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Epilepsy and vaccinations: Italian guidelines

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Summary

Reports of childhood epilepsies in temporal association with vaccination have had a great impact on the acceptance of vaccination programs by health care providers, but little is known about this possible temporal association and about the types of seizures following vaccinations. For these reasons the Italian League Against Epilepsy (LICE), in collaboration with other Italian scientific societies, has decided to generate Guidelines on Vaccinations and Epilepsy. The aim of Guidelines on Vaccinations and Epilepsy is to present recent unequivocal evidence from published reports on the possible relationship between vaccines and epilepsy in order to provide information about contraindications and risks of vaccinations in patients with epilepsy. The following main issues have been addressed: (1) whether contraindications to vaccinations exist in patients with febrile convulsions, epilepsy, and/or epileptic encephalopathies; and (2) whether any vaccinations can cause febrile seizures, epilepsy, and/or epileptic encephalopathies. Diphtheria-tetanus-pertussis (DTP) vaccination and measles, mumps, and rubella vaccination (MMR) increase significantly the risk of febrile seizures. Recent observations and data about the relationships between vaccination and epileptic encephalopathy show that some cases of apparent vaccine-induced encephalopathy could in fact be caused by an inherent genetic defect with no causal relationship with vaccination.

KEY WORDS: Epilepsy, Vaccination, Febrile seizures, Epileptic encephalopathy, Italian League Against Epilepsy, Guidelines.

Immunization is a very effective health intervention, but recently as immunization-preventable infectious diseases and their serious clinical complications have become rare, more interest has been focused on vaccine-related adverse events (Miller et al., 1993; Derrough & Kitchin, 2002; Ellenberg et al., 2005; Guida alle controndicazioni alle vaccinazioni, 2005; Friederichs et al., 2006; Salisbury et al., 2006; Ward et al., 2007; Shui et al., 2009; Gold et al., 2010). Many parents and doctors are increasingly concerned about worsening of neurologic problems after vaccination in children who have neurologic diseases (Turcotte et al., 2001; Kimmel, 2002; Wharton, 2010). Reports of childhood epilepsies in temporal association with vaccination had a great impact on the acceptance of vaccination programs by health care providers but little is known about this possible temporal association and about the types of seizures following vaccinations (Varricchio et al., 2004; Kroger et al., 2006; Marin et al., 2010; Von Spiczak et al., 2011). Finally, it is not easy to sort out whether febrile seizures result from nonspecific fever caused by vaccination or if these are secondary to an encephalitis or encephalopathy caused by the vaccine (Kohl et al., 2004; Gitiaux et al., 2006; Vestergaard & Christensen, 2009; Sugai, 2010; Cendes & Sankar, 2011).

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For these reasons the Italian League Against Epilepsy (LICE), in collaboration with other Italian scientific societies (SINP, Italian Society of Pediatric Neurology; SINPIA, Italian Society of Child Neuropsychiatry; and SIP, Italian Society for Pediatrics), has decided to create Guidelines on Vaccinations and Epilepsy.

Methods

The aim of Guidelines on Vaccinations and Epilepsy is to present recent unequivocal evidence from published reports on the possible relationship between vaccines and epilepsy in order to provide information about contraindications and risks of vaccinations in patients with epilepsy.

The recommendations given in these Guidelines have been elaborated in the following phases:

1 Group of distinguished members of scientific societies involved in the care of children with vaccination and epilepsy was appointed;
2 The main scientific issues for patients with epilepsy were identified;
3 The available medical literature was reviewed in order to identify all scientific data dealing with the specific topics;
4 The scientific data assigning recommendations based on levels of evidence.

The MEDLINE and Cochrane Library databases were used to identify pertinent original research (retrospective and, more rarely, prospective) studies, case–control and cohort studies, epidemiologic surveys, case reports, relevant reviews, and opinions of experts related to our topic. Reference sections of original reports and reviews were scanned to identify additional articles that were missed in the initial search. In the event that pediatric-specific reports were absent, adult studies have been evaluated.

The evaluation of the data from the literature has been carried out by Scottish Intercollegiate Guidelines (SIGN 50). Moreover, the Manual of the National Program for Guidelines (PNLG) of the Istituto Superiore di Sanità has been used (PNLG, 2002).

Guideline recommendations are graded to differentiate between those based on strong evidence and those based on weak evidence. This judgment is made on the basis of an assessment of the design and quality of each study and on the consistency, clinical relevance, and external validity of the entire body of evidence. The aim is to produce a recommendation that is evidence based. The recommendations are defined with a class of evidence expressed in Roman numerals from I (the highest) to IV and with the strength of the recommendation, expressed in letters from A (the highest) to E. (SIGN 50, 2008).

Levels of evidence

I^{++} High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I^{+} Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
I^{-} Meta-analyses, systematic reviews, or RCTs with a high risk of bias
II^{++} High quality systematic reviews of case–control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II^{+} Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II^{-} Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III Nonanalytic studies, for example, case reports, case series
IV Expert opinion

Grades of recommendation

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A At least one meta-analysis, systematic review, or RCT rated as I^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as I^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B A body of evidence including studies rated as II^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as I^{++} or I^{+}
C A body of evidence including studies rated as II^{+}, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as II^{++}
D Evidence level III or IV; or Extrapolated evidence from studies rated as II^{+}

The following main issues have been addressed:

1 Whether contraindications to vaccinations exist in patients with febrile convulsions, epilepsy, and/or epileptic encephalopathies.
2 Whether any vaccinations can cause febrile seizures, epilepsy, and/or epileptic encephalopathies.

The data from literature have been examined with respect to the possible evidence regarding:

(a) Whether vaccinations can cause febrile or nonfebrile convulsions;
(b) whether the vaccine-related febrile seizures are different from common febrile seizures;

(c) whether the vaccine-related febrile or afebrile seizures could be likely to progress to epilepsy earlier than it would have naturally occurred;
(d) whether some relationship exists between vaccinations and specific epileptic syndromes.

In addition, we collected all reports about possible side effects and/or complications following vaccinations in patients with the following:

1 Febrile seizures
2 Idiopathic and symptomatic epilepsies
3 Epileptic encephalopathies

The following vaccines have been taken into consideration: poliomyelitis; diphtheria-tetanus-pertussis (DPT), Haemophilus influenzae, pneumococcus; meningococcal conjugate; measles, mumps, and rubella (MMR), combined or not with chickenpox; influenza; hepatitis A and B; tuberculosis; and human papilloma virus (Wise et al., 2004; McMahon et al., 2005; Kerdpanich et al., 2008; Stehr-Green et al., 2008; Zangwill et al., 2008; Black et al., 2009; Rosenberg et al., 2009; Centers for Disease Control & Prevention, 2010; Moreira Gomes Monteiro et al., 2010; Sweet, 2010).

Part 1. Febrile seizures

(A) Are there contraindications to vaccination of children who have had febrile seizures?
(B) Is it necessary to avoid any vaccination because of significant association with a high risk of febrile seizures?

Relationship between DTP Vaccine and Febrile Seizures

Griffin et al. (1990) evaluated 38,171 vaccinated children, and the authors reported a statistically significant increase of vaccine-induced febrile seizures within 3 days following immunization, whereas no significant results was found with respect to vaccine-induced afebrile seizures. Only seven children had afebrile seizures within the 30 days following vaccine, and the risk of seizures was not significantly elevated in the 0–3, 4–7, 8–14, and 15–29 day time windows following vaccine compared with >30 days after vaccination.

Gale et al. (1994) conducted a case–control study in 358 children with new neurologic illness (including seizures). There was an increased risk of febrile seizures within 1 week after immunization, whereas no increased risks for afebrile seizures following vaccination were found. In fact, the risk of seizures was lowest in the periods following vaccination.

In the United Kingdom, Farrington et al. (1996), in a large cohort study, demonstrated that febrile seizures were three times more frequent in the 3 days after vaccination.

Barlow et al. (2001) published data from a cohort study on children enrolled in four large American regions (Vaccine Safety Datalink, VSD). The VSD study included >675,000 children younger than 6 years of age and >340,000 DPT vaccinations. The VSD study demonstrated that DTP vaccine increases the risk of febrile seizures by almost sixfold on the day of vaccination, but not thereafter. The strength of this study is the large number of children assessed and the enrollment of outpatient in the majority (three of four centers) of cases.

Jackson et al. (2002) reported a low risk of febrile convulsions (1 per 19,496 vaccinations), similar to any other causes of fever.

In 1985 , the U.S. Institute of Medicine published that immunization with DTP caused 7.2 million of minor reactions, 10.300 episodes of febrile seizures, 164 encephalopathies, 60 cases of chronic disabilities, and 2–4 deaths/year U.S. Institute of Medicine, 1985. In 1991, a new study estimated the rate of encephalopathy in children occurring within 7 days of DTP immunization to be 3.3 per million; 77% of these cases was attributable to DTP vaccine (Geier & Geier, 2004). In 1994, the Institute of Medicine concluded that there is no evidence that DTP immunization is associated with an increased risk of: (1) cerebral or developmental abnormalities, (2) triggering the onset of encephalopathy, or (3) causing an encephalopathy to which the child was predisposed (U.S. Institute of Medicine, 1994).

Another important debate has been about the differences between the potentially harmful effects of whole-cell and acellular DTP vaccine. The whole-cell vaccines are associated with a high frequency of adverse reactions, whereas the acellular vaccines are associated with lower rate of adverse reactions. For example, the rate of febrile seizures within 2 days of vaccination among children younger than 2 years of age was 1 per 19.496 vaccinations, which is much lower than the corresponding rate of 1 per 2,835 with the whole-cell vaccine (Cody et al., 1981).

More recently, David et al. (2008) collected information through questionnaires sent to parents of children from 1 to 11 months of age who were going to receive the four doses of DTP vaccine. This study compares whole-cell versus acellular vaccines and evaluates the occurrence of adverse effects. Among 15,069 children receiving whole-cell vaccine and 13,069 children receiving acellular vaccine (9,242 not combined with pneumococcus vaccine and 4,485 combined with pneumococcus vaccine), febrile seizures were identified rarely and only after the fourth immunization: 2 (0.06%) in whole-cell vaccinated children and 1 (0.02%) in acellular vaccinated children; one possible febrile seizure occurred following the third acellular vaccine exposure. The whole-cell vaccine was associated with a high frequency of adverse reactions, for example, fever and febrile seizures, especially after the fourth immunization. This study failed to show a statistically significant association with pneumococcus vaccine.

We must emphasize the limitations of this study: the authors have not evaluated the whole population, and the questionnaire is not the most precise and effective method for collecting data, with high risk of underreporting, ascertainment bias, and variability in report quality and completeness. Recently, when examining the risk of febrile seizures and epilepsy after DTaP-IPV-Hib vaccination, Sun et al. (2012) found that this vaccination was associated with an increased risk of febrile seizures on the day of the first two doses given at 3 and 5 months of age, mostly because of the occurrence of fever. Of interest, this study shows that the risk of febrile seizures was high after the first two vaccinations but not after the third one. The absolute risk to develop recurrent febrile seizures after vaccination turned out to be very low.

In conclusion, DTP vaccination increases significantly the risk of febrile seizures, and this increase appears to be related to the high incidence of fever as side effect of this immunization.

The relationship between dosage and age is not clear: some data demonstrate that children vaccinated in the first months of life (e.g., 2–4 months of age) show a lower risk of adverse effects including seizures (David et al., 2008).

Relationship Between MMR Vaccine and Febrile Seizures

In 2001, Barlow et al. published a large cohort study carried out in children belonging to the Vaccine Safety Datalink (VSD) Project of four U.S. regions (Washington, Oregon, and northern and southern California). The authors looked at the relationship between the MMR vaccination and the risk of first seizure, of recurrent seizures, and of possible abnormalities of neurologic development. The VSD study included >675,000 children younger than 6 years of age and >340,000 MMR vaccinations. The children who showed a febrile seizure following vaccination were followed in order to evaluate the risk of occurrence of epilepsy and/or neurologic diseases. Febrile seizures appear to be most common after 8–14 days following MMR vaccination, whereas there was no significantly increased risk of seizures in the 0–7 and 15–30 days following immunization. There was not even an increased risk of subsequent afebrile seizures or of neurologic illness. Study strengths include the large sample size and the inclusion of patients from outpatient clinics for three of the four sites.

In 2003, a Canadian retrospective study, performed by Le Saux et al. (2003), collected data from IMPACT (Immunization Monitoring Program-Active), a program of active surveillance that reported adverse events of vaccinations from 12 Canadian hospitals. The study cohort consisted of children who experienced fever >38.5°C in the 5–30 days after a single dose of MMR vaccine. Of the 107 cases of febrile convulsions subsequent to vaccination, 55 (51%) showed convulsions in the 5- to 10-day interval after immunization. The main limitation of this study is the inclusion of children admitted to hospitals with prolonged and recurrent seizures. The number of identified cases is extremely low in relation to the doses of vaccine in the period of time considered.

In the same year, Davis and Barlow (2003) published a meta-analysis to evaluate the risk of febrile and afebrile seizures following DTP and MMR immunizations; these authors evaluated the three major studies (Griffin et al., 1990; Farrington et al., 1996; Barlow et al., 2001). All studies found that immunization with MMR vaccine increases the risk of febrile seizures between 1.5- and 3.0-fold subsequent to vaccination, with a peak occurring 1–2 weeks after vaccination. In particular, Farrington et al. (1996) estimated that there were 33 additional febrile seizures per 100,000 children immunized with the MMR vaccine.

It is extremely difficult to confirm a clear relationship between vaccination and febrile seizures. It is also particularly difficult to compare a population of children who were immunized with a population of nonimmunized children because the majority of children received also optional vaccinations. Moreover, it is difficult to understand whether vaccination could cause febrile seizures or whether vaccine-induced febrile seizures were caused by a genetically determined susceptibility.

In Vestergaard et al., 2004 published a large retrospective cohort study; the study cohort consisted of children born in Denmark between 1991 and 1998 (data were collected from Danish Civil Registration System and from other four national registries). The study aimed at assessing the incidence and the risk of febrile seizures following MMR immunization and at estimating their clinical outcome. A total of 530,000 children were evaluated who were immunized with the first dose of MMR vaccine at the age of 15 months (82% of the population studied): 937 episodes of first febrile seizures within 2 weeks of the vaccination were ascertained. The percentage of risk of developing febrile seizures in the vaccinated population was 10% higher than the background rate. In the next 2 weeks following vaccination, the relative risk of febrile convulsions was 2.75 (95% confidence interval [95% CI] 2.55–2.97). The population studied has been subdivided into various subgroups (according to family history of epileptic seizures and febrile convulsions, premature birth, birth weight for gestational age, socioeconomic status, and so on): no significantly increased risks in the different subgroups were reported. In contrast, an increased risk in those patients with twins affected by epilepsy was found. The authors underscore that the children who had febrile seizures within the 15 days following immunization showed only a slightly elevated risk of recurrent febrile

seizures, but not of epilepsy, when compared to children with febrile seizures of different etiology.

More recently, Miller et al. (2007) conducted a cohort study to assess febrile convulsions after MMR immunization: data collection began in 1998, when, in England, Priorix vaccine (containing Schwarz attenuated strain of measles virus, RIT 4385 strain of mumps, derived from Jeryl Lynn strain and Wistar RA 27/3 strain of rubella virus) was licensed, and finished in 2002. Almost 900 children aged 12–23 months were enrolled in this study. An increased incidence of febrile seizures in the 6–11 days after MMR vaccination was found; these values are consistent with the data collected by Farrington et al. (1996) and by Barlow et al. (2001), confirming the lack of the increase of incidence of febrile seizure 15–35 days after immunization. There were no significant differences between the two strains (MMRII and Priorix).

In Jacobsen et al., 2009, for the first time, two groups of children: one immunized with MMRV vaccine and one immunized with MMR + varicella. From February 2006 to June 2007, the study enrolled more than 30,000 children/group, age 1–5 years, with a follow-up 30 days after administration of the new combined vaccine in order to evaluate the risk of febrile seizures. The study demonstrated that in 30 days of follow-up there was no significant difference of relative risk of febrile seizures between the two groups of children. On the other hand, within 5–12 days after immunization, the first group showed an increased risk of febrile convulsions (incidence 0.70/1,000) in comparison with the second group (incidence 0.32/1,000), with a relative risk of 2.20 (95% CI 1.04–4.65). Moreover, Klein et al. (2010), using 2000–2008 Vaccine Safety Datalink data, assessed seizures and fever visits among children aged 12 to 23 months after MMRV and separate MMR + varicella vaccines; the authors reported that in children who received their first dose of measles-containing vaccine, fever and seizures increased 7 to 10 days after vaccination. Vaccination with MMRV resulted in one additional febrile seizure every 2,300 doses. In 2008, the recommendations of the Advisory Committee on Immunization Practices about MMRV vaccine were published. Although data about febrile seizures after MMRV vaccination are still unavailable, data concerning MMR vaccination are applicable to MMRV vaccine. Advisory Committee suggests that children with a personal or family history of epileptic seizures of any etiology should be immunized with MMR and varicella vaccines independently. More recently, the American Academy of Pediatrics recommended that MMR and varicella vaccines should be used separately or MMRV can be used for the first dose of MMR and varicella vaccines administered between 12 and 47 months of age. For the first dose of MMR and varicella vaccines given from the age of 48 months and for the second dose at any age, use of MMRV vaccine should be preferred with separate injections of MMR and varicella vaccines (Committee on Infectious Diseases, 2011).

In conclusion, it is evident that the MMR vaccination increases significantly the risk of febrile seizures. This increase is correlated with the higher frequency of febrile reactions that are more common in the 2 weeks following vaccination, especially with the measles strain. Further studies are needed to resolve the question of the real rate of recurrence of febrile seizures and/or epilepsy following the first seizure after immunization.

From the critical appraisal of the literature, the following indications can be drawn:

(1) Some vaccinations, in particular DTP (especially whole-cell vaccine) and MMR (especially combined with varicella), can cause fever with possible febrile seizures.
(2) The rate of febrile seizures is similar in children with and without a personal history of previous febrile seizures.
(3) Vaccine-induced febrile seizures are no more frequent than febrile seizures with any other cause of fever.
(4) The risk of nonfebrile seizures following vaccine-induced febrile seizures is not higher than in children who have not shown vaccine-induced febrile seizures.

Recommendation 1

Vaccinations should be performed without contraindication in children with previous febrile seizures (class of evidence III; strength of recommendation A).

Recommendation 2

The risk of febrile seizures should not discourage parents from vaccinating their children (class of evidence III; strength of recommendation A).

Note: Parents should be informed that some vaccines could be associated with febrile reactions with consequent seizures, in particular in children with personal history of febrile seizures and/or younger than 6 years.

Part 2. Idiopathic and symptomatic epilepsy

(C) Are there contraindications to vaccinating children who are affected or were affected by epilepsy?
(D) Is it necessary to avoid any vaccination because of significant association with epilepsy?

The literature regarding the relationships between idiopathic or symptomatic epilepsies, epileptic encephalopathies, and vaccination is lacking.

Barlow et al. (2001) conducted a large cohort study on the occurrence of seizures among 679,942 children after 340,386 vaccinations with DTP vaccine, 137,457 vaccinations with MMR vaccine, or no recent vaccination. As compared with children with febrile seizures that were not associated with vaccination, children who had febrile sei-

zures after vaccination were not found to be at higher risk for subsequent seizures. Gold et al. (2000), in a review of 421 Australian children concluded that revaccination of children with a past history of an adverse event following immunization appears safe. The study by Huang et al. (2010) used the risk-interval cohort and self-controlled case series analyses to compare the incidence of seizures in the risk and control periods. There was no increased risk for seizures within 3 days after receipt of DTaP in early childhood and no mention of seizures or epilepsy in an older age. In an extensive review Shorvon and Berg (2008) conclude that the recent consensus is that the risk of vaccine-induced encephalopathy and/or epilepsy, if it exists, is extremely low. Risk estimates in the literature have included the following: risk of a febrile seizure, 1 per 19,496 vaccinations; risk of an afebrile seizure, 1 per 76,133 vaccinations; risk of encephalopathy after pertussis infection, three cases per million vaccinations.

From an appraisal of literature, the following indications can be drawn:

(1) Vaccinations do not cause afebrile seizures or epilepsy.
(2) No correlation exists between vaccinations and any specific epileptic syndrome.
(3) There is no higher risk of adverse events after vaccination in children with idiopathic or symptomatic epilepsy

Recommendation 3

Vaccinations should be performed without contraindication in children with idiopathic or symptomatic epilepsy (class of evidence III; strength of recommendation A).

Recommendation 4

The risk of epilepsy should not discourage parents from vaccinating their children (class of evidence III; strength of recommendation A).

Part 3. Epileptic encephalopathy

(E) Are there contraindications to vaccinating children who are affected or were affected by epileptic encephalopathy?
(F) Is it necessary to avoid any vaccination because of a significant association with an epileptic encephalopathy?

The literature comprises many reviews, case definitions, and data analyses regarding the relationship between epileptic encephalopathy and vaccination (American Academy of Pediatrics Committee on Infectious Diseases, 1996; Ball et al., 2002; Bonhoeffer et al., 2004, 2009; Poland et al., 2009).

Jefferson et al. (2003) performed a systematic review of studies published during the period from 1969–2003, aimed at assessing and assembling evidence on the type and frequency of unintended events associated with MMR vaccines compared with no vaccination or placebo or combinations of attenuated MMR vaccines. They did not find associations between vaccination and encephalopathy. Moore et al. (2004) showed the lack of evidence of encephalopathy related to pertussis vaccine (no attributable case following administration of 6.5 million doses of vaccine). Ray et al. (2006) in a retrospective case–control study including more than 2 million children, concluded that DTP and MMR vaccines were not associated with an increased risk of encephalopathy after vaccination. Shorvon and Berg in their review published in 2008 show that recent studies failed to demonstrate any causal association between vaccination and the occurrence of encephalopathy (Shorvon and Berg 2008). Vaccine-induced encephalopathy (or epilepsy) can be diagnosed only when other forms of childhood encephalopathy are excluded.

Infantile Spasms

Because infantile spasms typically start at about 6 months of age, onset of seizures might coincide with routine vaccination. Goodman et al. (1998) examined the time relationship between DTP immunization and infantile spasms (IS) onset using three statistical models (association, temporal shift, and no-effect) using the case–control data from the NCES (National Childhood Encephalopathy Study). IS cases classified as being previously abnormal showed a no-effect relationship, whereas in children classified as previously normal a temporal shift model was suggested, which means no increase in the total number of cases but a shortening of interval to the onset of seizures. No data fit the association model. Guggenheim et al. (2008) examined the temporal latency between an encephalopathic event and the onset of IS in previously normal infants and conclude that IS do not occur acutely following an encephalopathic event. The findings of this studies refute claims that a close temporal association between an immunization and the onset of infantile spasms establishes causation.

Doose Syndrome and Lennox-Gastaut Syndrome

The two entities of Doose syndrome and Lennox-Gastaut syndrome start later in childhood and therefore they are less likely to begin in the context of vaccination, as vaccination courses are mostly completed at this age. There is absence of significative studies except for isolated and questionable case reports (Ishikawa et al., 1999).

Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy)

The terms of the debate about the potentially harmful effects of vaccination has been dramatically changed by the publication of a pivotal study by Berkovic et al. (2006) followed by many comments (Sell & Minassian, 2006; Berg, 2007; Brown et al., 2007; Doja, 2008; Neville, 2010; Wisnitzer, 2010). Epidemiologic studies did not lend support to the view of a causal association between immunization and permanent brain damage. In individual cases, however, the perception of causality can be difficult to challenge, especially if no alternative cause is identified. The diagnostic features of vaccine encephalopathy have never been defined. Reported cases have an apparent temporal relation to vaccination (varying from <1 day to 14 days) and typically have multiple seizure types with developmental arrest or regression. In the Berkovic's retrospective study, 11 of 14 patients with alleged vaccine encephalopathy in whom the first seizure occurred within 72 h of vaccination have *SCN1A* mutations; a diagnosis of a specific epilepsy syndrome was made in all 14 cases.

Clinical-molecular correlation showed mutations in eight of eight cases with phenotypes of severe myoclonic epilepsy of infancy (SMEI), in three of four cases with borderline SMEI, but not in two cases with Lennox-Gastaut syndrome.

The interpretation of the authors is that cases of alleged vaccine encephalopathy could be a de novo genetically determined epileptic encephalopathy. These findings, more recently replicated by Reyes et al. (2011), have important clinical implications for the diagnosis and management of encephalopathy and, if confirmed in other cohorts, major societal implications for the general acceptance of vaccination. McIntosh et al. (2010) aimed to establish whether the apparent association of Dravet syndrome with vaccination was caused by recall bias and, if not, whether vaccination affected the onset or the outcome of the disorder. They retrospectively studied 40 patients with Dravet syndrome comparing clinical features, intellectual outcome, and *SCN1A* mutation between two groups according to whether seizure onset occurred shortly after vaccination (vaccination-proximate group) or not (vaccination-distant group). They found no differences in intellectual outcome, subsequent seizure type, or mutation type between the two groups, and they conclude that the vaccination might trigger earlier onset of Dravet syndrome in children who, because of an *SCN1A* mutation, are destined to develop the disease. However, vaccination should not be withheld in children with *SCN1A* mutations because there is no evidence that vaccinations before or after disease onset affect outcome. It is possible that the vaccine causes fever, which precipitates the manifestations of this condition, but the vaccine cannot be considered the primary cause in these cases.

Tro-Baumann et al. (2011) retrospectively investigated the occurrence of vaccination-related seizures in 70 patients with Dravet syndrome. Seizures following vaccination were reported in 27%, and in 58% of these patients the vaccination-related event was the first reported seizure, suggesting that vaccination-related seizures are common in Dravet syndrome, and represent a possible presenting feature of this condition.

However, larger studies in children with isolated febrile seizures and no history of epilepsy did not demonstrate an effect of prophylactic antipyretic or anticonvulsive treatment (Tanabe et al., 2004; Shafrir, 2010). Further studies are needed to evaluate preventive measures for seizures in the setting of vaccination or febrile illness, especially for patients with Dravet syndrome.

From the appraisal of literature, the following indications can be drawn:

(1) No pathologic correlation exists between vaccinations and epileptic encephalopathies with onset in the first year of life (Dravet syndrome, West syndrome). There is some evidence that the vaccination might trigger earlier onset of these syndromes.
(2) Vaccines were not associated with an increased risk of encephalopathy after vaccination.

Recommendation 5

Vaccinations should be performed without contraindication in children with epileptic encephalopathies (Dravet syndrome, West syndrome) (class of evidence III; strength of recommendation A).

Recommendation 6

The possible risk of epileptic encephalopathy should not discourage parents from vaccinating their children (class of evidence III; strength of recommendation A).

Note

There is no evidence that vaccination should be prevented in such patients but parents and caregivers of patients with Dravet syndrome should be carefully advised about immunization risks, and prophylaxis with antiepileptic drugs (AEDs) might be helpful in these patients.

In patients with *SCN1A* mutations, an earlier and more aggressive therapy (i.e., antipyretics and/or benzodiazepine for a short time before and after vaccination), associated with early AEDs therapy might prevent further vaccination-related seizures and contrast a negative evolution of the disease (class of evidence III; strength of recommendation D).

Discussion

Because of effective vaccination programs, several infectious diseases and their serious complications have become rare. Consequently, side effects of vaccinations assume a more important role for the acceptance of vaccination by the public (Alfredsson et al., 2004), and strategies focused on safety concerns and perceived risks are crucial to obtaining sufficient vaccination coverage. Cases of severe childhood epilepsies starting in the setting of vaccination might have great impact on the acceptance of vaccination programs by parents and health care providers. (Von Spiczak et al., 2011).

From the critical analysis of the literature, it is evident that DTP vaccination increases significantly the risk of febrile seizures and this increase seems to be related to the high incidence of fever as side effect of the immunization. The relationship between dosage and age is not clear: some data demonstrate that children vaccinated in the first months of life (e.g., 2–4 months of age) show a lower risk of adverse effects including seizures. Furthermore, it is evident that MMR vaccination increases statistically the risk of febrile seizures. This increase is correlated with the higher frequency of febrile reactions that are more common in the 2 weeks following vaccination, especially with the measles strain.

Recent observations and data about the relationships between vaccination and epileptic encephalopathy (Berkovic et al., 2006) shed new light on a controversy not only involving the medical community, but also the public interest and legislation in several countries since the emergence of a disorder of so-called "vaccine encephalopathy," in which a previously well infant experienced sudden onset of seizures and encephalopathy soon after vaccination. This disorder has resulted in significant legal battles in compensation for the alleged "damage" caused by vaccination. The entity of "vaccine encephalopathy" is poorly defined. No specific electroclinical features have been delineated, and the time of onset from vaccination has not been clearly specified. Nevertheless, large-scale epidemiologic studies have failed to confirm an association between vaccination and encephalopathy (Cendes & Sankar, 2011). About the possible link between Dravet syndrome and vaccinations, it is important to underscore that the presence of genetic mutations provide a compelling explanation of the cause of the encephalopathy; therefore, it is possible that some cases of apparent vaccine-induced encephalopathy could in fact be due to an inherent genetic defect with no causal relationship with vaccination (Shafrir, 2010). Moreover, there is no demonstration of a causal association between vaccination and the occurrence of encephalopathy. It is possible that vaccinations cause fever, which precipitates the manifestations (seizures) of the genetic condition.

Disclosures

The authors have no conflicts of interest to disclose.

We confirm that we have read the Journal position on issue involved in ethical publication and affirm that this report is consistent with these guidelines.

References

Alfredsson R, Svensson E, Trollfors B, Borres MP. (2004) Why do parents hesitate to vaccinate their children against measles, mumps and rubella? *Acta Pediatr* 93:1232–1237.

American Academy of Pediatrics Committee on Infectious Diseases. (1996) The relationship between pertussis vaccine and central nervous system sequelae: continuing assessment. *Pediatrics* 97:279–281.

Ball R, Halsey N, Miles Braun M, Moulton LH, Gale AD, Rammohan K, Wiznitzer M, Johnson R, Salive ME, the VAERS Working Group. (2002) Development of case definitions for acute encephalopathy, encephalitis, and multiple sclerosis reports to the vaccine: Adverse Event Reporting System. *J Clin Epidemiol* 55:819–824.

Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mulloly JP, Black SB, Shinefield HR, Ward JI, Marcy SM, DeStefano F, Chen RT, for the Centers for Disease Control, Prevention Vaccine Safety Datalink Working Group. (2001) The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N Engl J Med* 345:656–661.

Berg AT. (2007) Vaccines, encephalopathies and mutations. *Epilepsy Curr* 7:40–42.

Berkovic SF, Harkin L, McMahon JM, Pelekanos JT, Zuberi SM, Wirrell EC, Gill DS, Iona X, Mulley JC, Scheffer IE. (2006) De-novo mutations of the sodium channel gene *SCN1A* in alleged vaccine encephalopathy: a retrospective study. *Lancet Neurol* 5:488–492.

Black S, Eskola J, Siegrist CA, Halsey N, MacDonald N, Law B, Miller E, Andrews N, Stowe J, Salmon D, Vannice K, Izurieta HS, Akhtar A, Gold M, Oselka G, Zuber P, Pfeifer D, Vellozzi C. (2009) Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 infl uenza vaccines. *Lancet* 374:2115–2222.

Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, Vermeer P. (2004) The Brighton Collaboration Seizure Working Group. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. *Vaccine* 22:557–562.

Bonhoeffer J, Bentsi-Enchill A, Chen RT, Fisher MC, Gold MS, Hartman K, Heininger U, Hoet B, Jefferson T, Khuri-Bulos N, Kohl K, Marcy SM, Nalin D, Pless R, Sanabria-Rojas H, Sleeman K, Wise R. (2009) The Brighton Collaboration *Methods* Working Group. Guidelines for collection, analysis and presentation of vaccine safety data in surveillance systems. *Vaccine* 27:2289–2297.

Brown NJ, Berkovic SF, Scheffer IE. (2007) Vaccination, seizures and 'vaccine damage.' *Curr Opin Neurol* 20:181–187.

Cendes F, Sankar R. (2011) Vaccinations and febrile seizures. *Epilepsia* 52(Suppl. 3):23–25.

Centers for Disease Control and Prevention. (2008) Update: recommendations from the Advisory Committee on Immunization Practices (ACIP) regarding administration of combination MMRV vaccine. *MMWR Morb Mortal Wkly Rep* 57:258–260.

Centers for Disease Control and Prevention. (2010) Update: Recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding use of CSL seasonal influenza vaccine (Afluria) in the United States during 2010–11. *MMWR Morb Mortal Wkly Rep* 59:989–992.

Cody CL, Baraff LJ, Cherry JD, Marcy SM, Manclark CR. (1981) Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. *Pediatrics* 68:650–660.

Committee on Infectious Diseases. (2011) Policy Statement—Prevention of varicella: update of recommendations for use of quadrivalent and monovalent varicella vaccines in children. *Pediatrics* 128:630–632.

David S, Vermeer-de Bondt PE, van der Maas NAT. (2008) Reactogenicity of infant whole cell pertussis combination vaccine compared with acellular pertussis vaccines with or without simultaneous pneumococcal vaccine in Netherlands. *Vaccine* 26:5883–5887.

Davis RL, Barlow W. (2003) Placing the risk of seizures with pediatric vaccines in a clinical context. *Pediatri Drugs* 5:712–722.

Derrough TF, Kitchin NRE. (2002) Occurrence of adverse events following inadvertent administration of childhood vaccines. *Vaccine* 21:53–59.

Doja A. (2008) Genetics and the myth of vaccine encephalopathy. *Paediatr Child Health* 13:7–599.

Ellenberg SS, Foulkes MA, Midthun K, Goldenthal KL. (2005) Evaluating the safety of new vaccines: summary of a workshop. *Am J Public Health* 95:800–807.

Farrington CP, Nash J, Miller E. (1996) Case series analysis of adverse reactions to vaccines: a comparative evaluation. *Am J Epidemiol* 143:1165–1172.

Friederichs V, Cameron JC, Robertson C. (2006) Impact of adverse publicity on MMR vaccine uptake: a population based analysis of vaccine uptake records for one million children, born 1987–2004. *Arch Dis Child* 91:465–468.

Gale JL, Thapa PB, Wassilak SG, Bobo JK, Mendelman PM, Foy HM. (1994) Risk of serious acute neurological illness after immunization with diphtheria-tetanus-pertussis vaccine. A population-based case-control study. *JAMA* 271:37–41.

Geier DA, Geier MR. (2004) An evaluation of serious neurological disorders following immunization: a comparison of whole-cell pertussis and acellular pertussis vaccines. *Brain Dev* 26:296–300.

Gitiaux C, Poeyo S, Demazes S, Pedespan L, Pillet P, Husson M, Pedespan J-M. (2006) Vaccinal status in children with seizures: a retrospective study conducted in the Bordeaux child hospital. *Arch Pediatr* 13:1102–1106.

Gold M, Goodwin H, Botham S, Burgess M, Nash M, Kempe A. (2000) Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunisation service. *Arch Dis Child* 83:128–131.

Gold M, Dugdale S, Woodmanc RJ, McCaul KA. (2010) Use of the Australian childhood immunisation Register for vaccine safety data linkage. *Vaccine* 28:4308–4311.

Goodman M, Lamm SH, Bellman MH. (1998) Temporal relationship modeling: DTP or DT immunizations and infantile spasms. *Vaccine* 16:225–231.

Griffin MR, Ray WA, Mortimer EA, Fenichel GM, Schaffner W. (1990) Risk of seizures and encephalopathy after immunization with the diphtheria-tetanus-pertussis vaccine. *JAMA* 263:1641–1645.

Guggenheim MA, Frost JD, Hrachovy RA. (2008) Time interval from a brain insult to the onset of infantile spasms. *Pediatr Neurol* 38:34–37.

Guida alle controndicazioni alle vaccinazioni. (2005) 3° edizione maggio. Istituto Superiore di Sanità.

Huang WT, Gargiullo PM, Broder KR, Weintraub ES, Iskander JK, Klein NP, Baggs JM, for the Vaccine Safety Datalink Team. (2010) Lack of association between acellular pertussis vaccine and seizures in early childhood. *Pediatrics* 126:263–269.

Ishikawa T, Ogino C, Chang S. (1999) Lennox-Gastaut syndrome after a further attenuated live measles vaccination. *Brain Dev* 21:563–565.

Jackson LA, Carste BA, Malais D, Froeschle J. (2002) Retrospective population-based assessment of medically attended injection site reactions, seizures, allergic responses and febrile episodes after acellular pertussis vaccine combined with diphtheria and tetanus toxoids. *Pediatr Infect Dis J* 21:781–785.

Jacobsen SJ, Ackerson BK, Sy LS, Tran TN, Jones TL, Yao JF, Xie F, Cheetham TC, Saddier P. (2009) Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. *Vaccine* 27:4656–4661.

Jefferson T, Price D, Demicheli V, Bianco E, for the European Research Program for Improved Vaccine Safety Surveillance (EUSAFEVAC) Project. (2003) Unintended events following immunization with MMR: a systematic review. *Vaccine* 21:3954–3960.

Kerdpanich A, Warachit B, Kosuwon P, Gatchalian SR, Watanaveeradej V, Borkird T, Kosalaraksa P, Han HH, Hutagalung Y, Boutriau D, Dobbelaere K. (2008) Primary vaccination with a new heptavalent DTPw—HBV/Hib—Neisseria meningitidis serogroups A and C combined vaccine is well tolerated. *Int J Infect Dis* 12:88–97.

Kimmel SR. (2002) Vaccine adverse events: separating myth from reality. *Am Fam Physician* 66:2113–2120.

Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, Baxter R, Hambidge S, Nordin J, Naleway A, Belongia EA, Lieu T, Baggs J, Weintraub E, Vaccine Safety Datalink. (2010) Measles-mumps-rubella-varicella combinationvaccine and the risk of febrile seizures. *Pediatrics* 126:e1–e8.

Kohl KS, Marcy SM, Blum M, Jones MC, Dagan R, Hansen J, Nalin D, Rothstein E, Brighton Collaboration Fever Working Group. (2004) Fever after immunization: current concepts and improved future scientific understanding. *Clin Infect Dis* 39:389–394.

Kroger AT, Atkinson WL, Marcuse EK, Pickering LK; **Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). (2006) General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 55:1–48.

Le Saux N, Barrowman NJ, Moore DL, Whiting S, Scheifele D, Halperin S; Canadian Paediatric Society/ Health Canada Immunization Monitoring Program–Active (IMPACT). (2003) Decrease in hospital admissions for febrile seizures and reports of hypotonic-hyporesponsive episodes presenting to hospital emergency departments since switching to acellular pertussis vaccine in Canada: a report from IMPACT. *Pediatrics* 112:e348–e353.

Marin M, Broder KR, Temte JL, Snider DE, Seward JF; **Centers for Disease Control and Prevention (CDC). (2010) Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 59:1–12.

McIntosh AM, McMahon J, Dibbens LM, Iona X, Mulley JC, Scheffer IE, Berkovic SF. (2010) Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. *Lancet Neurol* 9:592–598.

McMahon AM, Iskander J, Haber P, Chang S, Woo EJ, Braun MM, Ball R. (2005) Adverse events after inactivated influenza vaccination among children less than 2 years of age: analysis of reports from the vaccine adverse event. *Pediatrics* 115:453–460.

Miller D, Madge N, Diamond J, Wadsworth J, Ross E. (1993) Pertussis immunisation and serious acute neurological illnesses in children. *BMJ* 307:1171–1176.

Miller E, Andrews N, Stowe J, Grant A, Waight P, Taylor B. (2007) Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom. *Am J Epidemiol* 165:704–709.

Moore DL, Le Saux N, Scheifele D, Halperin SA, Members of the Canadian Paediatric Society/Health Canada Immunization Monitoring Program, Active (IMPACT). (2004) Lack of evidence of encephalopathy related to pertussis vaccine*:* active surveillance by IMPACT, Canada, 1993–2002. *Pediatr Infect Dis J* 23:568–571.

Moreira Gomes Monteiro SA, Takanoa OA, Waldmanb EA. (2010) Surveillance for adverse events after DTwP/Hib vaccination in Brazil: sensitivity and factors associated with reporting. *Vaccine* 28:3127–3133.

Neville B. (2010) Dravet syndrome and 'immunization encephalopathy. *Dev Med Child Neurol* 52:590–591.

PNLG (Programma nazionale per le linee guida). (2002) Manuale Metodologico. Come produrre, diffondere e aggiornare racco-mandazioni per la pratica clinica. Istituto Superiore Di Sanità, maggio 2002.

Poland GA, Ovsyannikova IG, Jacobson RM.. Adversomics: (2009) The emerging field of vaccine adverse event immunogenetics. *Pediatr Infect Dis J* 28:431–432.

Ray P, Hayward J, Michelson D, Lewis E, Schwalbe J, Black S, Shinefield H, Marcy M, Huff K, Ward J, Mullooly J, Chen R, Davis R, Vaccine Safety Datalink Group. (2006) Encephalopathy after whole-cell pertussis or measles vaccination. Lack of evidence for a causal association in a retrospective case–control study. *Pediatr Infect Dis J* 25:768–773.

Reyes IS, Hsieh DT, Laux LC, Wilfong AA. (2011) Alleged cases of vaccine encephalopathy rediagnosed years later as Dravet syndrome. *Pediatrics* 128:e699–e702.

Rosenberg M, Sparks R, McMahon A, Iskander J, Campbell JD, Edwards KM. (2009) Serious adverse events rarely reported after trivalent inactivated influenza vaccine (TIV) in children 6–23 months of age. *Vaccine* 27:4278–4283.

Salisbury D, Ramsay M, Noakes K. (2006) Immunisation against infectious disease. In: *The green book*. Published by The Stationery Office under licence from the Department of Health, London.

Sell E, Minassian BA. (2006) Demystifying vaccination-associated encephalopathy. *Lancet Neurol* 5:465–466.

Shafrir Y. (2010) Vaccination and Dravet syndrome. *Lancet Neurol* 9:1147–1148.

Shorvon S, Berg A. (2008) Pertussis vaccination and epilepsy—an erratic history, new research and the mismatch between science and social policy. *Epilepsia* 49:219–225.

Shui IM, Shia P, Maya Dutta-Linna M, Weintraub ES, Hambidge SJ, Nordine JD, Lieu TA, for the Vaccine Safety Datalink Research Team. (2009) Predictive value of seizure ICD9 codes for vaccine safety research. *Vaccine* 27:5307–5312.

SIGN 50. (2008) A Guideline Developer's Handbook. Scottish Intercollegiate Guidelines Network. Revised Edition January 2008.

Stehr-Green P, Radke S, Kieft C, Galloway Y, McNicholas A, Reid S. (2008) The risk of simple febrile seizures after immunisation with a new group B meningococcal vaccine, New Zealand. *Vaccine* 26:739–742.

Sugai K. (2010) Current management of febrile seizures in Japan: an overview. *Brain Dev* 32:64–70.

Sun Y, Christensen J, Hviid A, Li J, Vedsted P, Olsen J, Vestergaard M. (2012) Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus and Haemophilus influenzae type B. *JAMA* 307:823–831.

Sweet M. (2010) Australian health authorities' response criticised after adverse events related to influenza vaccination in children. *BMJ* 341: c4470.

Tanabe T, Awaya Y, Matsuishi T, Nagai T, Yamamoto K, Kurihara M, Iyoda K, Maekawa K. (2004) Survey of vaccination and viral infections for children with severe myoclonic epilepsy in infancy. *No To Hattatsu* 36:318–323.

Tro-Baumann B, von Spiczak S, Lotte J, Bast T, Haberlandt E, Sassen R, Freund A, Leiz S, Stephani U, Boor R, Holthausen H, Helbig I, Kluger G. (2011) A retrospective study of the relation between vaccination and occurrence of seizures in Dravet syndrome. *Epilepsia* 52:175–178.

Turcotte K, Raina P, Moyer WA. (2001) Above all, do no harm. Assessing the risk of an adverse reaction. *West J Med* 174:325–329.

U.S. Institute of Medicine. (1985). *Adverse events associated with pertussis and rubella vaccines*. National Academy Press, Washington DC.

U.S. Institute of Medicine. (1994). *DPT vaccine and chronic nervous system dysfunction: a new analysis*. National Academy Press, Washington DC.

Varricchio F, Iskander J, DeStefano F, Ball ??, Pless R, Braun M, Chen RT. (2004) Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* 23:287–294.

Vestergaard M, Christensen J. (2009) Register-based studies on febrile seizures in Denmark. *Brain Dev* 31:372–377.

Vestergaard M, Hviid A, Madsen KM, Wohlfahrt J, Thorsen P, Schendel D, Melbye M, Olsen J. (2004) MMR vaccination and febrile seizures evaluation of susceptible subgroups and long-term prognosis. *JAMA* 292:351–357.

Von Spiczak S, Helbig I, Drechsel-Baeuerle U, Muhle H, Van Baalen A, Van Kempen MJ, Lindhout D, Scheffer IE, Berkovic SF, Stephani U, Keller-Stanislawski B. (2011) A retrospective population-based study on seizures related to childhood vaccination. *Epilepsia* 52:1506–1512.

Ward KN, Bryant NJ, Andrews NJ, Bowley JS, Ohrling A, Verity CM, Ross EM, Miller E. (2007) Risk of serious neurologic disease after immunization of young children in Britain and Ireland. *Pediatrics* 120:314–321.

Wharton M. (2010) Vaccine safety: current systems and recent findings. *Curr Opin Pediatr* 22:88–93.

Wise RP, Iskander J, Pratt RD, Campbell S, Ball R, Pless RP, Miles Braun MM. (2004) Postlicensure safety surveillance for 7-valent pneumococcal conjugate vaccine. *JAMA* 292:1702–1710.

Wisnitzer M. (2010) Dravet syndrome and vaccination: when science prevails over speculation. *Lancet Neurol* 9:559–561.

Zangwill KM, Eriksen E, Lee M, Lee J, Marcy SM, Friedland LR, Weston W, Howe B, Ward JI. (2008) A population-based, postlicensure evaluation of the safety of a combination diphtheria, tetanus, acellular pertussis, hepatitis B, and inactivated poliovirus vaccine in a large managed care organization. *Pediatrics* 122:e1179–e1185.