Review Article

Risk of Seizures after Immunization with Vaccine in Children

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Abstract:
Adverse neurological event particularly seizure after vaccination is not uncommon. The most linked vaccines are Diphtheria, Pertussis and Tetanus toxoid (DPT), Measles, Mumps and Rubella (MMR) and other combination vaccines. It is documented that increased febrile seizure after DPT and MMR vaccine is due to increase febrile episodes precipitating seizure and it is time related. Concomitant administration of vaccines cause seizure due to synergistic effect of those vaccines. When these vaccines are given separately, the risk of seizure is decreased. These type of vaccines are MMR + varicella (MMRV), DTaP-HepB-IPV etc. Regarding etiology, genetic mutation is most important. Some genes are closely related to vaccine induced FS and afebrile seizure like SCN1A, SCN2A, IFI44L, PCDH19 etc. Other causes are endotoxin mediated endothelial damage, IL-1β production and non CNS infection. It is well evident that consequences of not giving vaccine are far more than the adverse events. So Vaccinations should be performed without contraindication in children with previous febrile and afebrile seizures with proper counseling.

Key words: seizure, febrile seizure (FS), vaccine, epilepsy.

Introduction
Immunization is an important part of child care practice and millions of children are vaccinated every year. The vaccine is generally well tolerated but transient adverse events like seizures are rarely encountered after vaccination. There are many questions about vaccine related seizures making the parents and health care providers worried and concerned. This is discussed in brief in this article. Diphtheria, Pertussis and Tetanus toxoid (DPT) vaccination and relationship with febrile seizures (FS)

Adverse neurologic events were first linked to pertussis in 1933.¹ Later several studies have reported elevated risk of seizures associated with diphtheria and tetanus toxoids and whole-cell pertussis (DTP). One study found that vaccination with DPT was associated with an elevated risk of seizures (relative risk, 3.3; 95 percent confidence interval, 1.4 to 8.2).² In another study, an increased risk of febrile seizures (FS) was noted within three days after DPT vaccination (relative risk, 3.7; 95 percent confidence interval, 1.4 to 10.0).³ That was only in association with the third dose of vaccine. There were some studies which found no significant increase in the risk of FS after immunization with DPT vaccine.⁴⁻⁶ However, it is evident that DPT vaccination increases significantly the risk of FS, 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: but children vaccinated in the first months of life (e.g., 2–4 months of age) show a lower risk of seizures.⁷ The clinical studies noted 60 episodes of FS per 100,000 doses of DPT occurring within 3 days of DTwP vaccination but active surveillance studies have shown 8 episodes of FS per 100,000 doses of DPT.⁸⁻⁹ In another report

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convulsions (with or without fever) occur 1 per 750 doses within 48 hours after vaccination with DPT. Measles, Mumps and Rubella (MMR) vaccination and FS febrile seizure appear to be most common after 8–14 days but not in the 0–7 and 15–30 days following immunization with MMR vaccine. In a Canadian retrospective study, of the 107 cases of febrile convulsions subsequent to MMR vaccination, 55 (51%) showed convulsions in the 5 to 10 day interval after immunization. A meta analysis found that immunization with MMR vaccine increases the risk of FS between 1.5 and 3.0 fold with a peak occurring 1–2 weeks after vaccination. Farrington et al estimated that there were 33 additional FS per 100,000 children immunized with the MMR vaccine.

A large retrospective cohort study consisted of children born in Denmark between 1991 and 1998 to assess the incidence and the risk of FS following MMR immunization. The percentage of risk of developing FS in the vaccinated population was 10% higher than the background rate. The study assessed according to family history of epileptic seizures and febrile convulsions, premature birth, birth weight for gestational age, socioeconomic status. No significantly increased risks in the different groups were reported. Children who had FS within the 15 days following immunization showed only a slightly elevated risk of recurrent FS. Miller et al. conducted a cohort study of 900 children aged 12–23 months. An increased incidence of FS in the 6–11 days after MMR vaccination was found and there was lack of the increase of incidence of FS 15–35 days after immunization. It is evident that the MMR vaccination increases significantly the risk of FS. This increase is correlated with the higher frequency of febrile reactions that are more common in the 2 weeks following vaccination.

Pneumococcal vaccination and FS
Pneumococcal conjugate vaccine 7 (PCV7) increases the risk of FS in the 2 days post vaccination by itself regardless of concomitant vaccination. There is no difference in FS risk between PCV13 and PCV7.

Combinations of vaccines and risk of seizures
Several combination vaccines are now available to provide protection against more than one disease. For routine vaccination of children, the combined diphtheria, tetanus and pertussis (DTP) and MMR vaccines are in widespread use. Other examples of combination vaccines are hepatitis vaccine (HepA+B+HepA) + typhoid, inactivated polio vaccine (IPV) + DTP, IPV + DTP + Haemophilus influenzae type b (Hib), MMR + varicella (MMRV), IPV + DTP + HepB + Hib. Combination vaccines based on Haemophilus influenzae type b and Neisseria meningitidis C and Y vaccines (Hib + MenC or Hib + MenCY) are also available in some countries.

Influenza vaccine has been recommended for all children aged 6 to 23 months since the 2004–2005 influenza season. Before 2010, no increased FS risk had been observed after trivalent inactivated influenza vaccine (IIV3). Subsequent vaccine safety monitoring in the United States during the 2010–2011 influenza season detected an increased risk of FS for the IIV3. It was hypothesized that concomitant PCV13 administration might have played a role. PCV13 had been introduced in the United States in 2010. Additional epidemiologic investigation found the greatest risk of FS when both vaccines were given together.

So there was an increased risk of fever and FS on post vaccination days 0 and 1 when inactivated influenza vaccine and pneumococcal conjugate vaccine were given on the same day. A population-based self-controlled risk interval analysis of the risk of FS 0 to 1 day post vaccination for all routinely recommended vaccines among children aged 6 through 23 months during a period encompassing influenza seasons (2006–2007 through 2010–2011) was done. The administration of IIV3 on the same day with PCV or a DTaP-containing vaccine was associated with a greater risk of FS than when IIV3 was given on a separate day.

Only PCV 7-valent had an independent FS risk (incidence rate ratio [IRR], 1.98; 95% confidence interval [CI], 1.00 to 3.91). IIV3 had no independent risk (IRR, 0.46; 95% CI, 0.21 to 1.02), but risk was increased when IIV3 was given with either PCV (IRR, 3.50; 95% CI, 1.13 to 10.85) or a diphtheria-tetanus-acellular-pertussis (DTaP)-containing vaccine (IRR, 3.50; 95% CI, 1.52 to 8.07). In clinical trials, DTaP-HepB-IPV had higher rates of fever compared with its separately administered component vaccines.

An independent risk of FS in the 0 to 1 days post vaccination for any vaccines other than PCV was not observed. The 0- to 1-day risk interval is likely only biologically plausible for inactivated vaccines (ie, IIV3, PCV, DTaP, HepA, HepB, Hib, IPV, and influenza A
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A cell model of DPT vaccine affects cellular signaling, catecholaminergic and GABAergic systems and blood–brain barrier due to endotoxin-mediated endothelial damage. Animal studies have shown that whole cell pertussis vaccine induces the IL-1α production in the hippocampus and hypothalamus. This induce seizures by decreasing release of inhibitory neurotransmitters GABA and adenosine in the hippocampus. Acellular pertussis vaccine does not induce the IL-1α production. Whole-cell pertussis vaccines contain 3000 different proteins, whereas acellular pertussis vaccine (DTaP) contains 2–5 proteins. This may be the reason for less chances of seizures, with DTaP as compared to whole-cell vaccine. The whole-cell pertussis vaccine has now become highly unpopular and replaced by acellular type of pertussis vaccine in many countries. The efficacy of the acellular vaccine is comparable with the whole-cell vaccine and it has substantially fewer adverse effects.

There are some observations in some studies which provide evidence that underlying genetic causes are triggered by vaccine in vaccine related seizures. A study in the Netherlands of children under two year old who experienced seizures following vaccination found that 4.5% were diagnosed with epilepsy by age two years. Children who were subsequently diagnosed with epilepsy, had seizure onset within 24 hours after giving an inactivated vaccine or 5-12 days after a live attenuated vaccine. In those whose epilepsy onset had been temporally associated with vaccination, 65% had an identifiable genetic or structural cause. Identified causes were Dravet syndrome (associated with SCN1A mutation), genetic epilepsy with FS plus syndrome, a protocadherin 19 mutation, a 1qter microdeletion, PCDH19 mutation, a 1qter microdeletion, and other monogenic familial epilepsy. These syndromes may not be recognized at the time of the first seizure. In this study, two patients who initially had a seizure with fever went on to later have afebrile seizures and was diagnosed with epilepsy. So the diagnosis of an apparent FS in a child under six months who has a seizure with fever should be considered a provisional diagnosis, with the recognition that the diagnosis might change.

Etiologies for seizures around the time of vaccination

Pertussis component of DPT vaccine affects cellular signaling, catecholaminergic and GABAergic signaling, catecholaminergic and GABAergic signaling, catecholaminergic and GABAergic signaling.
as the child ages and additional syndromic features present. There is also an increased risk of epileptic seizure precipitated by fever following vaccination regardless of the underlying mechanism of seizure susceptibility. So vaccine may elicit fever and fever in turn may precipitate a seizure in susceptible individuals.34

In one study to determine the prevalence of SCN1A variants in children having their first FS either proximal to vaccination or unrelated to vaccination compared to controls, SCN1A sequencing was performed. Two pathogenic variants in vaccine proximate cases were detected who developed Dravet syndrome and febrile seizures plus. All had generalized tonic–clonic seizures lasting >15 minutes. There recommendation is, for early diagnosis, optimal management and outcome of Dravet syndrome, it is essential to do SCN1A sequencing in infants with prolonged FS, proximate to vaccination.35 Two loci were distinctly associated with MMR-related FS, harboring the interferon-stimulated gene IFI44L. Four loci were associated with FS in general, implicating the sodium channel genes SCN1A and SCN2A, a TMEM16 family gene and a region associated with magnesium levels (12q21.33).36

Vaccine-related seizures which later come out as epilepsy, initial vaccine-related seizures occurred at a lower body temperature of <38.5°C compared with all other children. It is thought that the immune response activated by vaccination triggered a seizure without necessarily producing a high fever or even a fever at all.37

**Time of FS after vaccination**

Barlow et al reported that the risk of FS was increased almost six fold on the day of DPT receipt and dropped off to a negligible increase thereafter.10 DTaP-IPV-Hib vaccination was associated with FS on the day of the first 2 vaccinations given at 3 and 5 months.28 Immunization with MMR vaccine increased the risk of FS during the first 7 to 14 days after vaccination.5 These findings are consistent with the timing of the onset of fever after vaccination with live attenuated measles virus. Besides this, significantly elevated risk of febrile and nonfebrile seizures were not found at any other time after vaccination with DTP or MMR vaccine.29

Risk of unprovoked seizures and other neuro-behavioral disorders

There were no differences in the long term incidence of unprovoked seizures and other neurobehavioral disorders between children whose FS were associated with MMR or DTP vaccinations compared with children whose FS occurred spontaneously. This lack of any association is reassuring.13 In Norway a self-controlled case series analysis was used to estimate incidence of epilepsy after pandemic influenza vaccination. The risk of epilepsy was not increased after pandemic influenza vaccination: hazard ratio: 1.07; 95% confidence interval: 0.94–1.23.38 Ray et al. 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.39 Vaccine induced encephalopathy (or epilepsy) can be diagnosed only when other forms of childhood encephalopathy are excluded. Because infantile spasms typically start at about 6 months of age, onset of seizures might coincide with routine vaccination. The findings of studies refute claims that a close temporal association between an immunization and the onset of infantile spasms establishes causation.40,41 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.

McIntosh et al. 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. 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.42-46
Vaccine encephalopathy
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 has resulted in controversies. The entity of “vaccine encephalopathy” is poorly defined. No specific electro-clinical 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. 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. So, apparent vaccine induced encephalopathy could in fact be due to an inherent genetic defect with no causal relationship with vaccination. It is possible that vaccinations cause fever, which precipitates the manifestations (seizures) of the genetic condition.

Risk of seizures after immunization in children with epilepsy
A retrospective study of 302 children <7 years of age with epilepsy in Nova Scotia, Canada from 2010 to 2014 was done to assess risk of seizures after immunization. A risk interval analysis was conducted to estimate the relative risk (RR) of seizure during risk periods 0–14, 0–2, and 5–14 days post-immunization versus a control period 21–83 days post-immunization. Among the children 36% had focal epilepsy, 33% had unclassified epilepsy, 18% had idiopathic generalized epilepsy (52% of whom had absence epilepsy), 5% had benign childhood epilepsy with centrotemporal spikes and 4% had severe epilepsy. Only 15 children had a severe epilepsy syndrome (severe myoclonic epilepsy of infancy, infantile spasms, or Lennox-Gastaux syndrome); therefore, they could not exclude a risk in this subgroup.

Children with immunizations had more seizures than either those with no immunizations or those with no records (mean 2.5 versus 0.7 versus 0.9, p < 0.001). The risk of medically attended seizure or seizures requiring medical help was not increased 0–14 days after any vaccine (RR = 1.1, 95% confidence interval (CI): 0.5–2.8) or 0–2 days after inactivated vaccines (RR= 0.9, 95% CI: 0.1–7.1) versus 21–83 days post-immunization. No seizure events occurred 5–14 days after live vaccines. So these children did not appear to be at increased risk of seizure requiring medical attention after any immunization or after inactivated vaccines, compared to their baseline risk. Parents and vaccine providers can be reassured that children with epilepsy do not appear to be at increased risk of medically attended seizure after immunization. While a small increased risk of seizure after immunization was balanced against the risk of seizure associated with a vaccine-preventable infection, the benefits appear to outweigh the risks.

The risk of FS should not obscure the benefits of vaccination
The study done by Duffy J et al. represents the best estimate of the risk of FS associated with immunization for children ageing 1 to 5 months. The absolute risk of FS following vaccination in this age range is small. Therefore, postvaccination FS should not be a concern for the vast majority of children receiving vaccines. However, clinicians might take this risk into consideration when managing children susceptible to seizures precipitated by fever.

Vaccination has reduced childhood morbidity and mortality resulting from diseases such as smallpox, poliomyelitis, and invasive infection with Haemophilus influenzae type b. Vaccination with DPT and MMR vaccines has also reduced the incidence of neurologic disabilities that would have resulted from pertussis or measles. It is reassuring that vaccination with DPT and MMR vaccines does not appear to increase the risk of nonfebrile seizures or long-term neurodevelopment problems among children who have FS after vaccination. Children with FS do not appear to differ from children without FS in terms of intelligence, behavior, and academic progress. Children who have vaccine-associated FS are not at greater risk for epilepsy or learning, behavioral, or psychiatric disorders than other children with FS. MMR vaccination is an effective health intervention. The 3 diseases and their neurological sequel are rarely observed today in countries with high vaccination coverage. Study showed that the transient increased rate of FS was restricted to two weeks following vaccination. The risk difference was small even in children at high risk of FS. The long-term rate of epilepsy was not increased in children who had FS following MMR vaccination compared with children who had FS of a different etiology.
Consequences of not giving vaccine on apprehension of adverse events

It is well documented that there are serious effects of the illness against which these vaccines protect. Encephalitis and encephalopathies from many of the diseases are prevented in many children following vaccination. Morbidity and mortality from vaccine preventable diseases would increase to an alarming level. It is pertinent to mention that immunization for pertussis was terminated in Sweden in 1979. Over a 2-year period, over 2000 children were hospitalized with pertussis. Four percent suffered neurologic complications, and three died. Another example is anti measles vaccine. Measles in developed countries escalating from 40 cases in France in 2006 to >22,000 cases during 2008–2011. Serious acute encephalitis caused by measles can occur in approximately 1 out of 1000 cases of measles and subacute sclerosing panencephalitis, a typically fatal complication of measles, occurs in approximately 1 in 1,000,000 cases. Such occurrences appear to be prevented through vaccination. So adverse effects of vaccination occur at an magnitude far smaller than the serious measurable effects of the illnesses they prevent.

Strategies to reduce the risk of vaccine related FS

Evidence is lacking for suggesting strategies to reduce the risk of FS. Giving prophylactic antipyretics before or at the time of vaccination is not recommended. Antipyretics given after a fever started do not prevent recurrent FS. Oral diazepam given at the onset of febrile illness may be effective in preventing recurrent FS. However, potential adverse effects of diazepam should be taken into account. Parents must inform about seizures during first dose of DPT vaccine to consultant physician to take necessary step. The acellular DPT vaccine may be preferred to DTwP vaccine in those children with history of severe adverse effects following DTwP vaccine or children with neurological disorders. In a case report of a sibling of the index case of Dravet syndrome, who died, with the same SCN1A variant was subsequently managed with prophylactic valproate and additional clobazam post vaccination. She successfully completed immunizations to 18 months with no seizures and was developmentally normal.

Conclusion

DPT and MMR or MMRV vaccination can cause seizure with fever. It is extremely difficult to confirm a clear causal relationship between vaccination and FS. It is not clearly evident that the risk of nonfebrile seizures following vaccine induced FS is higher than in children who have not shown vaccine induced FS. Vaccinations should be performed without contraindication in children with previous febrile and afebrile seizures. The risk of FS should not discourage parents from vaccinating their children. Parents should be informed that vaccines could be associated with FS. A transient increase in the risk of FS should not obscure the benefits of vaccination. However, the potential benefits of vaccination to prevent episodes of infection leading to FS over longer periods is less readily apparent than the short-term risk of FS. So vaccination must be carefully carried out and proper counseling is needed. Additional research to identify evidence-based strategies to mitigate the risk of post vaccination complications is a hope.

References:

1. Madsen T. Vaccination against whooping cough. JAMA 1933;101:187-8.
2. Miller D, Wadsworth J, Ross E. Severe neurologic illness: further analyses of the British National Childhood Encephalopathy Study. Tokai J Wxp Clin Med1988; l:145-55.
3. Walker AM, Jick H, Perera DR, Knauss TA, Thompson RS. Neurologic events following diphtheria –tetanus-pertussis immunization. Pediatrics 1988; 81:345-9.
4. Griffin MR, Ray WA, Mortimer EA, Fenichel GM, Schaffner W. Risk of seizures and encephalopathy after immunization with the diphtheria –tetanus-pertussis vaccine JAMA 1990; 263:1641-5.
5. Gale JL, Thapa PB, Wassilak SG, Bobo JK, Mendelman PM, Foy HM. Risk of serious acute neurological illness after immunization with diphtheria-tetanus-pertussis vaccine. A population-based case-control study. JAMA 1994; 271:37-41.
6. Farrington P, Pugh S, Colville A, Flower A, Nash J, Morgan-Capner P et al. A new method for active surveillance of adverse events from DTP and MMR vaccines. Lancet 1995; 345: 567–9.
7. David S, Vermeer de Bondt PE, van der Maas NAT. Reactogenicity of infant whole cell pertussis combination vaccine compared with acellular pertussis vaccines with or without simultaneous pneumococcal vaccine in Netherlands. Vaccine 2008;26: 5883– 7.
8. Cody CL, Baraff LJ, Cherry JD, Marcy SM, Manclark CR. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. Pediatrics 1981;68:650–60.

9. Vaccine side effects, adverse reactions, contraindications, and precautions. Morbidity and mortality weekly report. Centers for disease control and prevention 1996; September 6: Vol.45: No. RR-12.

10. Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mulloly JP, et al. Centers for Disease Control, Prevention Vaccine Safety Datalink Working Group. The risk of seizures after receipt of whole cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med 2001; 345: 656–61.

11. Le Saux N, Barrowman NJ, Moore DL, Whiting PH, Thompson RS, Mulloly JP, et al. Centers for Disease Control, Prevention Vaccine Safety Datalink Working Group. The risk of seizures after receipt of whole cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med 2001; 345: 656–61.

12. Davis RL, Barlow W. (2003) Placing the risk of hypotonic hyporesponsive episodes presenting to hospital emergency departments since switching to acellular pertussis vaccine in Canada: a report from IMPACT. Pediatrics 2003; 112: e348–e353.

13. Vestergaard M, Hvid A, Madsen KM, Wohlfahrt J, Thorsen P, Schendel D et al. MMR vaccination and febrile seizures evaluation of susceptible subgroups and long term prognosis. JAMA 2004; 292: 351–7.

14. Miller D, Madge N, Diamond J, Wadsworth J, Ross E. Pertussis immunisation and serious acute neurological illnesses in children. BMJ 1993; 307: 1171–6.

15. Committee on Infectious Diseases. Policy Statement—Prevention of varicella: update of recommendations for use of quadrivalent and monovalent varicella vaccines in children. Pediatrics 2011; 128: 630–2.

16. Shorvon S, Berg A. Pertussis vaccination and epilepsy—an erratic history, new research and the mismatch between science and social policy. Epilepsia 2008 49: 219–25.

17. Tseng HF, Sy LS, Liu IL, Qian L, Marcy SM, Weintraub E et al. Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children. Vaccine 2013;31(22):2578–83.

18. WHO guideline on the use of safety-engineered syringes for intramuscular, intradermal and subcutaneous injections in healthcare settings. Geneva: World Health Organization; 2015 (Document:WHO/HIS/SDS/2015.5;http://www.who.int/injection_safety/global-campaign/injection-safety_guideline.pdf, accessed 10 December 2016)).

19. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP).

20. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2004; 53(6):1–40.

21. Broder KR, Martin DB, Vellozzi C. In the heat of a signal: responding to a vaccine safety signal for febrile seizures after 2010-11 influenza vaccine in young children, United States. Vaccine 2012; 30(11):2032–4.

22. Hambidge SJ, Glanz JM, France EK, McClure D, Xu S, Yamasaki K et al; Vaccine Safety Datalink Team. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. JAMA. 2006; 296(16):1990–7.

23. Armstrong PK, Dowse GK, Effler PV, Carcione D, Blyth CC, Richmond PC et al. Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. BMJ Open. 2011;1(1):e000016.

24. Tse A, Tseng HF, Greene SK, Vellozzi C, Lee G; VSD Rapid Cycle Analysis Influenza Working Group. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. Vaccine 2012;30(11):2024–2031.

25. US Centers for Disease Control and Prevention. Childhood vaccines and febrile seizures. Available at: www.cdc.gov/vaccinesafety/concerns/febrile-seizures.html.

26. Duffy J, Weintraub E, Hambidge SJ, Jackson LA, Kharbanda EO, Klein NP, et al. Febrile Seizure Risk After Vaccination in Children 6 to 23 Months. Pediatrics 2016; 138:1-10.

27. Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P et al; Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics. 2010; 126(1):e1-8.

28. Jacobsen SJ, Ackerson BK, Sy LS, Tran TN, Jones TL, Yao JF, et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine 2009; 27(34): 4656– 61.
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29. Schink T, Holstiege J, Kowalzik F, Zepp F, Garbe E. Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR+V vaccination. Vaccine 2014; 32: 645–50

30. Stockwell MS, Broder K, LaRuska P, Lewis P, Fernandez N, Sharma D et al. Risk of fever after pediatric trivalent inactivated influenza vaccine and 13-valent pneumococcal conjugate vaccine. JAMA Pediatr. 2014;168(3):211–19.

31. Donnelly S, Loscher CE, Lynch MA, Mills KH. Whole-cell but not acellular pertussis vaccines induce convulsive activity in mice: Evidence of a role for toxin-induced interleukin-1beta in a new murine model for analysis of neuronal side effects of vaccination. Infect Immun. 2001; 69:4: 217–23.

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

33. Patel MK, Patel TK, Tripathi CB. Diphtheria, pertussis (whooping cough), and tetanus vaccine induced recurrent seizures and acute encephalopathy in a paediatric patient: possibly due to pertussis fraction. J Pharmacol pharmacother 2012; 3: 71-3.

34. Verbeek NE, Jansen FE, Vermeer-de Bondt PE, de Kovel CG, van Kempen MJ, Lindhout D et al. Etiologies for seizures around the time of vaccination. Pediatrics. 2014;134:658–66.

35. Damiano JA, Deng L, Li W, Burgess R, Schneider AL, Crawford N W, et al. SCN1A Variants in vaccine related febrile seizures: A prospective study. ANN NEUROL 2020; 46:1274–82.

36. Feenstra B, Pastermak B, Geller F, Carstensen L, Wang T, Huang F, et al. Common Variants Associated With General and MMR Vaccine–Related Febrile Seizures. Nat Genet 2014; 46:1274–82.

37. Scheffer IE. Vaccination Triggers, Rather Than Causes, Seizures. Epilepsy Curr. 2015 ; 15(6): 335– 7. doi: 10.5698/1535-7511-15.6.335

38. Håberg SE, Aaberg KM, Surén P, Trogstad L, Ghaderi S, Stoltenberg C, et al. Epilepsy in Children After Pandemic Influenza Vaccination. Pediatrics 2018; e20170752; DOI: https://doi.org/10.1542/peds.2017-0752

39. Ray P, Hayward J, Michelson D, Lewis E, Schwalbe J, Black S, et al. Vaccine Safety Datalink Group. 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 2006 ;25: 768–73.

40. Goodman M, Lamm SH, Bellman MH. Temporal relationship modeling: DTP or DT immunizations and infantile spasms. Vaccine 1998;16: 225–31.

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

42. McIntosh AM, McMahon J, Dibbens LM, Iona X, Mulley JC, Scheffer IE, et al. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. Lancet Neurol 2010; 9: 592– 8.

43. Tro Baumann B, von Spiczak S, Lotte J, Bast T, Haberlandt E, Sassen R, et al. A retrospective study of the relation between vaccination and occurrence of seizures in Dravet syndrome. Epilepsia 2011; 52: 175– 8.

44. Tanabe T, Aawaya Y, Matsuishi T, Nagai T, Yamamoto K, Kurihara M, et al. Survey of vaccination and viral infections for children with severe myoclonic epilepsy in infancy. No To Hattatsu 2004; 36: 318–23.

45. Shafrir Y. Vaccination and Dravet syndrome. Lancet Neurol 2010; 9: 1147– 8.

46. Pruna D, Balestri P, Zamponi N, Grosso S, Gobbi G, Romeo A, et al. Epilepsy and vaccinations: Italian guidelines. Epilepsia 2013;54 (7):13–22.

47. Berkovic SF, Harkin L, McMahan JM, Plekenkos JT, Zuberi SM, Wirrell EC, et al. De novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. Lancet Neurol 2006; 5: 488– 92.

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

49. Top KA, Brna P, Ye L, Smith B. Risk of seizures after immunization in children with epilepsy: a risk interval analysis. BMC Pediatr. 2018; 18: 134. doi: 10.1186/s12887-018-1112-0

50. Duffy J, Hambidge SJ, Jackson LA, Kharbanda EO, Klein NP, Naleway A, et al. Febrile Seizure Risk after Vaccination in Children One to Five Months of Age. Pediatr Neurol 2017 ; 76: 72–8.

51. Romanus V, Jonsell R, Bergquist SO. Pertussis in Sweden after the cessation of general immunization in 1979. Pediatr Infect Dis J 1987; 6:364–71.

52. Antona D, Levy-Bruhl D, Baudon C, Freymuth F, Lamy M, Maine C, et al. Measles elimination efforts for children with severe myoclonic epilepsy in 1979. Pediatr Infect Dis J 1987; 6:364–71.

53. Subacute sclerosing panencephalitis surveillance: United States. MMWR Morb Mortal Wkly Rep 1982; 31:585–8.

54. Deng L, Ma A, Wood N, Ardern-Holmes S. Vaccination management in an asymptomatic child with novel SCN1A variant and family history of status epilepticus following vaccination: A case report on a potential new direction in personalised medicine. Seizure 2020; 78:49-52.