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RISK FACTORS FOR ADVERSE EVENTS AFTER VACCINATIONS PERFORMED DURING THE INITIAL HOSPITALIZATION OF INFANTS BORN PREMATURELY*

CZYNNIKI RYZYKA WYSTĄPIENIA ZDARZEŃ NIEPOŻĄDANYCH PO SZCZEPIENIACH OCHRONNYCH WYKONANYCH PODCZAS PIERWSZEJ HOSPITALIZACJI U NOWORODKÓW PRZEDWCZEŚNIE URODZONYCH

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Abstract

Introduction: *There are significant delays in implementing vaccination among preterm infants.*

Objectives: *Description of the frequency and kinds of adverse events following immunization in preterms. Establishment of the group of preterms who will distinctively be susceptible to adverse events.*

Materials and methods: *Demographical, clinical data and the occurrence of adverse events after DTaP, HIB and pneumococcal vaccination among preterms during their initial hospitalization were prospectively collected with the use of an electronic data form between 1st June 2011 and 31st May 2015. The analysis was conducted on 138 patients. The groups were divided according to maturity (I: ≤ GA 28w n=73 and GA 29-36 w n=65).*

Results: *There were no statistically significant differences between the groups in the occurrence of adverse events. Out of the total group, following vaccination apnoea developed in 6 newborns (4%) and activity dysfunctions were observed in 13 newborns (10%). The occurrence of apnoea after vaccination positively correlated with the time of non-invasive ventilation and the occurrence of late infection. There were no statistically significant demographical or clinical risk factors for the development of activity dysfunctions following vaccination.*

Conclusions: *Term vaccination in clinically stable preterm infants is a safe medical procedure. However, long-term non-invasive respiratory support and late infections are risk factors for apnea following vaccinations. In these patients vaccinations should be considered during hospitalization.*

Key words: premature newborns, immunization, adverse effects

Streszczenie

Istnieją znaczące opóźnienia w realizacji programu szczepień ochronnych u noworodków przedwcześnie urodzonych.

Cel: *częstość występowania i rodzaj działań niepożądanych po szczepieniu ochronnym u wcześniaków. Określenie grupy noworodków szczególnie narażonych na wystąpienie działań niepożądanych.*

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Materiał i metody: *W okresie od 1.06.2011 do 31.05.2015 roku, przy użyciu elektronicznego formularza, prospektywnie gromadzono dane demograficzne i kliniczne dotyczące noworodków przedwcześnie urodzonych oraz występowana działań niepożądanych po szczepieniu ochronnym DTaP, HIB i przeciw pneumokokom, wykonanym w trakcie hospitalizacji po urodzeniu. Analizą objęto 138 pacjentów. Dzieci podzielono na dwie grupy, kryterium podziału stanowiła dojrzałość przy urodzeniu (grupa I: ≤28 i grupa II: > 28 tygodni).*

Wyniki: *Nie stwierdzono różnic istotnych statystycznie między grupami co do częstości występowania działań niepożądanych. Bezdechy po szczepieniu stwierdzono u 6 pacjentów (4%), zaburzenia aktywności wystąpiły u 13 wcześniaków (10% całej grupy badanej). Występowanie bezdechów po szczepieniu dodatnio korelowało z czasem trwania wspomagania oddychania i występowaniem infekcji późnych. Nie stwierdzono istotnych statystycznie korelacji między danymi demograficznymi i klinicznymi a wystąpieniem zaburzeń aktywności po szczepieniu ochronnym.*

Wnioski: *Szczepienie ochronne wykonane we właściwym terminie jest u stabilnego noworodka przedwcześnie urodzonego procedurą bezpieczną. Jednakże, długotrwałe nieinwazyjne wsparcie oddechowe oraz przebycie infekcji wtórnej to czynniki ryzyka wystąpienia bezdechów po szczepieniu. W tej grupie pacjentów należy rozważyć wykonanie szczepienia ochronnego w warunkach szpitalnych.*

Słowa kluczowe: noworodki przedwcześnie urodzone, szczepienie, działania niepożądane

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INTRODUCTION

Preterm infants should receive compulsory vaccination in compliance with their chronological age [1-4]. According to bibliographical data, such immunization is not properly implemented either in Poland, or the rest of the world [5-7].

Anti-vaccination movements play a great role in postponing the program of immunization. They are responsible for the negative attitude towards vaccination among newborns' parents [8]. It is common among medical personnel to believe that preterm infants are more susceptible to experiencing adverse events following immunization (AEFI) than other age groups.

However, a prospective observational study performed among preterm babies demonstrated a good immune response to the series of primary diphtheria, tetanus, pneumococcal, meningococcal and Haemophilus influenzae type b (Hib) vaccination [9-12].

Unless the effectiveness of vaccination among preterms raises no concerns, the safety of vaccination, especially among the most immature group, requires further examination. In order to determine whether the occurrence AEFI depends on the gestational age group, the infants studied were divided into two groups depending on their maturity at birth.

The objectives of the study were:

1. to perform an analysis of early dysfunctions in the clinical state among preterm infants following vaccination;

2. to determine the correlation between the incidence of AEFI and the demographical and clinical data of the population;

3. to attempt to create a list of pathological states the presence of which is a risk factor for early AEFI.

MATERIAL AND METHODS

The study involved preterm infants born in the Department of Neonatology in the Centre of Medical Postgraduate Education in Warsaw between 01.06.2011 and 01.06.2015. The total group examined was divided into two sub-groups depending on maturity at birth: extremely immature (group I) GA ≤28 w and immature (group II) GA>28w. The infants were vaccinated (Diphtheria, Tetanus, Pertussis, Haemophilus influenzae type b, Polio, Pneumococcus) and followed up according to a standardized protocol during their hospital stay. We used *Infanrix IPV HIB* (GSK, Belgium) and *Prevenar* (Wyeth Lederle, USA) vaccine.

The medical schedule for vaccination considered: the infant's age (>42 days of life), a stable clinical condition and the parents' written consent.

We monitored the newborns' cardiac and respiratory functions, as well as body temperature over 72 hours after vaccination. The Multidimensional Neonatal Infant Pain Scale (NIPS) was used to assess the changes in the infant's behavior (facial expression: relaxed-0, contracted-1, cry: absent – 0, mumbling – 1, vigorous – 1, breathing: relaxed – 0, different than basal – 1, arms and legs: relaxed – 0, flexed – 1, stretched – 1, alertness: sleeping – 0, calm – 0, uncomfortable. Three points were considered as activity abnormalities.

Electronically collected data included delivery type (natural, caesarean section), infant's sex, birth weight, gestational age and Apgar scale at 5th minute of life. We also documented early (EOS) and late (LOS) infection (diagnosed with the use of uniform algorithms [13, 14]), necrotizing enterocolitis, intraventricular haemorrhage (IVH), type (invasive, non-invasive) and length of respiratory support, number of days with

apnoea, caffeine administration, anaemia requiring red blood cells (RBCs) in the first week of life [15], bronchopulmonary dysplasia (BPD) and periventricular leukomalacia (PVL).

Excessive local skin reaction (swelling and redness >0.5 cm, increased temperature and tenderness) and systemic symptoms (hyperthermia, worsening or recurrence of apnoea, the necessitty to administer caffeine, activity dysfunctions, desaturations (SpO2<90%), the necessity of respiratory support) were considered as dysfunctions of the clinical condition.

The implementation of immunization at the Department was in accordance with current recommendations. The Bioethics Committee in Centre of Medical Postgraduate Education approved the study. All the parents contacted agreed to participate in the study, i.e. the response rate was 100%. All the preterm infants hospitalized (inborn and out-born) in the Department in the observational period were included in the study. There were no cases of the parents' refusal to perform vaccination, or use the child's data for the scientific report.

STATISTICAL ANALYSIS

Categorical variables were presented in the form of absolute numbers and percentages (%). Measurable traits were described by the median value (*Me*). Logistic regression was fitted in order to estimate the odds ratios in terms of an increase in an investigated trait between the infants born up to 28 weeks of gestational age versus those born after the 28th week.

Regarding the estimation of relationships between categorical variables (frequency measurements), the χ^2 test of independence or Fisher's exact test (two-tailed) were carried out in the groups examined. In estimating significant differences in numerical variables (medians) in the two independent groups, the Mann-Whitney *U* test was performed. Due to the possible small numbers of respondents in the independent groups, the exact Mann-Whitney U rank-sum test with or without bootstrapped standard errors was used in the course of statistical analysis. Exact tests return exact p-values, especially when one deals with the total size of the two samples, which is ≤25. The exact testing incorporates permutations, thus it yields exact p-values which are adequate for small sample statistics. Bootstrapping provides a way of estimating standard errors and other measures of statistical precision. It provides a way to obtain such measures when no formula is otherwise available or when available formulas make inappropriate assumptions [16, 17].

The level of $p<0.05$ was considered statistically significant. Some missing data were encountered during analyses. Therefore, cases of factorial analysis with blank cells were excluded from a given computation but not from the data basis. In other words, only cases that did not contain any missing data for any of the variables selected for the analysis would be included in the statistical procedure. During the statistical analyses the Stata®/Special Edition, release 14.1 package was employed (StataCorp LP, College Station, Texas, USA).

RESULTS

AEFI analysis was performed among 138 newborns: of whom group I – 73, group II – 65 infants. There were significant differences in their maturity ($p<0.001$), birth weight ($p<0.001$), weight on vaccination day ($p<0.001$), Apgar score at 5' ($p<0.001$) and age on vaccination day ($p=0,001$) between the groups. The demographic data is presented in table I.

As it is shown in Table IV and V, apnoea (called: *Apnea group*), and activity dysfunctions (called: *Activity dysfunctions group*) were the relatively most frequent AEFI. Both groups were further analyzed. Complications of prematurity were evaluated in each of these groups and compared with the prevalence of these diseases in the entire study population.

Apnea after vaccination occurred in 6 infants (4%). The *Apnoea group* presented no differences in either sex, delivery type, maturity at birth, birth weight and Apgar score at 5th minute, or in IVH, early anemia, EOS, NEC, length of mechanical ventilation, BPD and PVL in comparison to the *non-Apnea group*. The *Apnoea group* newborns experienced significantly more frequent LOS ($p=0.028$), as well as a history of CPAP which lasted significantly longer than in the general group ($p=0.033$). There were no significant differences in the length of caffeine administration, late anemia requiring erythropoietin and blood transfusions (data not presented in table IV), as well as body weight and age on the vaccination day.

Activity dysfunctions following vaccination regarded 13 preterm infants (9%). There were no significant differences in sex, maturity status at birth, delivery type in comparison to the *non-Activity dysfunctions group*. The newborns examined who revealed activity dysfunction unexpectedly gained a statistically significant higher Apgar score in the 5th minute after delivery. The Apgar score had been awarded strictly according to the rules, nevertheless the surprising, albeit significant difference, is supposed to have arisen due to the small sample size and purely random selection of the study subjects. There were no differences in IVH, EOS, LOS, PVL, BPD occurrence, the length of respiratory support of any type, the length of apnoea and caffeine administration, nor in either early or late anaemia, body weight and age on vaccination day.

DISCUSSION

In the present paper we tried to identify factors increasing the risk of the incidence of adverse events following DTaP, HiB and pneumococcal vaccination in prematurely born infants. The study included only hospitalized premature babies vaccinated in the hospital, which enabled the exact identification of AEFI. In order to determine whether the occurrence AEFI depends on the degree of immaturity at birth, the group were divided into two sub-groups ≤28 hbd and >28 hbd. The sample size is rather small, so the results have to be interpreted with caution.

The newborns in the group with lower maturity were vaccinated later, moreover their body weight on the day of vaccination was lower.

Table I. Demographic characteristics of the study groups.

Tabela I. Charakterystyka demograficzna badanej grupy.

Trait ***Cecha***	**GA ≤28 w** ***Wiek płodowy ≤28 tyg.*** **n=73 (%)**	**GA >28 w** ***Wiek płodowy >28 tyg.*** **n=65 [%]**	**p**
Birth weight* [g] *Urodzeniowa masa ciała [g]*	1000	1200	<0.001
Gestational age at birth [hbd]* *Wiek płodowy przy urodzeniu (tydzień ciąży)*	27	30	<0.001
Type of delivery: *Rodzaj porodu* caesarean section *cięcie cesarskie* vaginal delivery *poród drogami natury*	52 (71) 21 (29)	54 (84) 10 (16)	=0.067
Sex *Płeć* male *męska* female *żeńska*	44 (60) 29 (40)	38 (58) 27 (42)	=0.829
Apgar score at 5'* *Punktacja według Apgar w 5' życia**	6	7	<0.001
Body weight on the day of vaccination [g] * *Masa ciała w dniu szczepienia [g]**	1795	2100	=0.001
Day of life on the day of vaccination* *Doba życia w dniu szczepienia**	49	44	<0.001

*median
**mediana*

The frequency and intensity of IVH, including severe forms (III and IV°), incidence of PVL and NEC were comparable, but the younger group more often demonstrated EOS, LOS and BPD. Newborns with lower maturity required significantly longer respiratory support, both of the invasive and non-invasive kind. The apnoea period was longer and consequently caffeine was not administered any more (tab. II).

The objective of this work was to verify the doctors' and parents' concerns regarding the suitability of more frequent AEFI. We also tried to specify the risk factors for these events in order to determine if the newborns require vaccination in hospital.

According to general knowledge, there is no large prospective research which would identify the risk factors determining the necessity of vaccination in a hospital environment.

We have observed that general condition dysfunctions following vaccination are rare and they concern a low percentage of newborns. We note that vaccination was performed in the early days of the newborns' life compared to other reports [18, 19].

The analysis of the incidence of AEFI in preterm newborn infants has shown that the maturity level at birth and the differences in demographical and clinical measurements associated with it do not influence the incidence of adverse events following immunization. Only one child had increased body temperature, 13 children had activity dysfunctions (9%), 6 experienced apnoea (4%), half of them required respiratory support and one required additional caffeine administration (tab. III). Desaturation following vaccination was demonstrated in 3 newborns, which represents 2% of the whole group. None of the premature infants had an excessive local skin reaction following the intramuscular administration of vaccine. Table III presents no statistically significant differences in the incidence of adverse events between the groups of diverse maturity.

Ricardo E. Pfister's research has shown that bradycardia episodes, desaturation and apnoea at a time immediately prior to vaccination are risk factors for adverse events following immunization. The risk was higher in cases when the newborn was oxygen dependent. In the above-mentioned work the risk of an apnoea incident accounts for 12-20%. Among other risk factors for adverse events following immunization the work states the extremely early birth of a preterm infant, a severe clinical condition after birth, low weight at vaccination, infants born at

Table II. Clinical characteristics of the study groups.

Tabela II. Charakterystyka kliniczna badanych grup.

Trait ***Cecha***	**GA ≤28 w** ***Wiek płodowy ≤28 tyg.*** **n=73 (%)**	**GA >28 w** ***Wiek płodowy >28 tyg.*** **n=65 (%)**	**p**
Early onset sepsis *Zakażenie wczesne*	51 (70)	33 (51)	= 0.022
Late onset sepsis *Zakażenie późne*	36 (49)	16 (25)	= 0.003
Necrotizing enterocolitis *Martwicze zapalenie jelit* ≥ II° according to Bell *≥ II° wg Bella* surgical *chirurgiczne*	2 (3) 2 (3)	2 (4) 0 (0)	= 0.558
Early anaemia *Wczesna niedokrwistość*	35 (48)	11 (17)	< 0.001
Intraventricular haemorrhage *Krwawienie dokomorowe* no *nie* yes *tak* in it: *(w tym)* I° II° III° IV°	11 (16) 59 (84) 19 (32) 25 (43) 9 (15) 6 (10)	10 (18) 46 (82) 25 (54) 17 (37) 3 (7) 1 (2)	= 0.748 = 0.067
Periventricular leukomalacia *Leukomalacja okołokomorowa*	11 (17)	7 (10)	= 0.454
Bronchopulmonary dysplasia *Dysplazja oskrzelowo-płucna* including *(w tym):* mild *łagodna* moderate *umiarkowana* severe *ciężka*	43 (61) 31 (72) 6 (14) 6 (14)	6 (11) 3 (50) 2 (33) 1 (17)	< 0.001 = 0.327
Apnoea (No of days) *Bezdechy (liczba dni)*	30	4	< 0.001
Invasive respiratory support (No of days) Inwazyjne wspomaganie oddychania (*liczba dni)*	2	0	< 0.001
Non-invasive respiratory support (No of days) Nieinwazyjne wsparcie oddychania (*liczba dni)*	19	4	< 0.001
Caffeine (No of days) *Kofeina (liczba dni)*	45	22	< 0.001

GA <28 weeks, Bronchopulmonary dysplasia, earlier mechanical respiratory treatment [20].

Among all the adverse events analyzed, the most frequent ones are apnoea and activity dysfunctions. Newborns who developed the above-mentioned adverse events were further analyzed.

Based on the data acquired, the statistical significance in the younger group allows us to claim that late infection may be a risk factor for apnoea incidence following immunization. The period of respiratory support after birth, the length of which is positively correlated with apnoea incidence following vaccination, was also important in that group. The material analyzed has not shown that the immaturity level, type of delivery, clinical examination after birth or birth weight are not risk factors for apnoea incidence. It has also been shown that typical premature birth complications such as IVH, PVL, early infection occurrence, severe early anaemia and NEC or BPD incidence are not risk factors for apnoea following vaccination. The day of vaccination and actual body

Table III. Incidence of clinical events in each group and the total study population of premature (observation time 0-72 after vaccination).

Tabela III. Występowanie zdarzeń klinicznych w poszczególnych podgrupach i całej badanej grupie wcześniaków (czas obserwacji 72 godziny po szczepieniu).

Clinical event ***Zdarzenie kliniczne***	**GA ≤28 w** ***Wiek płodowy ≤28 tyg.*** **n=73 (%)**	**GA >28 w** ***Wiek płodowy >28 tyg.*** **n=65 (%)**	**Overall** ***Ogółem*** **n=138**	**p**
Local reaction *Reakcja miejscowa*	0 (0)	0 (0)	0 (0)	-
Increased body temperature >38°C *Wzrost ciepłoty ciała >38°C*	1 (1)	0 (0)	1 (1)	0.999
Activity dysfunctions NIPS scale ≥3 pts. *Zaburzenia aktywności ≥3 pkt w skali NIPS*	7 (10)	6 (9)	13 (9)	0.943
Apnoea *Bezdechy*	5 (7)	1 (2)	6 (4)	0.213
Necessity of respiratory support *Konieczność wsparcia oddechowego*	2 (3)	1 (2)	3 (2)	0.999
Desaturations *Desaturacje*	2 (3)	1 (2)	3 (2)	0.999
Necessity of the supply of caffeine *Konieczność włączenia kofeiny*	1 (1)	0 (0)	1 (1)	0.999

weight are not risk factors for AEFI. There are strong indications that appropriate clinical assessment is the most significant factor of the proper course of the post-vaccination period in preterm newborn infants.

A study of 411 Australian children with low and extremely low birth weight has shown that vaccination may require respiratory support in newborns with extremely low birth weight, with BPD and after sepsis [21].

The thorough analysis of contemporary literature performed by a research team from California and Boston has proved that there is a relation between vaccination and increased body temperature together with febrile convulsion. What is more, there is a higher risk of intussusception after vaccine against rotavirus; the incidence, however, is very rare (1.1 to 1.5 for 100 000 doses of RotaTeq and 5.1 for 100 000 doses of Rotarix). There is a risk of adverse events following varicella vaccination among children with immunodeficiency syndrome. Other adverse events following immunization (reddening, pain, swelling, thrombocytopenia, hypersensitivity to ingredients, vomiting, diarrhea) are rare and harmless. The possibility of low risk of adverse events indicates that the decision to vaccinate is reasonable, considering the health benefits of active immunization. While administering multiple vaccinations at one sitting (e.g. pneumococcal and influenza vaccination) the risk of AEFI increases. There is good evidence that eliminates the relation between vaccination and autism or leukemia [22].

Carbone et al, who conducted research comprising 191 preterm infants born in 10 American hospitals, did not record increased frequency of cardiovascular dysfunctions among vaccinated newborns compared with the control group [23]. Another multicenter study (13 926 preterm infants ≤GA 28 weeks) has shown the increased frequency of late infection incidence and intubation and respiratory support following vaccination, which implies the necessity of significant caution and careful qualification for vaccination [24]. Lee has described the increased frequency of cardiovascular and respiratory systems dysfunctions [25].

Impaired psychomotor skills are an additional, clearly visible symptom in newborns. This disorder developed in 12 newborns (11% of the group). The disorder included reduced activity (drowsiness, apathy, reluctance to suckle) and also agitation, hypersensitivity, anxiety. Recurring tachycardia combined with increased activity was also observed; at a calm time the heart rate normalized. Due to this fact, the above parameter was not included in the analysis. All the above newborns required their father's, mother's or a nurse's additional care and nursing. The duration of the above-mentioned dysfunctions did not exceed 2 days. It is interesting that this characteristic was observed among newborns with a higher Apgar score than the rest of the population. We believe, however, that it was just a coincidence.

The group with activity dysfunctions following vaccination did not present any statistically significant dependence on any analyzed demographical or clinical measurement. The newborns' medical history did not mention any febrile condition or the necessity of tranquilizers or administration of analgesics.

Our study has a few limitations. It was conducted only on prematurely born infants during their hospitalization, so there is no control group of term newborns. The

Table IV. Comparison of the occurrence of the most common adverse events following vaccination in preterms depending on the demographic characteristics.
Tabela IV. Porównanie częstości występowania najczęstszych niepożądanych zdarzeń poszczepiennych u wcześniaków zależnie od czynników demograficznych.

Trait ***Cecha***	**General population n=138 (%)** ***Populacja ogólna n=138 (%)***	**Apnoea** ***Bezdechy***		**Activity dysfunctions** ***Zaburzenia aktywności***		**Statistical significance of differences (p-value)** ***Istotność statystyczna (wartość p)***
		YES, n=6 (%) *TAK, n=6(%)*	NO, n=132 (%) NIE, n=132(%)	YES, n=13 (%) *TAK, n=13 (%)*	NO, n=125 (%) *NIE, n=125 (%)*	
	1	2	3	4	5	
Male sex *Płeć męska*	82 (59)	4 (67)	78 (59)	5 (38)	77 (62)	(2) vs. (3) ns (4) vs. (5) ns
GA ≤28 w *Wiek płodowy ≤28 tygodni*	73 (53)	5 (83)	68 (52)	6 (46)	67 (54)	(2) vs. (3) ns (4) vs. (5) ns
Caesarean section *Cięcie cesarskie*	106 (77)	3 (50)	103 (79)	10 (77)	96 (77)	(2) vs. (3) ns (4) vs. (5) ns
Body weight (g) *Urodzeniowa masa ciała (g)*	1095 (465-1900)	935 (490-1300)	1095 (465-1900)	1140 (740-1500)	1090 (465-1900)	(2) vs. (3) ns (4) vs. (5) ns
Apgar score in 5' *Ocena wg skali Apgar w 5'*	6 (1-10)	7 (4-8)	6 (1-10)	7 (4-10)	6 (1-10)	(2) vs. (3) ns **(4) vs. (5) p = 0,036**

Table V. Comparison of the occurrence of the most common adverse events following vaccination in preterms depending on clinical characteristics.

Tabela V. Porównanie częstości występowania najczęstszych niepożądanych zdarzeń poszczepiennych u wcześniaków zależnie od czynników klinicznych.

Trait ***Cecha***	**General population n=138 (%)** ***Populacja ogólna n=138 (%)***	**Apnoea** ***Bezdechy***		**Activity dysfunctions** ***Zaburzenia aktywności***		**Statistical significance of differences (p-value)** ***Istotność statystyczna (p)***
		YES, n=6 (%) *TAK, n=6 (%)*	NO, n=132 (%) *NIE, n=132 (%)*	YES, n=13 (%) *TAK, n=13(%)*	NO, n=125 (%) *NIE, n=125(%)*	
	1	2	3	4	5	
Late onset sepsis *Zakażenie późne*	52 (38)	5 (83)	47 (36)	3 (23)	49 (39)	**(2) vs. (3) p = 0,028** (4) vs. (5) ns
Non-invasive ventilatory support, No. of patients *Nieinwazyjne wsparcie oddechowe, Liczba pacjentów*	135 (98)	6 (100)	129 (98)	12 (92)	123 (98)	(2) vs. (3) - (4) vs. (5) ns
No. of days (*median value) *Liczba dni (*mediana)*	8 (1-121)	29,5 (7-31)	7 (1-121)	4 (1-30)	8 (1-121)	**(2) vs. (3) p = 0,033** (4) vs. (5) ns
Body weight on the day of vaccination (g) *Masa ciała w dniu szczepienia (g)*	1890 (1100-3490)	1790 (1180-2030)	1890 (1100-3490)	2030 (1480-3050)	1880 (1100-3490)	(2) vs. (3) ns (4) vs. (5) ns
Day of life on the day of vaccination *Doba życia w dniu szczepienia*	46 (17-99)	48,5 (42-70)	45,5 (17-99)	45 (42-66)	46 (17-99)	(2) vs. (3) ns (4) vs. (5) ns

sample size is rather small, so that the results have to be interpreted critically. Especially the data in table IV should be interpreted with caution. It is based on the empirical data we collected during the study, alas it is not possible to estimate the exact timespan between the vaccination and the onset of the clinical events analyzed.

Taking into account the higher incidence of AEFE in the literature than in our study, a group of 138 infants born prematurely was initially considered sufficient. We therefore believe that the study needs to be continued.

CONCLUSIONS

1. Appropriate clinical assessment of a child seems to be the most significant factor which qualifies the patient for vaccination at the right age and is a prerequisite for the proper course of the post-vaccination period in preterm newborn infants .
2. Factors increasing the risk of apnea following vaccination in this group of patients are long respiratory support and late infection.
3. The presence of risk factors for developing adverse events following immunization qualifies the child for performing the procedure in hospital.
4. The efficacy and safety of vaccinations in preterm newborn infants requires further analysis performed on a large group of patients and long-term prospective observation.

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