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Vaccination and neurological disorders

Anastasia Gkampeta, Efterpi Pavlidou, Evangelos Pavlou

2nd Pediatric Department, Aristotle University of Thessaloniki, "AHEPA" General Hospital, Greece

Abstract:

Active immunization of children has been proven very effective in elimination of life threatening complications of many infectious diseases in developed countries. However, as vaccination-preventable infectious diseases and their complications have become rare, the interest focuses on immunization-related adverse reactions. Unfortunately, fear of vaccination-related adverse effects can lead to decreased vaccination coverage and subsequent epidemics of infectious diseases. This review includes reports about possible side effects following vaccinations in children with neurological disorders and also published recommendations about vaccinating children with neurological disorders. From all international published data anyone can conclude that vaccines are safer than ever before, but the challenge remains to convey this message to society.

Keywords: immunization, vaccination, children, neurological disorders, infectious

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Corresponding author: Anastasia Gkampeta, St. Kyriakidi 1, Thessaloniki 54636 Phone: 00302310994815 Fax: 00302310993514 e-mail: anastagab@yahoo.gr

INTRODUCTION

Active immunization of children has been proven very effective in elimination of life threatening and disabling complications of many infectious diseases in developed countries. However, as vaccination-preventable infectious diseases and their complications have become rare, the interest focuses on immunization-related adverse reactions¹. Both doctors and parents are concerned about the increased risk of adverse effects in children with neurological disorders after vaccination, which can be attributed to insufficient understanding about vaccination-related adverse effects in those children^{1,2}. Unfortunately, fear of vaccination-related adverse effects can lead to decreased

vaccination coverage and subsequent epidemics of infectious diseases.

Usually parents concerning about vaccine-related complications choose to delay vaccinations. However, this delay puts children at risk without a clear benefit, as they are exposed to vaccine-preventable diseases. Although the majority of parents agree to have their children immunized, vaccine refusal appears to be increasing. Approximately 90 percent of pediatric healthcare providers annually encounter at least one parent who refuses some recommended vaccines, and 54 percent encounter a parent who refuses all recommended vaccines³. This review includes reports about possible side effects following vaccinations in children with neurological

disorders and also published recommendations about vaccinating children with neurological disorders.

Febrile seizures

Febrile seizures (FSs) occur in children between 3 months and 5 years of age, without a history of afebrile seizures, associated with fever but without evidence of central nervous system's infection or acute electrolyte imbalance. Their pathogenesis is multifactorial⁴. While febrile seizures are generally not associated with high morbidity or mortality, they are the most common cause of pediatric seizures and are very frightening for parents. Several vaccines have been associated with elevated risk of febrile seizures, including whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids (DTP), measles-containing vaccines, some formulations of inactivated influenza vaccines, and the 13-valent pneumococcal conjugate vaccine (PCV13)^{5,6,7,8,9,10}.

Most studies conducted from 1990 till nowadays revealed statistically significant increase of vaccine-induced febrile seizures within 3 days to 1 week following immunization with DTP (Diphtheria-Tetanus-Pertussis) vaccine^{5,6,11,12,13,14,15}. This increase is considered to be related to the high incidence of fever as adverse effect of DTP immunization. However, the relationship between age and dosage is not clear with some data demonstrated that vaccination in the first 2-4 months of life shows a lower risk of seizures¹.

Similar statistically significant increase of vaccine-related febrile convulsions within 5 to 14 days following immunization with MMR (Measles-Mumps-Rubella) vaccine was described by many studies worldwide^{6,7,15,16,17,18}. This increase can be attributed to the higher incidence of febrile reactions that appear frequently in the 2 weeks following vaccination

¹. A more recent extensive cohort revealed no association between the timing of vaccination and occurrence of seizures in the first year of life, while delayed vaccination with measles-containing vaccines post 15 months is associated with more post-vaccination seizures in the 7 to 10 days after vaccination up to 3 times greater than the on-time vaccine administration¹⁹. Moreover, receipt of MMRV (Measles-Mumps-Rubella-Varicella) compared with MMR has been described to double the incident rate ratio for post-vaccination convulsions, both at 12-15 months and at 16-23 months of age which can be attributed to the higher concentration of varicella virus in the MMRV formulation²⁰. To the same conclusion came two other recent studies, one by Klein et al. and the other by MacDonald et al., both of whom found that the use of MMRV vaccine instead of separate MMR plus varicella vaccines approximately doubles the risk for fever and febrile seizures^{21,22}. Similar results had the more recent study of Schink et al²³.

So, it is evident that both DTP and MMR vaccinations increase the risk of febrile seizures, but not the risk for afebrile seizures. Also, the rate of febrile seizures is similar in children with and without a history of previous febrile convulsions^{1,24}. The use of whole-cell pertussis vaccine has been associated with febrile and afebrile seizures. However there has been a reduction in postvaccination febrile seizures since the introduction of acellular pertussis vaccine²⁵. Also, a lower increased risk of seizures has been reported when measles-containing vaccines administered at 12 to 15 months of age²⁰.

Concerning Inactivated Poliovirus vaccine (IPV) and Haemophilus Influenzae Type b vaccine (Hib), a large population study conducted by Sun et al. revealed no increased risk of epilepsy after vaccination with combined DTaP-IPV-Hib vaccine. In the same study, authors found that

the relative risk of febrile seizures were increased on the day of the first and the second vaccinations and the overall risk of febrile seizures was not increased within 0 to 7 days after DTaP-IPV-Hib vaccinations. Besides, the prognosis of post-vaccination febrile seizures was similar to the prognosis of febrile seizures occurring after the risk period of vaccination¹⁴. Because of the fact that DTaP-IPV-Hib vaccine was given as a combined vaccine, authors were unable to identify which of the components caused febrile seizures. The estimates did not change with the addition of pneumococcal vaccine, as an increased risk of febrile seizures was shown 1 to 3 days after the second vaccination and on the day of the third vaccination²⁶.

Influenza and pneumococcal vaccines help the prevention of morbidity and mortality from influenza and severe pneumococcal infections. Several studies investigated the possible relationship between influenza vaccines and febrile seizures²⁷⁻³⁰. A large population based study on the risk of epileptic seizures in both adults and children of three Swedish countries revealed no evidence of increased risk of epileptic seizures after vaccination with a monovalent AS03 adjuvanted pandemic H1N1 influenza vaccine during the 2009-10 A/H1N1PDM09 pandemic³¹. However, Vaccine Safety Datalink (VSD) data revealed a statistically significant elevated risk for febrile seizures 0 to 1 days after vaccination in children aged 6 months to 5 years old who received first dose of season's trivalent inactivated influenza vaccine (TIV) during the 2010-2011 season, independent of concomitant 12-valent pneumococcal conjugate vaccine (PCV13). The highest risk appeared in children between 12 to 23 months who had been vaccinated with TIV and PCV13 concomitantly^{8,32}.

Japanese guidelines on vaccination for patients with febrile seizures recommend a 2-3 month observation period after the last seizure. Also, seizure frequency, time since the last seizure and electroencephalographic findings are considered to be unrelated to post-vaccination complications according to Japanese guidelines². According to LICE guidelines, vaccinations should be performed without concern in children with a history of febrile seizures, after the detailed information of parents that some vaccinations (in particular DTP and MMR) can cause fever with consequent febrile seizures, particularly in children with previous febrile convulsions and/or younger than 6 years old¹. Generally, most studies suggest that vaccination is safe for children with a personal or family history of seizures.

A more recent study conducted by Tartof et al. suggests that there may be immunogenetic differences underlying vaccine-related febrile seizures compared with other febrile seizures. According to their results, non-white race categories and children of younger mothers had higher risk of febrile seizures regardless of vaccine exposure. Moreover, while the risk for febrile seizures in females was lower than males outside of the vaccine risk window, females and males had equal risk in the post-vaccination period. For children with low Apgar scores, risk for febrile seizures was higher only after vaccination but not outside of the vaccine risk window³³. However, further studies are needed to understand and reinforce the mechanism by which vaccinations cause febrile seizures.

Dravet syndrome (severe myoclonic epilepsy of infancy)

Dravet syndrome is an infantile epileptic syndrome with intractable pleomorphic seizures, cognitive impairment, and a number of comorbidities including ataxia or gait

abnormalities and behavioral issues³⁴. At least 70% of children diagnosed with Dravet syndrome have a heterozygous mutation in the SCN1A gene³⁵. Onset age is around 6 months with prolonged febrile or afebrile generalized clonic or hemiclonic seizures, and coincidentally occurs at the same time as the vaccination are commonly given³⁶.

There are few studies about the relationship of Dravet syndrome and vaccination that show no correlation between vaccinations and Dravet syndrome (or other epileptic encephalopathies with onset in the first year of life) and reveal no increased risk of encephalopathy after the immunization^{35,37,38,39}. However, there is some evidence that earlier onset of these syndromes can be triggered by vaccination, especially in children with a SCN1A mutation^{1,14,40}. Moreover, vaccinations precede first seizures in about 7 to 57% of children with Dravet syndrome and mainly occur within 0-3 days after DTP and 6-11 days after MMR vaccination^{35,9}. However, a more recent study by Zamponi et al. revealed that vaccinations do not significantly affect clinical and cognitive evolution of Dravet syndrome and generalized epilepsy with febrile seizure plus patients even if they are carriers of SCN1A mutations⁴¹.

Japanese medical society encourages pediatricians to vaccinate children with Dravet syndrome as it has been confirmed that vaccination reduces the risk of suffering a viral infection in such patients⁴². According to LICE guidelines, vaccinations should be performed without concern in children with epileptic encephalopathies, after a detailed information of parents and an earlier and more aggressive antiepileptic therapy¹. Parents should understand that vaccination, although possible the trigger for first seizure, is not the cause of the child's genetic epileptic syndrome. Berkovic et al made the first steps to understanding whether

vaccination can elicit Dravet syndrome and mentioned that vaccination was only the trigger in the disease's onset⁴³.

Multiple sclerosis (MS)

Multiple sclerosis (MS) is considered to result from complex inflammatory processes with a background of interacting genetic and environmental factors. MS is rare in children, accounting for only 3% to 4% of all MS cases⁴⁴. There are several studies investigating the possible relationship between vaccination and MS. Unfortunately, these studies are merely case reports, poorly designed observational studies, or well designed studies with a small number of participants from which valid conclusions cannot be drawn. A very recent meta analysis by Farez et al. revealed no increase in risk of developing MS with BCG, hepatitis B, diphtheria, influenza, MMR, polio, tetanus and typhoid fever vaccines, while diphtheria and tetanus immunization may be associated with a decreased risk of developing MS⁴⁵.

Since the introduction of HPV (Human Papillomavirus) vaccines several vaccine-related neurological complications have been reported including Guillain-Barré syndrome, seizures, stroke, venous thromboembolism, anaphylaxis and other allergic reactions. While studies on HPV vaccine remain reassuring as they lack of evidence of any association between HPV vaccine and autoimmune or neurological complications, diseases like MS have been under careful investigation. Since now multiple studies have shown no increased risk of autoimmune diseases, including MS, among girls who have been vaccinated with HPV vaccine^{46,47,48,49}.

Several studies, mainly in adults, investigated the risk of MS associated with Hepatitis B (HepB) vaccine exposure, but failed to show any association^{44,50,51,52,53,54,55}. One recent study conducted by Mikaeloff et al shows that HepB

vaccination does not increase the risk of relapse and conversion to MS, either within 3 years of vaccination or at any time point after vaccination, in subjects with first episode of CNS inflammatory demyelination in childhood⁵⁶. So, it is generally accepted that vaccination against HepB does not increase the risk of a first episode of MS in childhood.

No association found between MMR vaccination and increased risk of MS⁵⁷. Moreover, a recent population-based case-control study by Ahlgren et al. found no significant associations between measles, mumps, rubella or varicella and MS risk⁵⁸.

This led to the recommendation issued by the American Academy of Neurology that patients with MS should follow Centers for Disease Control indications for immunization in the general population for all vaccinations, including HepB vaccine⁵⁹.

Autism Spectrum Disorders (ASD)

Since the 1980s, there has been an increase in the number of cases of ASD diagnosed in the United States and other parts of the world. Much attention was generated when the California Department of Developmental Services reported a 210% increase in the number of persons diagnosed with ASD between 1987 and 1998. The explanation for the increase was not clear, though it was considered that changes in diagnostic criteria and an increased awareness of the conditions among health-care providers and developmental specialists may have been contributing factors⁶⁰.

About 62% of children with Autism Spectrum Disorders (ASD) have been reported to experience a period of regression, characterized by loss of previously acquired skills. This period ranges between 6 and 36 months of age with the typical age of regression between 18 and 24 months^{61,62}. This period of regression occurs

within the same time period that children typically receive their required immunizations.

The possible relationship between the MMR vaccine and ASD was first described by Wakefield et al. in 1999 after they observed a regressive phenotype of autism that generally appeared after the administration of the first MMR vaccine⁶³. This study described 12 children from the United Kingdom and suggested that MMR damaged the intestinal lining, allowing encephalopathic proteins to enter the bloodstream and brain, thereby leading to the development of autism. However, by comparing the case descriptions in the paper with medical records, an investigative reporter found that the study was fraudulent⁶⁴. Three of the children did not have autism, five had developmental concerns before MMR vaccination, behavioral symptoms developed in some children months (rather than days) after MMR vaccination and colonoscopy results were altered from unremarkable findings to “nonspecific colitis” after “research review”. In addition, patients were recruited through an anti-MMR organization and the study was commissioned and funded for planned litigation. Consequently, 10 of the 13 authors of the study in 2004 published a statement retracting its interpretation, and the paper was retracted from the public record in 2010^{65,66}. Since then, there are few studies supporting the relationship between MMR vaccine and ASD^{67,68}, while several large epidemiologic studies have tested the possible relationship and failed to find supporting evidence^{69,70,71,72,73,74,75,76,77,78,79,80,81,82}.

A more recent study by Hooker provides new epidemiologic evidence showing that African American males receiving the MMR vaccine prior to 24 months of age or 36 months of age are more likely to be diagnosed with ASD⁸³.

Decreased viral immunity, caused by the MMR vaccine, has been proposed as a mechanism for the association between MMR and ASD⁶³. However, there is insufficient evidence to support this view^{84,85}. Persistent measles infection or abnormally persistent immune response to MMR is another mechanism that has been proposed to explain an association between MMR and autism. Support for this hypothesis was lacking in a case-control study in which measles virus and measles antibody were measured in 98 children (aged 10 to 12 years) with ASD, 52 children with special needs without ASD, and 90 typically developing children⁸⁶. Measles virus nucleic acid was detected in peripheral blood mononuclear cells of one child with ASD and two typically developing children. Antibody response did not differ between cases and controls and there was no correlation between antibody levels and autism symptoms. Multiple large, well-designed epidemiologic studies and systematic reviews have found insufficient evidence to support an association between the MMR vaccine and ASD. However, some parents remain concerned that the MMR vaccine is not safe. MMR immunization rates in the UK declined acutely (from 92 percent in 1995 to 79 percent in 2003). In June 2008, measles was again endemic in the UK, 14 years after it had been eliminated⁸⁷. Further studies are needed to evaluate the relationship between MMR vaccine and ASD.

Much controversy has been generated by allegations that vaccinations cause Autism Spectrum Disorders. Concerns were raised that thiomersal-containing vaccines result in a significant number of children developing neurodevelopmental disorders^{88,89,90,91}. Thiomersal, or sodium ethylmercury thiosalicylate, is an organic compound that has been used as a preservative since the 1930s. Thiomersal has been used as a preservative in

hepatitis B, diphtheria-tetanus-acellular-pertussis, and Haemophilus influenzae type b (Hib) vaccines, typically at concentrations from 0.005% to 0.01% (12.5 µg Hg or 25 µg Hg per 0.5 mL vaccine dose)⁹². A more recent study by Geier et al. supports the association between increasing organic-Hg exposure from Thiomersal-containing childhood vaccines and the risk of an ASD diagnosis⁹². However, multiple large, well-designed epidemiologic studies^{93,94,95,96,97,98} and systematic reviews^{84,99,100,101} have found insufficient evidence to support an association between thiomersal-containing vaccines and ASD or other developmental disorders. A more recent evidence-based meta-analysis of case-control and cohort studies conducted by Taylor et al. suggests that the components of the vaccines (thiomersal or mercury) or multiple vaccines (MMR) are not associated with the development of autism or autism spectrum disorder¹⁰².

Research to prove or disprove a possible relationship between the various components of recommended childhood vaccines and chronic diseases such as ASD is ongoing. However, to date, no scientific linkage has been established.

Inborn errors of metabolism (IEMs)

Inborn errors of metabolism (IEMs) are a large group of heterogeneous diseases. The impact of the available vaccines on children with IEMs may vary depending on the child's metabolic characteristics. Infections can be more severe in children with IEMs, than in healthy children because metabolic abnormalities can be worsened by the inflammation response and symptoms such as poor feeding, vomiting and diarrhea)¹⁰³. Consequently, vaccination plays an important role on prevention of infectious diseases in children with IEMs. However, vaccines can deteriorate the fragile metabolic equilibrium of children with IEMs. Moreover,

vaccines could be less effective in children with IEMs accompanied by immune deficiency than in healthy children.

Unfortunately, the number of studies evaluating the immunogenicity, safety and tolerability of vaccines in children with IEMs is very small^{104,105,106,107}. Recently, a close relationship between whole cell pertussis vaccine and metabolic deterioration in children with IEMs has been proposed¹⁰⁸. However, recently published studies indicate that the risk of severe metabolic deterioration is very low in children with stable or slowly progressive IEMs, suggesting that they could receive the recommended schedules of all vaccinations^{106,107}. The Committee on Infectious Diseases of the American Academy of Pediatrics recommends that all patients with metabolic disorders receive the vaccinations recommended for healthy children and yearly influenza vaccinations unless there is a contraindication to the specific components of the vaccines, and highlights the fact that the child's physician should seek guidance from a specialist before administering any preparation^{104,109}.

Finally, in a very recent review Menni et al state their concern about the necessity of a booster pneumococcal vaccination after the age of five years and yearly influenza vaccinations in children diagnosed with IEMs¹¹⁰.

Stroke

Stroke is an important cause of death and disability worldwide. Several case-control studies and have shown increased likelihood of respiratory symptoms 1 to 4 weeks before the occurrence of stroke, indicating that prevention of respiratory infection could decrease the risk of following stroke^{111,112}. However limited in number, case reports of children presented with stroke after influenza infection are indicative of necessity for vaccination against influenza,

particularly in children already at high risk^{113,114,115}. The protective role of vaccination on stroke incidence remains controversial with several studies supporting that influenza vaccination, either alone or combined with pneumococcal vaccine, associates with a reduced risk of stroke^{111,116-121,122}, while other studies do not support this protective role^{123,124,125}.

Several case reports and cohort studies have reported an increased risk of stroke in the year following zoster infection¹²⁶⁻¹²⁹. A more recent report by Langan et al. showed an increased risk of stroke within 6 months following zoster infection¹³⁰. To similar results came Askalan et al. who conduct a cohort study in young children (aged 6 months to 10 years) and found strong association between varicella infection and childhood arterial ischemic stroke¹³¹. These findings have implications for zoster vaccination programs, which may reduce stroke risk following zoster. However, Wirrell et al. reported two children presented with stroke after varicella vaccination, suggesting that immunization with the varicella vaccine may, in rare cases, predispose to stroke despite the fact that the vaccine appears efficacious and safe in controlled clinical trials¹³². A recent cohort study by Donahue et al. failed to reveal any association between varicella vaccine and ischemic stroke in children within 12 months after vaccination¹³³.

A more recent study by Daley et al. published in 2014 concerning the Safety of diphtheria, tetanus, acellular pertussis and inactivated poliovirus (DTaP-IPV) vaccine found no evidence of increased risk for stroke¹¹⁸. Further studies required to evaluate the impact of immunization for varicella on childhood stroke.

West syndrome (WS)

West syndrome refers to the classic triad of spasms, characteristic EEG, and

neurodevelopmental regression, with poor prognosis. Peak onset age of the epileptic syndrome is 3 to 7 months, which mainly occurs before 2 years of age in 93% of patients ¹³⁴.

It is generally considered that children with WS should not be vaccinated during therapy with adrenocorticotrophic hormone (ACTH), as it has various adverse effects, especially on the immune system. A multicenter questionnaire survey revealed that 36% of pediatricians vaccinate children with WS within 3 months and 55% of pediatricians vaccinate within 6 months after ACTH therapy. However, the appropriate timing of vaccination after ACTH therapy has not been reported yet ¹³⁵. In an effort to clarify the appropriate timing of vaccination after ACTH therapy, Ohya et al. investigated the changes in immunity levels before and after ACTH therapy. They clearly found significant decreases in lymphocyte levels and CD4+ T cell counts immediately after and at 1 and 3 months after ACTH therapy (which gradually recovered), while no decrease reported in CD8+ T cell counts ¹³⁵. Therefore, further study is necessary.

Guillain-Barré syndrome

Adverse events following influenza vaccines have been widely studied. Although causal associations have not been established, adverse events have been reported to occur in temporal association with influenza vaccines. During the H1N1 vaccination campaign in 1976 in United States a sevenfold risk of Guillain-Barré syndrome was reported. Subsequent studies did not replicate these results, even the most recent multinational case-control study in Europe ^{136,137,138,139,140,141}.

A more recent study by Daley et al. published in 2014 concerning the Safety of diphtheria, tetanus, acellular pertussis and inactivated poliovirus (DTaP-IPV) vaccine found no

evidence of increased risk for meningitis/encephalitis, seizures, stroke, Guillain-Barré syndrome, Stevens–Johnson syndrome, anaphylaxis, serious allergic reactions other than anaphylaxis, and serious local reactions ¹⁴².

In 2005, the Food and Drug Administration (FDA) and CDC published an advisory issue regarding the occurrence of Guillain-Barré syndrome in five recipients of quadrivalent meningococcal polysaccharide vaccine conjugated to diphtheria toxoid (MCV4) ¹⁴³. Through 2006, a total of 15 cases of Guillain-Barré syndrome were reported in persons aged 11 to 19 years with onset within six weeks after vaccination with MCV4; all patients recovered or were recovering ¹⁴⁴. However since then, more recent studies failed to show increased risk of Guillain-Barré syndrome in individuals who received MCV4.

Acute disseminated encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the central nervous system, principally affecting the white matter, associated with preceding infection or immunization. Post-vaccination ADEM, that accounts for less than 5% of present cases of ADEM, has been associated with several vaccines such as rabies, diphtheria–tetanus–polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, influenza, hepatitis B, and the Hog vaccine ¹⁴⁵⁻¹⁴⁹. The most common vaccinations associated with ADEM are the non-neural measles, mumps and rubella vaccines. ADEM following immunisation seems to occur significantly more frequently after primary vaccination as compared to revaccination ^{150,151}. In post-vaccination ADEM, the interval period from vaccination to the onset of illness is between 4 to 24 weeks ¹⁵². To our

knowledge, there are few case report of ADEM associated with tetanus vaccine^{152,153}. Generally, the international literature regarding the relationship between ADEM and immunization in children is lacking.

Posterior reversible encephalopathy syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) is a disorder with typical radiologic findings of bilateral white and gray matter abnormalities in the posterior regions of the cerebral hemispheres. Typical clinical symptoms include headache, convulsion, loss of consciousness and visual disturbance¹⁵⁴. Due to recent measles outbreaks in Japan, the Japanese government has mandated measles vaccination at ages 14 and 17 since April 2008. Since then, the number of people receiving measles vaccination has increased in Japan. The literature concerning association of PRES with vaccination is lacking, with only two reports describing the post-vaccination PRES. Aydin et al. reported a 9-year-old boy with PRES after measles vaccination¹⁵⁵. Hamano et al. described an adult case of PRES and myeloradiculoneuropathy following measles vaccination¹⁵⁴.

Conclusions

As vaccination-preventable diseases have become rare, the interest focuses on immunization-related adverse effects. This review contains published case reports and cohort studies from international literature regarding the relationship between immunizations and neurological disorders and also published recommendations about immunization of children with neurological disorders.

Most frequently described immunization-related neurological complications include seizures, shock, polyneuritis, transverse myelitis, optic neuritis, demyelinating brain lesions and

encephalopathy. Causal relationship between vaccinations and neurological disorders remains controversial. Also, not all immunization-related neurological complications have been confirmed to occur more frequently in children with neurological disorders². The main concerns of medical society include whether vaccinations cause febrile or afebrile seizures, whether vaccine-related febrile seizures differ from common febrile seizures, whether vaccine-related seizures could progress to epilepsy and whether vaccinations are related to epileptic syndromes. Italian League Against Epilepsy (LICE), in an effort to answer above mentioned concerns, published guidelines on vaccination and epilepsy¹. More information about contraindications and risks of vaccination in patients with epilepsy are needed.

The international literature regarding the relationship between vaccination and idiopathic or symptomatic epilepsies and epileptic encephalopathies is lacking. All conducted studies, however small in number, show no relationship between vaccinations and any specific epileptic syndrome, encephalopathy, afebrile seizures, neuromuscular disorders or any irreversible neurological damage, while children with idiopathic or symptomatic epilepsy do not have higher risk of adverse effects following vaccination^{1,6,156,157,158,159,160,161,162,163}. There are only few reports of children presented with afebrile seizures after vaccination with MMRV vaccine¹⁰. However, it is not possible based on these few sole cases to assess a causal relationship between nonfebrile seizures and vaccination. A cohort conducted by Payne et al. found that a full course of rotavirus vaccination was associated with statistically significant (about 18%–21%) reduction in the risk of childhood seizures during the year following last rotavirus vaccination, compared to unvaccinated children¹⁶⁴.

From all international published data anyone can conclude that vaccines are safer than ever before, but the challenge remains to convey this message to society. The resulting misinformation from media or internet leads to unnecessary parental

concerns. Healthcare providers need to understand these concerns in order to effectively address them and aid parents in choosing immunization for their children.

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