

# 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-1 $\beta$  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 vaccination against pertussis in 1933.<sup>1</sup> Later several studies have reported elevated risk of seizures

associated with diphtheria and tetanus toxoids and whole-cell pertussis (DTwP). 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).<sup>2</sup> 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).<sup>3</sup> 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.<sup>4-6</sup> 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.<sup>7</sup> 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.<sup>8,9</sup> In another report

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convulsions (with or without fever) occur 1 per, 750 doses within 48 hours after vaccination with DPT.<sup>9</sup>

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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup> Farrington et al estimated that there were 33 additional FS per 100,000 children immunized with the MMR vaccine.<sup>6</sup>

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.<sup>13</sup> 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.<sup>14</sup> 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.<sup>15,16</sup>

### **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.<sup>17</sup>

### **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 and 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.<sup>18</sup>

Influenza vaccine has been recommended for all children aged 6 to 23 months since the 2004–2005 influenza season.<sup>19,20</sup> Before 2010, no increased FS risk had been observed after trivalent inactivated influenza vaccine (IIV3).<sup>21–23</sup> Subsequent vaccine safety monitoring in the United States during the 2010–2011 in influenza season detected an increased risk of FS for the IIV3. It was hypothesized that concomitant PCV13 administration might have played a role.<sup>24</sup> 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.<sup>24</sup>

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.<sup>24</sup>

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.<sup>25</sup>

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

virus vaccine, 2009 (H1N1), were assessed in this study). In another study combination of vaccines received simultaneously by patients were rota virus vaccine pentavalent (RV5), DTaP-HepB-IPV, Hib, and PCV. Results indicate that FS risk may increase on the day of or the day after administration of an inactivated vaccine, but not all FS occurring during this time interval will necessarily be caused by vaccination.<sup>26</sup> Independent risk with RV5, MMR, varicella vaccine (VAR), or MMRV was also not observed. A previous study examined MMRV, MMR, and VAR using an appropriate 7- to 10-day risk interval.<sup>27</sup> The risk of FS 5-12 days after the first dose of MMRV vaccination in immunocompetent children is 2 fold higher than using non-combined vaccination (MMR+V). This resulted in one additional FS for every ~2300-2700 children vaccinated with MMRV vs MMR + V. This higher risk was documented in studies among children 12 (9) to 23 months of age.<sup>28,29</sup>

However, some combinations like DPT or MMR or DTaP cannot be separated. But combination like MMRV can be avoided to MMR+V. It was found that the concomitant administration of IIV3 with a DTaP-containing vaccine was associated with a risk of FS that was statistically significantly greater than the sum of the independent risks of each vaccine given separately. The relative excess risk due to the interaction between IIV3 and PCV was similarly elevated. The clinical significance of the IIV3-PCV interaction is due to a synergistic effect with concomitant administration of those 2 vaccines.<sup>30</sup> The maximum estimated absolute excess risk due to concomitant administration of IIV3, PCV, and DTaP-containing vaccines compared with administration on separate days was 30 FS per 100 000 persons vaccinated.<sup>26</sup> This is similar to the absolute risk of FS previously identified for the MMR vaccine of 25 to 34 FS per 100 000 persons vaccinated.<sup>10</sup> This absolute risk may be outweighed by the benefits of timely vaccination that can be achieved by giving IIV3 on the same day as other vaccines when needed. When benefits of vaccination are taken into consideration then IIV3, PCV, and DTaP vaccines each have the potential to prevent multiple episodes of infection, including fevers and FS caused by those infections. It is not recommended separating any of these vaccines to different days.<sup>26</sup>

### **Etiologies for seizures around the time of vaccination**

Pertussis component 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-1 $\alpha$  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-1 $\alpha$  production.<sup>31</sup> Whole-cell pertussis vaccines contain 3000 different proteins, whereas acellular pertussis vaccine (DTaP) contains 2–5 proteins.<sup>32</sup> This may be the reason for less chances of seizures, with DTaP as compared to whole-cell vaccine.<sup>33</sup> 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.<sup>32,33</sup> In one study, it was noted that patients with FS during the risk interval after vaccination had a non-CNS infection documented at the time of their FS. This infection might have contributed to FS.<sup>34</sup> Some of these seizures might also be due to noninfectious preexisting conditions that had not yet been diagnosed.

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 1 qter microdeletion, PCDH19 mutation, a neuronal migration disorder and other monogenic familial epilepsy.<sup>34</sup> 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.<sup>34</sup> 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

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.<sup>34</sup>

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. Their 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.<sup>35</sup> 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).<sup>36</sup>

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.<sup>37</sup>

#### 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.<sup>10</sup> DTaP-IPV-Hib vaccination was associated with FS on the day of the first 2 vaccinations given at 3 and 5 months.<sup>28</sup> Immunization with MMR vaccine increased the risk of FS during the first 7 to 14 days after vaccination.<sup>5</sup> 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.<sup>29</sup>

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.<sup>13</sup> 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.<sup>38</sup> 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.<sup>39</sup> 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.<sup>40,41</sup> 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.<sup>42-46</sup>

### 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.<sup>47</sup> 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.<sup>48</sup> 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.<sup>46-48</sup>

### 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 38% 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-Gastaut 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.<sup>49</sup>

### 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.<sup>50</sup>

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.<sup>5</sup> MMR vaccination is an effective health intervention. The 3 diseases and their neurological sequelae 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.<sup>37</sup>

### 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.<sup>51</sup> 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.<sup>52</sup> 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.<sup>43</sup> So adverse effects of vaccination occur at a magnitude far smaller than the serious measurable effects of the illnesses they prevent.<sup>53</sup>

### 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.<sup>26</sup> 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.<sup>54</sup>

### 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.

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