Seizures following vaccination in children

Risks, outcomes and management of subsequent revaccination

CPD

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Background
Seizures and status epilepticus can occur within 14 days following administration of inactivated and live-attenuated vaccines. These vaccine-proximate seizures can undermine parental confidence in vaccine safety and affect further vaccination decisions. Vaccine-proximate status epilepticus (VP-SE) is uncommon but may be the first manifestation of genetic developmental epileptic encephalopathies, including Dravet syndrome.

Objective
The aim of this article is to review current literature on the risks and outcomes of vaccine-proximate seizures and, using two clinical scenarios, outline management of subsequent revaccination.

Discussion
Vaccine-proximate seizures require careful evaluation of the vaccine(s) involved, seizure type and duration to determine a safe course for revaccination. Vaccine-proximate febrile seizures (VP-FSs) have similar outcomes to other febrile seizures and are not associated with increased developmental or behavioural concerns. Vaccination for children with VP-FSs can occur safely in the community. However, VP-SE cases warrant prompt specialist review, consideration of genetic epilepsy testing and referral to a specialist immunisation clinic for subsequent vaccination under medical supervision.

AS THE INCIDENCE of vaccine-preventable diseases and their consequences declines with successful vaccination programs, the public's focus has shifted to vaccine safety and potential adverse events following immunisation (AEFIs). AEFIs, particularly neurological events with risk of developmental sequelae, can particularly affect parental confidence in vaccine safety and influence further vaccination decisions. Seizures following vaccination are one such AEFI. While the child's initial seizure will most likely be managed in an emergency department, parents of these children often present to general practitioners (GPs) seeking advice about their child's subsequent vaccinations.

In this article, the authors present a review of what is known about seizures that occur following vaccination, known as vaccine-proximate seizures, in children. This is followed by two illustrative cases to highlight the clinical differences and management implications in relation to planning further vaccination in each case.

Vaccine-proximate febrile seizures

Febrile seizures are the most common type of childhood seizure, and they occur in association with a febrile illness.[1] They occur in 2–5% of children aged between six months and six years, with approximately half first occurring between 12 and 30 months of age.[2] Fever following vaccination usually occurs within 48 hours following administration of inactivated vaccines (eg diphtheria/tetanus/pertussis [DTP] or influenza vaccines) or 5–14 days following live-attenuated vaccines (eg measles/mumps/rubella [MMR], varicella or measles/mumps/rubella/varicella [MMRV] vaccines). During these defined periods, when fever is more likely following vaccination, vaccine-proximate febrile seizures (VP-FSs) can occur.[3–6] In this article, the authors present the known risk of febrile seizures following specific vaccines.

Live-attenuated vaccines

Measles-containing vaccines

The risk of febrile seizure 5–14 days following MMR vaccination[3,7] is double the risk of febrile seizure outside this period, with the peak incidence on day nine post-vaccination.[8] When a narrower risk period of 6–11 days post-vaccination was examined, an attributable risk of one febrile seizure per 1150–3000 vaccinations was reported.[9,10]

Febrile seizure risk is also elevated with MMRV vaccine when the vaccine is given as the first dose of measles-containing vaccine; however, this risk is not seen when the MMRV vaccine is given as the second dose. Studies have shown a twofold increased risk of febrile seizure 5–12 days following vaccination in children receiving

MMRV as their first dose of measles-containing vaccine when compared with children receiving MMR and varicella separately, equating to an additional one febrile seizure per 2600 children vaccinated.[6,11] This increased risk was not seen for MMRV or MMR plus varicella given to children aged 4–6 years,[12] and it was also not seen when MMRV was given as the second dose of measles-containing vaccine at 18 months of age.[5] As such, the Australian National Immunisation Program only recommends MMRV at 18 months of age as the second dose of measles-containing vaccine, and for use as the first dose of measles-containing vaccine only in children aged >4 years.

Inactivated vaccines

Pertussis vaccines

Acellular pertussis–containing vaccine (DTPa) has been in use in Australia, in replacement of the more reactogenic whole-cell pertussis vaccine, from 1997. A large population-based Danish study identified a small risk of febrile seizure on the day of vaccination for the first and second dose of DTPa only, at three and five months of age, of <1 febrile seizure per 28,000 vaccinations. There was no overall increased risk of febrile seizure within 0–7 days of vaccination across the three primary doses.[4] Importantly, the study found no increased risk of recurrent febrile seizures or subsequent epilepsy in children whose first febrile seizure occurred within 0–7 days of vaccination. Other studies have reported no attributable risk of febrile seizure on the day of, or 0–3 days following, DTPa vaccination.[13,14]

Influenza vaccines

Febrile seizure risk following influenza vaccination was first identified when the 2010 Southern Hemisphere seasonal trivalent influenza vaccine (TIV) of a single brand in Australia was associated with one febrile seizure per 300 vaccine doses administered,[15] which led to a temporary suspension of influenza vaccine for children in Australia for that season. Prior to this, a US study found one febrile seizure in 70,000 TIV doses in children aged <2 years in 2003–04.[16] In Northern Hemisphere influenza seasons subsequent to 2010, a fivefold increased risk was identified of febrile seizure 0–1 day following concomitant TIV and 13-valent pneumococcal conjugate vaccine (PCV13) administration in children when compared with receiving either vaccine separately.[17] Following the unexpected increase in febrile seizures associated with TIV in 2010, Australia established a national sentinel vaccine safety active surveillance system, AusVaxSafety (http://ausvaxsafety.org.au), to monitor the safety of vaccines in Australia. By analysing de-identified data reported directly from people receiving vaccines (or their parents or carers), AusVaxSafety monitors AEFIs and facilitates early detection of potential vaccine safety issues. There has been no increased risk of febrile seizure with influenza vaccines in Australia identified since. In 2015 and 2016, only six (0.08%) of 7198 responders reported seizures within three days of influenza vaccination, five of whom had a prior history of seizures.[18]

Table 1 summarises the timing and risk of febrile seizures following vaccination. Seizures occurring outside of these biologically plausible timeframes are not considered to be related to vaccination, and an alternative cause should be considered.

Clinical outcomes of vaccine-proximate febrile seizures

Most febrile seizures are simple, defined as a generalised tonic-clonic seizure lasting <15 minutes with no recurrence within 24 hours of the initial seizure or postictal pathology such as Todd's paresis.[19] Approximately 20–30% of febrile seizures have one or more complex features, with 4–16% having focal features.[20–22]

VP-FSs were found to be no different in seizure severity to febrile seizures of another cause (ie non–vaccine proximate febrile seizures [NVP-FSs]).

Table 1. Biologically plausible risk intervals for vaccine-proximate seizures

Vaccine type	Vaccines	Risk interval (days after vaccination)	Febrile seizure risk
Live-attenuated	MMR	5–14	One febrile seizure per 1,150–3,000 vaccinations[9,10]
	MMRV	5–14	One additional febrile seizure per 2,600 MMRV vaccinations when compared with MMR+V[6,11]
			No increased risk if administered as dose two[12]
Inactivated	DTPa	0–2	No increased risk[4,13,14]
	TIV	0–2	One febrile seizure per 70,000 vaccinations (2003–04)[16]
			One febrile seizure per 300 vaccinations (2010)[15]
			No increased risk with current formulation[18]
	TIV + PCV13	0–2	Fivefold increased risk of febrile seizure compared to having the vaccines separately[17]

DTPa, diphtheria/tetanus/acellular pertussis vaccine; MMR, measles/mumps/rubella vaccine; MMR+V, MMR vaccine given concomitantly with varicella zoster virus vaccine; MMRV, measles/mumps/rubella/varicella vaccine; PCV13, 13-valent conjugate pneumococcal vaccine; TIV, trivalent influenza vaccine

In a prospective Australian cohort study of 1022 children aged <6 years presenting to hospitals with their first febrile seizure, there was no increased risk found of prolonged febrile seizure or seizure recurrence in the first 24 hours following VP-FS when compared with NVP-FS. VP-FS and NVP-FS cases also had similar hospitalisation duration. In addition, the study found 12% of children with VP-FS had a laboratory-confirmed concomitant infection. Children who had both an infection and recent vaccination had a longer hospitalisation for infection treatment, compared with those with no coinfection. A US retrospective cohort study of children aged six months to three years supported these findings, identifying no difference in the risk of hospitalisation between first VP-FS and NVP-FS.[23] Both studies reported no difference in the risk of febrile seizure recurrence in the follow-up period of their cohorts.

Population-based studies show that most children aged 6–12 years with a history of febrile seizure have normal cognitive and academic performance.[24,25] Developmental and behavioural outcomes of children following their first VP-FS were assessed and compared with children with NVP-FS and those with no seizure history, 12–18 months following the initial febrile seizures, in a recent Australian prospective multicentre case-control study. The study found no difference between the three groups in their cognitive, motor, language, social-emotional or general adaptive functions on formal developmental assessment.[26] There was also no difference in executive function and behaviour of children with VP-FS or NVP-FS when compared with controls on parent-rated behaviour questionnaires.

Vaccine-proximate afebrile seizures and status epilepticus

In addition to febrile seizures, afebrile seizures and status epilepticus, a seizure lasting ≥30 minutes or multiple seizures over a 30-minute period with no return to normal level of consciousness between each seizure, have also been reported following vaccinations, though the risk is not as clearly defined. A retrospective review of the AEFI database in Germany from 2006–08[27] identified 247 seizure reports following vaccination, of which there were 21 cases of status epilepticus and 44 single afebrile seizures.

An Australian study identified that 11 of 14 children with epilepsy whose first seizure was vaccine-proximate (two febrile seizures, three afebrile seizures, six cases of status epilepticus, three unclear) had *SCN1A*-associated Dravet syndrome.[28] A further study of 40 children with Dravet syndrome found 12 had their first seizure within two days of DTP vaccination, five of which were status epilepticus, and all occurred in children aged <12 months (mean age 4.5 months).[29] A study of 1729 Dutch children with seizures following vaccination reported over a 10-year period identified that six of the 15 *SCN1A*-associated Dravet syndrome cases presented with status epilepticus.[30] In the abovementioned case-control study, two VP-FS cases were identified to have a pathogenic *SCN1A* variant on genetic testing, and both presented with status epilepticus following DTP vaccination aged <12 months.[31]

Dravet syndrome is a form of severe epilepsy in which 80% of patients have an *SCN1A* variant.[32–36] Features of Dravet syndrome are outlined in Box 1. Seizures typically present in the first year of life, often as prolonged seizures triggered by fever. Patients progress to have various seizure types, with common triggers being fever, heat and sunlight. Developmental stagnation and regression occur between the ages of one and four years, resulting in cognitive, motor and behavioural impairment, with some children displaying autistic and hyperactive traits.[37–39] Seizures in patients with Dravet syndrome are usually refractory to standard antiepileptic medication. As a result, screening for *SCN1A* variants in infants with vaccine-proximate status epilepticus (VP-SE) should be considered for early diagnosis and optimal management of subsequent vaccinations, especially to prevent recurrent VP-SE.

Children with VP-SE should be referred to the specialist immunisation clinic in their respective state or territory for assessment in conjunction with a paediatric neurologist to determine future vaccination plans. If vaccination can proceed and parents are agreeable, a vaccination protocol for children with VP-SE can be followed. The protocol, developed by The Royal Children's Hospital Melbourne's immunisation service together with expert neurologists, involves vaccination under medical supervision in hospital with prophylactic antiepileptic and antipyretic medication.

There are few data on clinical outcomes and the risk of seizure recurrence in children with afebrile seizures post-vaccination. Therefore, these children should also be referred to a specialist immunisation clinic for assessment for vaccination under medical supervision.

Children with neurological conditions, including epilepsy, are at increased risk of complications from vaccine-preventable diseases including influenza. Where possible, it is important to facilitate timely vaccination of these children by early referral to specialist immunisation services.

Table 2 summarises the features of the different types of vaccine-proximate seizures, recommended investigations and subsequent vaccination management.

CASE 1

Mary, a healthy infant aged 12 months, had a five-minute generalised tonic-clonic seizure with no focal signs at home. She was febrile to 39 °C at the time of the seizure. On review in the emergency department, Mary had a normal examination with no clear focus of infection. She had no significant medical or family history, though it was noted that she had received her 12-month vaccines (MMR, quadrivalent meningococcal conjugate vaccine [MenACWY] and PCV13) nine days prior. She was discharged home after a period of observation in the emergency department with a diagnosis of a simple febrile seizure.

This is an example of a simple febrile seizure nine days post-MMR vaccination, where the vaccine is a biologically plausible cause or trigger of the febrile seizure. On review at 18 months, Mary

had had no further febrile seizures and remained developmentally normal. Her GP reassured her parents regarding the long-term outcomes following a VP-FS, and she proceeded to have her 18-month MMRV vaccination in the clinic with no adverse reactions.

CASE 2

John, a boy aged four months, was brought in by ambulance to the emergency department in status epilepticus. Fifteen hours prior, he had received his four-month vaccinations (diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, hepatitis B and inactivated polio combination vaccine; PCV13; and oral rotavirus vaccine). The status was terminated after 40 minutes with four doses of midazolam (0.3 mg/kg/dose) and levetiracetam (20 mg/kg). John was a healthy infant with no previous seizures and no family history of febrile seizures or epilepsy. He was discharged with buccal midazolam for emergency seizure management out of hospital.

This is an example of status epilepticus following DTPa vaccination, where the vaccine is again a biologically plausible cause of the seizure. John had further febrile and afebrile seizures, unrelated to vaccination, and was referred to a neurologist for further assessment. He was diagnosed with Dravet syndrome after showing signs of developmental regression and genetic testing that confirmed an *SCN1A* variant. Through a specialist immunisation clinic and in consultation with his treating neurologist, his six-month scheduled vaccinations were safely administered as an inpatient under medical supervision using a hospital revaccination protocol that included additional prophylactic anti-epileptic therapy. He also safely received the influenza vaccine at the same time to ensure he was protected against influenza disease.

Box 1. Features of Dravet syndrome

- Frequent febrile and afebrile seizures in the first year of life, often prolonged
- Seizure triggers including fever, heat and sunlight
- High risk of vaccine-proximate seizures, particularly vaccine-proximate status epilepticus
- Other seizure types, including myoclonic and absence seizures, appearing between one and four years of age
- Developmental plateau or regression starting from the second year of life
- Cognitive, motor and behavioural impairment
- Movement and balance impairment
- Autistic and hyperactive traits

Table 2. Post-vaccination seizures

Seizure	Features	Investigations	Vaccination management
Simple febrile seizure[19]	• Documented fever • No evidence of central nervous system infection • No previous neonatal or unprovoked seizure • Generalised tonic-clonic seizure • ≤15 minutes' duration • No recurrence within 24 hours of initial seizure • No postictal pathology	Nil required	Continue vaccination in usual setting – general practice or community clinic
Complex febrile seizure[20]	One or more of the following: • >15 minutes' duration • focal features • recurrence within 24 hours of the initial seizure • presence of postictal pathology such as Todd's paresis	• Exclude other causes (electrolyte abnormality, CNS infection, structural abnormality) • EEG • CNS imaging	Where no other cause is found through investigation, can continue vaccination in usual setting – general practice or community clinic
Afebrile seizure	Seizure (generalised or focal onset) in the absence of a fever	As above	Referral to specialist immunisation clinic for review and vaccination under medical supervision
Status epilepticus[1]	• Seizure lasting >30 minutes OR • Multiple seizures over a 30-minute period with no return to normal level of consciousness between each seizure	• As above • If aged <12 months, consider referral to neurologist for genetic epilepsy panel	Referral to specialist immunisation clinic and vaccination under medical supervision as an inpatient using a revaccination protocol

CNS, central nervous system; EEG, electroencephalogram

Conclusion

These case studies highlight two types of seizures following vaccination. Where a simple VP-FS has occurred, immunisation providers and parents can be reassured that the clinical severity and neurodevelopmental outcomes following VP-FSs are no different to febrile seizures due to another cause. Further vaccinations can be safely administered for these children in their usual setting, either general practice or community clinic, and should not be delayed.

Children presenting with VP-SE or vaccine-proximate afebrile seizures should be referred for specialist review and consideration of investigations for an underlying genetic epileptic encephalopathy. It is important that subsequent vaccination occurs under medical supervision. Children diagnosed with Dravet syndrome or other genetic epilepsies are ideally vaccinated as an inpatient using a revaccination protocol.

In all instances, further vaccination should be prioritised if possible and can usually be safely achieved in consultation with immunisation specialists and neurologists through specialist clinics in each state and territory in Australia if required.

Key points

- Both live-attenuated and inactivated vaccines are associated with febrile seizures and, rarely, status epilepticus.
- Revaccination management of children with vaccine-proximate seizures is dependent on the seizure type.
- Clinical and neurodevelopmental outcomes of children with VP-FSs are no different to those of children with febrile seizures from another cause or children with no history of seizures.
- Children with febrile seizures can safely continue vaccination in the community.
- Young infants (particularly those aged <12 months) with febrile status epilepticus following vaccination could have an underlying genetic epilepsy, such as Dravet syndrome, and should be referred to a specialist immunisation clinic or neurologist for further investigations.
- It is important to refer children with afebrile seizures to a specialist immunisation clinic for review and vaccination under medical supervision.

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