.4%)	275 (89.9%)	0.058	0.46	0.20–1.05

postulated that lower post-vaccination seroprotection rates in children born preterm are not necessarily clinically relevant, since they are often high enough to provide immune protection until the time of booster immunization [15–18]. However, it is still unclear if immune memory after immunization of preterm infants is really persistent.

The majority of preschool children participating in our study, both those delivered preterm and at term, presented with seroprotective levels of post-vaccination antibodies against all analyzed antigens, and no statistically significant intergroup differences were found in the seroprotection rates. Serological studies were conducted 2.5–3 years after the last immunization, before recommended booster vaccinations. Importantly, all children delivered preterm had been immunized according to their chronological age and received all vaccinations listed in the National Vaccination Program. Moreover, none of the subjects born preterm had birth weight <2200 g. All these factors might contribute to the high seroprotection rates documented in preterm children.

Persistence of seroprotection after basic vaccination against HBV and the need for booster doses later in life still raise some concerns. Long-term studies of children vaccinated in early childhood demonstrated that the proportions of subjects with seroprotective levels of anti-HBV IgG at 5 and 10–15 years of age were 88% and 74–78%, respectively [19,20]. Importantly, high seroprotection rates against HBV were also documented in subjects born prematurely, but the level of the specific IgG was significantly correlated with body weight at the time of primary immunization [21–24]. In another study [25], proportions of subjects with seroprotective levels of anti-HBV antibodies (>10 mIU/mL) after primary vaccination with a polyvalent vaccine (DTaP-HBV-IPV/Hib) at 2, 4, and 6 months of age and booster immunization at 18 months were essentially the same, regardless of whether they were born preterm or full-term (93.4% *vs.* 95.2%). The same study did not demonstrate a significant association between gestational age or body weight at birth and humoral response to the vaccination [25]. Together, this evidence implies that vaccination of premature infants according to their chronological age is both justified and effective [20,22,25,26].

However, in other studies [27–29], 7-year-old children who were born at <29 weeks of gestational age, with birthweight <1000 g, and vaccinated in the first few weeks of life, presented with significantly lower concentrations of antibodies against diphtheria, tetanus, poliomyelitis, and HBV than their peers delivered at term. These findings suggest that gestational age and/or body weight at birth are determinants of post-vaccination immune response and IgG elimination rates. However, according to other authors, children born preterm at 25–35 weeks of gestation show adequate immune response after vaccination with diphtheria antigen and tetanus toxoid [30–32].

The type of vaccine used for primary immunization against pertussis (acellular or whole-cell) seems to be a key determinant

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of long-term immunity; according to the literature, acellular vaccines provide shorter seroprotection later in life [27,28]. It is estimated that only 10% of children born at term and vaccinated with the acellular vaccine present with seroprotective levels of anti-pertussis IgG at 8.5 years after the last immunization; this justifies implementation of earlier booster strategies to control spread of this infectious disease [28]. Nevertheless, many previous studies demonstrated that acellular vaccine against pertussis is effective and safe in children born prematurely, unless given earlier than at 2 months of age [29–33]. Indeed, in our study, the proportions of preterm and full-term children without seroprotective levels of anti-pertussis IgG did not differ significantly (10.9% *vs.* 11.8%).

According to the literature, immune response of infants born preterm and/or with low birthweight to inactivated polio vaccine (IPV), measured as an induction of neutralizing antibodies against poliovirus type 1 and 2, is essentially the same as in their full-term peers; however, preterm children presented with lower levels of neutralizing antibodies against poliovirus type 3 [22,25]. In our study, all preschool children, both those born preterm and full-term, maintained seroprotective levels of IgG against all 3 types of poliovirus.

Infections caused by *Haemophilus influenzae* type b may be fatal in young children, especially those born preterm, and negatively affect further development of the child [34]. Principal virulence factor of *Haemophilus influenzae* is its capsular antigen, which is composed of polyribosylribitol phosphate (PRP) [35]. According to the literature, minimal seroprotective levels of anti-PRP antibodies providing short- and long-term protection against infections with *Haemophilus influenzae* should exceed 0.15 µg/mL and 1 µg/mL, respectively [29,34]. Importantly, previous studies demonstrated that response to immunization against Hib is determined by age at time of vaccination, birthweight, and gestational age at birth [35], and is generally worse in preterm infants than in those delivered at term [29]. However, in our study, seroprotective levels of anti-Hib IgG were found in most subjects, both those born preterm and full-term (84.8% *vs.* 90.2%). This might be at least in part associated with the fact that our study group included preschoolers with gestational age at birth ≥32 weeks; according to the literature, the efficiency of immunization against Hib in preterm infants increases with their gestational age [36].

Published evidence from observational studies shows that up to 8.9% of healthy children who received 2 doses of a MMR vaccine do not show seroprotective levels of anti-measles IgG at 7.4 years after the last immunization, and post-vaccination seroconversion does not occur in 2–10% of the subjects [37–43]. However, in our study, seroprotective levels of anti-measles antibodies were found in all preschool children immunized with MMR vaccine, both those born preterm and full-term.

Timely vaccination is a key determinant of immune protection, especially in children born preterm, who present with lower levels of maternal antibodies [44,45]. The fact that in our study the proportions of timely vaccinated preschoolers from preterm and full-term group were essentially the same (67.4% *vs.* 74.5% and median vaccination delay 4.5 *vs.* 3 months) may be another reason behind the lack of statistically significant intergroup differences in persistent immunity. Our findings suggest that most available vaccines provide adequate seroprotection in preschoolers, including those born preterm, if administered at the appropriate time according to chronological age of the infant, and also show the need to continue the vaccination schedule by using boosting doses. This emphasizes the importance of educational activities promoting appropriate immunization strategies for preterm infants among their parents and pediatricians [14].

We are well aware of potential limitations of this study. We examined late preterm infants who on the whole would not necessarily be expected to have the same immune challenges that early preterm infants face in responding to vaccines. Defining late prematurity as an inclusion criterion, we kept in mind that 82% of Polish preterm neonates are delivered at 32–36 weeks of gestation. Nevertheless, the results of this study may not be generalizable to all preterm infants. It should also be noted that the immunization schedule followed in Poland, where, depending on a reimbursement scheme, either monovalent or polyvalent vaccines can be administered, may not be generalizable, and different results may be obtained for other schedules. Finally, vaccine responses to many antigens, especially pertussis, are known to decrease over time, which justifies use of 5-year boosters; since our study was performed within this window of time, its results may be biased. Consequently, future studies should also include children aged 10 years and older; optimally, seroprotection rates should be followed-up longitudinally.

The present research was aimed at the assessment of vaccine-induced immunity in preschool children at about 3 years after the administration of the recommended doses of basic vaccines against HBV, polio, tetanus, pertussis, diphtheria, Hib, measles, mumps, and rubella. Some of the children enrolled were born prior to the expected date of delivery. According to the medical documentation, the study group did not include children born before 32 weeks of pregnancy and their birthweight was above 2200 g. Some of the population had levels of IgG indicating lack of post-vaccine protection. Because the week of pregnancy is considered to be the main factor of fetal development, we sought to verify whether gestational age determines vaccine-induced immunity, and, consequently, whether preterm birth should be a cause of vaccination schedule modification. Our own research results are in accordance with those of other researchers, indicating that some children do not achieve the

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recommended post-vaccination antibody titer within a given period after immunization. Therefore, booster doses of some vaccines are necessary, which proves the legitimacy of booster administration for children at recommended periods provided by the National Vaccination Program.

Conclusions

Preschool children who were late preterm infants do not seem to present differences compared to those who were full-term infants, who were immunized according to their chronological age.

Conflict of interest

None.

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