Neurologic adverse events following vaccination

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ABSTRACT

The present review summarizes data on neurological adverse events following vaccination in the relation to intensity, time of onset, taking into account the immunological and non-immunological mechanisms. The authors described the physiological development of the immune system and the possible immune system responses following vaccination. Toxic property of thimerosal - a mercury-containing preservative used in some vaccines was presented. The neurological complications after vaccination were described. The role of vaccination in the natural course of infectious diseases and the current immunizations schedule in Poland was discussed.

Key words: vaccination, neurologic adverse events following vaccination, immunization schedules

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INTRODUCTION

Adverse reactions

In developed countries, the schedules of mandatory and recommended vaccination for children contain more and more components with a specific emphasis on the co-administration of multiple antigens in combined form. This direction on the one hand provides many benefits and on the other carries an increased risk of side effects, the immunopathogenesis of which is not fully explained in many cases [1].

An adverse event following immunization (AEFI) is an undesirable side effect occurring after the administration of a vaccine [2]. It is a temporary, local or general reaction of the organism to an administered vaccine. A postvaccinal complication (PC) is associated with an excessive or pathological reaction with the characteristics of postvaccinal disease, which in extreme cases can lead to permanent damage, threat to life or even death [3]. Complications affecting the nervous system raise the most controversy; the more so, as the children subjected to vaccination are healthy.

In annex no. 1 to the Ordinance of the Minister of Health of 23rd December 2002 on adverse events following vaccination (Journal of Law from 31/12/2002, no. 241, item 2097, as amended. Journal of Law from 2005, no. 232, item 1973), the following categories of AEFI are presented [4].

1) Local reactions, including:
a) local reactions after the BCG vaccine,
b) swelling,
c) lymphadenopathy,
d) abscess at the injection site;
2) Postvaccinal adverse events of the central nervous system:
a) encephalopathy,
b) febrile convulsions,
c) non-febrile convulsions,
d) paralytic *poliomyelitis* caused by vaccine virus,
e) encephalitis,
f) meningitis,
g) Guillain – Barre syndrome;
3) Other adverse events following immunization:
a) joint pain,
b) hypotonic-hyporesponsive episode
c) fever above 39^0C
d) thrombocytopenia,
e) continuous inconsolable crying.

Other classifications of postvaccinal reactions can be found in the literature, some of which put an emphasis on the neurological symptoms, while others emphasize the immunological mechanisms.

Byers et al. describing neurological complications, have included as "minor" - mild or severe postvaccinal reactions, occurring up to 48 hours after injection and disappearing without leaving permanent sequelae, the following: prolonged crying, restlessness and hyperactivity, apathy with increased sleepiness, high body temperature, a temporary mild increase in intracranial pressure manifested by a throbbing crown of the head, "cerebral cry" (sometimes included among "major" complications) [5-7].

Among the "major" neurological complications, usually manifesting more than 48 hours after vaccination and which might be the cause of permanent damage to the central nervous system (CNS), the following are listed: seizures - especially if there is no increase in body temperature, hypotonic-hyporesponsive episodes, postvaccinal encephalitis, postvaccinal encephalopathy [6, 8-11] and autism [10, 12-14].

Konior and Strózik [7] have proposed their own classification of postvaccinal reactions taking into account the contribution of the immune system in the vaccinated children. They divided the adverse events into two groups:

1. related to the immune system - patients with immunodeficiencies (mainly cellular) and atopic patients with hypersensitivity to certain vaccine components
2. unrelated to the immune system - patients whose postvaccinal reactions may be related to the toxic effects of the vaccine components or may result from the vaccine virus turning virulent, resulting in complete or abortive symptoms of the disease.

Another classification of adverse events following vaccination distinguishes:

- Local postvaccinal reactions (redness, swelling, pain at the injection site) occurring particularly often after the administration of live vaccines (10.8% -15.5% of reports) [15]
- Generalized postvaccinal reactions (fever, malaise, muscle pain, joint pain, headaches, flu-like symptoms, local lymphadenopathy, allergic reactions) - usually disappear spontaneously within 3 days of vaccination, do not require treatment [16].
- Early postvaccinal complications – anaphylactic reaction, described in one in about 1 million of vaccinated individuals, occurs most often after immunization against typhoid, tetanus, pertussis, measles, mumps, rubella [16].
- Late and long-term complications - determined by different immunological mechanisms, occur most often after the administration of preparations containing live micro-organisms (e.g., flaccid paralysis after an oral poliovirus vaccine OPV - 10 individuals annually per 1 million people vaccinated) [16].

Reports in many Polish and foreign medical journals lead us to conclude that postvaccinal complications among children can be observed in sporadic cases and that they are disproportionate to the benefits of vaccination in the elimination of dangerous diseases in childhood. This article focuses on several aspects related to overall immunization, including: the physiological development of the immune system, the possible immune system responses following vaccination, the site of vaccination in the natural course of infectious diseases and the current immunization schedule in Poland compared with other countries.

The immune system in terms of vaccination

Physiology

Immune system functioning in neonates is characterized by complex mechanisms to adapt to the changed conditions of postnatal life. In infancy and early childhood, the individual components of specific and nonspecific immunity gradually develop and mature [17].

The humoral immunity of neonates is acquired and is associated with active transport of maternal immunoglobulin G through the placenta (starting from the end of the first trimester of pregnancy) mainly in the last 5-6 weeks of pregnancy. A neonate's humoral response is therefore a state of physiological dysimmuno-globulinemia, i.e. it has an average concentration of its own IgG, minimal or low concentrations of IgA, IgM, IgE, IgD [13, 14]. The level of maternal IgG gradually decreases, while the level of the child's IgG increases reaching approximately 60% of the adult level after 12 months. In the 2-3 month of life, an intersection of curves takes place - the declining curve of maternal IgG concentration and the increasing curve of infant IgG concentration (graph). The infant's IgG level is the lowest then (Fig.1) [18].

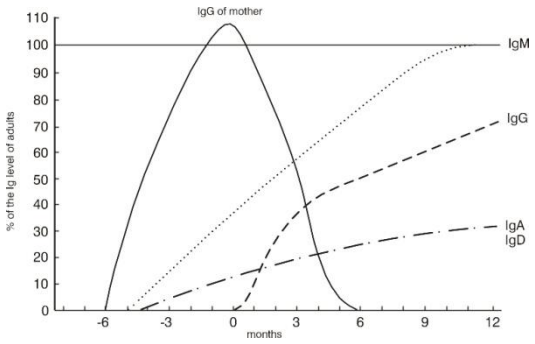


Fig. 1. Levels of antibodies in the blood serum of the fetus, neonate and infant [18]

From a physiological point of view, according to Jakóbisiak's [18] classification, the group of secondary immunodeficiency disorders includes conditions such as pregnancy and conditions associated with age (neonates, the elderly). Premature babies are a specific group, whose shortened period of maternal IgG influx leads to compromised anti-infective immunity.

On the other hand, according to the author, on account of the existing maternal antibodies, vaccination against certain microorganisms administered shortly after birth does not lead to long-lasting immunity. It should be emphasized that the immune system reaches full immunoregulatory and defensive maturity at about 3 years of age [19].

It is well established that early-life immune responses are weaker and of shorter duration than elicited in immunologically mature hosts. Consequently, vaccine efficacy in early infancy (particularly in the first 6 months of age) is limited [20]. Thus, in oder to provoke and sustain an adequate B-cell immune response in a neonate, strong immune adjuvants and repeated closely spaced booster doses are needed [21]. The problem with this approach is two-fold. First, experimental evidence clearly shows, that simultaneous administration of as little as two to three immune adjuvants, or repeated stimulation of the immune system by the same antigen can overcome genetic resistance to autoimmunity [22].

Second,while it is generally accepted that potency and toxicity of immune adjuvants must be adequately balanced so that the necessary immune stimulation is achived with minimal side effects, in practical terms, such a balance is very difficult to achieve. This is because the same adjuvanted-mediated mrchanisms which drive to the immune-stimulatory effects of vaccines have the capacity to provoke a variety of adverse reactions [23, 24]

Vaccinations and immune response

A vaccine is defined as a biological preparation containing antigen(s) of micro-organisms that cause specific stimulation of the immune response after administration which protects against infection by this microorganism, with safety precautions taken during administration [18, 25]. A vaccine may contain:

1. Microorganism antigens - bacterial or viral (live-attenuated, dead), isolated antigens - proteins, polysaccharides, DNA and anatoxins (diphtheria, tetanus) with retained immune-genicity but devoid of pathogenic properties,
2. Suspension: water, physiological saline, substrate protein, e.g. egg white, gelatin,
3. Preservatives: thiomerosal (mercury), anti-biotics, phenol,
4. Adjuvants, the aim of which is to enhance the immunogenicity of the vaccine - aluminum hydroxide or aluminum phosphate are the most commonly used.

According to the literature [18], it is believed that vaccines containing live micro-organisms are among the most effective means of inducing immunity against infectious disease. Attenuated microorganisms (viruses, BCG myco-bacteria) retain the ability to replicate in host cells, which stimulates cytotoxic T lymphocytes (Tc, CD8 +) that destroy cells infected by them. The way of impact of isolated antigens or antigens derived from whole inactivated microorganisms is different. In this case, a stimulation of the auxiliary Th (CD4+) lymphocyte response takes place. Th lymphocytes contain two distinct - in functional terms - subpopulations: Th1 and Th2. According to Jakóbisiak - with some simplification - it can be assumed that the Th1 lymphocytes perform auxiliary functions in cell-type response and Th2 in humoral response [18].

The mechanism of immune response to various types of vaccine antigens, especially to antigens in multicomponent vaccines, is not fully understood and researched. Figure 2 shows the hypothetical effect of vaccines and their additional components on the immunological balance of children.

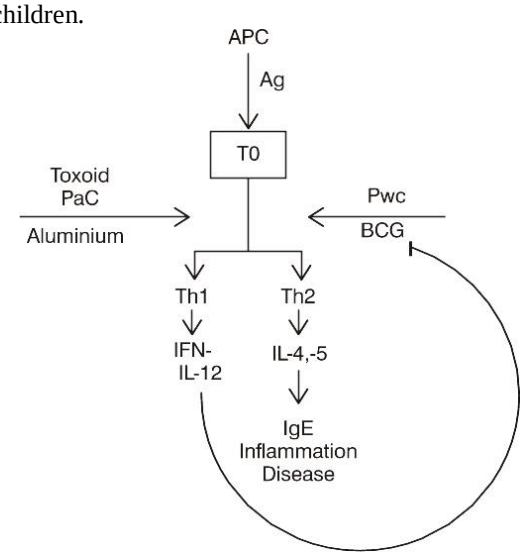


Fig. 2. Hypothetical effect of vaccines and their additional components on the immunological balance of children [25]
PaC – acellular pertussis used in most countries;
PwC – whole cell pertussis, more frequently used in Poland, APC – antigen-presenting cell; Ag – antigen; (Source: [25] Willak-Janc E.: Vaccination In children with allergic diseases. Alergia Astma Immunol 2003, 8, 3: 107-9; with permission MEDITON)

The vaccination-stimulated Th2 pathway responsible for the production of antibodies, the pathway which predominates in neonates and infants, in the absence of an adequate balance of Th1 response may lead to the development of allergic reactions [25]. This is symptomatic of the fact that allergic diseases are often referred to as "an epidemic of the XXI century" [26, 27]. As stated in the "European Allergy White Paper", the clinical symptoms of allergy are present in 35% of the population of developed countries, and according to the ISAAC (The International Study of Asthma and Allergies in Childhood) as many as 40%. Allergy is one of the major health problems on par with AIDS, cancer, cardiovascular diseases, injuries and accidents [28 - 30].

According to other authors, a restriction of the natural environmental infections stimulating Th1 response as well as change of their natural course resulting from mass immunization, an increase in general hygiene and widespread use of antibiotics ("Hygiene Theory") inhibiting and delaying the adjustment of Th2/Th1 could theoretically also contribute to the growth of the risk of allergic diseases [31, 32]. A confirmation of this thesis was the study of Swiss children from anthroposoic backgrounds, in which significantly less atopy was observed than in children from other backgrounds. In this group, a positive correlation of diseases with the MMR vaccination was found [33].

In addition, in a series of papers, Silverberg et al. have shown that wild type varicella zoster virus infection (WTVZV), but not varicella vaccine (VV), protects against asthma and atopic dermatitis (AD) in young children [34, 35].

The protective effect of WTVZV was attributed to its beneficial effect on stimulating Th1-primed immune responses and suppressing allergy-promoting Th2 responses. According to Silverberg et al. [34], "The introduction of widespread varicella vaccination and resultant decline of WTVZV in the United States may be a contributing factor in the increased prevalence of AD [atopic dermatitis] over the past few decades."

Notably, other than not providing an effective stimulus for proper immune system development, recent research has shown that vaccines are actually capable of disrupting it. For example, annual vaccination against influenza has been shown to hamper the development of virus-specific $CD8^+$T-cell immunity in children [36]

From the above observations it is clear that the proper functioning of the immune system involves a delicate balance between the two arms of the immune equilibrium (Th1/Th2), and its tilt to either side can be harmful for the body [30]. Furthermore, it appears that the necessary Th1/Th2 balance is better provided by natural challenges (i.e., in a form of relatively benign childhood diseases such as chickenpox and mumps) rather than vaccination.

Recent research by Singh of the Interna-tional Institute for Brain Research in the USA confirm the veracity of this statement. In the study, serum and cerebrospinal fluid (CSF) were analyzed in terms of viral and autoimmune markers in

patients with autism compared with a group of healthy children - both groups were vaccinated with MMR (measles, mumps, rubella vaccine) [37].

This is the first of this type of research examining a positive correlation between viral factors (viral serology) and autoimmune factors (brain autoantibodies). It was found that higher levels of measles antibodies were accompanied by Myelin Basic Protein (MBP) autoantibodies in children with autism (Figure.3). A similar serology was found in CSF.

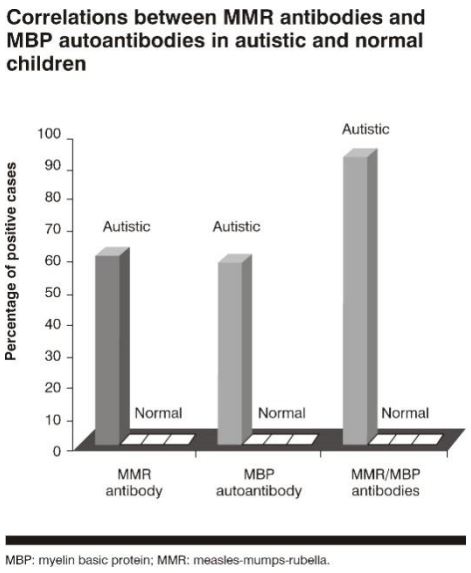


Fig. 3. Correlations between MMR antibodies and MBP autoantibodies in autistic and healthy children. (Source: [37] Singh VK. Phenotypic expression of autoimmune autistic disorder (AAD): A major subset of autism. Annals of Clinical Psychiatry, 2009, 21, 3,148-161; with permission: Healthy Impressions)

The results in Table 1 show a comparative study of antibodies against other viral pathogens in the studied population of children which confirmed the pathogenic role of the measles strain.

Table 1. Blood serum levels of antiviral antibodies in healthy and autistic children

Virus antibody (units)	Measles	Mumps	Rubella	HHV-6	CMV	EBV		
						EA	EBNA	VCA
Normal children	3.3±0.1	2.5±0.2	3.2±0.2	1.6±0.6	0.28±0.4	0.5±0.04	1.2±0.2	1.8±0.3
	(n=32)	(n=30)	(n=45)	(n=37)	(n=30)	(n=44)	(n=44)	(n=44)
Autistic children	4.2±0.1*	2.6±0.3	3.3±0.1	2.2±5.3	0.23+0.3	0.6±0.04	0.9±0.2	1.4±0.2
	(n=87)	(n=32)	(n=74)	(n=45)	(n=30)	(n=44)	(n=44)	(n=44)
p value	.003*	.76	.98	.5	.37	.76	.21	.15

(Source: [37] Singh VK. Phenotypic expression of autoimmune autistic disorder (AAD): A major subset of autism. Annals of Clinical Psychiatry, 2009, 21, 3,148-161; with permission: Healthy Impressions)

CMV: cytornegalovirus; EA: early antigen; EBNA: Epstein-Barr nuclear antigen; EBV: Epstein-Barr virus; HHV-6: human herpesvirus-6; VCA: viral capsid antigen; *Student t test was used to evaluate significance at a p value < 0.05

Significantly elevated levels of cytokines - IL-2, IL-12, IFN-γ (factors triggering autoimmune response) - and acute phase proteins were also found in patients [37].

Figure 4 shows a model of the development of autoimmune response as a result of viral infection, which is associated with the activation of Th1 cells and the production of interferon-γ - the only natural molecule able to change the permeability of the blood-brain barrier [37].

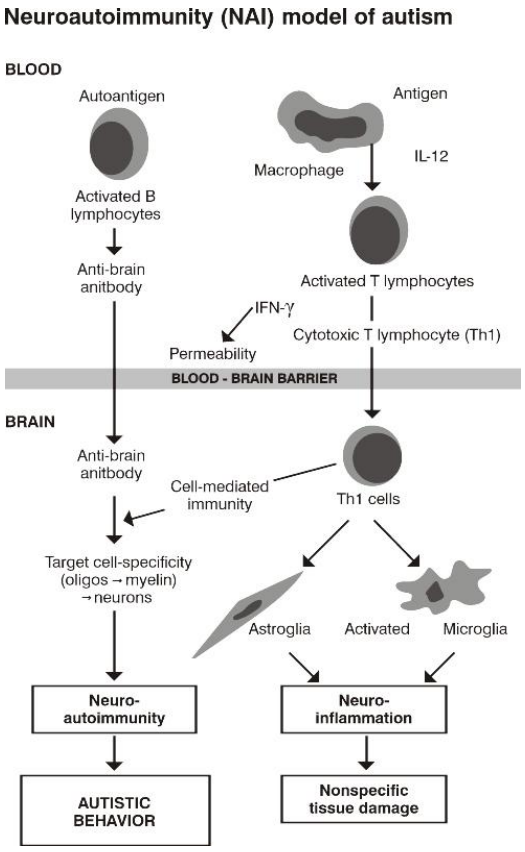


Fig. 4. Neuroautoimmunity (NAI) model of autism.

(Source: [37] Singh VK. Phenotypic expression of autoimmune autistic disorder (AAD): A major subset of autism. Annals of Clinical Psychiatry, 2009, 21, 3, 148-161; with permission: Healthy Impressions)

According to the authors of this study, subtle changes in the child's developing brain caused by an autoimmune reaction, changes in the myelin sheath, may ultimately lead to impairment

of higher brain functions such as speech, communication, social interaction, as well as other neurological symptoms occurring in children with autism. In this study, the measles viruses were researched, but under the immunization program children also receive vaccinations with simultaneous administration of several viral components. What then occurs in the brain of a child? Presently, there are no studies in this area.

In an earlier study concerning post-vaccinal adverse events of the immune system, Mannhalter et al. [38] presented an analysis of T lymphocyte (Th1/Th2) subpopulations in healthy adults before and after the administration of a vaccine containing the tetanus toxin. The result was a decrease in the Th1/Th2 ratio after vaccination, with maximum intensity 3 to 14 days after injection.

These reports present a picture of neuroimmune disorders which may be the result of vaccinations carried out on an increasingly wider scale. A clear answer to this hypothesis would require both large-scale epidemiological studies as well as in-depth laboratory research.

In Poland, multi-antigen combination vaccines are commonly administered at full cost with parental consent. Most often children are immunized at the same time with: diphtheria and tetanus toxoid, acellular pertussis antigen, polio and H.influenzae (Infanrix-IPV+Hib, Pentaxim vaccines) or with an additional antigen of hepatitis B virus (Infanrix hexa vaccine). These vaccinations are repeated from the second month of life 3 times every 6-8 weeks. The recommended vaccinations against rotavirus and pneumococcal (2-3 doses) are also proposed to children under 6 months of age. Together with the tuberculosis and hepatitis B vaccinations administered in the first 24h of life, an infant receives 24-26 doses of xenogenic antigens. According to Tsumiyama et al. [39] systemic autoimmunity appears to be the inevitable consequence of over-stimulating the host's immune 'system' by repeated immunization with antigen. Indeed, in adults multiple vaccinations have been associated with a variety of autoimmune phenolmena [40 - 42], yet children are regularly exposed to a much higher burden of vaccines than adults under the assumption that such exposures are safe [43] .

Vaccinations as an important "training" for the immune system lower its threshold of defense responses, which is a measure to prevent the development of infectious diseases. However, a question arises: how will the not fully mature, still developing immune system of a healthy child and the still forming central nervous system respond to such intense stimulation? Is it able to correctly respond with the same protective effect to so many different stimuli? Do the multi-antigen vaccine side effects change compared to the previously used vaccinations and how?

Thus far, these questions lack clear answers. Nonetheless, it is important to emphasize that a burgeoning body of evidence shows that immune molecules play integral roles in CNS development, affecting processes such as neurogenesis, neuronal migration, axon guidance, synaptic connectivity and synaptic plasticity [44 - 46]. Despite the dogma that peripheral immune responses do not affect CNS function, substantial evidence points exactly to the contrary [44, 47, 48].

Thus, it is not reasonable to assume that manipulation of the immune system through an increasing number of vaccinations during critical periods of brain development will not result in adverse neurodevelopmental outcomes [43, 49]

Neurological symptoms following vaccination

In recent years, attention has been brought to the mercury contained in vaccines as a component with toxic and allergic properties. The mercury compound is found in organic combinations in the form of sodium salt - thimerosal (sodium ethylmercuriothiosalicylate, merthiolate). The incidence of allergy to this compound is variously estimated from 13% in the Netherlands to 21% in Austria. Vaccinations are a primary cause of the initial allergic reactions to thimerosal [50]. Mercury's neurotoxicity (accumulation in the brain), cardiotoxicity, hepatotoxicity, nephrotoxicity, immunotoxicity, and carcinogenicity are mentioned as its toxic activity. It causes, among others, developmental disorders in children and neurodegenerative diseases in adults [7]. According to researchers [51, 52], a manifold incidence increase of psychoneurological diseases such as autism, ADHD, mental retardation, epilepsy and others have been observed all over the world over the past twenty years. As stated, from the 1990s new vaccines for infants containing thimerosal began to be used in America. In the DTP, Hib and Hep B vaccines, children received a dose of 62.5 ug of mercury, which is 125-fold more than the dose considered safe (0.1ug/kg/day). These reports were the reason that Scandinavian countries already prohibited the use of mercury in 1990 [53].

In 2005, a paper was published which describes the sudden death (SUD - Sudden Unexpected Death) of 19 infants within a few hours/days after vaccination with two hexavalent vaccines (DTP-Hib-HepB-IPV). The healthy prior to vaccination children died as a result of postvaccinal cerebral and lung edema and heart attacks. As the authors conclude, despite the lack of direct evidence for a causal relationship of the described SUDs with vaccination, it is a signal that brings to attention the need to monitor the course of vaccination and its complications [54].

In another study from 2004, Geier et al. [12] confirmed through epidemiological research the direct relationship between increasing doses of thimerosal and the incidence of autism in children in the US from the late 1980s through the mid-1990s. In addition, there was a potential correlation between the number of primary pediatric measles-containing vaccines (MMR) administered and the prevalence of autism during the 1980s. Geier et al. [12] also found a statistically significant odds ratios for the development of autism following increasing doses of mercury from thimerosal-containing vaccines (birth cohorts: 1985 and 1990-1995) in comparison to a baseline measurement (birth cohort: 1984). The contribution of thimerosal from childhood vaccines (>50% effect) was greater than that of the MMR vaccine on the prevalence of autism observed in the study.

In Poland, according to the documents "Characteristics of Pharmaceuticals", there are currently several permitted vaccines with significant thimerosal (THIM) content. These are: Euvax (Hepatitis B, LG Life Sciences, Korean manufacture) - 0.01% THIM-50μg/dose, DT (Biomed, Krakow) - 50μg/dose, Td (Biomed, Krakow) - 50μg/dose, DTP (Biomed, Krakow) - 50μg/dose, D,d (Biomed, Krakow) - 50μg/dose, TT (Biomed, Krakow) - 50μg/dose [4, 55].

The frequency of observed reactions and complications depend on the general condition, especially neurological, of the child, the age, immunological resistance status as well as family and genetic load. In the literature, neurological symptoms are usually connected with the pertussis component of the vaccines, including: cerebral cry, according to Cody, occurs in 1:1000 of vaccinated subjects; seizures - mild, feverish - triggered by the pertussis endotoxin, in 10% of vaccinated subjects the convulsions occur without elevated body temperature, and severe seizures occur according to Waller et al. in 1 in 106,000 children [25]. In serious complications, such as encephalitis (about 2.9/10,000,00 of those vaccinated with DTP), encephalopathy (1:140,000 - 1:300,000 of the vaccinated), which may result in mental retardation, recurrent seizures, epilepsy - particularly myoclonic and Lennox-Gastaut Syndrome, changes in the central nervous system comparable to those which occur in the course of meningitis and encephalitis were reported. In the early stages, perivascular lymphocytic infiltration and demyelination outbreaks were observed, then myelin atrophy with intact neuron axial fiber, degenerated microglia and macrophage cells. Some experimental studies suggest the pertussis toxin, which through the membrane receptors causes inhibitory neurotransmitter dysfunction and induces activity of excitatory neurotransmitters [56, 57].

In 2010, a case of a 6-month-old previously healthy boy admitted to hospital on day 6 after vaccination with DTwP (whole cell) was described. The child was in a coma, hypotonia, with focal clonic seizures. MRI of the central nervous system using proton spectroscopy revealed acute necrotizing encephalopathy [58]. Previously, epileptic seizures in children with asymptomatic CMV infection which occurred after vaccination with DTwP and OPV had also been described. In the case of hepatitis C virus (HCV) infection, DTaP (acellular) and IPV (inactivated) vaccinations are recommended [59]. As stated in the Polish literature, acellular vaccines are much better tolerated than whole cell - the risk of fever after the first dose is reduced by over 99%, the risk of hypotonic-hyporesponsive episodes by 56%, similar to seizures, and the risk of inconsolable crying after the first dose is reduced by 87% [4].

According to the current vaccination schedule in Poland, infants receive the first three doses of DTwP in the first 6-8 weeks of life every 6-8 weeks, the 4th dose in the 16th-18th month of life, and a DTaP booster at 6 years of age. Given the often reported neurological complications after whole-cell pertussis (DTwP, DTP) vaccine, most developed countries - European and the US - have introduced changes in their immunization schedules and the safer acellular (DTaP) vaccines are administered to children. Of these countries, the only exceptions are: Bulgaria, Malta and Poland. In Poland, the safe vaccine is paid in full.

Other neurological complications associated with the administered vaccination are listed, among others, as follows: multiple sclerosis after hepatitis B vaccine [60], Guillain-Barre syndrome - after vaccination against influenza, hepatitis, meningitis C, polio and HPV vaccines [61-65], transverse myelitis as a result of vaccination against cholera, typhoid, polio, and influenza, flaccid paralysis, meningitis, encephalitis, convulsions and facial palsy after live polio vaccine [65, 66], rapid progression of retinopathy in premature infants after BCG vaccination [67].

Monitoring

In the case of AEFI, the obligation of notification was described in article 21 of the Preventing and fighting infections and infectious diseases in humans Act. According to the Act, a physician who recognizes or suspects the occurrence of AEFI is required, within 24 hours after concluding the suspicion, to notify the State Sanitary Inspector of the suspected case [3]. In order for that to be possible, the child's guardian must also be accurately informed about the adverse symptoms following vaccination that may occur, then report the problem to the doctor or nurse who will take further steps. There was an attempt to trace the actual scale of the adverse events following vaccination reported by nurses and

doctors. The monitoring system was introduced in Poland in 1996 and is based on the WHO recommendations. In the Zieliński study, the number of AEFI reported in 1996-2000 from different provinces was analyzed and clear differences regarding the frequency of recorded entries were found. As the authors write, "they met astonishing examples of ignorance of the medical staff, including specialists, in their duty to report the AEFI" in their epidemiological practice [68]. On the other hand, there is no real possibility of laboratory tests to confirm a causal relationship between the clinical picture and the used vaccine. For example, only a few research laboratories in Poland, of the highest reference level, posses the microbiological methods for distinguishing mycobacteria from the BCG vaccine from other species of the *Mycobacterium tuberculosis* strain [69]. There are also no reports in the literature (except those listed above) of research work in immunology in the context of reactions following vaccination. It should also be noted that in more developed countries, there is little incentive for doing appropriate follow-up and laboratory tests on individuals who suffered serious adverse reactions following vaccinations [70]. The reason for such oversight is likely due to the fact that historically, vaccines have not been viewed as inherently toxic by the regulatory agencies [68] The resulting lack of evidence of causality between vaccinations and serious adverse outcomes has thus been filled with an assumption that vaccines are safe [71].

Natural history of infectious diseases/ immunizations

Based on statistics from the Federal Statistics Office in Wiesbaden, Buchwald published a paper containing long-term observations of morbidity and mortality from infectious diseases. The following charts present the collected data indicating the year of introduction of the vaccines [19].

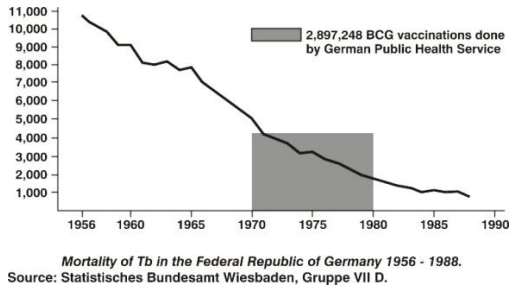


Fig. 5. Tuberculosis mortality in the Federal Republic of Germany (FRG) in the years 1956-1988.

Shaded area – the number of BCG vaccinations performed. (Source: Deggeller L.:Concerning Childhood Vaccinations Today. Journal of Anthrop Med, 1992, 9, 2,1-14; with permission: Phycicians' Association for Anthroposophical Medicine)

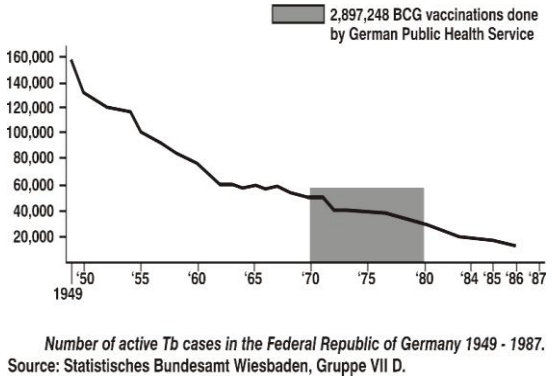


Fig. 6. Number of active tuberculosis cases in the years 1949-1987.

Shaded area – the number of BCG vaccinations performed. (Source: [19] Deggeller L. Concerning Childhood Vaccinations Today. Journal of Anthrop Med, 1992, 9, 2, 1-14; with permission: Phycicians' Association for Anthroposophical Medicine)

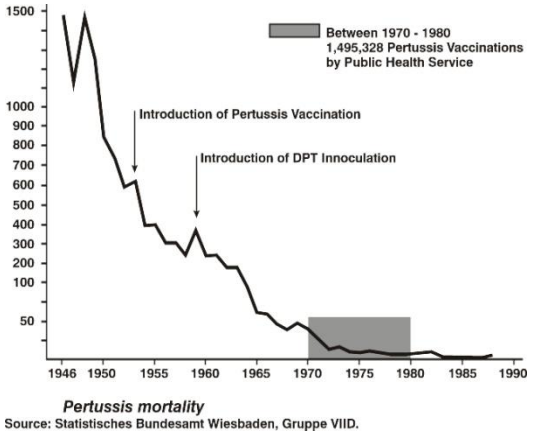
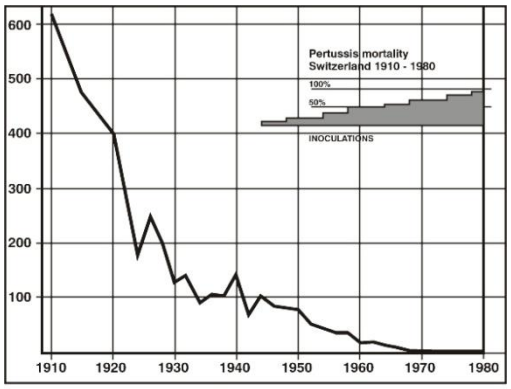


Fig. 7. Pertussis mortality. The arrows mark the year of introduction of the pertussis and DTP vaccines.

Shaded area - the number of vaccinations performed. (Source: [19] Deggeller L. Concerning Childhood Vaccinations Today. Journal of Anthrop Med, 1992, 9, 2,1-14; with permission: Phycicians' Association for Anthroposophical Medicine)

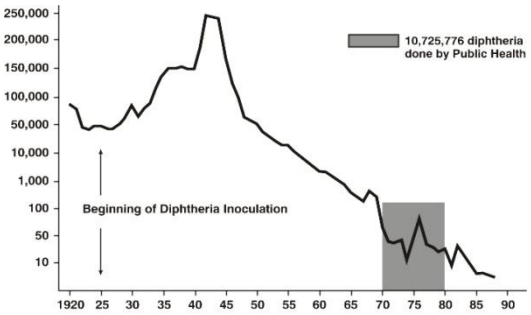


Pertussis mortality in Switzerland; more than 600 deaths at the beginning of the century, no deaths in last five years. The greatest decline occurred prior to introduction of general vaccination of infants.

Source: Tönz, O.:Keuchhustenimpfung. Therapeut. Umschau 40 (1983), S.203.

Fig. 8. Pertussis mortality in Switzerland in the years 1910-1980.

Shaded area – introduction of vaccination. (Source: [19] Deggeller L. Concerning childhood vaccinations today. Journal of Anthrop Med, 1992, 9, 2,1-14; with permission: Phycicians' Association for Anthroposophical Medicine)



Diphtheria Cases.

Source: Statistisches Bundesamt Wiesbaden.

Fig. 9. Number of diphtheria cases.

Shaded area – the number of vaccinations performed (Source: [19] Deggeller L.:Concerning Childhood Vaccinations Today. Journal of Anthrop Med, 1992, 9, 2,1-14; with permission: Phycicians' Association for Anthroposophical Medicine)

Figures 5 and 6 show tuberculosis morbidity and mortality, figures 7 and 8 contain data on pertussis, and figure 9 refers to the incidence of diphtheria. It is interesting that in recent decades a decrease of infectious diseases was generally reported, which took place before the introduction of inoculations against these diseases.

According to a 2002 report from *Lancet Infectious Diseases* [72] "the weight of evidence collectively suggests that personal and environmental hygiene reduces the spread of infection" and "Thus results from this review demonstrate that there is a continued, measurable, positive effect of personal and community hygiene on infectious". The same report showed that the crude death rate from infectious diseases decreased to nearly negligible levels long before introduction of universal vaccination practices. Currently, the developed countries introduce increasingly complex vaccination schedules. Forty years ago, children were immunized against five diseases (diphtheria, tetanus, pertussis, polio, smallpox), today this number has increased to eleven. At the same time, as mentioned previously, repeatedly administered multi-antigen vaccines are recommended.

Doctors and researchers point to the worsening state of health of the child population since the 1960s, which coincided with increasingly introduced vaccinations. Allergic diseases, including asthma, autoimmune diseases, diabetes and many neurological dysfunctions - difficulty in learning, ADD (attention deficit disorder), ADHD (attention deficit hyperactivity disorder), seizures, and autism - are chronic conditions, to which attention has been brought [73].

Proposals for modification of the vaccination schedule

European countries have different models of vaccination that have been modified in recent decades. In Scandinavian countries, which have the lowest infant mortality, vaccinations are voluntary and infants receive their first vaccination at 3 months of age. In the first year of life, they receive 9 recommended vaccinations, and at 18 months - MMR. The acellular pertussis vaccine (DTaP) is used, as well as IPV. BCG and Hepatitis B vaccines are administered to children from high risk groups. Similar vaccination schedules exist in other European countries, where the vaccination of neonates was abandoned and a ban on the use of thimerosal in vaccines was introduced [4, 74]. Note also that Scandinavian countries have the lowest rates of autism compared to other developed countries in which children are vaccinated much earlier and with greater number of vaccines [49].

Professor Majewska - a neurobiologist, Director of the Marie Curie Chairs Program at the Department of Pharmacology and Physiology of the Nervous System in Warsaw - together with pediatricians, drafted a proposal for changes to the vaccination program in Poland, which is based on an analysis of programs in other European Union countries. The propositions are as follows:

1. Eliminate thimerosal from all vaccines.
2. Discontinue the immunization of infants with the hepatitis B vaccine (vaccinate only newborns at high risk, i.e. of infected mothers).
3. Discontinue BCG vaccination of neonates (use only in children from regions where the

percentage of TB patients is over 40 per 100 thousand).
4. Begin vaccination from 4 months old in the remaining group of children.
5. Discontinue the whole cell pertussis vaccine.
6. Give a maximum of three types of vaccines in one day.
7. Discontinue the administration of live virus vaccines or give them one at a time at safe intervals.
8. Make monovalent vaccines accessible.
9. Commitment of the doctor administering the vaccine to conduct a preliminary interview with the parents about allergies, asthma and other autoimmune diseases and postvaccinal complications in family members, allowing them to predict whether a given child may experience severe postvaccinal reactions. Such a child should have an individual, very careful vaccination program developed.
10. Monitor the health status of children after vaccination in order to notice life- or health-threatening conditions in time.
11. Create a national program for compulsory registration of postvaccinal complications and deaths. These data should be reported to the WHO and information about complications should be provided in the child's health record book [51].

CONCLUSIONS

Despite the assurances of the necessity and safety of vaccinations, there are more and more questions and doubts, which both physicians and parents are waiting to be clarified. This paper describes several aspects of the immunization program of children. It includes: the physiological development of the immune system, the immunization schedule adopted in Poland in comparison with other countries, adverse reactions and complications following vaccination described in scientific publications, the natural course of infectious diseases in conjunction with the vaccination programs implemented and the problem of reporting adverse reactions following vaccination by medical personnel and parents. The proposal for changes in vaccination in Poland cited at the end of this paper is, according to the authors, part of the answer to the concerns and doubts. A second part would be extensive neuro-immunological research confirming or excluding the relationship of vaccines with the reported adverse events (early, late/long-term) and chronic diseases whose upward trend has been observed in recent decades in children.

It seems that it would be worthwhile to apply the precautionary principle - the ethical principle (from 1988) according to which if there is a probable, although poorly known, risk of adverse effects of new technology, it is better not to implement it rather than risk uncertain but potentially very harmful consequences.

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Conflicts of interest

We declare that we have no conflicts of interest.

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