

REVIEW ARTICLES/PRACE POGLĄDOWE

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VACCINATION OF PRETERM INFANTS BY POLYVALENT VACCINES: IMMUNOGENICITY AND SAFETY – REVIEW OF LITERATURE

SZCZEPIENIA DZIECI URODZONYCH PRZEDWCZEŚNIE SZCZEPIONKAMI WYSOKOSKOJARZONYMI: IMMUNOGENNOŚĆ I BEZPIECZEŃSTWO – PRZEGLĄD PIŚMIENNICTWA

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Abstract

The immunization of infants against infectious diseases still raises many controversies, not only with parents, but also among physicians. This refers particularly to preterm infants. Due to the increasing popularity of polyvalent vaccines, a number of studies has recently been conducted to verify their immunogenicity and safety in preterm infants. The aim of the present paper was to review the current literature dealing with the problem in question. The following recommendations regarding the use of polyvalent vaccines in preterm infants and neonates with low birth weight can be formulated on the basis of current evidence (1). Due to sufficient immunogenicity, polyvalent vaccines can be administered to preterm infants in accordance with their calendar age (2). Booster vaccination of preterm infants after completing 12 months of age is vital for achieving complete and persistent immunity against all vaccine antigens (3). In order to reduce the risk of adverse events after the administration of a polyvalent vaccine, it is essential to carefully consider the cardiorespiratory status of preterm infants during pre-immunization examination, as well as their history of any cardiorespiratory dysfunctions. In such cases administering the first dose of the vaccine in a hospital setting is strongly advised.

Key words: prematurity, low birth weight, immunity, adverse events

Streszczenie

Szczepienia niemowląt przeciwko chorobom zakaźnym wciąż budzą wiele kontrowersji i to nie tylko wśród rodziców, ale również w gronie lekarzy. Problem ten dotyczy w szczególności wcześniaków. Z uwagi na rosnącą popularność szczepionek wysokoskojarzonych, w ostatnich latach przeprowadzono szereg badań dotyczących ich immunogenności i bezpieczeństwa u wcześniaków. Celem niniejszego opracowania jest przegląd aktualnego stanu wiedzy w tym zakresie. Na podstawie powyższego przeglądu danych z piśmiennictwa można sformułować następujące zalecenia dotyczące stosowania szczepionek wysokoskojarzonych u wcześniaków i dzieci z małą urodzeniową masą ciała (1). Ze względu na wystarczającą immunogenność, szczepionki skojarzone należy podawać u wcześniaków zgodnie z ich wiekiem chronologicznym (2). Dla osiągnięcia przez wcześniaka pełnej i trwałej odporności przeciwko wszystkim antygenom szczepionkowym kluczowe znaczenie ma szczepienie przypominające po ukończeniu 12. miesiąca życia (3). W celu zmniejszenia ryzyka wystąpienia u wcześniaka działań niepożądanych po podaniu szczepionki wysokoskojarzonej, podczas badania przed szczepieniem należy zwrócić szczególną uwagę na stan układu krążenia i układu oddechowego pacjenta, a także na dane z wywiadu dotyczące ewentualnych nieprawidłowości tych układów. W takich przypadkach należy rozważyć podanie pierwszej dawki w warunkach szpitalnych.

Słowa kluczowe: wcześniactwo, mała masa urodzeniowa, odporność, działania niepożądane

INTRODUCTION

The immunization of infants against infectious diseases remains a controversial issue among parents and doctors alike. This is particularly true when it comes to preterm infants. It has been established that the proportion of vaccinated infants within these groups is lower than among children born between the 37th and 40th week of gestation; they are also delayed too often (1-3). The data reported in the available literature on the subject indicates that the most significant reason for delaying immunization in preterm infants is physicians' inadequate knowledge on the safety, efficacy, and proper administration of vaccines (4). A number of papers have therefore been published in recent years, addressing the issue of immunization in preterm children and some of the numerous concerns that are associated with it (5-10). These publications include the recommendations of a group of Polish experts (11). These guidelines clearly state that – with the exception of some rare cases – preterm infants should be immunized according to the same vaccination schedule that is valid for full-term children. The experts also emphasize that the number of required injections may be minimized by using polyvalent vaccines (11, 12). Due to the increasing popularity of such preparations, a number of investigations on their immunogenicity and safety in preterm infants have been carried out. The objective of the present study was to review the currently available knowledge on this subject.

Depending on the length of the gestation period, three groups of preterm infants are distinguished. The first group comprises children born between the 32nd and 36th week of pregnancy, while the second group consists of children born between the 29th and 32nd week. The third group are neonates born before the 29th week, i.e. children who are severely underdeveloped. Preterm birth is closely associated with *low birth weight* (LBW), which does not exceed 2,500 g. According to the data reported by the American Academy of Pediatrics (AAP), as many as 84% of all preterm infants are born between the 32nd and 36th week of pregnancy. A further 10% are born between the 28th and 31st week of the gestation period. Only around 6% of all preterm children are infants born before the 28th week (13).

Independently of the duration of pregnancy, neonates include children whose birth weight is too low, i.e. below the 10th percentile for a given gestational age. These children are considered *small for gestational age* (SGA). The children that are especially vulnerable, however, are neonates born with *very low birth weight* (VLBW; <1,500 g), and *extremely low birth weight* (ELBW; <1,000 g). Epidemiological data indicate that the incidence of preterm birth and low birth weight among neonates born in Poland has remained at a constant level for years. According to the data collected by the Institute of Mother and Child (Instytut Matki i Dziecka), 6.64% of births before the 37th week of gestation were registered in Poland in 2000; the incidence reported in 2010 was 6.68%. According to the same source, neonates with a birth weight of less than 2,500 g comprised 6.07% and 5.96% of all children born in 2000 and 2010, respectively (14).

RISK FACTORS FOR INFECTION IN PRETERM INFANTS

Despite considerable progress in the field of neonatology, preterm birth and low birth weight remain significant risk factors for death. The perinatal mortality rate for Polish full-term neonates born with adequate birth weight is 0.60 per mille; this value increases drastically for neonates with a birth weight of 2,500 g or less, or those born before the 37th week of pregnancy, reaching 83.7 and 88.3 per mille, respectively (14). The reason why the risk of perinatal mortality is so high in these groups is the functional underdevelopment of the majority of the body's vital systems, including the nervous, respiratory and circulatory systems; another factor is an increased susceptibility to infection. The latter issue is particularly important with regard to the immunization of preterm infants. It was proven that the risk of sepsis in neonates is higher for lower gestational age at birth; this type of infection develops in ca. 20% of hospitalized neonates with very low birth weight (15). Low birth weight is also one of the main risk factors for developing pertussis during infancy (16). Other diseases with increased risk associated with preterm birth include pneumococcal and influenza virus infections (16, 17).

The increased vulnerability of preterm infants to infections is related to several factors. These factors may be divided into at least three groups. The first group comprises factors associated with an underdeveloped immune system. Since the placental transfer of antibodies from the mother's body is at its maximum after the 33rd week of pregnancy, preterm infants – especially neonates with extreme underdevelopment – are born either with a deficiency of humoral immunity, or entirely without it (18). In addition, deficiencies in cell-mediated immunity also contribute to the afore-mentioned vulnerability. It was demonstrated that in the 8th week postpartum (i.e. at the age of the first vaccination) the peripheral blood of preterm infants contains fewer lymphocytes (including T cells, B cells, and Th cells) than the blood of full-term infants. Their ratio of CD4 cells to CD8 cells is lower as well. A lower level of peripheral blood lymphocytes, including T and Th cells, is also observed at 7 months of age (19). Moreover, the phagocytes and lymphocytes produced by the bodies of preterm infants never develop into fully functional cells. For example, the B cells of preterm infants recognize a far smaller number of antigens than their counterparts in full term neonates (20). Another group of risk factors for infection in preterm infants comprises situations that are the underlying cause of preterm birth, including infections or the carrying of pathogens by pregnant women as well as the premature rupture of the fetal membranes. In addition, infection in preterm infants may be promoted by iatrogenic factors such as invasive diagnostic-therapeutical procedures performed in the case of patients of neonatal intensive care units, pre- and postnatal steroid therapy as well as blood transfusion and administration of blood-based products or immunoglobulins (5).

However, there is no evidence that the afore-mentioned factors have an adverse effect on the immunogenicity of

vaccines administered to preterm infants. The congenital deficiencies in humoral immunity are made up for soon after birth and do not affect the immune response to the antigens contained in vaccines (18, 20). Although some studies have shown that the administration of corticosteroids immediately following birth may reduce the level of post-vaccination response to antigens (including the antigens of *Corynebacterium diphtheria*, *Clostridium tetani*, the hepatitis B virus (HBV), and *Haemophilus influenzae* type b (Hib), among others) and to the whole-cell pertussis component (21-26), the duration of the immunosuppressive effect of steroids is not sufficiently long to justify delaying immunization (5).

An interesting phenomenon which provides an argument against delaying vaccination in preterm infants is the accelerated differentiation of B cells that occurs when the preterm infant is exposed to vaccine antigens. As a result of this process, the degree of differentiation of B cells in children born in the 28th week of gestation is higher than in full-term children when evaluated at the time at which birth would normally occur; in the latter group of children, B cells undergo differentiation in utero during the third trimester (20).

GUIDELINES CONCERNING THE IMMUNIZATION OF PRETERM INFANTS

As previously mentioned, the Polish experts' guidelines published in 2011 state that – with some rare exceptions – preterm infants and neonates with low birth weight should be routinely vaccinated as per their chronological age and the universal vaccination schedule. Neither fetal age nor birth weight should delay the decision to commence the immunization of clinically stable preterm infants against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, poliomyelitis or the hepatitis B virus. The health of these children does not require constant medical care and the monitoring of vital signs, and they exhibit appropriate weight gain and good clinical condition (12). If such preterm infants remain hospitalized at the time at which they would normally be vaccinated, i.e. at six to eight weeks of age, they should receive their first vaccines in the neonatal ward. In the case of children born before the 28th week of gestation, preterm infants suffering from bouts of apnea and bradycardia, and children with severe bronchopulmonary dysplasia, it is particularly important to perform the initial vaccinations in a hospital setting. The post-vaccination function of these children's circulatory and respiratory systems should be monitored for 48 to 72 hours. British recommendations (27) state that if any respiratory dysfunctions are observed during the first vaccination, then the subsequent immunization must be carried out in a hospital setting, with respiratory function monitored for at least two days. Postponing vaccination is justified only in the case of clinically unstable children. Should doubts arise concerning the eligibility of preterm infants and LBW children for immunization or the vaccination procedure per se, the decision should be left to specialists working at an immunization advisory clinic. It is recommended that the so-called "cocoon strategy" (also known as "cocooning") is followed; this approach entails the parallel immunization of the parents of the preterm infant and other individuals from his or her immediate environment against influenza and pertussis. The significance of pertussis prophylaxis in individuals who come into close contact (e.g. at home) with infants who are not immune to the disease or with infants who are undergoing primary immunization and are at a particularly high risk of developing the disease with a severe course is underlined in the recommendations of the American Academy of Pediatrics and the Centers for Disease Control and Prevention (CDC). The group covered by the cocoon strategy includes those parents, grandparents, babysitters, and older siblings who had not received the Tdap vaccine. According to the guidelines referred to above, it would be optimal if the individuals from the surroundings of the preterm infant received this vaccine at least two weeks before contact. It should be stressed that at this point in time there is no minimum interval that needs to be maintained between immunization with Tdap and a prior tetanus or tetanus-diphtheria vaccination. The gold standard would therefore be to advise the parents well in advance to vaccinate household members against pertussis immediately after the birth of the child, or sufficiently early before the child is discharged from the neonatal ward (12).

Experts also emphasize the importance of booster doses after the child has reached 12 months of age. When administering six-component vaccines to children with extremely low birth weight who were immunized several weeks after the date set in the vaccination schedule due to their unstable clinical condition, booster doses should be given as initially planned. However, a minimum interval of six months should be kept between the last dose of the primary vaccination and the booster dose. Furthermore, in such circumstances it is important to keep the shortest possible intervals of four weeks between consecutive doses of the primary vaccination in order to compensate for any delays in immunization (12).

As previously mentioned, the guidelines formulated by the Polish group of experts (11) suggested that the number of injections administered to preterm infants may be reduced by using polyvalent vaccines. The goal of recently conducted studies was to investigate whether such vaccines provide an appropriate level of immunogenicity in prematurely born neonates and whether they do not cause adverse effects.

IMMUNOGENICITY OF POLYVALENT VACCINES

The results of studies conducted in recent years indicate that in the case of most antigens the immunogenicity of polyvalent vaccines in preterm infants is similar to that in full-term neonates.

Faldella et al. (28) compared the immunogenicity of a quadrivalent DTPa-HBV vaccine in a group of 34 preterm infants (mean gestational age of 32 weeks) and a group of 28 full-term neonates. Their primary immunization was carried out at three, five and eleven weeks of age. After two doses of the vaccine, two children (one from each group) did not develop a concentration

of antibodies sufficient to confer protection for any of the antigens contained in it. However, after the full primary immunization cycle had been completed the antibody concentrations of all infants were sufficiently high to protect them against the respective diseases. Nevertheless, the concentrations of antibodies against pertussis and diphtheria antigens were lower in preterm infants. In addition, the researchers observed that children born before the 31st week of gestation had significantly lower concentrations of antibodies against *Bordetella pertussis* and HBV than preterm infants who were born after this point.

Slack et al. (29) evaluated the immunogenicity of the Hib antigen in 107 preterm infants born before the 32nd week of gestation. Children from this group who received the DTPa-Hib vaccine at two, three, and four months of age had a significantly lower concentration of antibodies than children from the control group of 54 full-term neonates. The minimum antibody concentration sufficient to confer protection (≥0.15 μg/ml) was reported in only 55% of preterm infants and in 80% of children from the control group, while the concentration of ≥1 μg/ml was reported in 21% and 46% of the children from the respective groups. No significant relation between the immunogenicity of the Hib antigen and either gestational age or weight at birth was observed. However, a significant positive correlation between the calendar age of the child at the time of the third vaccination and the concentration of anti-Hib antibodies was demonstrated.

Yet another study (26) compared the immune response after the administration of a quadrivalent DTPa-Hib vaccine to 130 preterm infants (mean gestational age at birth equal to 29.1 weeks) and 54 full-term neonates. Subsequent doses of the vaccine were administered according to an accelerated schedule, at an age of two, three, and four months. After primary immunization had been completed, the children did not differ significantly in terms of the concentration of antibodies against *Corynebacterium diphtheriae* and *Clostridium tetani* antigens and against filamentous hemagglutinin (FHA) and pertactin of *Bordetella pertussis*. The preterm group did, however, exhibit a significantly lower concentration of antibodies against pertussis toxin (PT). It was also demonstrated that the immunogenicity of tetanus and pertactin increases with age at the time of the third vaccination, while the immunogenicity of all antigens except for diphtheria antigens is positively correlated with gestational age evaluated at birth. In addition, a significant inverse correlation between the immunogenicity of tetanus antigens and the number of corticosteroid doses administered to pregnant women at risk of premature labour was reported. On the other hand, the post-vaccination response did not appear to be significantly affected by postnatal steroid therapy.

The same group of researchers (30) investigated the effects of primary immunization with a pentavalent DT5Pa-Hib-IPV vaccine in a group of 50 preterm infants (mean gestational age at birth equal to 28.5 weeks) and in a control group of full-term children. The vaccinations were performed according to the accelerated schedule, at an age of two, three, and four months. After primary immunization had been completed, antibody concentrations conferring protection against the antigens of *Corynebacterium diphtheriae*, *Clostridium tetani*, and all three serotypes of poliovirus were reported. Moreover, between 80 and 96% of preterm infants exhibited a sufficient concentration of antibodies against pertussis antigens, and 80% of them had sufficient concentrations against Hib antigens. The immune responses of preterm infants and neonates from the control group did not appear to differ significantly.

Omenaca et al. (31) compared the post-vaccination response of 94 preterm infants born between 24 and 36 weeks of gestation (mean gestation age at birth equal to 31 weeks, mean birth weight of 1420 g) and that of 92 full-term neonates. Each child received three doses of the hexavalent DTPa-HBV-IPV/Hib at an age of two, four, and six months. One month after the last vaccination, all infants exhibited antibody levels sufficient to confer protection against *Corynebacterium diphtheriae Clostridium tetani*, and poliovirus. In addition, the compared groups did not differ in terms of immunity against pertussis antigens (≥98.9% in both groups). The preterm infants did, however, exhibit reduced immunogenicity against Hib and HBV antigens. In the case of Hib antigen, sufficient antibody concentrations were reported for 92.5% of preterm infants and 97.8% of full-term neonates. For HBV antigens, these numbers were equal to 93.4% and 95.2%, respectively. Full-term children also exhibited higher concentrations of anti-Hib and anti-HBV antibodies as well as antibodies against the antigens of poliovirus type 3.

Vazquez et al. (32) demonstrated that as many as 92.4 to 100% of preterm infants born between the 24th and 36th week of gestation and with a birth weight of below 2000 g exhibit a sufficiently high antibody level to confer protection for all antigens contained in the hexavalent DTaP-HBV-IPV/Hib vaccine. The vaccine was administered at an age of two, four, and six months, and its immunogenicity was evaluated one month after the last dose. The administration of a booster dose at an age of 18 to 24 months yielded a further increase in the level of antibodies against the above-mentioned antigens, with the exception of the HBV antigen.

Vermeulen et al. (33) analyzed the possibility of conferring a sufficiently high level of non-specific immune response against the antigens of *Bordetella pertussis* in preterm infants born before the 31st week of gestation. 48 preterm infants received a quadrivalent DTPa-IPV vaccine at an age of two, three, and four months. The level of non-specific immune response against pertussis antigens was measured at an age of two, three, and six months. At three and six months of age the majority of the group of preterm infants exhibited a level of interferon gamma that was sufficient to confer protection. According to this report the level of non-specific immune response was not adversely affected by low birth weight, severe infections, or the administration of corticosteroids or immunoglobulins.

Baxter et al. (34) analyzed the immunization history of preterm infants born before the 32nd week, who had been vaccinated with DTPa-Hib or DTPw-Hib at an age of two, three, or four months. A protective *Corynebacterium*

diphtheriae and *Clostridium tetani* antibody titer was reported in 98.3% and 100% of the preterm infants, respectively. However, only around one third of children (34.7%) had a protective level of antibodies against the Hib antigen (≥1 μg/ml), while 32.2% had no anti-Hib antibodies whatsoever.

SAFETY OF POLYVALENT VACCINES IN PRETERM INFANTS

According to the available literature data, the risk of adverse events after the administration of polyvalent vaccines is not dependent on gestational age and/or weight at birth, or on the calendar age at the time of vaccination. On the other hand, the condition of the infant's circulatory and respiratory systems at the time of vaccination appears to be a risk factor for complications. In an observational study involving 78 preterm infants who received the pentavalent DTPa-IPV-Hib vaccine, 47% of the children developed transient circulatory-respiratory dysfunctions: apnea (15%), bradycardia (21%), and decreased saturation (42%). The relative risk of these complications proved to be between five and eight times higher in infants who had previously experienced cardiorespiratory problems (35). In another retrospective involving a group of 53 preterm infants, episodes of transient apnea and bradycardia were reported in 13% of the children who had received a pentavalent (DTPa-IPV-Hib) or hexavalent (DTPa-HBV-IPV/Hib) vaccine (36). It is worth noting that the adverse effects of polyvalent vaccines are more frequent and more pronounced in preterm infants who receive preparations that include a whole-cell pertussis component (37) instead of an acellular one (35, 38-41).

In conclusion, preterm infants should receive all of the vaccines indicated by the vaccination schedule. Experts recommend that preterm infants should be administered vaccines with an acellular pertussis component (11).

THINGS TO CONSIDER WHEN IMMUNIZING PRETERM INFANTS WITH POLYVALENT VACCINES

The Polish national vaccination schedule (Program Szczepień Ochronnych, PSO) for 2013 (42) entails the administration of a vaccine with an acellular pertussis component (DTPa) and a pneumococcal conjugate vaccine after 6 weeks of age. The prophylaxis that is offered as part of free health care therefore requires administering four injections during the first appointment. In addition, a PSO regulation concerning the prevention of HBV infections was changed in 2013. It was recommended that children with a birth weight of less than 2,000 g should be immunized with a monovalent vaccine, according to the 0-1-2-12 month schedule, i.e. as per the registration data concerning the use of such preparations. As a consequence of these changes, it has become extremely important to discuss the realization of the vaccination schedule with the parents of children with extremely low birth weight who are bound for a prolonged hospitalization lasting several weeks. The adoption of the afore-mentioned cocoon strategy at this stage and reducing the number of required injections to a minimum by using hexavalent vaccines makes it possible to avoid the second dose of the HBV vaccine. In our opinion this is important, since the administration of the second dose of the HBV vaccine precludes the use of a hexavalent vaccine.

In the case of preterm infants it is difficult according to our experience to set the date of the first visit at the office of a pediatrician or a primary care physician. The child's hospital discharge summary received in the neonatal ward should include information about the recommended date of the next appointment, during which the child is to be immunized. The date is set depending on the age of the infant at the time of discharge, the number of doses of the HBV vaccine administered during the hospitalization, and the time elapsed from the last vaccination.

The child may receive the first dose of the hexavalent vaccine in the neonatal ward after reaching an age of six weeks, but not before at least four weeks have elapsed from the administration of the first dose of the HBV vaccine. The second dose of the hexavalent vaccine may be administered at the primary care physician's office (in accordance with the vaccination schedule), four to eight weeks after the first immunization.

It is important to pay due attention to the prevention of rotavirus infections; at the time of the first visit at the primary care physician's office the child's age may exceed 12 weeks, i.e. the deadline for the administration of the first dose of the rotavirus vaccine. For this reason the immunization of preterm infants with rotavirus vaccines should be commenced upon discharge, or during the first few days at home.

Technical issues connected with vaccination concern not only preterm infants with extremely low birth weight, but all prematurely born neonates weighing less than 2,500 g. During the first appointment, which involves vaccination (six to eight weeks of age), the body mass of such children does not generally exceed 4,000 g. Consequently, it may be difficult to administer two injections into the anterolateral aspect of the thigh (vaccines: HBV, DTPa, Hib, PNC) at one visit. There are two ways of solving this problem. The vaccination may either be performed during two separate visits, with the second one taking place within two weeks of the initial one, or a polyvalent vaccine may be used instead, reducing the number of required visits and injections (3 visits, each with 2 injections).

CONCLUSIONS

The results of the cited studies indicate that – when administered as appropriate for the child's chronological age – polyvalent vaccines provide a sufficient level of protection against infection with *Corynebacterium diphtheriae*, *Clostridium tetani*, and poliovirus. At this time there is no consensus on whether a full cycle of primary immunization provides protective levels of antibodies against pertussis toxin and HBV antigens. It is very likely that primary vaccination is also insufficient to provide

full protection against Hib antigens in the case of preterm infants. The fourth (booster) dose, administered six months after the third dose of the primary vaccination, is therefore particularly important. This dose should be administered by 18 months of age. In view of the quoted data, preterm birth does not appear to be inherently associated with an increased risk of adverse effects after the administration of polyvalent vaccines. It is nevertheless recommended that this group of neonates should receive vaccines that contain an acellular pertussis component.

Based on the presented review of literature data, we suggest the following recommendations concerning the use of polyvalent vaccines in preterm infants and children with low birth weight:

1. Due to sufficient immunogenicity, polyvalent vaccines should be administered to preterm infants in accordance with their chronological age.
2. Receiving a booster dose after 12 months of age is essential for the development of complete and persistent immunity against all vaccine antigens.
3. To reduce the risk of adverse effects after the administration of polyvalent vaccines, the condition of the child patient's circulatory and respiratory systems and any related medical history should be evaluated with due care during the pre-vaccination examination. In such cases the administration of the first dose in a hospital setting should be considered.

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