



## REVIEW PAPER

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# Safety and efficacy of vaccinations in patients from high-risk groups: new challenges in the era of vaccine hesitancy

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## ABSTRACT

**Introduction.** Vaccinations are one of the most effective medical interventions that protect people against infectious diseases. It should be noted that a new vaccine licensing is always preceded by clinical trials assessing its safety and efficacy. Anti-vaccine propaganda carried out by vaccination opponents has become an international problem with a global reach.

**Aim.** To review the literature on vaccinations of patients from high-risk groups.

**Material and methods.** A literature review of the following databases has been conducted: EBSCO, PubMed, Science Direct, and Springer Link.

**Results.** High-risk groups in the paediatric population include pre-term born infants, patients after stem cell transplantations, children with allergies and other chronic diseases. Vaccinations in the examined groups are generally safe and are an effective method of preventing infections.

**Conclusion.** At a time when the level of vaccine skepticism is high and the epidemiological situation of many diseases is unstable, patients who are more susceptible to infection are particularly endangered. High level of knowledge of health care professionals and their personal positive attitude towards vaccinations are important for improving the vaccination coverage rates. In the light of measles epidemic outbreaks and an almost geometric increase in the number of pertussis cases noted recently, actions are needed to achieve herd immunity.

**Keywords.** allergy, immunogenicity, preterm, safety, transplantation, vaccination, vaccine hesitancy

## Introduction

Vaccinations are one of the most effective medical interventions that protect people against infectious diseases. Many of these diseases posed a significant threat to health or life of children and adults just a few decades ago. Immunization procedures are considered to be expensive, and European Union member states

spend on average 3% of their health budgets on protection against infectious diseases by vaccinations. Twenty different vaccines are currently being used in vaccination schedules in Europe, and a number of further new or improved vaccines are subject to advanced clinical trials.<sup>1</sup> It should be noted that vaccine safety and efficacy is always demonstrated during clinical tri-

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als conducted under ideal conditions prior to licensing, but also after the introduction of a new vaccine. This applies to both monovalent and multivalent vaccines. In addition to the assessment of the effectiveness and safety of individual preparations, the design of national vaccination schedules is also important. It must ensure maximally simplified and safe co-administration of vaccines in order to reduce the risk of adverse events that may be caused by the interaction of simultaneously administered antigens. Nevertheless, since the very beginning the use of vaccines is accompanied by a large group of sceptics and determined opponents. With widespread and unlimited access to various, often unreliable sources of information, anti-vaccine propaganda carried out by opponents of vaccination has become an international problem with a global reach.<sup>2</sup> The false data and conclusions spread by those people or institutions are based on non-scientific argumentation. The problem manifests itself among others in an increase in the number of parents refusing to immunize their children or unjustifiably postponing the administration of vaccines. One of the most frequently attacked vaccines used in the pediatric population is the measles, mumps and rubella (MMR) vaccine. Information disseminated by vaccine opponents concern not only pediatric, but also adult population, which for example negatively influences the number of vaccinations against influenza carried out every year. In 2012 World Health Organization (WHO) together with the United Nations Children's Fund (UNICEF) established the Strategic Advisory Group of Experts (SAGE) on Vaccine Hesitancy. The purpose of this group is to recognize the reasons for vaccine hesitancy and to assess why children and adults are under-vaccinated or unvaccinated. Vaccine hesitancy results in the slowing of realization of vaccination schedules in the WHO Regions and individual countries even when the availability of appropriate vaccines is guaranteed.<sup>3</sup> The level of knowledge of health care professionals performing immunizations (doctors and nurses) and their personal attitude towards vaccinations are also important in the process of improving the rates of vaccine uptake.<sup>4</sup>

### Aim

At a time when the level of vaccine skepticism is high and the epidemiological situation of many diseases is unstable, patients who are more susceptible to infection (high risk patients) are particularly endangered. Paying attention to the consequences of poor vaccine coverage including unreasonable delay of vaccinations has been the subject of my scientific and clinical interest for many years. The importance of safe administration of individual vaccines and the need to prepare recommendations for their use should also be stressed. The aim of the present work is to briefly review the literature available in this field.

### Infectious Diseases Threats in Poland

In recent years the above-mentioned epidemiological instability concerned primarily measles. This highly contagious disease, until recently, had been the next eradication candidate after polio virus infections. A significant decrease in the incidence of measles between 2000 and 2015 (estimated at 75%) was a consequence of the introduction of routine vaccinations against this disease in a two-dose scheme. In Poland these vaccinations were started in 1975. In contrast to expectations, in 2015 an unprecedented growth in the number of measles cases was observed. WHO estimated the number of measles cases in 2015 at 9.7 million, the number of deaths from measles was estimated at over 130,000. At the same time, only 254,928 cases were reported to six regional WHO centers. This discrepancy is best illustrated by German data, where the number of measles cases reported to the mandatory notification system was three times lower compared to health insurance claim submissions by doctors.<sup>5</sup> In Poland, the number of cases of measles increased significantly at the end of 2018. Until October that year 148 cases were noted, in November 2018, 79 new cases were registered. A further 112 cases were observed in December, and eventually 339 people were diagnosed with measles in 2018 in Poland according to the official WHO report. As for 2019, as of 28/02/2019, 314 cases of this disease were reported in our country. In Poland, as in other European Union countries, measles affects mostly people who were not vaccinated against this disease (78%) or vaccinated with only one dose of MMR vaccine (16%).<sup>6</sup> Thus, in the current epidemiological situation, a significant increase in the number of people avoiding immunizations or refusing to have their children vaccinated is particularly alarming. The number of patients refusing vaccinations in Poland has increased more than ten-fold between 2010 and 2018 from 3,437 to 40,342 respectively.<sup>7</sup> This phenomenon is a direct threat to population immunity, which requires vaccine coverage rate at the level of at least 90%. In some provinces, the vaccination rate in children aged 2-3 years already does not reach this limit.

For many years, very low influenza vaccine coverage rates were noted in Poland, which applies also to the patients from the risk groups. Yearly updated global recommendations suggest that 75% of the population should be vaccinated against influenza every year which, however, is achieved only in a few countries. In Poland, in the age group above 50 years, less than 10% of people are vaccinated, and the total vaccine coverage in the 2016/2017 season has reached only 3.3%. Meanwhile, in the same season, over 2.5 million flu cases were registered in Poland in the group aged 0-14 years (over 5 million in the entire population), with approximately 10,000 hospitalizations and 48 deaths due to this disease.<sup>8</sup>

Recently a significant increase in the number of pertussis cases was also observed in Poland. A constant, almost geometric increase of incidence of this disease is noted in epidemiological reports of the National Institute of Public Health - National Institute of Hygiene in Warsaw. In 2014, 2,102 cases of pertussis were reported in Poland (incidence 5.46/100,000), in the following year this number has grown to 4,959 cases (incidence 12.89/100,000). In 2016, an increase by over 138% was reported (6,856 cases of pertussis, incidence 17.84/100,000). In these years the number of pertussis cases has grown almost fourfold (390%). Infectious diseases including pertussis are a significant threat to health and even to lives of infants. Pertussis infections are particularly dangerous to pre-term born children, including those with extremely low birth weight (ELBW) who are especially susceptible to infectious diseases. This is why early initiation of active prevention of infectious diseases (according to the chronological age of these children) is of great importance.<sup>9</sup> But epidemiological data show that vaccinations (also against pertussis) in the group of ELBW infants are started with a delay, which is associated with an increased risk of diseases that can be prevented in many cases.<sup>10</sup> Epidemiological data show that infants are particularly prone to bacterial or viral infections. Acute symptoms occurring in this age group usually require hospitalization and antibiotic therapy.<sup>11</sup> Pre-term born infants have a higher risk of hospitalization in the clinical course of pertussis compared to full term infants with normal body weight.<sup>12</sup> In addition to the immediate risk to health or life of a child, one should not forget about various complications of infectious diseases that can cause damage or permanent dysfunction of the nervous, circulatory, respiratory and muscular systems.<sup>13,14</sup>

### **Vaccinations in high-risk groups - pre-term born infants**

In 2008, as a first in Poland, together with my colleagues from The Clinic of Neonatology at the Collegium Medicum of the Jagiellonian University, we proposed early vaccination of ELBW (<1000 g) infants born before 32 weeks of pregnancy. We postulated immunization of these children before their discharge, in the clinical setting.<sup>15</sup> This resulted from the observed unjustified delay in starting vaccinations in outpatient clinics after discharge from the neonatal intensive care units. Our proposal was based on studies of the American Academy of Pediatrics recommending starting vaccinations of pre-term infants during hospitalization in neonatal wards.<sup>16</sup> Three years later – in 2011, I participated in the work of the Polish Expert Group, which issued recommendations concerning the vaccination of pre-term born infants in neonatal units. This recommendation was included in the Polish Vaccination Schedule for 2012.

Thanks to these recommendations, it became possible to vaccinate pre-term born infants against diphtheria, tetanus, pertussis, poliomyelitis, Haemophilus influenzae type b and pneumococcal infections in addition to standard hepatitis B and tuberculosis vaccinations before their discharge from the neonatal intensive care units.<sup>17</sup> Despite the fact of developing the abovementioned recommendations a significant delay of vaccinations conducted by GPs after hospitalization is still observed in this group of patients. On the other hand only half of Polish neonatal units began administration of DTPa, IPV, Hib and PVC vaccines in pre-term infants in the clinical setting. It should be noted that the average duration of hospitalization of a pre-term born infant in Poland is 72 days.<sup>18</sup> Our own research shows that only 13% of 109 infants hospitalized between 2009 and 2014 in the Clinic of Neonatology at the University Hospital in Kraków ( gestational age at birth 22-30 weeks, mean weight 953.4 g.) received the DTPa vaccine in accordance with the national vaccination schedule. Delays in the administration of vaccines in the studied group most often resulted from the unstable clinical condition of the patients. Despite a longer stay at the hospital, which was associated with various issues in the perinatal stage, the administration of the first dose of the DTPa vaccine took place sooner in the hospital setting than in the outpatient clinics (80 vs. 153.4 days).

In the analyzed group of patients vaccinated in the neonatological clinic 73.7% of children received a multivalent vaccine DTPa-IPV-Hib-HBV, which significantly improved the implementation of vaccinations, compared to children receiving vaccines purchased by the state. The use of standard vaccines used for mandatory vaccinations increases the number of required injections.

The assessment of the response to primary immunizations against hepatitis B, diphtheria, tetanus, pertussis in the group of ELBW infants showed the achievement of antibody concentration sufficient to provide adequate protection. The results of safety assessment were also positive – infants in the study group did not develop any adverse symptoms such as bradycardia, apnea, or drops in saturation.<sup>19,20</sup> Vaccinations in the risk group of pre-term born infants are not a frequent subject of prospective studies with a control group. During one of three multicenter clinical trials, carried out in 2015 in our clinic, the safety and efficacy of a conjugate vaccine against pneumococcal infections was assessed. The results obtained confirmed full safety and optimal efficacy of PCV13 vaccine in the group of pre-term born children. In the study conclusions the importance of protection against pneumococcal infections in this risk-group was emphasized together with the need of implementation of these vaccinations without delays.<sup>21,22</sup>

### Vaccinations in high-risk groups – children with allergic diseases

Children with allergic diseases are often vaccinated with significant delays. In my everyday practice in the vaccination outpatient clinic in Kraków, the most frequent reason for consultations of patients with allergies is egg protein allergy. Parents of children allergic to egg proteins are afraid of allergic reactions after measles, mumps and rubella MMR vaccine administration. In view of the epidemiological situation outlined above, postponing the administration of the first dose of MMR vaccine should be qualified as a medical error. Since 2012, the recommendations of the American Academy of Pediatrics and the British recommendations indicate that MMR vaccine should be administered to children with an allergy to egg proteins in an outpatient setting, without special precautions. These recommendations have been fully approved by the World Allergy Organization since 2016. The analysis of a group of 138 patients with allergies consulted in our clinic because of the MMR vaccine administration postponement showed that in 101 cases (73.2%). The reason for immunization postponing was an allergy to hen egg protein. In this group the average delay in performing these vaccinations has reached 12.3 months. Vaccinations performed in our outpatient clinic, extended period of observation after the vaccine administration, as well as monitoring of the post-vaccination period demonstrated full safety MMR vaccination in the study group. There was no need for conducting any additional medical consultations or interventions.<sup>23</sup>

### Vaccinations in high-risk groups - children after bone marrow stem cell transplantation

Attention should be paid to the particular importance of vaccination in reducing the risk of infectious diseases among patients in the early post-transplant period. In 2007-2010 in our Clinic we carried out medical qualification and vaccinations of children and adolescents referred to us by the Center for Transplantation of the Children's University Hospital in Kraków after autologous and allogeneic hematopoietic stem cell transplantations. In our hospital, we evaluated the seroprotection of 38 patients both before and after vaccination against diphtheria, tetanus, *Haemophilus influenzae* type b and against hepatitis B (HBV). The results of observation of these patients confirmed the efficacy and safety of performed vaccinations.<sup>24,25</sup>

The heterogeneity of this group is important to note, being the result of different indications for transplantation and various courses of the period after the transplantation.

For the aforementioned reasons, despite the recommendations to start immunization as soon as possible (3-6 months after autologous transplantation and 6-12

months after allogeneic transplantation), only a few patients started vaccinations according to the study protocol. The average time of the vaccination after auto-HSCT was 29 months (6-67 months) and 13 months after allo-HSCT (8-33 months). Parents of the patients even after being informed about the importance of the prevention of infectious diseases for their children's health both in the transplantation center and at the vaccination outpatient clinic were not fully convinced. It was due to some information of unknown origin that reached them from other, external sources and undermined their trust in vaccination of their children. As a result, five children did not receive the prescribed vaccines. Vaccinations were carried out in accordance with the European Group for Blood and Marrow Transplantation guidelines, which resulted from the lack of appropriate national recommendations.<sup>26,27</sup>

### Vaccination safety

In each group of patients with an increased risk of developing infectious diseases vaccination recommendations include vaccination against measles, mumps and rubella (MMR) and against varicella (VZV). Immunosuppressed patients should always meet the conditions for the safe use of live vaccines prior to the vaccine administration. In order to maximally simplify the implementation of vaccination schedules and to ensure on-time vaccine administration, multi-component preparations for the pediatric population are created. Preparations created for this purpose are the 6-component DTPa-IPV-Hib-HBV vaccine and the 4-component vaccine against measles, mumps, rubella and chickenpox MMRV.

In view of high incidence of varicella in many countries with simultaneous occurrence of measles epidemic outbreaks concomitant use of two doses of MMR and VZV vaccine is required.<sup>24</sup> To simplify the vaccination schedule and to shorten the time of achieving protection MMRV vaccine was developed.<sup>25</sup> The safety analysis of its application, based on 8 clinical trials, showed that the administration of the first dose of MMRV, compared to separate administration of MMR and VZV vaccines, results in statistically more frequent occurrence of elevated body temperature within 15 days after MMRV administration.<sup>28</sup> This difference was not observed when MMRV vaccine was used as the second dose. These results led to conclusions and recommendations that the MMRV vaccine should be used as a second dose after first administering MMR and VZV vaccines separately.<sup>29-32</sup>

The safety of vaccinations is a priority task when creating vaccination schedules, but also during their implementation. The medical qualification for vaccination of patients who have previously had an adverse event after vaccine administration is a particular chal-

lenge. At the beginning of the 21st century, the lower percentage of infants received diphtheria, tetanus and pertussis (DTP) vaccine with acellular pertussis component. More frequent cases of hypotonic-hyporeactive syndrome (HHE) after vaccination with a full cellular component of pertussis were noted at that time. A group of 49 infants with a confirmed onset of HHE syndrome were given a DTPa vaccine to complete the vaccination schedule. No adverse reactions were observed. A further analysis of patients history, diagnoses and referrals to the vaccination outpatient clinic revealed poor level of knowledge concerning HHE as an adverse post-vaccination reaction among pediatricians as well as GPs.<sup>33</sup>

Vaccinations belong to everyday, routine practice of general practitioners. Hence, knowledge of current recommendations, contraindications to vaccination and adverse post-vaccination reactions is necessary for the proper implementation of the vaccination schedules and building confidence in vaccination among parents of our patients. According to CBOS research from 2017, the most common reason for refusing vaccinations was the fear of adverse events caused by vaccines. Therefore, better education of parents / guardians of children and providing full, reliable information by health care professionals is necessary. Improvement in the medical staff training is also crucial to meet these expectations. It is advisable to extend education programs at the level of studies of all faculties whose graduates may have an impact on individual parents' decisions concerning vaccinations.

## Conclusions

Parents of children with chronic diseases usually have greater concerns regarding vaccinations compared with the general population. In such a case physicians should be able to explain to the parents that their child is more susceptible to infection. It is important to provide comprehensive information about the diseases that can be prevented by vaccination and about different prevention options. Such a conversation requires time, sufficient level of knowledge and communication skills.

Globally observed activity of anti-vaccine movements, vaccine hesitancy and low vaccine coverage rates may have a negative impact on the health of patients whose delays in the implementation of vaccinations result from objective medical causes. Knowledge about the scale of epidemiological threats and the effects of diseases that can be prevented by vaccination may promote the emergence of pro-health social behaviors.

Popularization of knowledge about the clinical trials assessing safety and efficacy of vaccines is one of the ways of trust-building and active vaccine hesitancy prevention.

There is a need to improve the qualifications of medical staff by highlighting the importance of vaccinations in the syllabuses of all medical faculties, whose graduates may influence patient's and caregiver's individual decisions related to vaccination.

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