Seizures following vaccination: risk, outcome and recurrence

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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Contents

Tables and figures

This list only includes tables and figures not contained in published manuscripts.

Statement of originality

I certify that, to the best of my knowledge, the content of this thesis is the product of my own work and that all assistance received in preparing this thesis and all sources have been acknowledged. I declare that appropriate ethical review and approval was sought for this work and that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Lucy Deng

25 October 2021

Executive summary

Background

An adverse event following immunisation is any untoward medical occurrence that follows immunisation and does not necessarily have a causal relationship with the usage of the vaccine. Seizures, ranging from the common and mostly benign febrile seizure to the life-threatening status epilepticus, that occur following immunisation are considered adverse events following immunisation. Febrile seizures have been observed to occur in defined periods following vaccination when a fever is most likely to occur. The magnitude of risk attributed to specific vaccines varies, with no known increased risk seen for some vaccines. Status epilepticus, continuous seizure activity for 5 minutes or more without return of consciousness, or recurrent seizure activity without a return to baseline consciousness in between, has also been reported following vaccination, though the magnitude of attributable risk is unclear. Both seizure types are rare, but serious adverse events, that can follow and sometimes be triggered by immunisation. Because of the potential risk of neurodevelopmental sequalae, seizures can affect both provider and consumer confidence in vaccine safety and therefore immunisation coverage.

Knowledge gaps on seizures following vaccination include their clinical severity, developmental outcomes, genetic risks and revaccination outcomes. In my thesis, I aimed to address these gaps to better inform immunisation providers about the risks and outcomes of these potentially serious adverse events following immunisation, to improve guidance on their assessment and management, and ultimately to improve parent and consumer confidence in vaccine safety.

Febrile seizures following vaccination

In this thesis, I set out to assess the clinical severity, neurodevelopmental outcome and genetic risk of febrile seizures following vaccination, to supplement the known attributable risk of febrile seizures following specific vaccines. Vaccine proximate seizures were defined as VPS was defined as a seizure within 14 days of a vaccination encounter, based on previous studies on the timing of fever and febrile seizures following specific vaccines. I examined the clinical severity of vaccine-proximate

febrile seizures through a multi-site prospective cohort study. I discovered that febrile seizures most commonly occurred following the first dose of measles-containing vaccine, and were not clinically any different to febrile seizures due to another cause such as a viral illness. The only factor that prolonged hospitalisation in children with a vaccine-proximate febrile seizure was the presence of concomitant laboratory-confirmed infection. A subsequent prospective case-control study was conducted to assess developmental and behavioural outcomes, and to identify the presence of genetic variants in children with vaccine-proximate febrile seizures compared to children with non-vaccine-proximate febrile seizures and no history of seizures. Using standardised developmental tests administered by certified assessors blinded to the child's medical history and standardised parent-completed questionnaires, this study found no increased risk of developmental or behavioural problems in children with vaccine-proximate febrile seizures compared to children with non-vaccine-proximate seizures or no history of seizures. Genetic variants in the sodium channel gene, *SCN1A*, associated with a severe form of epilepsy were only identified in children with prolonged vaccine-proximate febrile seizures.

Status epilepticus following vaccination

Prior to this thesis, there were only case reports and case series on vaccine-proximate status epilepticus, presenting an incomplete and potentially biased picture of the risk and severity of vaccine-proximate status epilepticus that may not be generalisable to the whole population. Using a retrospective, population-based, record-linked cohort linking birth, immunisation, hospitalisation and death data, I was able to determine that less than 4% of first episode status epilepticus in children was vaccine proximate. Similar to vaccine-proximate febrile seizures, status epilepticus was found to occur most commonly following the first dose of measles-containing vaccine, but at a rate 35 times lower than that of vaccine-proximate febrile seizure for the same risk window. There was no difference in clinical severity, measured by duration of hospitalisation, intensive care unit admission or death, between vaccine-proximate and non-vaccine-proximate status epilepticus cases. The predictor for ongoing seizures subsequent to the first status epilepticus was seizure onset prior to the status epilepticus episode. Importantly, vaccination uptake decreased following status epilepticus, regardless of the proximity of the status epilepticus episode to vaccination. These findings were confirmed in a second retrospective cohort study I conducted using medical record review to validate the findings from the larger population-based retrospective study that relied on hospital administrative

data. The retrospective cohort study also found morbidity following vaccine-proximate status epilepticus was associated with the presence of an underlying genetic epilepsy, where the seizures are the result of a known or presumed genetic defect.

Revaccination outcomes following vaccine-proximate seizures

Following the identification of the risk and outcome of seizures following vaccination, the next logical clinical question to address was can these children safely proceed with subsequent vaccinations and, if so, how? I, therefore, examined the risk of seizure recurrence following revaccination in children with a previous vaccine-proximate seizure. Through a 5-year multi-site retrospective cohort study, I reviewed the clinical management and outcomes of children with a history of vaccine-proximate seizures who presented to a Specialist Immunisation Clinic, a specialist clinic at tertiary paediatric hospitals where children with a vaccine proximate seizure are provided specialised medical assessment and management for subsequent vaccinations. Vaccine-proximate seizure recurrence was found to be more likely in children with an underlying genetic epilepsy, in particular Dravet syndrome. Reassuringly, the risk of seizure recurrence decreased with the use of prophylactic benzodiazepine with vaccination in these children.

Conclusions

Vaccination is one of the most effective public health measures for reducing the burden of infectious diseases. However, the success of vaccination programs has been threatened by vaccine hesitancy, that is, the reluctance or refusal to vaccinate despite vaccine availability. Concerns regarding the safety of vaccines and their potential long-term neurological sequalae are amongst the complex reasons why people choose not to vaccinate.

My doctoral research has contributed to vaccine safety knowledge globally, specifically in the understanding of seizures, specifically febrile seizures and status epilepticus, as severe acute neurological events following vaccination. In this thesis, I not only identified the children most at risk of neurological sequelae following a vaccine-proximate seizure, but also a revaccination management plan that would allow these children to continue vaccinations without placing them at risk of further

vaccine-proximate seizures. These are children aged <12 months, whose underlying genetic epileptic encephalopathy is unmasked by a vaccination event. These children typically present with status epilepticus following vaccination, and are most likely to have further seizures with revaccination if it is given without additional precautions in the form of prophylactic benzodiazepine. My thesis finding highlights the importance of, and future work required to better understand, adversomics – the immunogenetics and immunogenomics of vaccine adverse events at the individual and population level, respectively – and its implications on vaccine safety, confidence and uptake.

Finally, my thesis incorporates a variety of research methods, from retrospective record-linked cohort studies to examine whole-of-population risk, retrospective multi-site clinic-based cohort studies to examine detailed clinical management and outcomes, and prospective case-control studies to test hypotheses. I have demonstrated the unique contribution of each of these research methods and the strength in combining these to form a broader pharmacovigilance program of research that can help inform both risk and outcome at a population and individual level. By applying the doctoral research skills I have acquired, I aim to continue my work as a vaccine safety clinician researcher in the monitoring and investigation of vaccine safety signals for novel vaccines, including the multiple COVID-19 vaccines currently in early use globally, to ensure the continued safe and effective use of vaccines in the years to come.

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This thesis arose from a vision from my inspiring, practical, patient- and clinical-care-oriented supervisor A/Prof Nicholas Wood. I am enormously grateful for the opportunity that Nick granted to me to pick up his NHMRC-funded project and “run with it”. Nick is the best ship’s captain you could ever ask to learn from, masterfully balancing the opportunities for self-discovery and growth, all the while watching the direction of the ship, ensuring I was not sailing astray. It has been an honour to be guided and supported by an amazing leader, a visionary who is constantly reminding me to ask the “Why?” and “So what?” questions in research.

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Authorship attribution statement

I, Lucy Deng, was the first author and corresponding author* for the following six published and one submitted manuscripts contained in the body of this thesis:

Chapter 2 of this thesis includes four peer-reviewed first author published manuscripts:

Deng L, Gidding H, Macartney K, Crawford N, Buttery J, Gold M, Richmond P, Wood N. Postvaccination febrile seizure severity and outcome. Pediatrics. 2019;143(5):e20182120. doi:10.1542/peds.2018-2120

Deng L, Wood N, Macartney K, Gold M, Crawford N, Buttery J, Richmond P, Barton B. Developmental outcomes following vaccine-proximate febrile seizures in children. Neurology. 2020;95(3):e226–38. doi:10.1212/WNL.0000000000009876

Damiano JA*, **Deng L***, Li WH, Burgess R, Schneider AL, Crawford NW, Buttery J, Gold M, Richmond P, Macartney KK, Hildebrand MS, Scheffer IE, Wood N, Berkovic SF. *SCN1A* variants in vaccine-related febrile seizures: a prospective study. Annals of Neurology. 2020;87(2):281–8. doi:10.1002/ana.25650. (*joint first authors, Prof Samuel Berkovic as corresponding author)

Deng L, Wood N, Danchin M. Seizures following vaccination in children: risks, outcomes and management of subsequent revaccination. Australian Journal of General Practice. 2020;49(10):644–9. doi:10.31128/AJGP-02-20-5236

I analysed the data, wrote the initial drafts of the manuscripts and revised the manuscripts with input from co-authors.

Chapter 3 of this thesis includes one published and one submitted first author manuscript:

Deng L, Ma A, Wood N, Ardern-Holmes S. Vaccination management in an asymptomatic child with a 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. doi:10.1016/j.seizure.2020.03.005

Deng L, Macartney K, Gill D, Fathima P, Wood N, Gidding H. Clinical outcomes and risk of status epilepticus following vaccination in children: a retrospective, population-based, record-linked cohort study. Developmental Medicine and Child Neurology. *Manuscript under review.*

I designed the study, analysed the data, wrote the initial draft of the manuscript and revised the manuscript with input from co-authors.

Chapter 4 of this thesis includes one submitted first author manuscript:

Deng L, Danchin M, Lewis G, Cheung A, Campbell A, Wadia U, Ewe K, Wood N. Revaccination outcomes of children with vaccine proximate seizures. Vaccine. 2021;39(11):1565–71. doi:10.1016/j.vaccine.2021.02.016

I designed the study, analysed the data, wrote the initial draft of the manuscript and revised the manuscript with input from co-authors.

Lucy Deng

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As a supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

A/Prof Nicholas Wood

25 October 2021

Publications and presentations arising from this thesis

The following are listed in chronological order.

Publications

1. **Deng L**, Gidding H, Macartney K, Crawford N, Buttery J, Gold M, Richmond P, Wood N. Postvaccination febrile seizure severity and outcome. Pediatrics. 2019;143(5):e20182120. doi:10.1542/peds.2018-2120
2. Damiano JA*, **Deng L***, Li WH, Burgess R, Schneider AL, Crawford NW, Buttery J, Gold M, Richmond P, Macartney KK, Hildebrand MS, Scheffer IE, Wood N, Berkovic SF. *SCN1A* variants in vaccine-related febrile seizures: a prospective study. Annals of Neurology. 2020;87(2):281–8. doi:10.1002/ana.25650. (*joint first authors)
3. **Deng L**, Ma A, Wood N, Ardern-Holmes S. Vaccination management in an asymptomatic child with a 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. doi:10.1016/j.seizure.2020.03.005
4. **Deng L**, Wood N, Macartney K, Gold M, Crawford N, Buttery J, Richmond P, Barton B. Developmental outcomes following vaccine-proximate febrile seizures in children. Neurology. 2020;95(3):e226–38. doi: 10.1212/WNL.0000000000009876
5. **Deng L**, Wood N, Danchin M. Seizures following vaccination in children: risks, outcomes and management of subsequent revaccination. Australian Journal of General Practice. 2020;49(10):644–9. doi:10.31128/AJGP-02-20-5236
6. **Deng L**, Danchin M, Lewis G, Cheung A, Campbell A, Wadia U, Ewe K, Wood N. Revaccination outcomes of children with vaccine proximate seizures. Vaccine. 2021;39(11):1565–71. doi:10.1016/j.vaccine.2021.02.016

Submitted manuscripts

1. **Deng L**, Macartney K, Gill D, Fathima P, Wood N, Gidding H. Clinical outcomes and risk of status epilepticus following vaccination in children: a retrospective, population-based, record-linked cohort study. Submitted to: Developmental Medicine and Child Neurology

Presentations

1. Research e-poster presentation (international): European Society of Paediatric Infectious Disease Society Meeting, Malmo, May 2018.

   Deng L, Wood N, Macartney K, Crawford N, Buttery J, Gold M, Richmond P, Barton B. Post vaccination febrile seizures: clinical severity and long-term developmental outcome data.

2. Research oral presentation (national): Public Health Association Australia National Immunisation Conference, Adelaide, June 2018.

   Deng L, Macartney K, Crawford N, Buttery J, Gold M, Richmond P, Wood N. Post vaccination febrile seizures: clinical severity and outcome data is reassuring.

3. Research oral presentation (international): New Zealand Immunisation Conference, Auckland, September 2019.

   Deng L, Wood N, Macartney K, Blyth C, Fatima P, Gidding H. Status epilepticus following vaccination is rare.

4. Research poster presentation (international): American Academy of Pediatrics Conference, New Orleans, October 2019.

   Deng L, Wood N, Macartney K, Crawford N, Buttery J, Gold M, Richmond P, Barton B. Febrile seizures following vaccination do not impact on young children's development or behaviour.

5. Research oral presentation (national): Public Health Association Australia National Immunisation Conference, Perth, June 2020 (accepted abstract; postponed due to COVID-19)

   Deng L, Campbell A, Wadia U, Wen S, Bhatia R, Wood N, Danchin M. Status epilepticus following vaccination: a five-year retrospective review.

6. Research poster presentation (national): Public Health Association Australia National Immunisation Conference, Perth, June 2020 (accepted abstract; postponed due to COVID-19)

Deng L, Macartney K, Crawford N, Buttery J, Gold M, Richmond P, Scheffer I, Berkovic S, Barton B, Wood N. Developmental outcomes and *SCN1A* variants in children with vaccine-proximate febrile seizures.

Abbreviations

AED	antiepileptic drug
AEFI	adverse event following immunisation
AEFI-CAN	Adverse Event Following Immunisation Clinical Assessment Network
CI	confidence interval
COVID-19	coronavirus disease
DNA	deoxyribonucleic acid
DTP	diphtheria-tetanus-pertussis
DTPa	diphtheria-tetanus-acellular pertussis
DTPa-IPV-Hib	diphtheria-tetanus-acellular pertussis, inactivated polio and *Haemophilus influenzae* type b combination vaccine
DTPa-IPV-Hib-HBV	diphtheria-tetanus-acellular pertussis, inactivated polio, *Haemophilus influenzae* type b and hepatitis B combination vaccine
DTPw	diphtheria-tetanus-whole-cell pertussis
EEG	electroencephalogram
FS	febrile seizure
FSE	febrile status epilepticus
GEFS+	generalised epilepsy with febrile seizure plus
HHV	human herpesvirus
Hib-MenC	combination *Haemophilus influenzae* type b and meningococcal C conjugate vaccine
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases Ninth Revision, Clinical Modification
ICD-10-AM	International Classification of Diseases Tenth Revision, Australian Modification
ICU	intensive care unit
IL	interleukin
ILAE	International League Against Epilepsy
IQR	interquartile range
IRR	incident rate ratio
IV	intravenous

MMR	measles-mumps-rubella vaccine
MMRV	measles-mumps-rubella-varicella vaccine
mRNA	messenger ribonucleic acid
NSW	New South Wales
NVP	non-vaccine-proximate
NVP-FS	non-vaccine-proximate febrile seizure
NVP-SE	non-vaccine-proximate status epilepticus
OR	odds ratio
PAEDS	Paediatric Active Enhanced Disease Surveillance
PCV13	13-valent pneumococcal conjugate vaccine
RI	relative incidence
RNA	ribonucleic acid
RR	relative risk
SCCS	self-control case series
SE	status epilepticus
TIV	trivalent influenza vaccine
UK	United Kingdom
US/USA	United States
VP	vaccine-proximate
VP-FS	vaccine-proximate febrile seizure
VP-SE	vaccine-proximate status epilepticus
VPS	vaccine-proximate seizure

Thesis overview

An adverse event following immunisation (AEFI), as defined by the World Health Organization, is an untoward medical occurrence that follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine.(1) While most AEFIs are mild and resolve quickly, rare serious AEFIs can be life threatening, and lead to hospitalisation, significant or permanent disability, or even death. When the risks and outcomes of AEFIs are not appropriately and effectively managed, vaccine confidence may decline, with dramatic consequences for immunisation coverage and disease incidence.(2)

The research in this thesis explores seizures as a rare serious AEFI. This work arose from an unprecedented vaccine safety event in Australia and its subsequent impact on vaccine safety confidence and vaccination uptake, which coincided with an insidious growth of vaccine hesitancy that was threatening the success of immunisation programs worldwide. In the 2010 influenza season, an unexpected and alarming increase in the rate of fever and febrile seizures following that year's influenza vaccination in children led to a temporary suspension of the influenza vaccination program, the initiation of a coronial and a parliamentary inquiry (Stokes Ministerial Review and Horvath Review), and subsequent alteration of guidelines for vaccine use and surveillance, both nationally and internationally.(3-5) In Australia, the causally associated vaccine was withdrawn from use in children <5 years old, who were at risk of febrile seizures,(6) and a national sentinel vaccine safety active surveillance system for rapid signal detection was established.

As demonstrated by the sustained decrease in influenza vaccination uptake in the years subsequent to 2010,(7) AEFIs, particularly severe acute neurological events with risk of developmental sequelae, can particularly affect parental and provider confidence in vaccine safety and influence further vaccination decisions.(8)

In an era where incidence, morbidity and mortality of vaccine-preventable diseases have declined with successful vaccination programs and the public's focus on vaccination has shifted to vaccine safety, a better understanding of the risk and sequelae of severe acute neurological events following vaccination and subsequent revaccination outcomes was needed. This has become even more

pertinent in the face of the COVID-19 pandemic where the introduction of a novel vaccine is inevitable.

The body of work in this thesis aims to address two forms of severe acute neurological events following vaccination: febrile seizures and status epilepticus. The work is presented “by publication” with six published manuscripts and one submitted manuscripts, supplemented by chapter sections. The thesis chapters, studies undertaken, and published or submitted manuscripts are summarised below and in Figure 1.1.

Chapter 1 is a **literature review** on existing knowledge on febrile seizures and status epilepticus, the known attributable risk of vaccines to these severe acute neurological events, and the known clinical characteristics and outcomes. The chapter concludes with the aims of the thesis that arose from the knowledge gaps identified, a summary of the studies proposed to address these gaps, and the potential impact for providers and policymakers.

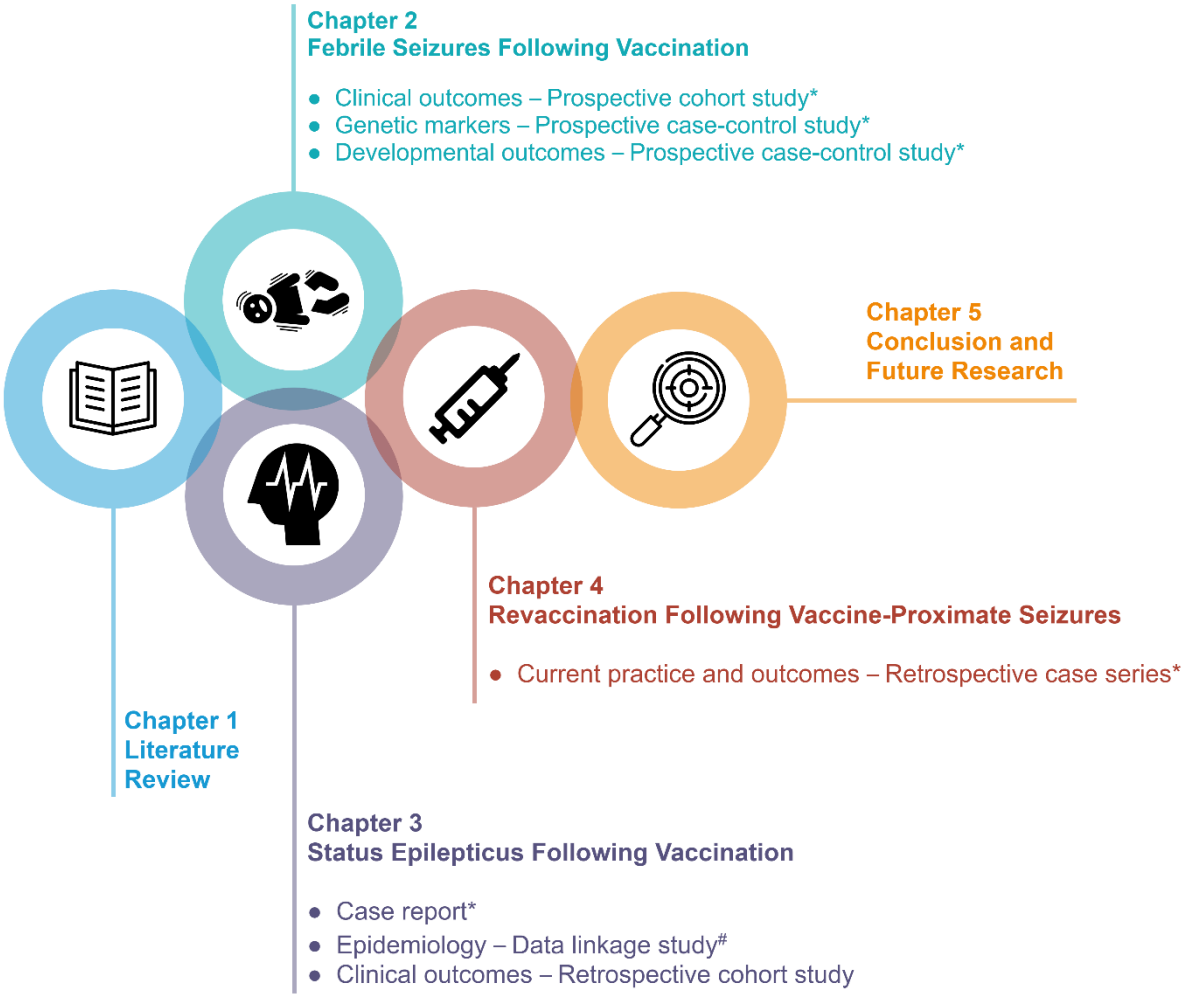
Chapter 2 examines **febrile seizures following vaccination**, presenting data on the immediate clinical outcomes, genetic markers and longer-term developmental outcomes of children with vaccine-proximate febrile seizures compared to children with non-vaccine-proximate febrile seizures, through two prospective cohort studies. The study findings are then summarised in a narrative review with illustrative clinical scenarios to assist with translation into clinical practice.

Chapter 3 examines **status epilepticus following vaccination**, with a case study, followed by a population-based study on the incidence and hospitalisation outcomes of vaccine-proximate status epilepticus, and a retrospective cohort study on its clinical severity and outcomes.

Chapter 4 examines the risks of revaccination in children who have had vaccine-proximate seizures, through a retrospective review of **revaccination practices and outcomes** for children with vaccine-proximate seizures managed through specialist immunisation services in Australia.

Finally, **Chapter 5** discusses the key findings of this thesis and offer suggestions for **future research**.

Figure 1.1 Thesis outline



*Designates sections containing published manuscripts
#Designates sections containing submitted manuscripts

Chapter 1 Literature review

1.1 Introduction

An epileptic seizure is defined by the International League Against Epilepsy (ILAE) as a “transient occurrence of signs and/or symptom due to abnormal excessive or synchronic neuronal activity in the brain”. It can manifest as any combination of involuntary muscle contractions, sensory disturbances, autonomic dysfunction, behavioural abnormalities, or impaired or loss of consciousness.(9) The causes of seizures are numerous and vary from a febrile illness to a structural, metabolic, inflammatory, infectious, toxic or genetic process affecting the central nervous system. The occurrence of a seizure in association with a “disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition” is diagnosed as epilepsy.(9) The impact of seizures and epilepsy on neurodevelopment is the major driver for both management of and mitigation of risk from seizure occurrences.(10)

This thesis focuses on two forms of epileptic seizures that can occur following, and in some cases are causally related to, vaccination – febrile seizures (FSs) and status epilepticus (SE). This chapter outlines the existing knowledge on these two common forms of seizures in childhood, the emerging knowledge on their association with vaccination, and the research gaps that form the rationale and aims of this thesis.

1.2 Febrile seizures

1.2.1 Definition

An FS, as defined by ILAE, is a seizure occurring in children aged >1 month that is associated with a febrile illness with no evidence of a central nervous system infection, no history of previous neonatal or unprovoked (in the absence of an identifiable acute brain disturbance) seizure and not fulfilling the criteria for another acute symptomatic seizure, caused by a known disorder such as a structural, metabolic, inflammatory, infectious, toxic or genetic process.(11)

FSs are divided into two types: simple and complex.(12) A simple FS is a generalised tonic-clonic seizure lasting <15 minutes, with no recurrence within 24 hours of the initial seizure and no postictal pathology. A complex FS is an FS with one or more of the following features: seizure lasting >15 minutes, focal features (seizure activity affecting one part of the brain), recurrence within 24 hours of the initial seizure, and presence of postictal pathology such as Todd's paresis (temporary weakness in part or all of the body). The majority of FSs are simple, with nearly 90% of FSs lasting <10 minutes.(13) However, approximately 20–30% of FSs have one or more complex features(14-16): 4–16% have focal features,(12, 14, 17) 9% last >15 minutes and 5% progress to febrile status epilepticus (FSE), where the FS lasts >30 minutes.(14)

1.2.2 Aetiology and epidemiology

FS is the most common type of childhood seizure. The median age of onset is 18 months and approximately half of all first FSs will occur between 12 and 30 months of age.(14, 18-20)

FSs commonly arise from febrile illnesses caused by a viral infection, including upper respiratory tract infections, otitis media and gastroenteritis.(15, 21-23) Epidemiological studies show a seasonal variation in FS incidence with peaks over the winter months,(24-26) and incidence is most closely correlated to influenza infection and influenza-like illnesses.(27-29) Other viruses implicated in FSs include human herpesvirus 6 (HHV-6), adenovirus, parainfluenza, respiratory syncytial virus and rotavirus.(30) HHV-6 was isolated in one-third of first FS presentations in children up to 2 years of age

in a USA study,(31) and was found in 35% of children with FSs in a study from Italy.(32) HHV-6B and HHV-7 infections have also been associated with FSE.(33)

In addition to environmental triggers, geographic and genetic factors play a role in FS aetiology. The reported FS incidence varies geographically, ranging from 2–5% in the US and Western Europe(34, 35) and 6–9% in Japan, to as high as 10% in India and 14% in Guam.(18) However, differences in case ascertainment and study design may contribute to these variations in reported incidence. Studies have also identified a genetic predisposition to FSs. Twenty-four percent of children with FSs have a family history of FSs, and 4% have a family history of epilepsy.(19) Those with a family history are also more susceptible to recurrent FSs,(36, 37) and specific genes have been associated with recurrent FSs.(17, 38-43) A case-control population-based study identified existing developmental delay, hospitalisation of more than 30 days as a neonate, and attendance in day care as additional risk factors for having an FS.(44) The study reported that children with two of these risk factors have a 28% chance of having at least one FS. Risk factors for FSs are summarised in Table 1.1.

1.2.3 Management

Management of children with a simple FS focuses on finding and, where possible, treating the underlying cause of the fever using thorough clinical assessment. Generally, in high-resource settings including Australia, a lumbar puncture is only recommended in children with signs of meningitis or intracranial infection, or in children aged 6–12 months who have not received *Haemophilus influenzae* type b or pneumococcal vaccination, on the basis that *Haemophilus influenzae* type b and *Streptococcus pneumoniae* were the most common causes of meningitis in this age group prior to the introduction of vaccination.(45) Other laboratory tests should only be considered if the cause of the fever requires further investigation and should not be used for the diagnosis of FS itself. Neuroimaging is not required unless there is a clinical suspicion of a space-occupying lesion. In simple FS cases, an electroencephalogram (EEG) is also not indicated as does not predict recurrent FS or development of epilepsy in the following 2 years.(46, 47) An EEG may, however, play a role in FSE cases. An EEG performed within 72 hours of an FSE presentation showing focal slowing or attenuation was found to be highly associated with acute hippocampal injury on subsequent magnetic resonance imaging of the brain.(48)

Antipyretics are recommended for symptomatic relief to comfort children during their acute febrile illness, but are not recommended as prophylaxis for reducing the risk of FS recurrence in future febrile illnesses. A study comparing regular use versus intermittent use of antipyretics showed no difference in the incidence of FS recurrence.(49) A randomised double-blind placebo-controlled trial comparing paracetamol to placebo and low dose oral diazepam to placebo also showed no reduction in recurrence risk.(50) While prophylactic antipyretics do not reduce the risk of FS in future febrile illnesses, a recent randomised controlled trial in 423 patients aged 6-60 months found a reduction in FS recurrence within the same febrile illness with the use of regular rectal paracetamol for the first 24 hours following the initial FS, compared to placebo (9.1% vs 23.5%, $P<0.001$).(51)

A Cochrane review on prophylactic drug management for prevention of FS in children(52) reported no reduction in the risk of FS with the use of phenobarbitone, phenytoin, valproate, pyridoxine, ibuprofen or zinc sulphate (compared to placebo or no treatment) during the period of a febrile illness. Intermittent diazepam(53, 54) and clobazam(55) have been shown to be effective in reducing the risk of FS compared to placebo or no treatment. However, in the clobazam versus placebo study, a higher than expected proportion of children in the control group had FS recurrence (83% compared to 30% in population studies), and therefore the effect of the treatment arm should be interpreted with caution. The Cochrane review concluded that for every 100 children treated with either intermittent diazepam or continuous phenobarbitone, 10 children were prevented from FS recurrence while 33 children will have unwanted side effects.

Management of children with FS should therefore primarily focus on education of carers in first aid management for seizures rather than prophylaxis for subsequent febrile illnesses.

1.2.4 Recurrence and epilepsy risk

In children who have experienced an FS, there is a 30–50% risk of FS recurrence with subsequent febrile illnesses depending on the number of risk factors the child has. These factors include onset of the first FS before 18 months of age, lower degree of fever (38°C) at time of first FS, shorter duration of fever (<1 hour) before onset of first FS and having a first-degree family history of FS.(14, 37, 56-58) Children who have all these risk factors have a 76% risk of FS recurrence, while those with no risk

factors have a 14% recurrence risk.(37) The risk of recurrence is 20% for a 3-year-old compared to 50% for a child aged 12 months or younger at their first FS. The type or duration of the FS, however, are not significant predictors of recurrence.(59) Half of recurrences will occur within 6 months, 75% within the first year and 90% within the first 2 years of the initial FS.(14, 19)

While most children who have an FS will not progress to develop epilepsy, having an FS increases the risk of developing epilepsy from a background rate of 1.4% to 2.4%.(17) This increases to 10% if one or more of the following risk factors are present: FS having a complex feature, presence of a neurological or neurodevelopmental abnormality, first-degree family history of epilepsy, and short duration of fever before onset of seizure.(12) Having a prolonged FS or all three features of a complex FS further increases this risk.(17, 35, 60, 61) Table 1.1 summarises the risk factors for first and recurrent FSs and subsequent development of epilepsy.

Table 1.1 Predictors of first and recurrent febrile seizures and subsequent diagnosis of epilepsy

Predictor	First FS	Recurrent FS	Epilepsy
Neonatal nursery admission for >30 days	+	Unknown	Unknown
Day care attendance	+	Unknown	Unknown
Developmental delay or neurological problems	+	−	+
Family history of FS in first-degree relative	+	+	−
Family history of epilepsy in first-degree relative	−	−	+
Age of onset <18 months	−	+	−
Lower temperature (38°C) at first FS	−	+	−
Short duration (<1 hour) of fever before seizure	−	+	+
Complex FS (focal, prolonged, multiple seizures in 24 hours)	−	−	+

FS=febrile seizure, +=predictor, −=not a predictor

Adapted from Chung S. Febrile seizures. *Korean J Pediatr*. 2014;57(9):384-395(62)

1.2.5 Developmental outcomes

Evidence from population-based studies indicates that children who experience an FS, from any cause, generally have normal cognitive and developmental outcomes.(63-68) Children's cognitive or motor function 12 months following their first FS did not differ when compared to controls in a case-control study.(63) A history of FS in preschool children was not associated with an increased risk of parent-reported executive impairments.(64) A Taiwanese study of 87 age-matched children followed to 6 years of age showed no association between FS and impairment in cognitive attention or early academic performance on neuropsychological testing.(65) A sibling-control study of 431 sibling pairs in the USA found no intellectual or academic performance difference at 7 years of age, as assessed using the Wechsler Intelligence Scale for Children and Wide Range Achievement Test.(66) For older children, a study of South Indian children aged 8–12 years showed no association between FS and poor intellectual outcomes on psychometric assessments.(67) Similarly, a UK study comparing 381 children with FS to 13,009 children without FS found no difference in academic progress, intelligence or behaviour at 10 years of age, irrespective of FS recurrence.(68)

While these studies found no immediate or longer-term adverse effect of FS on cognitive function in children who experience a FS overall, children who experience an FS before 12 months of age or have recurrent or prolonged FSs were found to be at an increased risk for poorer cognitive and developmental outcomes.(64, 68-75) Neuroimaging studies have shown that prolonged and focal FS may be associated with acute hippocampal injury(69, 70) and potential cognitive impairment.(71, 72) Children aged 6–8 years with FS onset before 12 months of age showed significantly poorer performance on a learning task and on delayed recognition when compared to those with later FS onset in one study,(73) while another study showed a higher proportion of children with FS onset before 12 months of age required special schooling.(68) In a US study of children admitted for their first FS, there was a fall in Griffith's developmental quotient in those with recurrent FSs between their initial and 24-month post-FS assessments.(74) The impact of early-onset FS may be long-lasting, with a study of conscripted Danish men reporting that those who were hospitalised for an FS before 1 year of age had poorer cognitive function as young adults.(75) Delayed vocabulary development has been reported in children with recurrent FSs,(64) and lower non-verbal intelligence on neuropsychological testing has been reported in children with prolonged FSs compared to those with simple FSs and

healthy controls.(76) Children with FSE also showed poorer performance on receptive language and weaker psychomotor performance at 12 months post seizure compared to those with simple FSs.(77)

Finally, there are conflicting data for behavioural outcomes following FS. Some studies report no difference between children with FSs and children without,(64, 65, 67, 73) while others report higher levels of externalising (impulsivity, aggressiveness, disruptiveness) and internalising (anxiety, withdrawal, dysphoria) behaviours in children who have had FSs.(68, 76) Behavioural outcomes from these studies were mostly based on parental report which may account for the variability in the results compared to more objective psychometric testing.

1.2.6 Febrile seizures and genetic epilepsy syndromes

Recurrent FSs are associated with two epilepsy syndromes. These syndromes are now believed to be on the spectrum of a single condition,(41) with the milder generalised epilepsy with febrile seizure plus (GEFS+) on one end, and the severe developmental epileptic encephalopathy Dravet syndrome on the other, as described in this section.(17, 41)

Generalised epilepsy with febrile seizure plus (GEFS+)

GEFS+ is a familial epilepsy syndrome with a heterogeneous phenotype,(42, 43) which can manifest in mild to severe phenotypes within the same family. Genetic variants in *SCN1A*, a sodium channel encoding gene, account for 20% of familial cases of GEFS+,(17, 41) while variants in *SCN2A, SCN1B, SCN9A, GABRG2* and *STX1B* genes account for an additional 10% of cases.(38-40) The genetic variants for the remaining cases remain unknown.

The most common phenotype in family members with GEFS+ is characterised by recurrent FSs, followed by FSs starting before but occurring beyond 6 years of age (known as FS+, given FS by definition should not occur beyond 6 years of age). Rarer and more serious phenotypes have FS or FS+ in conjunction with other seizures including afebrile generalised tonic-clonic seizures, or absence, myoclonic, atonic or focal seizures.(41) Neurodevelopment in family members with GEFS+

depends on the severity of their phenotype. Those with the milder phenotype have normal intellect, while some with myoclonic-atonic seizures have impaired cognition.(41)

Dravet syndrome

Dravet syndrome is a rare form of epilepsy, with an estimated prevalence of 1:40,000.(78, 79) Approximately 80% of children with Dravet syndrome have an *SCN1A* variant, of which 95% are de novo mutations.(80-84)

Children with Dravet syndrome typically present with their first seizure around 6 months of age. They have prolonged FSs, which are often misdiagnosed as complex FSs initially. However, these children progress to have polymorphous seizure types including prolonged, febrile and afebrile, generalised and/or hemiclonic epileptic seizures, with common triggers including fever, heat and sunlight. Between 1 and 4 years of age, they develop myoclonic, focal and atypical absence seizures and begin to show stagnation and regression of their development over this period, resulting in cognitive, motor and behavioural impairment; some children also display autistic and hyperactive traits.(85-87) Seizures in children with Dravet syndrome are usually refractory to standard antiepileptic medication, with some medications, such as carbamazepine(87) and lamotrigine,(88) having the potential to exacerbate seizures.

1.3 Status epilepticus

1.3.1 Definition

Status epilepticus (SE) was traditionally defined as a “seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur”.(11) The duration meeting this definition was considered to be ≥30 minutes based on studies on permanent neuronal damage with prolonged seizures in primates.(11, 89) Numerous systemic and metabolic changes occur in association with prolonged seizures, including tachycardia, hypertension, hyperglycaemia and lactic acidosis. Most of these changes are thought to result from a surge in catecholamine release that accompanies the seizure, and resolve with seizure resolution. When seizure duration goes beyond 30 minutes, cerebral autoregulation may become impaired and cerebral perfusion will fall as hypotension occurs, causing ischaemic injury and cerebral oedema.

Unlike a simple FS, SE is therefore a major medical and neurological emergency, with potentially significant long-term complications if not treated in a timely manner. To better reflect this, the definition of SE has since been revised by ILAE(90) to “a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after timepoint t_1) … which can have long-term consequences (after timepoint t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.” This new definition incorporates the operational timepoint when intervention should be initiated (t_1 = 5 minutes from start of seizure) to prevent irreversible neuronal damage, and the conceptual timepoint used to prognosticate long-term sequelae (t_2 = 30 minutes from start of seizure). While the timepoints are clearly defined for convulsive (generalised tonic-clonic) SE, the timepoints are not known for non-convulsive SE.

1.3.2 Aetiology and epidemiology

The causes of SE can be broadly divided in two groups: (1) a known or “symptomatic” cause, where the SE is caused by a known disorder such as a structural, metabolic, inflammatory, infectious, toxic or genetic process; or (2) an unknown or “cryptogenic” cause, where no symptomatic cause can be

identified.(90) Symptomatic causes can be further categorised into acute, remote, progressive and electroclinical syndromes as outlined in Table 1.2. In the most recent classification categories, ILAE(90) removed the use of “idiopathic” as an aetiology, as it only reflects the aetiology of the underlying epilepsy syndrome but not the cause of the SE itself, such as inadequate antiepileptic medication. FSE is classified as an electroclinical epilepsy syndrome, a group of clinical entities with characteristic and distinct seizure types and EEG findings which have implications for treatment, management and prognosis.

Table 1.2 Categories of symptomatic causes of status epilepticus

Aetiology category	Definition	Example
Acute	Seizure occurring during acute illness involving a neurological insult or metabolic dysfunction	• Infection (e.g. malaria, encephalitis) • Metabolic (e.g. electrolyte abnormality, intoxication) • Trauma (e.g. head injury, haemorrhage) • Anoxia
Remote	Seizure without acute provocation in someone with history of central nervous system insult which increases their risk of seizures	• Post-traumatic • Post-encephalitic • Post-stroke
Progressive	Seizure occurring as part of a progressive neurological disease	• Brain tumour • Neurodegenerative disease • Neurocutaneous syndrome
Defined electroclinical syndromes	Seizure occurring as part of an epileptic syndrome with distinctive electroencephalogram and clinical features	• West syndrome • Dravet syndrome • Febrile status epilepticus

Population studies on SE using the traditional definition of SE (seizure lasting >30 minutes or repeated seizures over 30 minutes with no recovery of consciousness)(91) have shown the incidence

of SE is highest in children aged <12 months, with an acute symptomatic cause being the most common.

The reported incidence of convulsive SE in children has varied widely globally.(92-98) In the earliest epidemiological study of SE that included children, in Rochester, Minnesota, from 1965 to 1984, Hesdorffer et al.(92) reported an SE incidence in children aged <14 years of 24.1/100,000 person-years. The highest incidence was in children aged <1 year at 135.2/100,000 person-years, followed by children aged 1–4 years at 35.3/100,000 person-years.(92) In a subsequent study in Richmond, Virginia, from 1989 to 1991, De Lorenzo et al.(94) reported a higher incidence in children aged <15 years of 41/100,000 person-years (150/100,000 person-years in those aged <1 year, 60/100,000 person-years in those aged 1–4 years). The difference in incidence rates between the studies was attributed to the racial distribution of the two populations, with SE incidence in non-Caucasians (mostly African Americans) being more than double that of Caucasians for all ages (57/100,000 person-years vs 20/100,000). In contrast, Wu et al.(99) reported a lower incidence in California using ICD-coded hospital data from 1991 to 1998 (7.52/100,000 person-years for children aged 0–4 years and 2.57/100,000 for those aged 5–19 years). In Europe, the reported SE incidence in children aged <15 years in North London(98) was 17–23/100,000 person-years, and in French-speaking Switzerland it was 38.7/100,000 for children 0–4 years of age and 10.9/100,000 person-years for those aged 5–14 years.(97) A wide incidence variance is also seen in Asian populations. For 2000–2011, Taiwan reported an SE incidence of 10.18/100,000 person-years for children 0–4 years of age and 2.26/100,000 for those aged 5–19 years(100), and Japan reported an incidence of 42.0/100,000 person-years in children aged <15 years over 2003–2005.(101) Studies using ICD-coded data only reported the lowest incidence, which is likely to reflect an under-ascertainment in this methodology. While there is a wide variance in overall reported SE incidence in children, the age distribution is more consistent across the studies, with all reporting the highest incidence in children aged <2 years. In three studies,(92, 94, 98) the incidence peaked in <12-month-olds, while another showed a peak in 12–23-month-olds.(101)

While SE incidence in children is much higher than the reported incidence of 4–6/100,000 person-years in the adult population,(92, 97, 102) the SE mortality rate in children of 3%(93, 94, 98) is much

lower than in young adults (13%) and the elderly (38%).(103) SE outcome is closely related to the duration of the seizure, with mortality increasing by up to five times in SE lasting >24 hours (refractory SE).(95, 104)

In terms of seizure aetiology, Hesdorffer et al.(92) found that half the SE cases in children had an acute symptomatic cause and 8% were FSE without an acute symptomatic cause. Similarly, De Lorenzo et al.(94) found febrile acute infection accounted for 52% of cases, with remote symptomatic (39%) and low antiepileptic drug levels (21%) being the next two most common causes. Aetiology also changes with age; while acute symptomatic SE accounted for half of SE in children <12 months old, FSE accounted for >60% of cases in children in the second year of life.(96) Less than 15% of cases in children aged <2 years had remote symptomatic or idiopathic causes, compared to over 60% in children aged ≥4 years. The North London Convulsive Status Epilepticus in Childhood Surveillance Study (NLSTEPSS) found a similar distribution, with FSE most common in children aged <4 years and remote symptomatic SE most common in children aged 5–15 years.(98) The causes of acute symptomatic SE from the NLSTEPSS cohort were, in order of frequency, acute bacterial meningitis, viral meningitis, acute metabolic or electrolyte derangement, and medication-related causes.

1.3.3 Investigation and management

Current acute seizure management guidelines recommend initiation of treatment when the seizure lasts ≥5 minutes,(105, 106) in line with the new operative definition of SE. A prospective study of 407 children with their first unprovoked afebrile seizure found that seizures lasting 7 minutes or more were likely to be prolonged and therefore would warrant seizure cessation medication.(107)

The first-line acute seizure management is a benzodiazepine. Buccal midazolam is the medication of choice for out-of-hospital management, with rectal diazepam as an alternative. Several paediatric studies have shown buccal midazolam to be more effective at seizure termination than rectal diazepam.(108-110) Once intravenous (IV) access is obtained, IV midazolam, diazepam or lorazepam can be used.(105, 106) A double-blind randomised controlled trial found no significant difference in the effectiveness or safety of lorazepam over diazepam in the treatment of paediatric SE.(111) If the seizure continues after two doses of first-line treatment (including pre-hospital administration),

second-line treatment using IV phenytoin, phenobarbital or levetiracetam should be initiated. IV levetiracetam has also been successfully used to terminate SE.(112-115) Two recent randomised controlled trials found no significant difference between the use of phenytoin or levetiracetam in both seizure cessation 5 minutes post infusion(116) or median time to seizure cessation.(117) IV midazolam infusion, or thiopental and intubation are recommended for refractory SE. For non-convulsive SE where management is considered less urgent, titration of usual antiepileptic therapy, IV benzodiazepine with EEG monitoring and neurological team guidance are recommended.

Seizure management of status epilepticus is the same regardless of aetiology. However, investigations for aetiology should be carried out simultaneously, including glucose level, serum electrolytes, arterial blood gas, anticonvulsant levels, and evidence of infection or sepsis. Specific treatment for these, including glucose, electrolyte replacement and antibiotics, should be initiated concurrently. Further investigations including EEG, neuroimaging, lumbar puncture and urine metabolic screen should be considered depending on the clinical scenario.

1.3.4 Recurrence and epilepsy risk

Approximately half of the children with SE have a history of one or more unprovoked afebrile seizures before their SE episode.(11) The proportion of children with prior unprovoked seizures increases with age: 35% of children aged <2 years have a preceding unprovoked seizure compared to 75% of children aged ≥10 years.(96)

Early studies reported that 10–18% of children who have an SE episode will experience at least another.(118-120) A follow-up of 92 children from the Bronx in New York (mean follow-up period 29 months, range 4–60 months) found the mean time to the next SE was 10.4 months. The reported SE recurrence rate ranged from 11–16% at 12 months following the initial SE to 13–18% at 24 months and 20% at 48 months, with the risk of recurrence highest in those with remote symptomatic or progressive cause of their initial SE.(94, 98, 121) Children with existing neurological abnormalities were more likely to have SE recurrence than those with no history of neurological abnormalities.(98, 121-123) While 10–12% of children present with SE as their first unprovoked

seizure,(124, 125) SE as a first seizure was, however, not found to be a risk factor for seizure recurrence.(126)

1.3.5 Developmental outcomes

SE is associated with structural abnormalities in the hippocampal region(127, 128) and neurocognitive and memory impairments,(129) with aetiology being the major determinant of outcome.(93, 130)

A cohort study of 193 children by Maytal et al.(93) found young children with acute symptomatic SE had the highest rate of neurological sequalae; 29% of children with SE aged <12 months developed neurological sequalae, compared to 11% in those aged 1–3 years and 6% in those aged >3 years. Children with idiopathic, remote symptomatic or febrile SE, however, did not develop new neurological deficits.

A prospective case-control study of 27 FSE and 27 non-febrile SE cases, and 17 healthy controls of similar age (1–42 months) found both SE groups performed below normal compared to controls on Bayley's developmental assessment within 6 weeks of their SE, with the non-febrile SE group performing worse than the FSE group. In the 70% of children (22 FSE, 16 non-febrile SE) who were followed up, there was no change in their developmental assessment outcomes at 12 months compared to their initial assessment, suggesting SE has some lasting effect on development in previously neurodevelopmentally normal children.(129)

A follow-up of 83 participants from the NLSTEPSS study for 8.1 years (range 5–10 years) to 2016 was the first prospective study to examine the long-term behavioural outcomes following SE.(131) Clinically significant behavioural problems were identified in 37% of participants and 28% had a DSM-IV psychiatric disorder on standardised questionnaire assessment. In children with epilepsy, diagnosed either before or after the SE episode, 43% had behavioural problems; this rate is similar to psychiatric disorders found in children with epilepsy, regardless of SE history.(132-134) In comparison, in children with SE and no epilepsy diagnosis, 31% still had behavioural problems, suggesting that SE itself can cause behavioural problems, irrespective of aetiology. Seizures prior to

SE and SE recurrence were associated with worse behavioural outcomes in children with epilepsy-related SE.(127)

1.4 Seizures following vaccination

Seizures of any kind can occur following vaccination. They are a rare but serious adverse event following immunisation (AEFI), defined by the Brighton Collaboration as a witnessed sudden loss of consciousness with generalised, tonic, clonic, tonic-clonic or atonic motor manifestations.(135)

1.4.1 Vaccine-proximate febrile seizure risk

The occurrence of fever following vaccination is a well-documented, expected and usually minor adverse event that varies in frequency and timing by vaccine type and age of the vaccine recipient. A fever, defined as the elevation of at least one measured body temperature to ≥38°C,(136) is known to occur within 48 hours following inactivated vaccines such as diphtheria-tetanus-pertussis (DTP) or influenza vaccine, or within 5–14 days following live attenuated vaccines such as measles-mumps-rubella (MMR). FSs can occur during these defined periods following vaccination when the fever peaks.(137, 138) They are considered plausibly related to the vaccine if no alternate aetiology is found.(139) Such seizures are referred to as vaccine-proximate febrile seizures (VP-FSs).(137, 140-142) FSs following vaccination but occurring outside of these periods are considered non-vaccine-proximate febrile seizures (NVP-FSs). VP-FS risks following specific vaccine types are outlined in this section and summarised in Table 1.3.

Table 1.3 Vaccine-proximate febrile seizure rates in children and biologically plausible risk intervals

Vaccine type	Vaccine	Risk interval (days after vaccination)	Febrile seizure rate
Inactivated	DTPw	0–2	1 FS per 11,000 to 17,000 vaccinations(141, 143)
	DTPa	0–2	No increased risk(142, 144, 145)
	TIV	0–2	1 FS per 70,000 vaccinations (2003–2004)(146) 1 FS per 227 vaccinations (Fluvax, CSL; 2010)(147) No increased risk with any formulation currently in use(148)
Live attenuated	MMR	5–14	1 FS per 1,150 to 3,000 vaccinations(143, 149)
	MMRV	5–14	1 additional FS per 2,600 MMRV vaccinations compared to MMR+V(138, 150) No increased risk as dose 2(137, 151)

DTPa= diphtheria-tetanus-acellular pertussis, DTPw= diphtheria-tetanus-whole-cell pertussis, FS=febrile seizure, MMR=measles-mumps-rubella, MMR+V=MMR plus varicella vaccine (given concomitantly), MMRV=measles-mumps-rubella-varicella, TIV=trivalent influenza vaccine

Pertussis-containing vaccines

Whole-cell pertussis vaccines were introduced in Australia in the 1940s and included in the first National Immunisation Program in 1975 as DTPw (diphtheria-tetanus-whole-cell pertussis) vaccine. DTPw vaccines were associated with high rates of AEFIs including fever, FS and occasional reports of encephalopathy.(152) An increased relative risk (RR) of FS following DTPw has been shown in several studies, with a range of reported RRs depending on the study's sample size, days post vaccination and dose number examined. A meta-analysis of three early studies reported an RR of 1.8 (95%CI 1.2–2.7), though the comparison group was not consistent across the studies.(153) Farrington et al. found an RR of 3.0 (95%CI 1.6–5.5) in the first 3 days following the third dose of DTPw(143) compared to time outside this risk period, while Barlow et al. reported an RR of 5.70 (95%CI 1.98–16.42) on the day of administration only with no subsequent increased risk compared to age-, time- and location-matched FS cases with no vaccinations in the preceding

30 days.(141) The increased risk reported from these two studies is equivalent to 1 additional FS per 11,000–17,000 children vaccinated, or 6–9 FS attributable to DTPw vaccination per 100,000 children vaccinated.

DTPw, composed of the whole inactivated organism, was subsequently replaced with the less reactogenic acellular pertussis-containing vaccine (DTPa), consisting of up to five purified antigenic components, in 1997. A large population-based Danish study(142) identified a small risk of FS on the day of vaccination only for the first and second dose of DTPa, compared to non-vaccinated children and children who were not in the 0–7-day risk period of vaccination (hazard ratio [HR] 6.02 [95%CI 2.86–12.65] and HR 3.94 [95%CI 2.18–7.10], respectively). However, no overall increased risk of FS within 0–7 days of vaccination was found across the three primary doses. In the same study, a secondary analysis using the self-control case series (SCCS) method confirmed the cohort analysis findings. Using the SCCS method, the FS cases act as their own controls with time classified into risk and control periods and relative incidence (RI) calculated by incidence in the risk period over incidence in the control period. Importantly, the study found no increased risk of recurrent FSs or subsequent epilepsy in children whose first FS occurred 0–7 days following vaccination. A UK study, also using the SCCS method, following the introduction of DTPa-IPV-Hib vaccine showed a doubling of seizure risk on the day of vaccination (RI 2.05, 95%CI 0.65–6.46), though it was not statistically significant. The risk was also lower than the reported seizure risk with DTPw (RI 4.14, 95%CI 1.92–8.92).(144) A US SCCS study showed a 30% increased risk of seizures on the day of the first DTPa vaccination, which was also not considered significant (incident rate ratio [IRR] 1.32, 95%CI 0.68–2.54).(145) Both studies, however, did not differentiate FSs from afebrile seizures. In summary, several studies using different methodologies in different populations have found no statistically significant attributable risk of FS following DTPa vaccination.

Measles-containing vaccines

In contrast to DTPa vaccines, a consistently significant but low risk of FS following measles-mumps-rubella (MMR) vaccination has been identified in several studies. The risk of FSs occurring within 5–14 days following MMR vaccination(141, 154) is double the risk of having an FS outside of this period, with peak incidence on day 9 post vaccination.(155) A cohort study of 18,364 children from

Tennessee found an RR of 2.1 (95%CI 0.7–6.4) for FSs in the 7–14-day period following MMR or measles-rubella vaccination.(156) A larger cohort study of 679,942 children reported an RR of 2.83 (95%CI 1.44–5.55) in the 8–14 day period following vaccination, compared to the background rate of FS in the second year of life.(141) When a narrower risk period of 6–11 days post vaccination was examined, an RI of 4.09 (95%CI 3.14–5.33) was reported in one study (equating to 1 FS per 1,150 to 3,000 vaccinations) and an RI of 3.04 (95%CI 2.27–4.07) in another.(143, 149)

FS risk is also elevated following measles-mumps-rubella-varicella (MMRV) vaccine when it is given as the first dose of measles-containing vaccine. An observational study showed an additional two-fold increase in risk of FS at 5–12 days following vaccination in children receiving MMRV as their first dose of measles-containing vaccine, compared to a historical cohort of children receiving MMR and varicella as separate vaccines given concomitantly in the same visit (MMR+V) (RR 2.20, 95%CI 1.04–4.65).(157) This equates to 1 additional FS per 2,600 children vaccinated with MMRV compared with MMR+V. A subsequent matched cohort study in Germany confirmed this increased risk for FS 5–12 days following the first dose of MMRV vaccine; adjusted odd ratios (aOR) were 4.1 (95%CI 1.3–12.7) relative to MMR, 3.5 (95%CI 0.7–19.0) relative to MMR+V, and 4.1 (95%CI 1.5–11.1) relative to MMR and MMR+V combined.(150) Klein et al. reported an RR of 1.98 (95%CI 1.43–2.73) for days 7–10 following MMRV compared to MMR+V as the first dose of measles-containing vaccine.(138) This increased risk was not seen for MMRV or MMR+V given to children aged 4–6 years, the recommended age for administration of the second dose of vaccine in the USA, and at which the background rate of FS is low.(151) An elevated FS risk was also not seen when MMRV was given as the second dose of measles-containing vaccine at 18 months of age, with an RI of 1.08 (95%CI 0.55–2.13) in the 5–12 days following MMRV using an SCCS analysis.(137) As such, the Australian National Immunisation Program only recommends MMRV as the second dose of measles-containing vaccine at 18 months of age and for use as the first dose of measles-containing vaccine in children aged >4 years.

In summary, measles-containing vaccines have a two-fold increased risk of FS in the 2 weeks following vaccination. This risk is elevated another two-fold with MMRV compared with MMR when given as a first dose of measles-containing vaccine but not when given as a second dose.

Influenza vaccines

FS risk following influenza vaccination was first identified in 2010 when there was an increase in cases of children with FS following the seasonal trivalent influenza (TIV) vaccine in Australia. A vaccine attributable risk of 1 FS per 227 vaccine doses(4, 147) led to a temporary suspension of influenza vaccine for children in Australia for that season. Prior to this, a US study in 2003–2004 found 1 FS in 70,000 TIV doses in children under 2 years of age.(146) Investigations identified that the increased rate of fever and FS in the 2010 influenza season was attributed to a single TIV brand (Fluvax and Fluvax Junior, manufactured by CSL). A similar rate of FS following the CSL-manufactured TIV was found in New Zealand.(158) The vaccine was subsequently withdrawn from use in children <5 years old in Australia.(6)

In vitro investigations concluded that the use of the inactivating agent β-propiolactone instead of formaldehyde(159, 160) and the increased fragments of viral RNA retained during the manufacturing process(161) was contributory to the higher rates of fevers and FS. It was also established that had increased levels of the agent sodium taurodeoxycholate been used to split the B strain, it could have resulted in decreased levels of residual lipids and attenuated proinflammatory cytokine signals.(161) An elevated level of the pyrogenic cytokines interferon alpha (IFN-α), interleukin (IL)-6 and IL-1β was stimulated in peripheral blood mononuclear cells by ex vivo exposure to the CSL 2010 southern hemisphere TIV, compared to other brands.(162) While this elevated cytokine response was also found in in vitro studies of CSL's 2009/10 and 2010/11 northern hemisphere TIV, no increase in FS cases was reported in 2009.(163) A lower cytokine response was found when CSL replaced the H1N1 A/California/7/2009 strain with H1N1 A/Brisbane/59/2007. It was therefore suggested that the combination of B/Brisbane/60/2008 and H1N1 A/California/7/2009 vaccine strains in the CSL 2010 TIV stimulated a higher than expected immune response, resulting in the increased risk of FS in children aged <5 years.

Following this unexpected increase in FS, the US Vaccine Adverse Event Reporting System identified increased cases of FS in children aged <24 months 0–1 days following vaccination with the Fluzone brand of TIV during the 2010–2011 influenza season.(164) Concurrently, near real-time surveillance conducted in children aged 6–59 months by the Vaccine Safety Datalink Project during the same

season identified 1 FS per 4,387 TIV doses, equating to an elevated IRR of FS occurring 0–1 days following TIV of 2.4 (95%CI 1.2–4.7) using a self-controlled risk interval (SCRI) design. A higher risk of FS was also found in children receiving TIV and 13-valent pneumococcal conjugate vaccine (PCV13) at the same time, equating to 1 additional FS per 5,555 doses (IRR 5.9, 95%CI 3.1–11.3).(165) A subsequent SCRI study for the 2013–14 and 2014–15 seasons also found a five-fold increased risk of FS 0–1 day following concomitant TIV and PCV13 administration (RR 5.3, 95%CI 1.87–14.75) in children, compared to receiving either vaccine separately.(166) In contrast, a larger SCRI study of 142 FS cases in 842,325 US children in 2010–2011 found no added risk of FS associated with TIV (IRR 1.36, 95%CI 0.78–2.39) after adjusting for age, seasonality and administration of other vaccines. In this larger study, concomitant administration of TIV and PCV13 was also not associated with increased risk of FS compared to separate-day vaccination, reporting 1.08 fewer FSs per 100,000 same-day vaccinations (95%CI −5.68 to 6.09).(167)

Seasonal influenza vaccine is different to routine vaccines as its composition can change annually to match the circulating influenza virus strains. As a result, adjustments in the manufacturing process may lead to an altered vaccine safety profile, which may not be detected during large-scale pre-licensure clinical trials. More recently, the influenza vaccine also changed from a trivalent to a quadrivalent formulation, adding a second B strain in 2016. Following the unexpected increase in FSs associated with CSL's TIV in 2010, Australia established a national sentinel active vaccine safety surveillance system, AusVaxSafety (http://ausvaxsafety.org.au/), to enable rapid signal detection by analysing participant-based post-vaccination responses using Bayesian methods. In 2015 and 2016, only 6 of 7,198 (0.08%) responders (parents/carers) reported a seizure in their child within 3 days of vaccination, of whom 5 had a history of seizures.(148)

In summary, there was an unexpectedly high FS risk associated with the CSL 2010 southern hemisphere TIV that was not seen in subsequent influenza seasons both in Australia and internationally. Similarly, while there are some studies suggesting an increased risk of FS with concomitant administration of TIV and PCV13, this has not been detected in the Australian active vaccine safety surveillance system.

1.4.2 Vaccine-proximate febrile seizure outcomes

While the risk of FS following specific vaccines is well known, little is known about the clinical severity and outcomes of VP-FS compared to FS due to another cause (NVP-FS). There are only two retrospective studies of the same cohort of 3,348 US children with FS, aged 6 months to 3 years, that directly compare the risk factors and clinical outcomes of VP-FS to those of NVP-FS.(168, 169) The first study, which focused on the risk factors for VP-FS, found that children with a first VP-FS (defined in the study as an FS within 15 days of any vaccination) were more likely to be female, younger, and have a lower birthweight, a lower Apgar score at 1 minute and a higher chance of FS recurrence compared to children with NVP-FS.(168) The second study, which focused on clinical outcomes, showed no difference in risk of hospitalisation between first VP-FS and first NVP-FS presentations.(169) These studies did not examine other markers of seizure severity such as seizure duration, seizure recurrence within the same admission, antiepileptic administration or need for readmission. There are also no studies examining the proportion of VP-FS that have an alternate biological cause, such as a concomitant infection, and how that affects the seizure severity of VP-FS.

While epidemiological studies outlined in **Section 1.3.5** describe favourable intellectual and developmental outcomes following FSs in children, these studies do not differentiate whether the FS was related to a vaccination event or another cause. Only one study has examined long-term outcomes of children following a VP-FS. Barlow et al.(141) reviewed a cohort of 562 children from 1991 to 1993, of which 41 had a VP-FS (18 DTPw, 22 MMR and 1 with both) and found no VP-FS cases developed afebrile seizures or epilepsy in the 2-year follow-up. A subgroup of 273 children were further followed up to 6 years following their first FS, and no increased risk of developmental disabilities was identified following VP-FS compared to NVP-FS (RR 0.56, 95%CI 0.07–4.2). No other studies comparing VP-FS and NVP-FS have been conducted, despite the introduction of many new vaccines, including acellular pertussis vaccines, to immunisation schedules worldwide. It is not known if the predictors of poorer outcomes in children with VP-FS are the same as those described in previous FS studies.

1.4.3 Vaccine-proximate febrile seizure and genetics

There is emerging evidence that host genetic factors contribute to an individual's susceptibility to AEFIs. For example, post-vaccination body temperatures were demonstrated to be higher in Amerind populations (indigenous peoples of the Americas) compared to Caucasian populations following measles vaccination.(170) Fever following smallpox vaccination was found to be associated with a specific set of inherited genes (haplotypes) in the IL-1 and IL-18 gene complexes, whereas a specific IL-4 haplotype was found to be protective against fever following vaccination.(171)

The substitution of a specific nucleotide (single nucleotide polymorphism) in *SCN1A* (IVS5N+5G>A, rs3812718) has been found to be associated with FS.(172) Adults with epilepsy and a history of FS (*n*=90) had an odds ratio (OR) of 3.9 (95%CI 1.9–8.0) of having the polymorphism compared to ethnically matched controls (*n*=701). This association was not found when comparing adults with epilepsy and no history of FS to controls. The same Austrian study also found the polymorphism in a cohort of children with FS and no epilepsy (*n*=144), with an OR of 3.1 (95%CI 1.7–5.5) compared to population controls. However, a replication of this study in Australia with 76 epilepsy cases and 482 controls, published in the same year, could not confirm the findings of the Austrian study.(173)

Feenstra et al. conducted genome-wide association scans comparing Danish children with MMR-related FSs (*n*=929), children with FSs unrelated to vaccination (*n*=1,070) and controls with no FS history (n=41,118).(174) Four gene positions (loci) were found to be associated with FSs in general (*SCN1A*: rs6432860, *SCN2A*: rs3769955, *ANO3*: rs114444506, and 12q21.11: rs11105468) and two were found to be associated with MMR-related FS only (*IFI44l*: rs273259, and *CD46*: rs1318653). This finding supports the concept that there is an immunogenetic mechanism to severe acute neurological events following immunisation such as VP-FS.

"Vaccine encephalopathy", where an individual's seizure disorder was thought to be precipitated by a vaccination event, was found to be associated with *SCN1A* variants in a ground-breaking retrospective study by Berkovic et al. in 2006.(175) Of 14 children in whom the onset of refractory epilepsy and subsequent developmental delay followed vaccination, 12 cases fit the clinical diagnosis of Dravet syndrome and 11 cases had a *SCN1A* variant. Five additional cases of vaccine

encephalopathy, with the onset of first seizure (3 febrile, 2 afebrile seizures) within 24 hours of vaccination in children under 12 months old, were subsequently reported by Reyes et al., all of whom were also diagnosed with *SCN1A*-associated Dravet syndrome.(176) McIntosh et al.(177) examined an additional 40 cases of *SCN1A*-associated Dravet syndrome and found children whose first seizure was within 2 days of vaccination were significantly younger than cases whose first seizure was not vaccine proximate (18.4 vs 26.2 weeks, *P*=0.004), suggesting that vaccination may trigger an earlier onset of their underlying genetic epilepsy. The younger age at presentation of these children compared to the peak incidence of FS in general has been confirmed in several subsequent studies.(78, 175, 178, 179)

Reassuringly, McIntosh et al.(177) found no difference in intellectual outcomes in children with*SCN1A*-associated Dravet syndrome between those whose first seizure was following vaccination and those whose first seizure was unrelated to vaccination.(177) Similarly, a Dutch study of 77 cases of *SCN1A*-associated Dravet syndrome found no difference in age of onset of developmental delay (24 vs 21 months, *P*=0.68) or proportion with poor cognitive outcome defined as IQ <50 (*P*=0.38) in those with vaccine-associated first seizures, despite the earlier age of onset of seizures.(179)

Analysis of all passive AEFI reports over 10 years in the Netherlands by Verbeek et al. found 1.2% (15/1,269) of children presenting with seizures following vaccination in the first 2 years of life had *SCN1A*-associated Dravet syndrome.(180)

These retrospective studies add to the growing evidence of immunogenetics and immunogenomics of AEFIs at both the individual and population level. However, further studies into genetic markers in children who have VP-FS compared to those with NVP-FS and healthy controls are needed to validate Feenstra et al.'s(174) findings outside of a Danish population.

1.4.4 Vaccine-proximate status epilepticus

While FS risk within a defined period after vaccination when body temperature peaks is well recognised,(4, 141, 154, 165) as outlined in **Section 1.4.1**, few studies have specifically examined SE following vaccination.

The British National Childhood Encephalopathy Study(181) identified 2 SE cases in previously normal children, aged 2 to 35 months, within 7 days following DTPa vaccine. The German AEFI database identified 21 SE cases out of 247 reported seizures following vaccination from 2006 to 2008, (182) but with no details of the vaccine or seizure timing.

Vaccine-proximate SE (VP-SE) as the first seizure presentation in children with *SCN1A*-associated Dravet syndrome has also been reported by Berkovic et al. (5 VP-SE cases)(175) and McIntosh et al. (6 VP-SE cases).(177) In Verbeek et al.'s retrospective study of 1,729 children with seizures following vaccination in the Netherlands, 6 out of the 15 *SCN1A*-associated Dravet syndrome cases presented with SE.(180) In an Italian cohort study of 72 patients with Dravet syndrome or GEFS+,(183) 3 of 17 vaccine-proximate seizures reported were SE. Those who had a vaccine-proximate seizure and were positive for *SCN1A* variants were more likely to have subsequent SE events.

These studies describe small case series of VP-SE, with a focus on *SCN1A*-associated Dravet syndrome. The overall proportion of SE cases that are vaccine proximate at a population level remains unknown. It is also not known if the clinical severity, subsequent seizure recurrence or vaccination rates following VP-SE are different to those for SE from any another cause (non-vaccine-proximate SE; NVP-SE).

1.4.5 Vaccine safety confidence

Concerns about the impact of vaccine-proximate seizures on neurocognitive development can affect parent and provider confidence in vaccine safety and influence future vaccination uptake.

Influenza vaccination uptake in children aged <5 years in Western Australia decreased significantly from 45% in 2009 to <10% in 2012 following the unexpected increase in FSs associated with the CSL 2010 southern hemisphere TIV in 2010.(7) Parents in the study reported more concern over the risk of vaccine side effects and safety than the risk of severe influenza disease.

While there are no studies examining vaccination coverage for routine scheduled vaccines in children with a history of seizures or epilepsy, children with neurological conditions are less likely to be fully

immunised and are at increased risk of delayed vaccinations compared to children with no neurological conditions.(184, 185) Parents of children with neurological conditions report safety concerns as a major barrier to vaccinating their children, with “concerns about how the vaccine would affect my child” being the most common concern.(8) Physicians have also reported a lower likelihood of recommending vaccination to children with neurological conditions,(186) despite neurological conditions not being a contraindication to vaccination.

1.5 Summary, research gaps and thesis aims

Seizures range from the common and mostly benign FS to the life-threatening SE. In this chapter, I have presented the existing knowledge on FS and SE, their aetiology, epidemiology, clinical severity, management, long-term developmental outcome and epilepsy risk. I have outlined the risk of VP-FS attributable to specific vaccines and presented the limited existing data on VP-SE, which focuses on children with Dravet syndrome.

I have identified knowledge gaps in the risk, clinical severity, developmental outcome and genetic risk of vaccine-proximate seizures, and their impact on vaccination coverage. Table 1.4 outlines these knowledge gaps, the respective thesis aims, and proposed studies to address these gaps (which form my thesis), and the potential impact for providers and policymakers.

Through the specified studies, I hope to better define the risks and outcomes across the spectrum of seizures following vaccination, to use this evidence to better inform immunisation providers and counsel parents on vaccine safety, and to provide guidance on safe revaccination.

Table 1.4 Knowledge gaps, thesis aims and research studies

Knowledge gap	Thesis aim	Proposed study	Thesis section	Policy and provider relevance
Clinical severity of VPSs	To determine the difference in clinical outcomes in children with VP-FS or VP-SE compared to children with NVP-FS or NVPS-SE	Prospective cohort study comparing VP-FS and NVP-FS hospital presentations	2.3	Inform stakeholders (individual and public health) of clinical outcomes of AEFIs Improve vaccine confidence
		Retrospective population-based record-linked cohort study on SE hospitalisations	3.3	
		Retrospective cohort study comparing VP-SE and NVP-SE hospital presentations	3.4	
Genetic risk for VPS	To determine if there is a genetic risk in children with VP-FS	Prospective case-control study in children with VP-FS, NVP-FS and no seizures, screening for pathogenic SCN1A variants	2.4	Identify at-risk individuals and need for tailored vaccination approach
Developmental outcome following VPS	To determine the difference in the developmental outcomes of children with VP-FS compared to children with NVP-FS or no seizures	Prospective case-control study in children with VP-FS, NVP-FS and no seizures, comparing developmental and behavioural outcomes	2.5	Inform stakeholders (individual and public health) of long-term outcomes following AEFIs

Knowledge gap	Thesis aim	Proposed study	Thesis section	Policy and provider relevance
Vaccination coverage following VPS	To compare the impact of VP-SE and NVP-SE on subsequent vaccination uptake	Retrospective population-based record-linked cohort study on SE hospitalisations	3.3	Inform stakeholders (providers and public health) of impact of AEFI on vaccination coverage
Risk of VPS recurrence	To quantify the risk of VPS recurrence	Retrospective cohort study of children with VPS presenting for revaccination	4.3, 4.4	Assist immunisation providers in risk stratification of VPS recurrence
Factors that reduce risk of VPS recurrence	To identify factors that reduce the risk of VPS recurrence	Retrospective cohort study of children with VPS presenting for revaccination	4.3, 4.4	Development of clinical practice guidelines

AEFI=adverse event following immunisation, NVP-FS=non-vaccine-proximate febrile seizure, NVP-SE=non-vaccine-proximate status epilepticus, SE=status epilepticus, VP-FS=vaccine-proximate febrile seizure, VP-SE=vaccine-proximate status epilepticus, VPS=vaccine-proximate seizure

Chapter 2 Febrile seizures following vaccination

2.1 Introduction

In my literature review, I identified knowledge gaps in the clinical and developmental outcomes and genetic markers in children with VP-FS compared to children with NVP-FS.

While studies on FS in general report that most FSs are brief and self-resolving, and children with a history of FS generally progress to have normal intelligence, academic achievement and behaviour,(13, 63-68) there were only two retrospective studies, of the same cohort, that specifically compared outcomes following VP-FS and NVP-FS.(168, 169) These studies found no difference in the risk of hospitalisation between groups,(169) but a higher chance of FS recurrence in children with VP-FS compared to children with NVP-FS.(168) However, the studies did not examine markers of seizure severity such as seizure duration, seizure recurrence within the same admission, the use of antiepileptics or the need for readmission. They also did not examine the proportion of VP-FS that has an alternate biological cause, such as a concomitant infection, and how that may affect the severity of the VP-FS. There were also no studies examining the genetic risk of VP-FS or the developmental outcomes following a VP-FS.

Through two prospective studies, this chapter aims to address the following knowledge gaps:

1. Clinical severity differences between VP-FS and NVP-FS cases
2. Developmental outcomes of children with VP-FS compared to children with NVP-FS and healthy children
3. Genetic markers in children with VP-FS compared to children with NVP-FS and healthy children

2.2 Methods

In **Section 2.3** (Paper 1), clinical outcomes following VP-FS were examined through a multi-centre prospective cohort study conducted through the Paediatric Active Enhanced Disease Surveillance (PAEDS) Network(187) across five Australian tertiary paediatric hospitals (The Children's Hospital at Westmead, Sydney; The Royal Children's Hospital Melbourne; Princess Margaret Hospital for Children, Perth [now Perth Children's Hospital]; Women's and Children's Hospital, Adelaide; and Lady Cilento Children's Hospital, Brisbane [now Queensland Children's Hospital]). The outcomes examined were seizure duration, seizure recurrence in the subsequent 24 hours, requirement for antiepileptic medication, hospital length of stay, intensive care unit (ICU) admission, death, and readmission for FS recurrence within 48 hours of the initial FS. Children aged ≤6 years presenting with FSs between 1 May 2013 and 30 June 2014 were prospectively recruited into the cohort study to compare the clinical outcomes of VP-FS and NVP-FS.

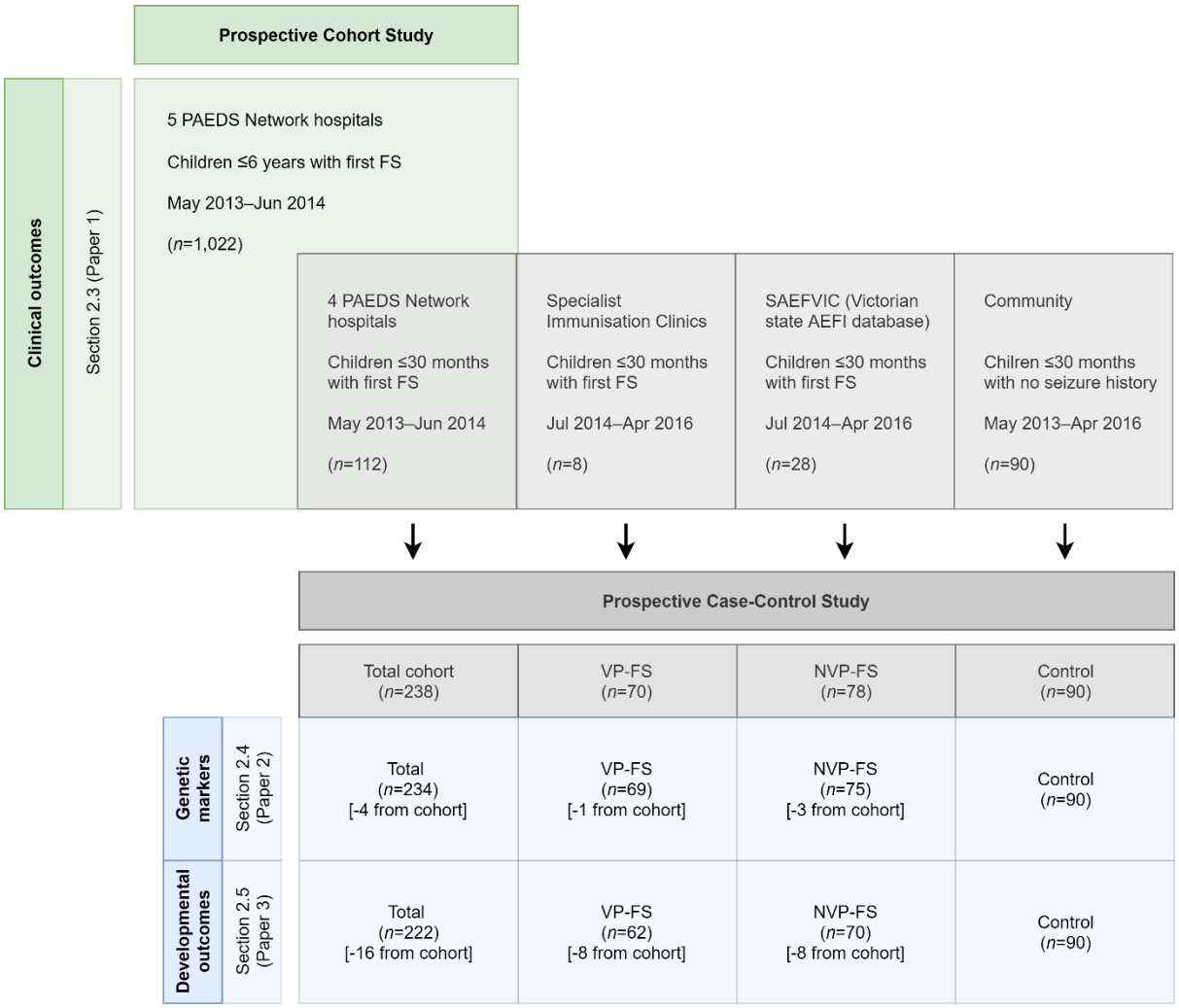
In **Sections 2.4** and **2.5** (Papers 2 and 3), the genetic markers of and developmental outcomes following VP-FS were examined through a prospective case-control study. The study protocol can be found in **Appendix 1**. Four of the five PAEDS hospitals (The Children's Hospital at Westmead, The Royal Children's Hospital Melbourne, Princess Margaret Hospital for Children, and Women's and Children's Hospital) involved in the prospective cohort study on clinical outcomes (Paper 1) recruited children from that study into a prospective case-control study to compare children with VP-FS to children with NVP-FS and healthy controls. Children aged ≤30 months at the time of their first FS were recruited from the cohort study between 1 May 2013 and 30 June 2014. From July 2014 to April 2016, additional FS cases were identified from children (outpatients) attending Specialist Immunisation Clinics at any of the participating hospitals for review of their VP-FS, or through reports of VP-FS to the Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) service responsible for the recording and follow-up of all adverse events after immunisation in Victoria. Children with no history of seizures or neurological conditions were recruited from the community across the entire study period (May 2013 to April 2016) as controls.

Recruited participants for both studies and the participant overlap across the study cohorts are outlined in Figure 2.1. **Section 2.3** is the published manuscript (Paper 1) of the larger prospective

cohort study comparing the clinical outcomes following VP-FS and NVP-FS. **Sections 2.4** and **2.5** are the published manuscripts (Papers 2 and 3) of the genetic markers of and the developmental outcomes following VP-FS from the prospective case-control study. Four participants were excluded from the genetic component of the case-control study (Paper 2) due to either consent or DNA sample for genetic testing not being provided. Sixteen participants were excluded from the developmental outcome component of the study (Paper 3); 2 withdrew participation from the VP-FS group, and 14 did not complete follow-up assessment within the specified time frame (6 from the VP-FS group and 8 from the NVP-FS group).

Finally, the findings of Papers 1–3 are summarised in a narrative review (Paper 4).

Figure 2.1 Study cohorts for Sections 2.3 to 2.5



FS=febrile seizure, NVP-FS=non-vaccine-proximate febrile seizure, PAEDS=Paediatric Active Enhanced Disease Surveillance, SAEFVIC=Surveillance of Adverse Events Following Vaccination in the Community, VP-FS=vaccine-proximate febrile seizure

2.3 Clinical outcomes (published manuscript)

Postvaccination febrile seizure severity and outcome.

Deng L, Gidding H, Macartney K, Crawford N, Buttery J, Gold M, Richmond P, Wood N.

Pediatrics. 2019;143(5):e20182120. doi:10.1542/peds.2018-2120

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Postvaccination Febrile Seizure Severity and Outcome

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abstract

BACKGROUND: Febrile seizures (FSs) are a common pediatric condition caused by a sudden rise in temperature, affecting 3% to 5% of children aged ≤6 years. Although vaccination can cause FSs, little is known on whether FSs occurring in the time soon after vaccination (vaccine-proximate febrile seizures [VP-FSs] differ clinically from non–vaccine-proximate febrile seizures [NVP-FSs]). We compared the clinical profile and outcomes of VP-FS to NVP-FS.

METHODS: Prospective cohort study of children aged ≤6 years presenting with their first FS at 1 of 5 Australian pediatric hospitals between May 2013 and June 2014. Clinical features, management, and outcomes were compared between VP-FS and NVP-FS.

RESULTS: Of 1022 first FS cases (median age 19.8 months; interquartile range 13.6–27.6), 67 (6%) were VP-FSs. When comparing VP-FS to NVP-FS, there was no increased risk of prolonged (>1 day) hospitalization (odds ratio [OR] 1.61; 95% confidence interval [95% CI] 0.84–3.10), ICU admission (OR 0.72; 95% CI 0.10–5.48), seizure duration >15 minutes (OR 1.47; 95% CI 0.73–2.98), repeat FS within 24 hours (OR 0.80; 95% CI 0.34–1.89), or requirement for antiepileptic treatment on discharge (OR 1.81; 95% CI 0.41–8.02). VP-FS patients with a laboratory-confirmed infection (12%) were more likely to have a prolonged admission compared with those without.

CONCLUSIONS: VP-FS accounted for a small proportion of all FS hospital presentations. There was no difference in outcomes of VP-FS compared with NVP-FS. This is reassuring data for clinicians and parents of children who experience FS after vaccination and can help guide decisions on revaccination.

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Dr Wood conceptualized and designed the study, coordinated, and supervised the project; Dr Deng conducted the initial analyses and drafted the initial manuscript; Dr Gidding assisted in the statistical analyses; Drs Macartney, Crawford, Buttery, Gold, and Richmond contributed to the interpretation of the results; and all authors reviewed and revised the final manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Febrile seizures are the most common childhood seizure disorder, triggered by a sudden increase in temperature from any cause, including vaccination. Previous studies revealed no difference in risk of hospitalization for vaccine-proximate febrile seizures (VP-FSs) compared to non–vaccine-proximate febrile seizures (NVP-FSs).

WHAT THIS STUDY ADDS: Comparing VP-FSs to NVP-FSs, we identified no difference in ICU admission rates, seizure duration, recurrent seizures during admission, or need for antiepileptics at discharge. VP-FS cases with laboratory-confirmed coexisting infection had longer admissions compared with VP-FS cases without.

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Febrile seizures (FSs) are the most common type of childhood seizures, occurring in 3% to 5% of children between 6 months and 6 years of age, with peak incidence in the second year of life. They are familial in some cases and sporadic in others, suggesting both genetic and environmental factors play a role. A sudden rise in temperature is often described, and FSs are most commonly associated with a febrile viral illness.[1–4] They are frightening to parents and often lead to medical consultation. In addition, ~30% of children with a first FS will have a second episode,[5] with risk factors for recurrence being younger age at first FS and family history of FS.[6] Epidemiological studies reveal that most children with a history of FS have normal behavior, intelligence and academic achievement, and do not later develop epilepsy.[7,8]

Whole-cell pertussis and measles-containing vaccines[9] as well as some influenza vaccines in combination with pneumococcal vaccines[10] are associated with an increased rate of FSs within a defined period of time after vaccination when fever peaks.[11,12] FS associated with a vaccination can decrease parent and provider confidence in vaccine safety and impact future vaccination of the child and other family members. When 1 seasonal influenza brand in Australia was withdrawn in 2010 because of increased risk of FS,[13] it led to an overall reduction in influenza vaccine confidence and coverage despite no further FS signal being detected in subsequent years.[14,15] While that particular influenza vaccine was associated with significant sequelae, it is unclear whether other vaccine-proximate febrile seizures (VP-FSs), occurring within a time frame when the fever may have been caused by vaccination, are any different to FSs due to another cause.

Although data to define the attributable risk of VP-FS are becoming increasingly available, only 2 previous studies, within the same cohort of US children aged 6 months to 3 years, directly compared VP-FS to non–vaccine-proximate febrile seizure (NVP-FS).[16,17] In the first study, children with a first VP-FS were more likely to be girls, younger, have a lower birth weight, a lower Apgar score at 1 minute, and a higher chance of FS recurrence compared with children with NVP-FS.[16] The second study revealed no difference in risk of hospitalization for first FS.[17] However, the authors of these retrospective studies did not examine other markers of seizure severity such as duration, recurrence within the same admission, or use of antiepileptics. The effect of a laboratory-confirmed coexisting infection on VP-FS has also never been examined. We conducted a prospective cohort study of children aged ≤6 years to examine differences in and contributors to first FS severity and FS recurrence in the 6 months after the initial FS presentation in VP-FS and NVP-FS cases.

METHODS

Case Ascertainment and Study Population

Active prospective FS surveillance was conducted from May 1, 2013, to June 30, 2014, through the Pediatric Active Enhanced Disease Surveillance (PAEDS) Network at 5 Australian tertiary hospitals: the Children's Hospital at Westmead Sydney, Royal Children's Hospital Melbourne, Princess Margaret Hospital for Children Perth, Women's and Children's Hospital Adelaide, and Lady Cilento Children's Hospital Brisbane, as previously described in another study using the same study cohort.[11]

Specialized surveillance nurses systemically identified potential FS cases by screening emergency department and inpatient databases and reviewing all records with *International Classification of Diseases, 10th Revision, Australian Modification* diagnosis code for FS (R56.0).

Children aged ≤6 years were included in the study if they presented with their first seizure, where the seizure fulfilled the Brighton Collaboration case definition[18] and was associated with a fever, defined as a temperature of >38°C, reported by their caregiver or documented by paramedics or health care worker on presentation to the hospital. Per the International League Against Epilepsy definition of FS,[19] children were excluded if they had a previous seizure and/or existing neurologic condition reported by their caregiver or if they were found to have a central nervous system infection by cerebrospinal fluid (CSF) analysis.

Clinical details were collected through caregiver interviews and included age at time of FS, aboriginal and Torres Strait Islander status, country of birth (Australia or other), birth weight, gestational age at birth, history of meningitis or encephalitis or other chronic medical conditions, family history of FSs or epilepsy, and clinical symptoms on seizure presentation. Investigations when performed included blood, urine, CSF culture, nasopharyngeal aspirate (NPA), EEG, and imaging (computed tomography [CT] or MRI), with these results being obtained through medical record review. Subsequent FS presentations of the same child within the study period were also recorded. Receipt of immunizations were verified for all children by using data from the Australian Immunization Register.[11,20]

Participants recruited between May 1 and December 31, 2013, were contacted via phone to assess FS recurrence 6 months after the initial FS presentation. Because of study

resource constraints, follow-up of cases recruited between January 1 and June 30, 2014, was not performed.

Case Definitions and Outcome Measures

On the basis of previous studies on timing of fever onset after specific vaccines, VP-FS was defined as an FS that occurred from day 0 to 2 after receipt of an inactivated vaccine, day 5 to 14 after a live-attenuated vaccine, or day 0 to 14 after a combination of inactivated and live-attenuated vaccines.[9,11,21,22] An FS outside of this period was considered an NVP-FS.

The primary outcome measures were seizure severity defined as seizure duration >15 minutes, further seizures in the subsequent 24 hours, and antiepileptic drug (AED) use; secondary outcome measures were length of stay (LOS) in hospital >1 day, transfer from a peripheral hospital, ICU admission, death, and readmission for FS recurrence within 48 hours of initial FS.

Cases were defined as having a coexisting infection if ≥1 laboratory investigations (blood, urine or CSF culture, CSF polymerase chain reaction, or NPA polymerase chain reaction) detected viral or bacterial pathogens. Investigations performed on readmission within 48 hours of initial presentation were considered as the same illness and were combined with any initial investigations in the analysis. Investigations were performed at the clinicians' discretion.

Statistical Analysis

Demographic data on and reported symptoms from patients with VP-FS and NVP-FS were compared by using a χ^2 or Fisher's exact test for categorical values, as appropriate, and the Mann-Whitney *U* test for nonparametric continuous values. Logistic regression was performed for each clinical outcome measure, with the exposure of interest categorized as either VP-FS or NVP-FS and adjusted for age categories (<12, 12–24, 24–36, ≥36 months) and sex. VP-FS cases with coinfection were compared with cases with no coinfection or not tested by using Fisher's exact test. Statistical analyses were performed with SAS (SAS Institute, Inc, Cary, NC) version 9.3.

TABLE 1 Baseline Profile of Patients Presenting With First FS (*n* = 1022)

Patient Characteristic	All Cases (*n* = 1022)	NVP-FS (*n* = 955)	VP-FS (*n* = 67)	*P*[a]
Male sex, *n* (%)	545 (53.3)	516 (54.0)	29 (43.3)	.09
Age, median (IQR), mo	19.8 (13.6–27.6)	20.3 (14.2–28.1)	13.0 (12.4–17.6)	<.001
<12, *n* (%)	164 (16.0)	151 (15.8)	13 (19.4)	—
12–24, *n* (%)	505 (49.4)	455 (47.6)	50 (74.6)	—
24–36, *n* (%)	214 (20.9)	213 (22.3)	1 (1.5)	—
≥36, *n* (%)	139 (13.6)	136 (14.2)	3 (4.5)	—
Indigenous, *n* (%)	25 (2.4)	25 (2.6)	0 (0.0)	.40
Country of birth, *n* (%)				
Australia	929 (90.9)	865 (90.6)	64 (95.5)	.38
Other	40 (3.9)	39 (4.1)	1 (1.5)	—
Unknown	53 (5.2)	51 (5.3)	2 (3.0)	—
Birth weight, *n* (%), g				
<1500	10 (1.0)	10 (1.0)	0 (0.0)	.11
1500–2500	42 (4.1)	39 (4.1)	3 (4.5)	—
2500–4000	737 (72.1)	683 (71.5)	54 (80.6)	—
>4000	98 (9.6)	90 (9.4)	8 (11.9)	—
Unknown	135 (13.2)	133 (13.9)	2 (3.0)	—
Gestation, *n* (%), wk				
<28	5 (0.5)	5 (0.5)	0 (0.0)	.24
28–31	4 (0.4)	4 (0.4)	0 (0.0)	—
32–36	72 (7.0)	70 (7.3)	2 (3.0)	—
>36	880 (86.1)	816 (85.4)	64 (95.5)	—
Unknown	61 (6.0)	60 (6.3)	1 (1.5)	—
Past medical history, *n* (%)				
Meningitis and/or encephalitis (resolved)	10 (1.0)	10 (1.0)	0 (0.0)	.99
Chronic medical conditions	115 (11.3)	107 (11.2)	8 (11.9)	.84
Family history, *n* (%)				
FSs	382 (37.4)	353 (37.2)	29 (43.3)	.30
Epilepsy	171 (16.7)	164 (17.2)	7 (10.4)	.18

Indigenous represents aboriginal and/or Torres Strait Islanders. —, not applicable.
[a] χ^2 or Fisher's exact test for categorical values and Mann-Whitney *U* test for nonparametric continuous values; unknown categories were not included in the statistical analyses.

RESULTS

Patient Characteristics

There were 1735 potential FS episodes in 1504 children aged 0 to 6 years identified through screening between May 1, 2013, and June 30, 2014, across the 5 PAEDS sites. Twenty-one patients with a previous afebrile seizure, 45 with an existing neurologic condition, and 7 confirmed meningitis cases were excluded from the study. Of the 1662 FS cases remaining, 640 were excluded because they were not the first FS episode, leaving 1022 first FS cases of which 67 (6%) were VP-FSs and 955 (94%) were NVP-FSs. A subset of 638 cases recruited between May 1 and December 31, 2013, were contacted for follow-up at 6 months, and 398 responded (62% overall response rate, 62% [373 of 598] for NVP-FS; 63% [25 of 40] for VP-FS).

Children with their first VP-FS were younger than children with their first NVP-FS (13 vs 20 months; $P < .001$) (Table 1). There was no difference in family history of FS or epilepsy between VP-FS and NVP-FS groups.

There were no differences in birth weight, gestational age at birth, country of birth, Aboriginal and/or Torres Strait Islander background, or past medical history of meningitis or encephalitis or other chronic medical conditions between the 2 groups.

VP-FS

Of the 67 VP-FS cases, 56 (84%) were after vaccination with measles-containing vaccines (of which 40 were measles-mumps-rubella [MMR] with *Haemophilus influenzae* type b and meningococcal C conjugate [Hib-MenC] vaccine, 12 measles-mumps-rubella-varicella [MMRV], 3 MMR with diphtheria-tetanus-acellular pertussis and inactivated polio combination vaccine [DTaP-IPV], and 1 MMR only). The remaining 11 VP-FSs occurred after diphtheria-tetanus-acellular pertussis, *H influenzae* type b, hepatitis B, and inactivated polio combination vaccine (DTaP-Hib-HepB-IPV) with 13-valent pneumococcal conjugate vaccine (PCV13) and rotavirus (n = 7), varicella (n = 2), DTaP-Hib-HepB-IPV (n = 1), and influenza (n = 1) vaccines.

The peak incidence of FS was 9 days postvaccination, of which 13 were after vaccination with MMR and 1 after MMRV (Fig 1).

Seizure Severity and Outcome

Univariate and multivariate analyses revealed no increased risk of a severe seizure associated with a VP-FS compared to an NVP-FS (Table 2). Most VP-FSs and NVP-FSs were short (≤15 minutes) with a LOS of 1 day or less, and no differences in FS recurrence within the first 24 hours of the initial FS were observed. There was an increased risk of AED use for seizure termination for VP-FSs compared to NVP-FSs (adjusted odds ratio [aOR] 2.24; 95% confidence interval [CI] 1.07–4.67; P = .03) but no difference at discharge. An AED was used for seizure termination in all 10 cases of prolonged VP-FS compared to only 47 cases (59%) of prolonged NVP-FS. Children with VP-FS were more likely to be transferred from a peripheral hospital than children with NVP-FS (aOR 2.36; 95% CI 1.09–5.11; P = .03). Compared to the VP-FS group overall, the 9 VP-FS cases requiring transfer had a higher proportion of patients with prolonged seizures (44% vs 15%), repeat seizures within 24 hours of initial (33% vs 9%), and AED use for initial management (56% vs 15%).

There was no FS recurrence within 48 hours after all first VP-FS. There was also no increased risk of FS recurrence 6 months after the initial VP-FS compared to NVP-FS (aOR 1.17; 95% CI 0.46–2.94; P = .75) in the subset of 398 patients followed-up at 6 months (Table 2).

Clinical Symptoms and Investigation of Outcomes

Respiratory symptoms were the most commonly reported symptom, with similar proportions in each group (62.7% VP-FS vs 62.8% NVP-FS). There was also a similar proportion of patients in each group who had a rash (9.0% vs 6.6%) or irritability and/or lethargy (11.1% vs 8.6%). Vomiting and diarrhea were less frequently reported in VP-FS than in NVP-FS cases (vomiting: 3.7% vs 22.0%; diarrhea: 7.5% vs 11.6%).

Laboratory investigations were performed in a subset of patients at the treating clinicians' discretion (24% of VP-FS versus 35% of NVP-FS had 1 or more laboratory tests; P = .3). A larger proportion of children with prolonged seizures (56% [61 of 108] vs 33% [285 of 880]; $P < .001$) or repeat seizures within 24 hours of the initial FS (74% [71 of 96] vs 31% [274 of 892]; $P <$ .001) had investigations performed. FS cases with respiratory symptoms were less likely to have investigations, although the difference was not statistically significant for VP-FS cases. There was no difference in other reported symptoms comparing VP-FS cases that had laboratory investigation to VP-FS cases that did not.

Laboratory-confirmed infection was found in similar proportions in those

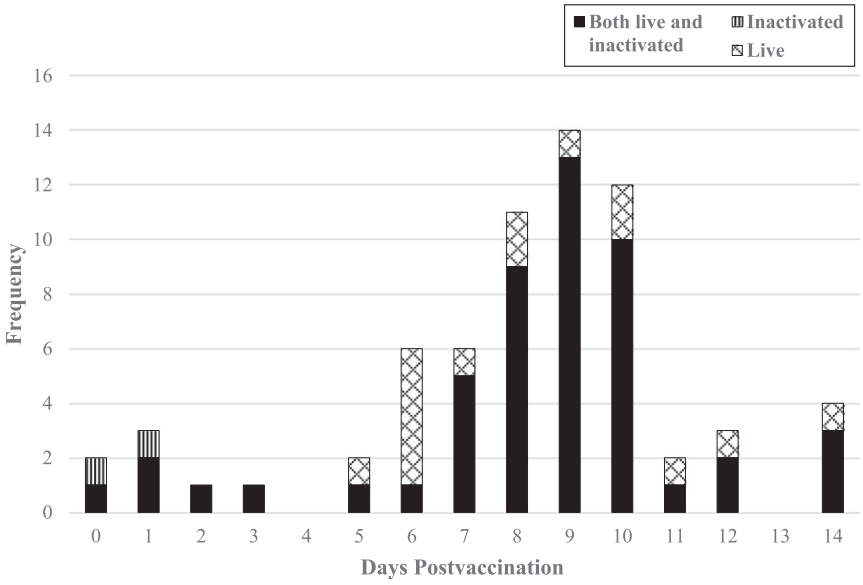

FIGURE 1
Timing of first FS after vaccination by type of vaccination received.

TABLE 2 Seizure Severity and Risk Estimates for Each Severity Indicator, Comparing VP-FS and NVP-FS Cases

	All (n = 1022)	NVP-FS (n = 955)	VP-FS (n = 67)	Univariate		Multivariate	
	n (%)	n (%)	n (%)	OR (95% CI)	P	aOR[a] (95% CI)	P
Admission details							
LOS >1 d	126 (12.3)	114 (11.9)	12 (17.9)	1.61 (0.84–3.10)	.15	1.50 (0.76–2.94)	.24
Transfer from peripheral hospital	61 (6.0)	52 (5.4)	9 (13.4)	2.70 (1.27–5.74)	.01	2.36 (1.09–5.11)	.03
ICU admission	20 (2.0)	19 (2.0)	1 (1.5)	0.72 (0.10–5.48)	.75	0.67 (0.09–5.16)	.70
Death	1 (0.1)	1 (0.1)	0 (0.0)	NC	—	—	—
Seizure details							
Seizure duration >15 min	108 (10.6)	98 (10.3)	10 (14.9)	1.47 (0.73–2.98)	.28	1.40 (0.70–2.79)	.34
Repeat seizures 24 h after presentation	96 (9.4)	90 (9.4)	6 (9.0)	0.80 (0.34–1.89)	.61	0.88 (0.59–1.31)	.44
AED use							
AED for termination of seizure	80 (7.8)	70 (7.3)	10 (14.9)	2.22 (1.09–4.53)	.03	2.24 (1.07–4.67)	.03
AED on discharge	18 (1.8)	6 (1.7)	2 (3.0)	1.81 (0.41–8.02)	.44	1.68 (0.37–7.66)	.50
Follow-up details							
Readmission within 48 h with FS	8 (0.8)	8 (0.8)	0 (0.0)	NC	—	—	—
FS recurrence[b] at 6 mo	88 of 398 (22.1)	81 of 373 (21.7)	7 of 25 (28.0%)	1.40 (0.57–3.47)	.47	1.17 (0.46–2.94)	.75

NC, not calculated; OR, odds ratio; —, not applicable.

[a] Multivariate analysis adjusted for age group (<12, 12–24, 24–36, ≥36 mo) and sex.

[b] Subset of 398 patients who were followed-up 6 mo after initial FS.

tested in both groups (30% VP-FS versus 28% NVP-FS; P = .82) (Table 3). Eight out of 27 VP-FS cases tested had a laboratory-confirmed infection (5 respiratory illnesses, 2 *Escherichia coli* urinary tract infections, and 1 enterovirus gastroenteritis). Four were after the first dose of MMR and 4 after the combination of DTaP-Hib-HepB-IPV, PCV13, and rotavirus vaccine.

Patients with VP-FS with a coinfection were younger compared with patients with VP-FS without coinfection and those not tested (9.8, 13.8, 13.2 months, respectively; P = .02), and a larger proportion required an LOS >1 day (75%, 26%, 2.5%, respectively; $P < .001$).

Six (9%) VP-FS and 41 (5%) NVP-FS cases had either EEG and/or CT or MRI on the brain. All VP-FS cases that had an EEG or imaging were either prolonged or recurrent FS cases.

DISCUSSION

We present a comprehensive comparison of seizure severity between young children with VP-FS and NVP-FS that should be valuable for counseling parents of children, who, in Australia, will have received 13 vaccinations by the time they reach

TABLE 3 Investigations and Diagnosis of Infection in NVP-FS and VP-FS Cases

	NVP-FS (n = 921)		VP-FS (n = 67)		P
	Tested (All Cases)	Positive (All Tested)	Tested (All Cases)	Positive (All Tested)	
n (%)	319 (34.6)	88 (27.6)	27 (40.3)	8 (29.6)	.82
Laboratory investigations, n (%)					
NPA	92 (10.0)	50 (54.3)	8 (11.9)	6 (75.0)	.13
Stool culture	44 (4.8)	11 (25.0)	5 (7.5)	1 (20.0)	.81
Urine culture	218 (23.7)	43 (19.7)	19 (28.4)	4 (21.1)	.89
Blood culture	221 (24.0)	6 (2.7)	14 (20.9)	0 (0.0)	.86
Neurologic investigations,[a] n (%)	41 (4.5)	—	6 (9.0)	—	—
EEG	29 (3.1)	8 (27.6)	3 (4.5)	1 (33.3)	.83
CT or MRI brain	28 (3.0)	4 (14.3)	4 (6.0)	0 (0.0)	.70
Diagnosis of infection,[b] n					
Bacteraemia and/or sepsis	—	3	—	0	—
Gastroenteritis (viral)	—	5	—	0	—
Gastroenteritis (bacterial)	—	6	—	1	—
Respiratory infection	—	49	—	5	—
Urinary tract infection	—	25	—	2	—

$P = \chi^2$ test comparing the proportion cases that tested with positive results in each FS group for each investigation. —, not applicable.

[a] Positive for neurologic investigations refers to an abnormality found on the investigation.

[b] Laboratory isolates in VP-FS group include 2 cases of *E coli* and 1 case of each of the following: rhinovirus; rhinovirus, respiratory syncytial virus, and adenovirus combination; enterovirus; human metapneumovirus; parainfluenza virus; and parechovirus.

2 years of age as part of the National Immunization Program. Our study reveals that VP-FSs are no different in seizure severity to NVP-FSs, with the majority being brief (<15 minutes) seizures with no recurrence in the acute period, no prolonged LOS (>1 day), and not requiring AED use at discharge.

Our study supports the findings of Tartof et al's[17] retrospective cohort study, which also revealed no difference in LOS between VP-FS and NVP-FS. Using detailed individual clinical note review, we have better defined the severity of VP-FS with our study. We expand on the Tartof et al[17] study to demonstrate no difference in other clinical severity measures, including rate of ICU admission, seizure duration, recurrence within the initial 24 hours, and requirement of AED use at discharge, which has not been studied before. With our study, we are the first to report no increased risk of prolonged or recurrent FS after VP-FS compared to NVP-FS even after adjusting for age and sex. We found the higher proportion of VP-FS cases transferred from peripheral hospitals compared to NVP-FS cases was associated with other markers of seizure severity, with a higher proportion of children with prolonged seizures or recurrence within the initial 24 hours being transferred. We also found a higher proportion of AED use for seizure termination in VP-FS cases. An AED was used for seizure termination in all prolonged VP-FSs, in accordance to international acute seizure management guidelines,[23] compared to only 59% of prolonged NVP-FSs. It is unclear whether there was a difference in semiology or duration of the prolonged seizures in either group, which may account for the difference in AED use for seizure cessation. Reassuringly, we found no difference in risk of prolonged seizures or the requirement of AED use on discharge between VP-FS and NVP-FS.

The majority of VP-FSs in our study were after measles-containing vaccines, in keeping with a known twofold risk in FS after measles vaccination.[24–26] They were mostly after the first dose of MMR, and because the first dose of MMR is given at 12 months of age in Australia, this has caused a left shift to a younger mean age of first FS in VP-FS compared to NVP-FS (mean age 13 vs 20 months; $P < .0001$). A similar age difference between groups was seen in the Tartof et al study.[17]

To our knowledge, this is the first study used to examine the presence of clinical symptoms and the effect of coexisting infections on VP-FS. We identified a large proportion (63%) of VP-FS cases with respiratory symptoms and some with vomiting, diarrhea, or abdominal pain, suggesting some may have an infective contributory cause of the FS in addition to a vaccine. Authors of previous studies examining the risk of vaccines and seizures have not reported on the presence of concomitant infection. It is not possible to determine whether an infection or vaccine is the dominant cause of the FS; however, it is reassuring that the presence of these infective symptoms did not impact seizure severity of VP-FS compared to NVP-FS. Of the 12% of VP-FS cases with laboratory-confirmed coinfection, the only clinical difference was a longer LOS compared with those with no laboratory-confirmed coinfection because of the need for treatment of the underlying infection. Because less than half of VP-FS cases were investigated for infection, it is possible that the proportion of VP-FS with a coinfection is underestimated, and the proportion of FS that is solely attributable to vaccination is lower than previously reported[17,24] where only the temporal relation with vaccination was considered.

Although risk factors for FS such as family history, prematurity, and fetal growth retardation have been well documented,[27–30] we did not find any differences in sex, birth weight, or gestational age between VP-FS and NVP-FS, which contrasts with Tartof et al[17] study findings. Study population differences may have contributed to the difference in findings because Tartof et al[17] only included first FS occurring at <3 years of age and more broadly defined VP-FS as an FS 0 to 15 days after any vaccine. The absence of differences in our study is reassuring given our more biologically plausible VP-FS definition and wider capture of all FSs up to 6 years of age that is more in line with FS incidence.[4]

In those followed up to 6 months, the recurrence rate in both VP-FS (23.6%) and NVP-FS (28%) was slightly lower than the 30% recurrence rate reported in previous FS studies.[5,30] The short follow-up period and small sample size may account for this difference. Although earlier onset of FS is a risk factor for recurrence,[5,6] there was no increased risk in the younger VP-FS group compared with the NVP-FS group. This was also reported by Tartof et al,[17] whose study had a longer mean follow-up duration of 2.2 years.

The strength of this study lies in the prospective case ascertainment through an established robust active surveillance network in which comprehensive clinical data were collected for analysis. Our strict case definition for VP-FS accounted for differences in fever risk window of specific vaccines allowing for more accurate delineation between VP-FS and NVP-FS. Our ability to collect clinical symptoms and investigation data allowed us to examine

the impact of coinfections on VP-FS, which was not examined in the comparative research studies.[16,17]

A limitation of case ascertainment from sentinel tertiary pediatric hospitals is that it may not be representative of all FSs in Australia. Differences in health care–seeking behavior could also contribute to bias. Patients with existing medical conditions may be more likely to present for assessment, and families who are familiar with FS may not. However, as we examined first FS only, we feel that this bias is less likely than for subsequent FS.

Given the small proportion of VP-FS cases and limited cohort size, the study would have been able to detect a true difference in the proportion of prolonged seizure in the VP-FS group if it was double the 11.9% in the NVP-FS group, with a power of 0.8. The 6.0% difference between the groups, however, would not be considered clinically significant. Finally, our follow-up data are limited by the high proportion lost to follow-up and short duration. Although it is unclear if there are any differences between those who responded and those who did not, the response rates between NVP-FS and VP-FS were comparable. Larger studies with a longer follow-up period would be useful in confirming our findings and improving recurrence rate estimates.

CONCLUSIONS

This study confirms that VP-FSs are clinically not any different from NVP-FSs and should be managed the same way. Our findings can be used to counsel concerned parents that although some vaccines have a known associated risk of FSs, clinical severity and outcomes of these FSs are no different to an FS from another cause. This information helps support the recommendation to these patients and their families that additional required vaccinations can be administered in the future.

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ABBREVIATIONS

AED: antiepileptic drug
aOR: adjusted odds ratio
CSF: cerebrospinal fluid
CT: computed tomography
DTaP-Hib-HepB-IPV: diphtheria-tetanus-acellular pertussis, *H influenzae* type b, hepatitis B, and inactivated polio combination vaccine
DTaP-IPV: diphtheria-tetanus-acellular pertussis and inactivated polio combination vaccine
FS: febrile seizure
Hib-MenC: *Haemophilus influenzae* type b and meningococcal C conjugate vaccine
LOS: length of stay
MMR: measles-mumps-rubella vaccine
MMRV: measles-mumps-rubella-varicella vaccine
NPA: nasopharyngeal aspirate
NVP-FS: non–vaccine-proximate febrile seizure
PAEDS: Pediatric Active Enhanced Disease Surveillance
PCV13: 13-valent pneumococcal conjugate vaccine
VP-FS: vaccine-proximate febrile seizure

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REFERENCES

1. Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. I—prevalence and recurrence in the first five years of life. *Br Med J (Clin Res Ed)*. 1985; 290(6478):1307–1310
2. Van der Berg BJ, Yerushalmy J. Studies on convulsive disorders in young children. I. Incidence of febrile and nonfebrile convulsions by age and other factors. *Pediatr Res*. 1969;3(4): 298–304
3. Johnston MV. Seizures in childhood. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BMD, eds. *Nelson Textbook of Pediatrics*. 18th ed. Philadelphia, PA: Elsevier Saunders; 2006:2457–2475
4. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. *Pediatrics*. 2008;121(6): 1281–1286
5. Berg AT, Shinnar S, Darefsky AS, et al. Predictors of recurrent febrile seizures. A prospective cohort study. *Arch Pediatr Adolesc Med*. 1997;151(4): 371–378
6. Pavlidou E, Tzitiridou M, Kontopoulos E, Panteliadis CP. Which factors determine febrile seizure recurrence? A prospective study. *Brain Dev*. 2008; 30(1):7–13
7. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. *N Engl J Med*. 1998;338(24): 1723–1728
8. Chang YC, Guo NW, Huang CC, Wang ST, Tsai JJ. Neurocognitive attention and behavior outcome of school-age children with a history of febrile convulsions: a population study. *Epilepsia*. 2000;41(4):412–420
9. Barlow WE, Davis RL, Glasser JW, et al; Centers for Disease Control and 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(9):656–661
10. Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM; 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
11. Macartney K, Gidding HF, Trinh L, et al; Paediatric Active Enhanced Disease Surveillance Network. Evaluation of combination measles-mumps-rubella-varicella vaccine introduction in Australia. *JAMA Pediatr*. 2017;171(10): 992–998
12. Klein NP, Fireman B, Yih WK, et al; Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics*. 2010;126(1). Available at: www.pediatrics.org/cgi/content/full/126/1/e1
13. Armstrong PK, Dowse GK, Effler PV, 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
14. Blyth CC, Richmond PC, Jacoby P, et al. The impact of pandemic A(H1N1)pdm09 influenza and vaccine-associated adverse events on parental attitudes and influenza vaccine uptake in young children. *Vaccine*. 2014;32(32): 4075–4081
15. Pillsbury A, Quinn H, Cashman P, Leeb A, Macartney K; AusVaxSafety Consortium. Active SMS-based influenza vaccine safety surveillance in Australian children. *Vaccine*. 2017;35(51): 7101–7106
16. Tartof SY, Tseng HF, Liu AL, et al. Exploring the risk factors for vaccine-associated and non-vaccine associated febrile seizures in a large pediatric cohort. *Vaccine*. 2014;32(22):2574–2581
17. Tartof SY, Tseng HF, Liu IL, et al. Inpatient admission for febrile seizure and subsequent outcomes do not differ in children with vaccine-associated versus non-vaccine associated febrile seizures. *Vaccine*. 2014;32(48):6408–6414
18. Bonhoeffer J, Menkes J, Gold MS, et al; 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*. 2004; 22(5–6):557–562
19. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. *Epilepsia*. 1993; 34(4):592–596
20. Hull B, Hendry AJ, Dey A, Beard FH, Brotherton JM, McIntyre PB. Immunisation coverage annual report, 2014. *Commun Dis Intell Q Rep*. 2017; 41(1):E68–E90
21. Rowhani-Rahbar A, Klein NP, Dekker CL, et al; Risk Interval Working Group of the Clinical Immunization Safety Assessment Network. Biologically plausible and evidence-based risk intervals in immunization safety research. *Vaccine*. 2012;31(1):271–277
22. Sun Y, Christensen J, Hviid A, et al. Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type B. *JAMA*. 2012;307(8):823–831
23. Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. *Epilepsy Curr*. 2016; 16(1):48–61
24. Macartney KK, Gidding HF, Trinh L, et al; PAEDS (Paediatric Active Enhanced Disease Surveillance) Network. Febrile seizures following measles and varicella vaccines in young children in Australia. *Vaccine*. 2015;33(11): 1412–1417
25. Gold M, Dugdale S, Woodman RJ, McCaul KA. Use of the Australian Childhood Immunisation Register for vaccine safety data linkage. *Vaccine*. 2010;28(26):4308–4311
26. Hanf M, Quantin C, Farrington P, et al. Validation of the French national health insurance information system as a tool in vaccine safety assessment: application to febrile convulsions after pediatric measles/mumps/rubella

immunization. *Vaccine*. 2013;31(49):5856–5862

27. Visser AM, Jaddoe VW, Hofman A, et al. Fetal growth retardation and risk of febrile seizures. *Pediatrics*. 2010;126(4). Available at: www.pediatrics.org/cgi/content/full/126/4/e919
28. Kjeldsen MJ, Kyvik KO, Friis ML, Christensen K. Genetic and environmental factors in febrile seizures: a Danish population-based twin study. *Epilepsy Res*. 2002;51(1–2):167–177
29. Herrgård EA, Karvonen M, Luoma L, et al. Increased number of febrile seizures in children born very preterm: relation of neonatal, febrile and epileptic seizures and neurological dysfunction to seizure outcome at 16 years of age. *Seizure*. 2006;15(8):590–597
30. Offringa M, Bossuyt PM, Lubsen J, et al. Risk factors for seizure recurrence in children with febrile seizures: a pooled analysis of individual patient data from five studies. *J Pediatr*. 1994;124(4):574–584

Postvaccination Febrile Seizure Severity and Outcome

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2.4 Genetic markers (published manuscript)

***SCN1A* variants in vaccine-related febrile seizures: a prospective study.**

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(*joint first author; I analysed the clinical data, JAD analysed the genomic sequencing; we jointly drafted the manuscript, figures and tables)

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SCN1A Variants in Vaccine-Related Febrile Seizures: A Prospective Study

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Objective: Febrile seizures may follow vaccination. Common variants in the sodium channel gene, *SCN1A*, are associated with febrile seizures, and rare pathogenic variants in *SCN1A* cause the severe developmental and epileptic encephalopathy Dravet syndrome. Following vaccination, febrile seizures may raise the specter of poor outcome and inappropriately implicate vaccination as the cause. We aimed to determine the prevalence of *SCN1A* variants in children having their first febrile seizure either proximal to vaccination or unrelated to vaccination compared to controls.
Methods: We performed *SCN1A* sequencing, blind to clinical category, in a prospective cohort of children presenting with their first febrile seizure as vaccine proximate (n = 69) or as non–vaccine proximate (n = 75), and children with no history of seizures (n = 90) recruited in Australian pediatric hospitals.
Results: We detected 2 pathogenic variants in vaccine-proximate cases (p.R568X and p.W932R), both of whom developed Dravet syndrome, and 1 in a non–vaccine-proximate case (p.V947L) who had febrile seizures plus from 9 months. All had generalized tonic–clonic seizures lasting >15 minutes. We also found enrichment of a reported risk allele, rs6432860-T, in children with febrile seizures compared to controls (odds ratio = 1.91, 95% confidence interval = 1.31–2.81).
Interpretation: Pathogenic *SCN1A* variants may be identified in infants with vaccine-proximate febrile seizures. As early diagnosis of Dravet syndrome is essential for optimal management and outcome, *SCN1A* sequencing in infants with prolonged febrile seizures, proximate to vaccination, should become routine.

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Vaccination is a highly effective public health intervention that has led to a dramatic reduction in childhood morbidity and mortality from many infectious diseases. Whereas vaccines have an excellent safety profile and usually only cause mild adverse reactions such as a fever, some individuals experience more serious adverse events, such as febrile seizures (FS).

FS following pertussis and measles–mumps–rubella (MMR)-containing vaccines, as well as influenza vaccines in combination with pneumococcal vaccines, are well

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recognized, albeit uncommon.[1–4] Whereas epidemiological studies show that the vast majority of children with a history of FS develop normally,[5,6] a small proportion develop epilepsies,[7] including the severe developmental and epileptic encephalopathy (DEE) Dravet syndrome.[8,9]

Pathogenic variants in the sodium channel alpha-1 subunit gene, *SCN1A*, cause Dravet syndrome in at least 80% of cases[8] and in 20% of cases of the milder syndrome of genetic epilepsy with FS plus (GEFS+).[10,11] Vaccinations have been implicated in triggering earlier seizure onset in children with epilepsy with Dravet syndrome.[12–15] We found that 30% (12/40) of a cohort of children with Dravet syndrome and *SCN1A* mutations had their first seizure within 2 days after vaccination.[13] In terms of the frequency of *SCN1A*-associated Dravet syndrome among children with vaccination-related seizures, Verbeek et al retrospectively identified 15 of 1,269 (1.2%) children with Dravet syndrome presenting with seizures following vaccination in the first 2 years of life.[16] Thus, rare variants in *SCN1A* are associated with genetic epilepsies and DEEs that present with FS. Conversely, common variants have been implicated in the pathogenesis of FS alone, with a common *SCN1A* exonic variant (rs6432860) associated with increased risk of FS in general, but not with MMR-related FS.[17]

Aside from these retrospective studies, little is known about genetic variants in children with vaccine proximate FS (VP-FS) and whether FS differ from those triggered by another cause. It is also unknown whether the common rs6432860 variant, only identified in one population to date, is also a risk factor in non-Danish subjects with FS.

This study is the first to prospectively identify the presence and proportion of sodium channel variants among infants with VP-FS or non–vaccine proximate FS (NVP-FS) compared with controls who have no history of seizures.

Subjects and Methods

Study Design and Participants

This prospective study was conducted across 4 Australian tertiary pediatric hospitals that participate in the Paediatric Active Enhanced Disease Surveillance network[18]: Children's Hospital at Westmead, Sydney; Royal Children's Hospital, Melbourne; Princess Margaret Hospital for Children, Perth; and Women's and Children's Hospital, Adelaide. Participant recruitment occurred between May 1, 2013 and April 30, 2016.

From May 2013 to June 2014, children presenting with FS at these sites were identified through daily surveillance nurse screening of emergency presentations or hospital admissions coded with the International Classification of Diseases, Tenth Revision, Australian Modification diagnosis code for FS (code R56.0) as part of a larger cohort study.[19] All VP-FS cases aged <30 months from this larger cohort study were invited to participate in this prospective study, and an equivalent number of NVP-FS cases of similar age were invited. Due to low numbers of VP-FS presentations during the initial recruitment period, additional VP-FS cases were recruited from July 2014 to April 2016 through outpatient attendance at specialist immunization clinics at any of the participating hospitals for review of FS following vaccination, or through VP-FS reports to the Serious Adverse Events following Vaccination in the Community service, which is responsible for recording and follow-up of all adverse events following immunization in Victoria. Vaccine exposure was confirmed using immunization records obtained from the Australian Immunisation Register, a national population-level register.[20]

We defined a first FS case in this study as a child aged <30 months at the time of their first FS; the FS had to fulfill the Brighton Collaboration case definition as verified by clinician review of hospital records[21] and be associated with a temperature of ≥38°C measured by the parents or documented in the medical records in a child with no previous history of seizures. To capture all seizures associated with a fever following vaccination, including those following the 6-week and 4-month vaccination time points, a lower age limit restriction was not used in this study. FS were categorized as VP-FS, defined as within 48 hours of an inactivated vaccine, between 5 and 14 days of a live vaccine, or within 14 days of a combination of inactivated and live vaccine. NVP-FS were defined as FS outside of this period.[20]

Control participants were defined as children aged 12 to 42 months with no personal or family history of febrile or afebrile seizures. They were recruited through friends of children with FS already recruited into the study, children participating in other clinical trials at each recruitment site, and advertisements placed in local community newspapers, childcare centers, and hospital notices.

Children were excluded from the study if they had a preexisting diagnosis of developmental delay, intellectual disability, or a medical or genetic condition that may affect cognition.

Thus, the phenotypic data allowed classification of participants into 3 groups: VP-FS, NVP-FS, and aged-matched controls without febrile seizures. This study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (HREC/14/SCHN/135).

Clinical Details and Follow-up

For FS cases, initial seizure details were collected from medical records and parent/carer interviews. Cases were contacted 12 to 24 months following the initial FS. Data on the occurrence, type (febrile or afebrile), and frequency of subsequent seizures following the initial FS and developmental progression were obtained from parent/carer interview and review of medical records, where available. Participants' development, executive function, and behavior were formally assessed using standardized assessment tools 12 to 24 months following their initial FS. Participants were assessed using Bayley Scales for Infant and Toddler Development, Third Edition, Woodcock-Johnson Tests of Achievement, Third Edition, Behavior Rating Inventory of Executive Function–Preschool Version, and Child Behaviour Checklist–Preschool. Outcomes of these assessments will be reported separately. Additional history regarding subsequent developmental progression was obtained via medical records for cases with *SCN1A* variants.

DNA Extraction

For gene variant screening, whole blood was obtained and genomic DNA was extracted using QIAamp DNA Maxi Kits (Qiagen, Valencia, CA). In some cases, saliva samples were obtained using Oragene kits and genomic DNA was extracted using prepIT•L2P kits (DNA Genotek, Ottawa, Ontario, Canada).

Polymerase Chain Reaction and Sanger Sequencing

Coding regions of *SCN1A* (chromosome 2: 165,984,641-166,149,214, NM_001165963, ENST00000303395.8) including splice sites and up to 200 base pairs of intronic sequence were sequenced. Amplicons were polymerase chain reaction amplified using gene-specific primers designed according to the reference human gene transcript.[22] Primer sequences are available upon request. Amplification reactions were cycled using a standard protocol on a Veriti Thermal Cycler (Applied Biosystems, Carlsbad, CA). Bidirectional sequencing of all exons and flanking regions including splice sites was completed with a BigDye TM v3.1 Terminator Cycle Sequencing Kit (Applied Biosystems) according to the manufacturer's instructions. Sequencing products were resolved using a 3730xl DNA Analyzer (Applied Biosystems). All sequencing chromatograms were compared to published cDNA sequence and flanking intronic sequences. Nucleotide changes were detected using CodonCode Aligner (CodonCode Corporation, Dedham, MA). Molecular analysis was performed blind to the patients' clinical status.

Variant Classification

Each variant detected in *SCN1A* was classified as pathogenic, likely pathogenic, uncertain significance, likely benign, or benign, according to American College of Medical Genetics (ACMG) consensus guidelines.[23]

The following online genetic databases were used to help determine classification of variants: Database of Single Nucleotide Polymorphisms,[24] ClinVar,[25] Genome Aggregation Database (gnomAD),[26] and Guangzhou Medical University Institute of Neuroscience *SCN1A* Mutation Database.[27]

Statistical Analysis

The 3 groups were compared using Pearson chi-squared or Fisher exact test for categorical values and independent *t* test for parametric continuous values. The primary outcome measure was the proportion of pathogenic and likely pathogenic *SCN1A* variants between groups compared using Fisher exact test. Pearson chi-squared or Fisher exact tests were also used to compare allele frequencies and genotype differences for synonymous and intronic variants between all 3 groups and between all FS subjects and controls. The Bonferroni–Holm method was applied to control the error rate for multiple comparisons.

Results

Study Cohort

Of the 269 participants initially recruited, 35 were excluded: 26 for history of previous FS, 6 for no DNA sample collected or no consent given for genetic testing, 1 for lack of documented fever on case review, and 2 for withdrawal from the study. Of the remaining 234 subjects, 69 had VP-FS, 75 had NVP-FS, and 90 were controls (Fig).

There were no differences in proportion of FS cases with a family history of FS or epilepsy between the VP-FS and NVP-FS groups. Participants with VP-FS were younger at time of first FS than those with NVP-FS (12.8 months vs 14.3 months, $p = 0.05$) and more frequently had complex FS, defined by 1 of 3 criteria: lasting >15 minutes, focal features, or > 1 FS in 24 hours (39.1% vs 22.7%, $p = 0.03$; Table 1). There was no difference in the proportion of patients with recurrent FS or afebrile seizures over a similar follow-up period (VP-FS vs NVP-FS: 37.7% vs 34.7%, $p = 0.66$ for FS; 11.6% vs 5.3%, $p = 0.17$ for afebrile seizures; follow-up 16.1 [standard deviation (SD) = 4.8] vs 17.2 [SD 3.2] months, $p = 0.09$).

Variant Detection

We detected 90 variants in *SCN1A* in the 234 subjects. The variants were comprised of 1 nonsense (stop gain), 8 missense, 9 synonymous, and 28 intronic variants; 44 variants were observed more than once. Table 2 shows the distribution of variants according to clinical group and ACMG guidelines.[23]

There were 3 pathogenic or likely pathogenic variants found. Two were in the VP-FS group (2.9%) and 1 was in the NVP-FS group (1.3%), with no difference between the 3 groups. Case 1 with VP-FS had a recurrent nonsense mutation, p.R568X, that was pathogenic in a patient with Dravet syndrome.[28] Case 2 with VP-FS and case 3 with NVP-FS had novel missense variants, p.W932R and p.V947L, respectively, both classified as "likely pathogenic" (variant details according to ACMG guidelines in footnotes to Table 3).

Three missense changes were classified as "unknown significance": p.A1161T (rs201079458), p.E1957G (rs121918802), and p.T1250M (rs140731963); all were previously reported with a minor allele frequency (MAF) < 0.01 in gnomAD; each had low predictions of functional effect from in silico tools or are reported as inherited.[29–31] In our study, all 3 were found in the NVP-FS group, and none of the cases had a family history of FS; segregation data were not available. A further 3 missense variants (p.R542Q [rs121918817], p.A1067T [rs2298771], p.T1174S [rs121918799]) were classified as "likely benign" or "benign."

The remaining variants of unknown significance comprised 3 previously unreported intronic variants (c.4339-96delC, c.1-182delT, c.4339-110 delT) and a further 9 rare intronic changes (rs571600918, rs749370340,

TABLE 1. Clinical Details for VP-FS, NVP-FS, and Control Groups

Detail	VP-FS	NVP-FS, n (%)	Control, n (%)	p[a]
n	69	75	90	
Sex, M, n (%)	37 (53.6%)	32 (42.7%)	55 (61.1%)	0.06
Family history of FS, n (%)				
FS	25 (36.2%)	25 (33.3%)	NA	0.72
Epilepsy	9 (13.0%)	13 (17.3%)	NA	0.47
First FS				
Age, mo	12.8 (SD = 3.8)	14.3 (SD = 5.2)	NA	0.05
Complex FS, n (%)	27 (39.1%)	17 (22.7%)	NA	0.03
FS recurrence				
Follow-up duration, mo	16.1 (SD = 4.8)	17.2 (SD = 3.2)	NA	0.09
FS recurrence, n (%)	26 (37.7%)	26 (34.7%)	NA	0.71
AFS following initial FS, n (%)	8 (11.6%)	4 (5.3%)	NA	0.23

[a]Where there is no value for control group, p value compares VP-FS and NVP-FS groups only.
AFS = afebrile seizure; Complex FS = FS > 15 minutes, focal seizure, or repeat seizure within 24 hours of initial FS; FS = febrile seizures; M = male; NA = not applicable; NVP-FS = non–vaccine proximate FS; SD = standard deviation; VP-FS = vaccine proximate FS.

rs73969742, rs549232924, rs75022359, rs76220226, rs8191989, rs773635222, rs148640356). We also identified 6 synonymous variants (rs140237315, rs141051370, rs374087499, rs144679294, rs569598595, rs145101180) with an MAF < 0.01 according to the Exome Aggregation Consortium database.[26] The significance of these rare variants to FS is unknown.

TABLE 2. *SCN1A* Variants by Group Allocation and Variant Class

ACMG Variant Class[23]	VP-FS, n = 69	NVP-FS, n = 75	Control, n = 90
Pathogenic	1	0	0
Likely pathogenic	1	1	0
Unknown significance[a]	4	8	4
Likely benign	2	2	4
Benign	20	22	21

[a]Variants of unknown significance were all intronic in VP-FS and control groups; NVP-FS group had 3 missense, 1 synonymous, and 4 intronic variants.
ACMG = American College of Medical Genetics; NVP-FS = non–vaccine proximate febrile seizures; VP-FS = vaccine proximate febrile seizures.

Common Variant Burden

Three common coding variants (c.3199 G > A, p.A1067T [rs2298771]; c.1212 A > G, p.V404V [rs7580482]; c.2292 T > C, p.V764V [rs6432860]) and 2 intronic variants — 1 previously implicated as a risk allele for FS in a genome-wide study (c.603-91 G > A [rs3812718])[17] and 1 in close proximity (c.603-106 T > G [rs3812719]) — were investigated for differences in allele frequencies and genotype frequency between the groups (Table 4). The synonymous change (c.2292 C > T, p.V764V [rs6432860]), was more frequently found in FS cases compared to controls (odds ratio = 1.91, 95% confidence interval = 1.31–2.81, p = 0.004). There was, however, no difference in frequency between the VP-FS and NVP-FS groups (Table 5).

SCN1A Pathogenic Variant Cases: Phenotype and Outcome

The phenotypes of the 3 children with pathogenic or likely pathogenic *SCN1A* variants are described in Table 3. The 2 VP-FS cases had seizure onset within 24 hours of receiving their 4-month vaccinations with Infanrix Hexa (hexavalent vaccine with diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus, and *Haemophilus influenzae* type B), Prevenar13

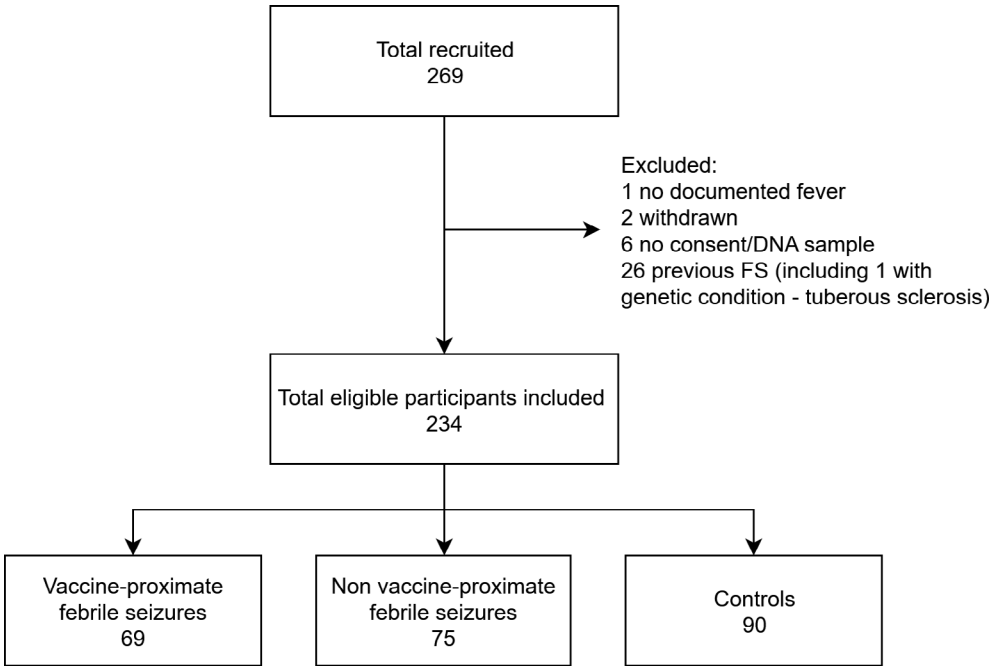

FIGURE : Study cohort. FS = febrile seizures.

(13-valent pneumococcal conjugate vaccine), and Rotarix (oral live-attenuated rotavirus vaccine). Both had prolonged generalized tonic–clonic seizures, lasting 30 and 15 minutes, respectively, and developed later seizure types that were not vaccine proximate, including myoclonic, absence, hemiclonic, generalized clonic seizures,

TABLE 3. Clinical Characteristics of Participants with Pathogenic/Likely Pathogenic Variants

Case/ Sex	Group	Age, mo	First FS Duration, min	Description	Vaccine (seizure onset time postvaccination)	Later Seizures	Epilepsy Syndrome	*SCN1A* Variant[a]
1/M	VP-FS	4.0	30	GTCS	DTPa-IPV-HepB-HiB, PCV13, rotavirus (10 hours)	MS, Ab, GTCS	Dravet	c.1702 C>T, p.R568X, pathogenic[b]
2/M	VP-FS	4.4	15	GTCS	DTPa-IPV-HepB-HiB, PCV13, rotavirus (18 hours)	MS, GCS, GTCS, H, SE	Dravet	c.2794 T>A, p.W932R, likely pathogenic[c]
3/M	NVP-FS	9.7	57	GTCS	NA	GTCS	FS+	c.2839 G>T, p.V947L, likely pathogenic[d]

[a]Classification according to American College of Medical Genetics guidelines[23] is listed, and qualifying criteria are specified.
[b]Null variant, previously reported.[8,29]
[c]Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before[39]; located in a mutational hot spot; absent from controls.
[d]Located in a mutational hot spot; absent from controls; multiple lines of computational evidence support a deleterious effect on the gene; missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease.
Ab = absences; DTPa-IPV-HepB-HiB = hexavalent diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B, haemophilus influenza B vaccine; FS = febrile seizure; FS+ = FS plus; GCS = generalized clonic seizures; GTCS = generalized tonic–clonic seizures; H = hemiclonic; M = male; MS = myoclonic seizures; NA = not applicable; NVP-FS = non–vaccine proximate FS; PCV13 = 13 valent pneumococcal conjugate vaccine; SE = status epilepticus; VP-FS = vaccine proximate FS.

TABLE 4. Allele Frequency Differences for the 5 Common Single Nucleotide Polymorphisms Detected within *SCN1A*

Variant	Location	Rs Number	Minor Allele Frequency		p[b]
			Febrile Seizures[a]	Controls	
c.2292 C>T, p.V764V	Exon 13	rs6432860	148/288 (0.51)	64/180 (0.36)	0.004
c.1212 A>G, p.V404V	Exon 9	rs7580482	137/288 (0.48)	67/180 (0.37)	0.14
c.3199 G>A, p.A1067T	Exon 16	rs2298771	75/288 (0.26)	54/180 (0.30)	1.00
c.603-91 G>A	Intron 4	rs3812718	117/288 (0.41)	81/180 (0.45)	1.00
c.603-106 T>G	Intron 4	rs3812719	55/288 (0.19)	53/180 (0.29)	0.50

[a]Includes both vaccine proximate febrile seizure and non–vaccine proximate febrile seizure cases.
[b]Probability value corrected for multiple comparisons using Bonferroni method and 5 tests.

TABLE 5. Allele Frequency Comparisons for Single Nucleotide Polymorphism c.2292 C>T, p.V764V, rs6432860 according to Clinical Group Assignment

Analyses	Minor Allele Frequency		OR (95% CI)	*p*[a]
	Cases, n (%)	Controls, n (%)		
VP-FS vs controls	74/138 (53.6%)	64/180 (35.5%)	2.10 (1.33–3.30)	0.17
NVP-FS vs controls	74/150 (49.3%)	64/180 (35.5%)	1.77 (1.13–2.75)	0.40
VP-FS vs NVP-FS	74/138 (53.6%)	74/150 (49.3%)	1.19 (0.75–1.89)	1.00
All FS vs controls	148/288 (51.4%)	64/180 (35.6%)	1.91 (1.31–2.81)	0.003

[a]Probability value corrected for multiple comparisons using Bonferroni method and 4 tests.
CI = confidence interval; FS = febrile seizures; NVP-FS = non–vaccine proximate febrile seizures; OR = odds ratio; VP-FS = vaccine proximate febrile seizures.

and status epilepticus in the first 2 years of life. Case 1, with nonsense mutation p.R568X, had developmental stagnation from 12 to 18 months with subsequent regression and developmental delay. Case 2, with the novel p.W932R mutation, had significant speech delay with no language or social–emotional developmental progression from age 18 months. The classical electroclinical history led to a diagnosis of Dravet syndrome in both children. Both cases have subsequently received further vaccinations under close medical supervision, with regular antipyretic and benzodiazepine administration following vaccination in addition to their regular antiepileptic medication, without experiencing a seizure.

The NVP-FS case with a "likely pathogenic" novel variant, p.V947L, was a dizygous twin who had his first FS at 9 months, a 57-minute episode of tonic–clonic status epilepticus in the context of an upper respiratory tract infection. He proceeded to have frequent (up to 10 per year) tonic–clonic seizures, many but not all associated with fever. His co-twin did not have seizures, but their father had a history of frequent FS. His last known seizure was at age 5 years. Bayley-III assessment at 18 months revealed mild fine motor delay and language delay. The diagnosis was FS plus (FS+) in the setting of a family with GEFS+.[10,11]

Discussion

This is the first prospective study examining the frequency of *SCN1A* variants in children with FS triggered by vaccination compared those with FS unrelated to vaccination, and controls with no history of seizures. Of 144 patients with FS, only 3 (2%) had pathogenic variants in *SCN1A*. There was no statistical difference in the frequency of pathogenic *SCN1A* variants between the groups from our cohort. It is of clinical relevance, however, that all 3 infants

with pathogenic variants had prolonged FS and the 2 infants with VP-FS both developed the features of Dravet syndrome. The third child with FS unrelated to vaccination had complex FS and afebrile seizures with a diagnosis of FS+. Our data suggest that a prolonged VP-FS in the first 6 months of life, lasting 15 minutes or more, in the presence of a pathogenic *SCN1A* variant, is suggestive of Dravet syndrome.

These findings are congruent with the retrospective analysis of a Dutch passive reporting database,[16] which found that 1.2% (15/1,269) of children with seizures, including febrile, afebrile, and unclassified seizures, after vaccination in the first 2 years of life had *SCN1A*-related Dravet syndrome. Our 2 Dravet syndrome patients presented with prolonged seizures at 4 months occurring within 24 hours of vaccination, similar to the Dutch cases. The younger age at presentation of these children, compared to the median onset of FS at age 18 months, mirrors our finding of vaccine-proximate onset in Dravet syndrome being associated with seizure onset at 4 months rather than the mean onset of Dravet syndrome of 6 months.[8,13] The reported vaccine-related first seizures in Verbeek's study involved whole-cell pertussis vaccines, whereas the *SCN1A*-related Dravet cases in our cohort had their first FS following acellular vaccines, suggesting that the genetic immunological interaction may be independent of the type of pertussis vaccine involved. Although a follow-up study by Verbeek et al[32] showed a reduction in risk of subsequent vaccine-related seizures with acellular pertussis vaccines, as with the general pediatric population,[33] the type of vaccine does not appear to affect the initial vaccine-related seizure presentation in children with Dravet syndrome.

In addition to the pathogenic and likely pathogenic variants identified, we confirmed a higher frequency of the common *SCN1A* variant allele c.2292 C > T, p.V764V in FS cases compared to controls. This FS risk allele was first identified in a Danish genome-wide association study,[17] and we are the first to confirm the association of this allele with FS outside of a Danish population. As our study only examined *SCN1A* variants, we could not verify the other loci reported to be associated with MMR-related FS and FS in general.

This study has some limitations. With the yield of pathogenic variants that we found, our sample size was not powered to detect a significant difference between the groups using Fisher exact test in the frequency of *SCN1A* variants. The *SCN1A* mutation rate may also be underestimated, as Sanger sequencing cannot reliably detect intragenic deletions[34] and mosaicism rates of <20% that have been previously found in *SCN1A*-associated FS.[35] Other genes associated with FS, including other sodium channel genes (*SCN1B*, *SCN8A*, and *SCN2A*), the γ2-subunit of γ-aminobutyric acid receptor subunit (*GABRG2*),[36] and protocadherin 19 (*PCDH19*), were not examined.

Our prospective study suggests that in an infant with vaccine-proximate, prolonged FS, the detection of a pathogenic *SCN1A* variant should raise the suspicion of Dravet syndrome. Given that a higher rate of seizures with subsequent vaccinations occurs in Dravet syndrome,[32] screening for *SCN1A* variants in children 12 months and younger with prolonged VP-FS should be considered for early diagnosis and optimal management. Early initiation and appropriate choice of antiepileptic medication for children with Dravet syndrome can lead to better long-term outcomes.[37,38] As children receive multiple vaccines in the first 18 months of life, early identification of this at-risk group can also assist in the planning of safe administration of subsequent vaccinations in these children to reduce the risk of vaccine-preventable diseases and associated complications.

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Author Contributions

N.W., S.F.B., and I.E.S. contributed to the conception and design of the study. J.A.D., L.D., W.L., R.B., A.L.S., N.W.C., J.B., M.G., P.R., K.K.M., and M.S.H. contributed to the acquisition and analysis of data. J.A.D. and L.D. drafted the text, figure, and tables with support from S.F.B., N.W., and I.E.S.

Potential Conflicts of Interest

The institution of S.F.B. and I.E.S. (University of Melbourne) receives payments for a patent for *SCN1A* testing held by Bionomics and licensed to various diagnostic companies. The remaining authors have nothing to report.

References

1. Barlow WE, Davis RL, Glasser JW, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med 2001;345:656–661.
2. Gold MS, Effler P, Kelly H, et al. Febrile convulsions after 2010 seasonal trivalent influenza vaccine: implications for vaccine safety surveillance in Australia. Med J Aust 2010;193:492–493.
3. Tse A, Tseng HF, Greene SK, et al. 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;30:2024–2031.
4. Macartney KK, Gidding HF, Trinh L, et al. Febrile seizures following measles and varicella vaccines in young children in Australia. Vaccine 2015;33:1412–1417.
5. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. N Engl J Med 1998;338:1723–1728.
6. Chang YC, Guo NW, Huang CC, et al. Neurocognitive attention and behavior outcome of school-age children with a history of febrile convulsions: a population study. Epilepsia 2000;41:412–420.
7. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med 1987; 316:493–498.
8. Marini C, Mei D, Temudo T, et al. Idiopathic epilepsies with seizures precipitated by fever and SCN1A abnormalities. Epilepsia 2007;48: 1678–1685.
9. von Spiczak S, Helbig I, Drechsel-Baeuerle U, et al. A retrospective population-based study on seizures related to childhood vaccination. Epilepsia 2011;52:1506–1512.
10. Zhang YH, Burgess R, Malone JP, et al. Genetic epilepsy with febrile seizures plus: refining the spectrum. Neurology 2017;89:1210–1219.
11. Myers KA, Scheffer IE, Berkovic SF, ILAE Genetics Commission. Genetic literacy series: genetic epilepsy with febrile seizures plus. Epileptic Disord 2018;20:232–238.
12. Berkovic SF, Harkin L, McMahon JM, et al. De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. Lancet Neurol 2006;5:488–492.
13. McIntosh AM, McMahon J, Dibbens LM, et al. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. Lancet Neurol 2010;9:592–598.
14. Zamponi N, Passamonti C, Petrelli C, et al. Vaccination and occurrence of seizures in SCN1A mutation-positive patients: a multicenter Italian study. Pediatr Neurol 2014;50:228–232.
15. Wong PT, Wong VC. Prevalence and characteristics of vaccination triggered seizures in Dravet syndrome in Hong Kong: a retrospective study. Pediatr Neurol 2016;58:41–47.
16. Verbeek NE, van der Maas NA, Jansen FE, et al. Prevalence of SCN1A-related Dravet syndrome among children reported with seizures following vaccination: a population-based ten-year cohort study. PLoS One 2013;8:e65758.
17. Feenstra B, Pasternak B, Geller F, et al. Common variants associated with general and MMR vaccine-related febrile seizures. Nat Genet 2014;46:1274–1282.
18. Zurynski Y, McIntyre P, Booy R, et al. Paediatric active enhanced disease surveillance: a new surveillance system for Australia. J Paediatr Child Health 2013;49:588–594.
19. Deng L, Gidding H, Macartney K, et al. Postvaccination febrile seizure severity and outcome. Pediatrics 2019;143. pii: e20182120.
20. Hull BP, Hendry AJ, Dey A, et al. Immunisation coverage annual report, 2014. Commun Dis Intell Q Rep 2017;41:E68–E90.
21. Bonhoeffer J, Menkes J, Gold MS, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004;22:557–562.
22. National Center for Biotechnology Information, US National Library of Medicine. Gene. 2018. Available at: https://www.ncbi.nlm.nih.gov/gene. Accessed November, 2019.
23. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17: 405–424.
24. National Center for Biotechnology Information, U.S. National Library of Medicine. dbSNP. 2018. Available at: http://www.ncbi.nlm.nih.gov/SNP/. Accessed November, 2019.
25. Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res 2018;46(D1):D1062–D1067.
26. Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature 2016;536:285–291.
27. Institute of Neuroscience and the Second Affiliated Hospital of Guangzhou Medical University, Key Laboratory of Neurogenetics and Channelopathies of Guangdong Province and the Ministry of Education of China, Collaborative Innovation Center for Neurogenetics and Channelopathies. SCN1A Mutation Database. 2014. Available at: http://www.caae.org.cn/gzneurosci/scn1adatabase/index.php. Accessed November, 2019.
28. Ohmori I, Ohtsuka Y, Ouchida M, et al. Is phenotype difference in severe myoclonic epilepsy in infancy related to SCN1A mutations? Brain Dev 2003;25:488–493.
29. Orrico A, Galli L, Grosso S, et al. Mutational analysis of the SCN1A, SCN1B and GABRG2 genes in 150 Italian patients with idiopathic childhood epilepsies. Clin Genet 2009;75:579–581.
30. Escayg A, Heils A, MacDonald BT, et al. A novel SCN1A mutation associated with generalized epilepsy with febrile seizures plus—and prevalence of variants in patients with epilepsy. Am J Hum Genet 2001;68:866–873.
31. Wallace RH, Hodgson BL, Grinton BE, et al. Sodium channel alpha1-subunit mutations in severe myoclonic epilepsy of infancy and infantile spasms. Neurology 2003;61:765–769.
32. Verbeek NE, van der Maas NA, Sonsma AC, et al. Effect of vaccinations on seizure risk and disease course in Dravet syndrome. Neurology 2015;85:596–603.
33. Le Saux N, Barrowman NJ, Moore DL, et al. 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 2003;112:e348.
34. Marini C, Scheffer IE, Nabbout R, et al. SCN1A duplications and deletions detected in Dravet syndrome: implications for molecular diagnosis. Epilepsia 2009;50:1670–1678.
35. Myers CT, Hollingsworth G, Muir AM, et al. Parental mosaicism in "de novo" epileptic encephalopathies. N Engl J Med 2018;378: 1646–1648.
36. Audenaert D, Van Broeckhoven C, De Jonghe P. Genes and loci involved in febrile seizures and related epilepsy syndromes. Hum Mutat 2006;27:391–401.
37. Wirrell EC, Laux L, Donner E, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American consensus panel. Pediatr Neurol 2017;68:18–34.e3.
38. Cetica V, Chiari S, Mei D, et al. Clinical and genetic factors predicting Dravet syndrome in infants with SCN1A mutations. Neurology 2017;88:1037–1044.
39. Zuberi SM, Brunklaus A, Birch R, et al. Genotype-phenotype associations in SCN1A-related epilepsies. Neurology 2011;76:594–600.

2.5 Developmental outcomes (published manuscript)

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ARTICLE

Developmental outcomes following vaccine-proximate febrile seizures in children

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Abstract

Objective

To compare the developmental and behavioral outcomes of children experiencing an initial vaccine-proximate (VP) febrile seizure (FS) to those having a non–VP-FS (NVP-FS) and controls who have not had a seizure.

Methods

In this prospective multicenter cohort study, children with their first FS before 30 months of age between May 2013 and April 2016 were recruited from 4 Australian pediatric hospitals and classified as having VP-FS or NVP-FS. Similar-aged children with no seizure history were recruited as controls. The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) was administered to participants with FS 12 to 24 months after their initial FS and to controls 12 to 42 months of age at the time of assessment. The primary outcome was the Bayley-III cognitive score. Children's preacademic skills were assessed with the Woodcock-Johnson Tests of Achievement, Third Edition, and their behavior and executive functioning were obtained from parent questionnaires.

Results

There was no significant difference in cognitive function between children with VP-FS (n = 62), those with NVP-FS (n = 70), and controls (n = 90) ($F_{2,219} = 2.645$, $p = 0.07$). There were no differences between the groups for all other measures and no increased risk of borderline/significant impairment or behavior in the clinical range in children with VP-FS compared to those with NVP-FS or controls.

Conclusion

VP-FS was not associated with an increased risk of developmental or behavioral problems in young children compared to children with NVP-FS or controls. Parents and providers should be reassured by the absence of adverse effects of VP-FS on the development of children.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ANOVA = analysis of variance; **Bayley-III** = Bayley Scales for Infant and Toddler Development, Third Edition; **BRIEF-P** = Behavior Rating Inventory of Executive Function, Preschool Version; **CBCL** = Child Behavior Checklist–Preschool; **DSM** = *Diagnostic and Statistical Manual of Mental Disorders*; **DTP** = diphtheria-tetanus-pertussis; **FS** = febrile seizure; **ICD** = *International Classification of Diseases*; **MMR** = measles-mumps-rubella; **NVP** = non–vaccine-proximate; **SES** = socioeconomic status; **VP** = vaccine-proximate; **WJ-III** = Woodcock-Johnson Tests of Achievement, Third Edition.

A febrile seizure (FS) is the most common form of childhood seizure, occurring in association with fever from any cause.[1] An increased risk of FS after vaccination is well recognized, particularly in the 5 to 12 days after measles-containing vaccines and within 3 days after inactivated vaccines such as concomitant influenza and pneumococcal vaccination.[2–5] FS after immunization can generate concerns regarding vaccine safety and affect parental confidence and therefore immunization uptake.[6]

Evidence from population-based studies indicates that children who experience an FS, from any cause, generally have normal cognitive and developmental outcomes.[7–12] However, some studies found that children were at an increased risk of poor outcomes if the FS occurred before 12 months of age or if FSs were recurrent or prolonged. Children with FS onset before 12 months of age were reported to have poorer working memory[13] and were more likely to require special primary schooling[11] compared to children with later FS onset. Recurrent FS has been associated with delayed vocabulary development,[8] while children with prolonged FS (lasting >15 minutes) demonstrated lower nonverbal intelligence compared to cases with brief self-resolving FS and controls.[14,15] behaviorally, it is unclear whether FSs may be associated with social-emotional difficulties. Some studies indicate that FSs are associated with more externalizing and internalizing problems such as anxiety in school-aged children[11,14] and subsequent development of attention-deficit/hyperactivity disorder,[16] while other studies have found no association between FS and behavior.[8,10–13]

Few studies have reported the neurodevelopmental outcomes of children who had FS after vaccination. One study[17] reported no increased risk of neurologic or developmental abnormalities 36 months after FS following diphtheria-tetanus-pertussis (DTP) vaccination in 10 children. Another study[2] found no increased risk of learning or developmental disabilities after FS from measles-mumps-rubella (MMR) and DTP vaccination in a larger cohort of 273 children followed up for up to 7 years. However, both studies identified neurodevelopmental abnormalities using the ICD[18] coded diagnoses recorded on inpatient or outpatient claims databases only and hence may be clinically inaccurate or may underestimate the occurrence of abnormalities.

In this study, we therefore aimed to objectively assess the developmental and behavioral outcomes of children with vaccine-proximate (VP) FS compared to children with non-VP (NVP) FS and to controls and to identify factors associated with poorer cognitive outcomes in children with FS. We hypothesized that the outcomes of children with VP-FS would be favorable and comparable to those of NVP-FS and to controls.

Methods

Study design and participants

A prospective multicenter case-control study was conducted across 4 Australian tertiary pediatric hospitals that participate in the Paediatric Active Enhanced Disease Surveillance network[19]: The Children's Hospital at Westmead Sydney, Royal Children's Hospital Melbourne, Princess Margaret Hospital for Children Perth, and Women's and Children's Hospital Adelaide. Participant recruitment occurred between May 1, 2013, and April 30, 2016.

From May 2013 to June 2014, children presenting with FS at these sites were identified through daily surveillance nurse screening of emergency presentations or hospital admissions coded with the ICD, 10th revision, Australian modification diagnosis code for FS (code R56.0) as part of a larger cohort study.[20] From July 2014 to April 2016, additional cases with VP-FS were identified through outpatient attendance to Specialist Immunisation Clinics at any of the participating hospitals for review of an FS after vaccination or through VP-FS reports to the Serious Adverse Events Following Vaccination in the Community service responsible for the recording and follow-up of all adverse events after immunization in Victoria. Vaccine exposure was confirmed with immunization records obtained from the Australian Immunisation Register, a national population-level register,[21] and participants with VP-FS and NVP-FS were classified as per the following inclusion criteria. For a VP-FS case, criteria were the following: (1) age of ≤30 months at the time of the first FS; (2) the seizure fulfilled the Brighton Collaboration case definition[22] as verified by clinician review of hospital records; (3) FS was associated with a caregiver-reported fever or documented temperature of >38°C; (4) FS occurred from day 0 to 2 after receipt of an inactivated vaccine, day 5 to 14 after a live-attenuated vaccine, or day 0 to 14 after a combination of inactivated and live-attenuated vaccines, according to previous studies on timing of fever onset after specific vaccines[2,23–25]; and (5) no history of seizures. For a case with NVP-FS, the inclusion criteria were the same as for VP-FS except the FS had to occur in a period outside of the VP-FS defined time periods in relation to the most recently received vaccine.

For controls, the inclusion criteria were age between 12 and 42 months at the time of assessment and no personal or family history of FS or afebrile seizures. To ensure that controls represented the general population, children were recruited from the community rather than the emergency or outpatient department through contacts of families of children already enrolled in the study and children participating in other clinical trials at each recruitment site and through advertisements placed in local community newspapers, childcare centers, and hospitals. Parents either were contacted by or were invited to contact research staff to obtain study information.

Children were excluded from the study if they (1) had a preexisting diagnosis of developmental delay or medical or genetic condition or injury that may affect cognition, including intracranial pathology; (2) had a significant hearing or visual impairment that precluded them from completing the assessment; or (3) were not learning or speaking English or if their caregivers were not fluent in English because the assessment and parent questionnaires were in English. Signed informed consent was obtained from the child's parent/legal guardian.

Demographic and medical and seizure history

Sociodemographic data, perinatal history, maternal education as a measure of socioeconomic status (SES), medical history, and family history of all participants were collected via parent interviews. For cases of FS, the presence of complex FS features, including seizure duration >15 minutes, focal signs, and recurrence within 24 hours of the initial seizure, was obtained from medical records. Investigations performed were also obtained from medical records. Subsequent seizures after the initial FS presentation by type (febrile or afebrile) and frequency were obtained at the time of follow-up assessment by parent interview.

Follow-up assessment

All participants were assessed at 12 to 42 months of age, with participants with FS assessed 12 to 24 months after their initial FS.

Children's development was assessed with the Bayley Scales for Infant and Toddler Development, Third Edition (Bayley-III)[26] (all ages) and Woodcock-Johnson Tests of Achievement, Third Edition (WJ-III)[27] (children ≥24 months of age) by a psychologist or a health care professional certified to administer the Bayley-III at each participating hospital. The assessor was blinded to the participant's group. The duration of the assessment was on average 60 minutes.

Children's executive function and behavior were assessed through parent-completed standardized questionnaires: Bayley-III socioemotional and general adaptive subscales,[28] the Behavior Rating Inventory of Executive Function, Preschool Version (BRIEF-P)[29,30] (≥24 months), and the Child Behavior Checklist–Preschool (CBCL)[31] (≥18 months) (table 1).

SCN1A gene variant screening was performed on participants who consented to this at time of recruitment using whole blood or saliva samples. Additional history regarding subsequent developmental progression was obtained via medical records for cases with *SCN1A* variants identified. The results of the gene testing have been reported separately.[32]

Standard protocol approvals, registrations, and patient consents

This study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (HREC/14/SCHN/135).

Statistical analyses

To detect a small to medium effect size (f = 0.18) between the 3 groups using 1-way analysis of variance (ANOVA) with a power of 0.80 and $\alpha = 0.05$ for the Bayley-III cognitive scale, we aimed to recruit 100 participants in each group.[33,34]

For parametric continuous variables, independent *t* tests or ANOVA was conducted with post hoc testing using the Tukey honestly significant difference. We calculated η^2 for ANOVAs, with 0.01 considered a small effect size, 0.06 considered medium, and 0.14 considered large.[34,35] ANOVAs for Bayley-III and WJ-III scores included maternal education as a fixed factor, a measure of SES that is most associated with cognitive function.[36–38] For BRIEF-P and CBCL syndrome scales, only composite scores were analyzed to minimize the number of statistical comparisons made. For missing data (≤10%), when parents did not complete the questionnaires, only available data for each assessment were reported. All tests were 2 tailed with the level of significance set at 0.05, and the Holm (modified Bonferroni) procedure was applied to control the familywise error rate.

For categorical variables, comparisons were made with χ^2 tests or odds ratio. The proportion of participants in the borderline/impaired or clinical range, defined by test guidelines (table 1) for the Bayley-III, BRIEF-P, and CBCL, was reported for each group. Odds ratio, adjusted for SES, was calculated for the risk of impairment in the VP-FS or NVP-FS groups compared to controls and in the VP-FS group compared to the NVP-FS group.

To identify potential risk factors associated with cognitive impairment in all participants with FS, a multiple linear regression was conducted with the Bayley-III cognitive score as the dependent variable. Possible predictor variables based on previous studies[13,14,39] included age at FS (<12 vs ≥12 months), presence of a complex feature (seizure duration >15 minutes, focal signs, recurrence within 24 hours of the initial FS), number of subsequent seizures between the first FS and assessment, and any baseline characteristics that were significantly different between the groups. FS group (VP or NVP) was included as a predictor to examine any difference between FS groups. Statistical analysis was performed with SPSS version 24.0 (IBM SPSS Statistics, IBM Corp, Chicago, IL).

Table 1 Assessments of children

Domain	Assessment	Assessment modality	Scales	Age range	Age-standardized mean scores (SD)	Clinical impairment[c]
Development	Bayley Scales for Infant and Toddler Development, Third Edition	Blinded certified assessor: cognitive, motor, language scales Parent questionnaire: socioemotional, general adaptive scales	Cognitive Motor Language Social-emotional General adaptive	All ages	100 (15)[a]	70–79: Borderline impairment ≤69: Significant impairment
Preacademic skills	Woodcock-Johnson Tests of Achievement, Third Edition	Blinded certified assessor	Letter word identification Understanding directions Applied problems	≥24 mo	100 (15)[a]	
Executive function	Behavior Rating Inventory of Executive Function, Preschool Version	Parent questionnaire	Inhibitory self-control Flexibility Emergent meta-cognition Global executive (composite)	≥24 mo	50 (10)[b]	≥65: Clinically significant
Emotional, behavioral, and social concerns	Child Behavior Checklist–Preschool[d]	Parent questionnaire	Emotionally reactive Anxious/depressed Somatic complaints Withdrawn Sleep problems Attention problems Aggressive behavior	≥18 mo	50 (10)[b]	Summary scale ≥64: clinically significant DSM-oriented scales ≥70: clinically significant

Abbreviation: DSM = *Diagnostic and Statistical Manual of Mental Disorders*.
[a] Scaled scores.
[b] T scores.
[c] Clinical impairment as defined by test manual guidelines.
[d] Scales in Child Behavioral Checklist–Preschool are used to generate internalizing, externalizing, and total composite summary scale and DSM-oriented scale scores.

Data availability

Anonymized data can be made available on request to the corresponding author.

Results

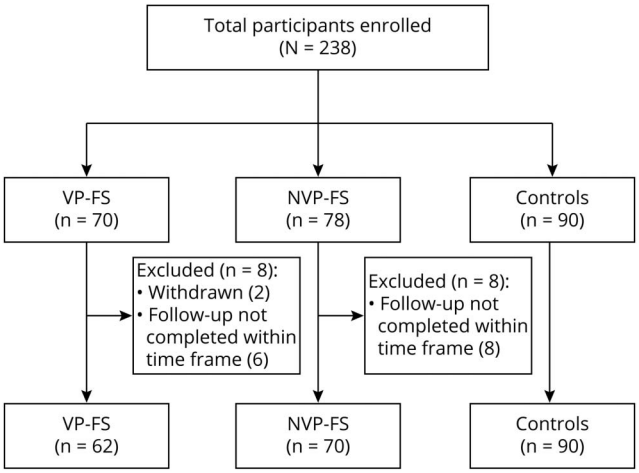
Study population

Within the defined recruitment period, 238 participants were enrolled in the study (70 with VP-FS, 78 with NVP-FS, and 90 controls); 16 were excluded from the analysis (2 cases with VP-FS withdrew, and 14 did not complete follow-up assessment within the specified time frame [6 with VP-FS, 8 with NVP-FS]), leaving 222 participants (62 with VP-FS, 70 with NVP-FS, and 90 controls) (figure).

Participant characteristics are reported in table 2. There was no significant difference between the 3 groups in sex, country of birth, gestational age at birth, birth weight, or Apgar score at 1 and 5 minutes. There was a significant difference between groups for SES (table 2), with a greater proportion of mothers in the control group having a higher level of education compared to the 2 FS groups. There was no significant difference for SES between the 2 FS groups [$\chi^2(2, n = 132) = 0.8701$, $p = 0.93$]. There was no significant difference in family history of FS or epilepsy between the VP-FS and NVP-FS groups (table 2).

Of the 62 cases with VP-FS, 53 (85%) occurred after measles-containing vaccines (43 were MMR with Haemophilus influenzae type b and meningococcal C conjugate vaccine, 9 MMR-varicella, and 1 MMR with meningococcal C only). The remaining 9 VP-FSs occurred after hexavalent diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, hepatitis B, and inactivated polio combination vaccine with 13-valent pneumococcal conjugate vaccine and rotavirus (n = 7), with 13-valent pneumococcal conjugate vaccine only (n = 1), and with rotavirus vaccine only (n = 1).

Figure Flowchart of patient recruitment



FS = febrile seizure; NVP = non–vaccine-proximate; VP = vaccine-proximate.

Participants with VP-FS were younger at the time of their first FS compared to cases with NVP-FS (table 2). A greater proportion of cases with VP-FS had ≥1 complex FS feature, including prolonged FS and repeat seizures within the first 24 hours after the initial FS. EEG was performed on 9 complex FS cases (8 VP-FS and 1 NVP-FS), all of which were normal.

There was a significant difference in the mean age at follow-up assessment between the 3 groups (table 2), with the mean age of cases with VP-FS at follow-up being significantly lower than that of participants with NVP-FS ($p = 0.002$). There was no difference between cases with VP-FS and controls ($p = 0.49$). The follow-up duration in VP-FS group was significantly shorter than in the NVP-FS group (table 2).

Developmental assessment outcomes

The Bayley-III scores for cognitive, language, motor, social-emotional, or general adaptive function did not differ significantly between the groups after application of the Holm procedure (table 3). The effect size between the groups was small for language and small to moderate for the other Bayley-III domains.

There was no significant difference in preacademic skills (WJ-III) (table 3), executive function (BRIEF-P), or emotional or behavioral problems (CBCL) between the 3 groups (table 4). The effect size between groups was small for all BRIEF-P and CBCL syndrome scales.

The proportion of cases with VP-FS with borderline or significant cognitive, motor, or language impairment was similar to that of controls, with no significant increased risk of impairment (table 5). There was a higher proportion of cases with NVP-FS with borderline or significant cognitive, motor, or language impairment compared to those with VP-FS and controls. This was, however, not significant (table 5). There were 6 participants with significant impairment in ≥1 domains (2 controls, 1 with VP-FS, and 3 with NVP-FS) and 9 participants with borderline impairment (3 with VP-FS and 6 with NVP-FS). Of the cases of FS, 4 with NVP-FS and 2 with VP-FS had further seizures between their first FS and the time of developmental assessment. A higher proportion of cases of VP-FS and NVP-FS had clinical impairment in inhibitory self-control (BRIEF-P) and oppositional defiant behavior (CBCL DSM-oriented scales) domains compared to controls. Similarly, a higher proportion of cases of NVP-FS had behavioral impairment (total composite) and affective and anxiety problems compared to the other groups. However, the increased risk of clinically significant executive function, emotional, or behavioral problems in cases of VP-FS or NVP-FS compared to each other or to controls was not statistically significant (table 5).

While SES was the only significant predictor of cognitive functioning of children with FS, the overall regression model was not statistically significant and accounted for none of the variance in cognitive scores (table 6). Time to follow-up from first FS, while statistically significantly different between the FS groups, was not included in the model because it did not significantly correlate with cognitive scores ($r = -0.007$, $p = 0.93$).

Discussion

This is the first prospective study to objectively examine the developmental and behavioral outcomes of children after a VP-FS. Consistent with our hypothesis, we found no significant difference between children who had experienced a VP-FS and children with NVP-FS or no history of seizures on the primary outcome, the Bayley-III cognitive scale. In addition, there was no significant difference between groups for the Bayley-III scales of motor, language, social-emotional, or general adaptive functioning.

Our findings are consistent with the case-control study by Leaffer et al.[7] that showed no significant difference in cognitive or motor skills or adaptive behavior between cases with all-cause FS 1 year after their initial FS and controls. While their cohort was larger (159 cases of FS and 142 controls), they did not differentiate cases with VP-FS from cases with NVP-FS. By differentiating between FS cases, we identified that the proportion of borderline or significant impairment was highest, although not significantly, in the NVP-FS group compared to the VP-FS and control groups. We found that there was no increased risk of impairment in the VP-FS group compared to the NVP-FS group. In addition, the Leaffer et al.[7] study combined standardized scores from the Bayley-II for children up to 3 years of age with Developmental Indicators for the Assessment of Learning–Third Edition[40] scores for children >3 years of age. In our study, we compared the developmental outcomes across all ages using the same measure, the Bayley-III, thereby minimizing multimodality variability across ages and allowing direct comparison of outcomes between groups across 5 different areas of functioning.

Table 2 Sociodemographic data and perinatal, medical, and family history of study participants according to group

Characteristic	VP-FS (n = 62), n (%)	NVP-FS (n = 70), n (%)	Control (n = 90), n (%)	*p* Value
Male sex	35 (56.5)	31 (44.3)	54 (60.0)	0.13
Australian born	61 (98.4)	68 (97.1)	86 (95.6)	0.61
English as first language	57 (91.9)	64 (91.4)	87 (96.7)	0.32
Birth data				
Gestational age, wk				
<28	0 (0.0)	1 (1.4)	0 (0.0)	0.18
28–31	0 (0.0)	0 (0.0)	0 (0.0)	
32–36	2 (3.2)	8 (11.4)	2 (2.2)	
>36	60 (96.8)	61 (87.1)	88 (97.7)	
Birth weight, g				
<1,500	0 (0.0)	1 (1.4)	1 (1.1)	0.10
1,500–2,500	2 (3.2)	5 (7.1)	0 (0.0)	
2,500–4,000	49 (79.0)	57 (81.4)	73 (81.1)	
>4,000	9 (14.5)	5 (7.1)	16 (17.8)	
Unknown	2 (3.2)	2 (2.9)	0 (0.0)	
Apgar score at 1 min				
≤3	0 (0.0)	2 (2.9)	2 (2.2)	0.79
4–6	3 (4.8)	3 (4.3)	4 (4.4)	
≥7	49 (79.0)	54 (77.1)	73 (86.7)	
Unknown	10 (16.1)	11 (15.7)	11 (12.2)	
Apgar score at 5 min				
≤3	0 (0.0)	1 (1.4)	0 (0.0)	0.52
4–6	1 (1.6)	0 (0.0)	1 (1.1)	
≥7	51 (82.3)	58 (82.9)	78 (86.7)	
Unknown	10 (16.1)	11 (15.7)	11 (12.2)	
Maternal data				
Maternal perinatal history				
Smoking	4 (6.5)	6 (8.6)	1 (1.1)	0.08
Alcohol consumption	5 (8.1)	3 (4.3)	3 (3.3)	0.39
Maternal education (SES)				
Up to year 10	4 (6.5)	5 (7.1)	2 (2.2)	0.01[a]
Year 12	11 (17.7)	10 (14.3)	3 (3.3)	
TAFE	10 (16.1)	11 (15.7)	13 (14.4)	
Undergraduate	24 (38.7)	25 (35.7)	30 (33.3)	
Postgraduate	13 (21.0)	19 (27.1)	42 (46.7)	
Seizure data				
First-degree family history				
Developmental concerns	10 (16.1)	12 (19.4)	11 (12.2)	0.64

Continued

Table 2 Sociodemographic data and perinatal, medical, and family history of study participants according to group *(continued)*

Characteristic	VP-FS (n = 62), n (%)	NVP-FS (n = 70), n (%)	Control (n = 90), n (%)	*p* Value
FS	26 (41.9)	24 (34.3)	NA	0.82[a]
Epilepsy	9 (14.5)	13 (18.6)	NA	0.39[a]
Initial seizure details				
Age at first FS (SD), mo	13.1 (3.7)	14.7 (5.1)	NA	0.04[a,c]
Age <12 mo	12 (19.4)	22 (31.4)	NA	0.11[a]
Complex FS[b]	28 (45.2)	14 (20.0)	NA	0.002[a,d]
Initial FS >15 min	15 (24.2)	7 (10.0)	NA	0.03[a,c]
Focality	4 (6.5)	4 (5.7)	NA	0.86[a]
Repeat seizure within 24 h after initial	15 (24.2)	6 (8.6)	NA	0.04[a,c]
Follow up details				
Age at follow-up (SD), mo	27.7 (4.9)	31.5 (5.1)	28.9 (7.4)	0.001[d]
Time to follow-up (SD), mo	14.7 (2.1)	16.7 (2.6)	NA	<0.001[a,d]
FS recurrence	23 (37.1)	21 (30.0)	NA	0.75[a]
Afebrile seizures	8 (12.9)	5 (7.1)	NA	0.27[a]

Abbreviations: FS = febrile seizure; NA = not applicable; NVP = non–vaccine-proximate; SES = socioeconomic status; TAFE = technical and further education; VP = vaccine-proximate.
[a] Comparing VP-FS and NVP-FS groups only.
[b] Complex FS includes any FS >15min or focal features or repeat seizure within 24 h following initial.
[c] $p < 0.05$.
[d] $p < 0.01$.

Previous studies have relied on ICD diagnosis codes only, with no individual assessments for developmental abnormalities in children with seizures after DTP or MMR vaccination.[2,17] Our study is the first to objectively compare the developmental outcomes of children with VP-FS after any vaccination event, including the receipt of multiple concurrent vaccines as per most national immunization program schedules, to those of children with NVP-FS using standardized clinical assessment tools. The absence of any difference in developmental subscale scores between children with VP-FS and controls using this rigorous approach should help reassure parents that a VP-FS will not affect their child's developmental functioning and should assist in decision-making in regard to completion of the immunization schedule.

In our study, type of seizure (VP-FS or NVP-FS), FS onset before 12 months of age, or having a complex FS, including prolonged FS, or subsequent FS did not significantly predict the cognitive functioning of children. This is in contrast to the findings of Kolfen et al.[14] that children with prolonged FS from any cause had deficits in nonverbal intelligence compared to controls. However, mean scores for both groups in the Kolfen et al. study were in the average range and thus do not reflect a clinically significant impairment.[41] In addition, children with prolonged FS did not significantly differ in performance from controls for any other cognitive or motor domains, with the authors concluding the result from their small sample needed to be replicated in a larger sample.[41]

There was a higher proportion of children with complex FS in the VP-FS compared to the NVP-FS group. This contrasts with the larger cohort study[20] from which a subset of our participants was recruited. Results from the cohort study indicated no significant difference in proportion of prolonged or recurrent FS within the initial 24 hours between the groups.[20] However, because most of the cases of complex VP-FS (21 of 28) in our study were recruited through VP-FS reports or Specialist Immunisation Clinics attendance, it is possible that more severe VP-FSs were more likely to be reported or referred to a specialist clinic. Despite this, our results indicated that the type of seizure (complex vs simple) did not predict the cognitive functioning of children.

Our finding that SES, measured by maternal education, was a significant predictor of cognitive function is consistent with previous studies that have examined the relationship between cognitive functioning and SES in children.[36–38,42–44] Maternal education level has been shown to be most strongly associated factor with infant development[42,43] and early cognitive development[36–38] of all SES factors.

Table 3 Mean (SD) scores and estimated marginal mean scores (SE) for Bayley-III and WJ-III assessments for VP-FS, NVP-FS, and control groups

	Unadjusted						Estimated marginal means									
	VP-FS		NVP-FS		Control		VP-FS		NVP-FS		Control		ANOVA[a]			
Assessment	N	Mean (SD)	n	Mean (SD)	n	Mean (SD)	N	Mean (SE)	n	Mean (SE)	N	Mean (SE)	*df*	*F* value	η^2 Value	*p* Value
Bayley-III																
Cognitive	61	101.72 (9.95)	70	101.21 (11.62)	89	105.73 (11.52)	61	100.60 (1.52)	70	100.35 (1.43)	89	104.28 (1.48)	2, 219	2.645	0.024	0.07
Language	59	104.25 (14.41)	70	104.56 (17.32)	89	107.42 (12.10)	59	103.25 (2.00)	70	103.13 (1.86)	89	104.69 (1.92)	2, 217	2.002	0.003	0.76
Motor	62	104.16 (13.05)	69	102.86 (15.61)	88	109.08 (12.87)	62	102.85 (1.88)	69	101.50 (1.79)	88	106.90 (1.85)	2, 218	1.054	0.028	0.05[c]
Social-emotional[b]	53	104.25 (16.5)	63	108.17 (18.12)	86	107.79 (14.79)	53	103.90 (2.39)	63	107.69 (2.27)	86	106.37 (2.27)	2, 201	1.036	0.021	0.39
General adaptive[b]	52	100.96 (14.57)	63	99.51 (17.38)	86	103.13 (13.40)	52	101.71 (2.24)	63	100.29 (2.11)	86	103.58 (2.11)	2, 200	0.832	0.013	0.63
WJ-III[d]																
Letter word	43	98.79 (11.15)	58	103.88 (13.34)	60	99.85 (13.53)	43	97.92 (2.15)	58	102.70 (1.87)	60	97.71 (2.14)	2, 160	2.325	0.029	0.10
Understand directions	43	100.72 (12.07)	58	100.81 (13.10)	60	102.68 (15.28)	43	100.89 (2.27)	58	100.74 (2.03)	60	101.92 (2.27)	2, 159	0.359	0.005	0.70
Applied problems	43	93.59 (13.58)	58	98.96 (17.03)	60	101.22 (15.87)	43	97.83 (2.61)	58	98.47 (2.33)	60	99.39 (2.61)	2, 159	0.637	0.008	0.53

Abbreviations: ANOVA = analysis of variance; Bayley-III = Bayley Scales for Infant and Toddler Development, Third Edition; FS = febrile seizure; NVP = non–vaccine-proximate; VP = vaccine-proximate; WJ-III = Woodcock-Johnson Tests of Achievement, Third Edition.
Composite scale score and standard score mean = 100, SD = 15, with lower scores indicating impairment.
[a] For η^2, 0.01 = small, 0.06 = medium, 0.14 = large effect size.
[b] Completion of Bayley-III social-emotional and general adaptive subscale depended on parents returning the questionnaires.
[c] $p = 0.05$ is not statistically significant after application of the Holm procedure.
[d] WJ-III performed only in children ≥24 months of age at the time of assessment; eligible participant numbers: VP-FS = 53, NVP-FS = 65, control=68, number of participants completed shown in table.

Table 4 Mean, SD, and 95% CI T scores for BRIEF-P and CBCL questionnaires for VP-FS, NVP-FS, and control groups

Assessment	VP-FS		NVP-FS		Control		η^2 Value	*p* Value
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI		
BRIEF-P (≥24 mo), n (%)	50/53 (94.4)		61/65 (93.8)		65/68 (95.6)			
Inhibit self-control	49.28 (9.89)	46.47–52.09	48.74 (12.45)	45.55–51.93	47.15 (9.44)	44.81–49.49	0.007	0.53
Flexibility	48.14 (9.33)	45.49–50.79	47.34 (11.19)	44.48–50.21	46.14 (9.35)	43.82–48.46	0.007	0.56
Emergent meta-cognition	49.50 (11.25)	46.30–52.70	51.44 (13.13)	48.08–54.80	49.86 (11.84)	46.93–52.80	0.005	0.66
Global executive	49.36 (10.83)	46.28–52.44	50.10 (13.92)	46.53–53.66	48.17 (11.35)	45.36–50.98	0.005	0.67
Inhibit	49.90 (8.96)	47.35–52.45	50.08 (12.30)	46.93–53.23	48.08 (10.09)	45.58–50.58	0.008	0.51
Shift	48.12 (9.24)	45.50–50.74	48.02 (11.02)	45.19–50.84	46.54 (9.59)	44.16–48.91	0.005	0.62
Emotional control	48.76 (9.74)	45.99–51.53	47.28 (11.20)	44.41–50.15	46.60 (8.12)	44.59–48.61	0.008	0.49
Working memory	50.72 (10.61)	47.74–53.73	52.69 (12.25)	49.55–55.82	51.37 (11.60)	48.50–54.24	0.005	0.65
Plan/organize	47.78 (10.59)	44.77–50.79	49.07 (12.04)	45.95–52.15	47.88 (10.98)	45.16–50.60	0.003	0.79
CBCL syndrome scales (≥18 mo), n (%)	55/60 (91.7)		65/70 (92.9)		76/81 (93.8)			
Internalizing	45.24 (9.32)	42.70–47.78	45.71 (11.94)	42.85–48.67	44.05 (10.24)	41.71–46.39	0.005	0.63
Externalizing	47.44 (9.51)	44.85–50.04	47.89 (11.51)	45.04–50.74	45.80 (9.59)	43.62–47.99	0.008	0.44
Total composite	46.69 (9.85)	44.00–49.37	45.55 (12.65)	42.42–48.69	43.75 (10.42)	41.37–46.13	0.012	0.31
Emotionally reactive	53.78 (5.79)	52.22–55.35	53.54 (6.56)	51.91–55.16	52.70 (4.36)	51.70–53.69	NC	NC
Anxious depressed	51.46 (2.72)	50.72–52.20	52.75 (5.35)	51.43–54.08	51.46 (3.18)	50.73–52.19	NC	NC
Somatic complaints	52.35 (5.49)	50.86–53.83	53.45 (5.70)	52.03–54.86	52.21 (4.08)	51.28–53.14	NC	NC
Withdrawn	52.45 (3.87)	51.41–53.50	53.25 (6.33)	51.68–54.82	53.17 (5.35)	51.95–54.39	NC	NC
Sleep problems	55.44 (9.24)	52.94–57.93	56.46 (9.96)	53.99–58.93	53.66 (5.13)	52.48–54.83	NC	NC
Attention problems	53.73 (5.85)	52.15–55.31	54.29 (7.16)	52.52–56.07	52.80 (4.22)	51.84–53.77	NC	NC
Aggressive behavior	52.96 (5.86)	51.38–54.55	54.08 (7.34)	52.26–55.89	52.30 (4.04)	51.38–53.23	NC	NC
CBCL DSM-oriented scales (≥18 mo), n (%)	55/60 (91.7)		65/70 (92.9)		76/81 (93.8)			
Affective problems	54.49 (6.19)	52.82–56.16	55.72 (7.59)	53.84–57.60	53.45 (4.62)	52.39–54.50	0.024	0.10
Anxiety problems	52.78 (4.71)	51.51–54.06	53.26 (6.44)	51.68–54.86	52.25 (4.58)	51.20–53.30	0.007	0.53
Pervasive developmental	52.82 (5.05)	51.45–54.18	53.31 (6.43)	51.72–54.90	53.54 (7.24)	51.89–55.19	0.002	0.82

Continued

Table 4 Mean, SD, and 95% CI T scores for BRIEF-P and CBCL questionnaires for VP-FS, NVP-FS, and control groups *(continued)*

Assessment	VP-FS		NVP-FS		Control		η^2 Value	*p* Value
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI		
ADHD	53.07 (4.51)	51.85–54.29	53.52 (5.71)	52.11–54.94	52.07 (3.06)	51.37–52.76	0.020	0.14
Oppositional defiant	53.58 (5.99)	51.96–55.20	54.23 (6.59)	52.60–55.86	53.14 (5.21)	51.95–54.33	0.006	0.55

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; BRIEF-P = Behavior Rating Inventory of Executive Function, Preschool Version; CBCL = Child Behavior Checklist–Preschool; CI = confidence interval; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; FS = febrile seizure; NC = not calculated; NVP = non–vaccine-proximate; VP = vaccine-proximate.
n = the number completed/number of age-appropriate participants for the assessment (percent completion rate). T score mean = 50, SD = 10, with higher scores indicating impairment.

For executive function and behavior, results from parent-rated questionnaires, the BRIEF-P and CBCL, found no significant difference in the scores of children with VP-FS or NVP-FS compared to controls. Our findings support the study by Visser et al.,[8] which showed no increased risk of behavioral problems on the CBCL at 3 years of age and no difference in BRIEF-P T-scores at 4 years in children with a history of FS of any cause compared to controls. It also supports Chang et al.,[10] who found no increased risk of behavioral problems in those with a history of FS of any cause based on parent and teacher ratings. While we found differences in the proportion of clinically significant executive function, emotional, or behavioral problems between groups in our study, the difference was not statistically significant. This is in contrast to the Bertelsen et al.[16] study, which found that FS were associated with a 30% increased risk of developing attention-deficit/hyperactivity disorder in Danish children, and the Verity et al.[11] study, which found that children with FS were rated by parents as being slightly more impulsive, excitable, and anxious compared to controls. However, these studies had 22- and 10-year follow-up periods, respectively, during which other factors such as other neurologic conditions or intracranial insults may have affected their behavioral outcomes. Both studies had a large cohort, >900,000 (>33,000 with FS) and >14,000 (398 with FS) respectively, and were therefore powered to detect smaller differences between groups.

The strengths of this prospective cohort study included the use of detailed clinical data, the use of objective and subjective standardized measures to assess development and behavior, and a high completion rate for all outcome measures, allowing detailed comparison of outcomes in children after VP-FS or NVP-FS and controls. Because our FS cases were recruited prospectively at the time of first FS, we believe our sample accurately represents the target population of children <30 months of age after their initial FS.

While we did not reach our target sample size during the recruitment period, the observed effect sizes were generally small, including the effect size ($\eta^2 = 0.024$) between the groups for Bayley-III cognitive scores. Post hoc power analysis shows that for an effect of this size to be detected (power 0.80) as significant ($\alpha = 0.05$), a sample of 16,731 participants would be required.[33] Such a small effect is unlikely to represent a clinically significant difference, especially when the mean of all groups was within the normal range and standard error of measurement for the Bayley[45] cognitive subscale. This study, however, was not powered to detect small differences in proportions of borderline or clinically significant impairment in development, executive function, and behavior between groups. While it is reassuring that the overall proportion of impairment was low and similar across groups, a larger cohort is required to reduce the possibility of a type II error.

Another possible limitation of our study was that the VP-FS group was younger on average by 2 months at the time of their first FS and younger at follow-up by ≈4 months compared to the NVP-FS group, reducing the duration over which developmental or behavioral concerns may manifest. However, because the absolute difference in follow-up duration between the 2 groups was minimal, this is unlikely to have had an impact on our study findings. In addition, there was a higher proportion of mothers with a postgraduate degree in the control group compared to 2015 Australian Bureau of Statistics data, which reported 39.6% of 25- to 29-year-old and 44% of 30- to 35-year-old women reported obtaining a Bachelor degree or higher.[46] Despite the higher proportion of educated mothers, the cognitive functioning of control participants was in the average range and not significantly different from either FS group.

Finally, our study assessed the development and behavior only in the early toddler years, from 12 to 42 months. Because we did not reach our target sample size, it would be valuable for our study results to be replicated with a larger cohort. Our study also does not address the potential longer-term impact of FS (single or recurrent) that may appear later in childhood. Previous studies suggest that the timing of brain insult, particularly when it occurs at a time of rapid neural or critical cognitive growth, will determine the nature and severity of impairments. It has been proposed that those skills already developed at the time of insult will remain intact, while skills emerging or partly developed are at risk of damage, which may result in temporary or permanent sequelae.[47,48] Executive functions emerge during

Table 5 Proportion of children in each group with test scores below cutoff levels for borderline impairment for the Bayley-III and clinical range for BRIEF-P and CBCL assessments

Assessment	NVP-FS, % (n)	VP-FS, % (n)	Control, % (n)	NVP-FS vs control aOR (95% CI)[a]	*p* Value	VP-FS vs control aOR (95% CI)[a]	*p* Value	VP-FS vs NVP-FS aOR (95% CI)[a]	*p* Value
Bayley-III (scaled score <80) (all ages)									
Cognitive	4.3 (3/70)	1.6 (1/61)	1.1 (1/89)	4.54 (0.45–46.19)	0.20	0.94 (0.03–28.00)	0.97	0.33 (0.03–3.32)	0.34
Language	10.0 (7/70)	5.1 (3/59)	2.2 (2/89)	3.94 (0.75–20.59)	0.10	1.47 (0.19–11.32)	0.71	0.42 (0.10–1.73)	0.23
Motor	10.1 (7/69)	3.2 (2/62)	2.2 (2/88)	3.51 (0.66–18.81)	0.14	1.46 (0.16–13.34)	0.74	0.27 (0.05–1.40)	0.12
BRIEF-P (T score ≥65) (≥24 mo)									
Inhibit self-control	13.1 (8/61)	8.0 (4/50)	1.5 (1/65)	7.62 (0.88–65.83)	0.07	4.38 (0.44–44.03)	0.21	0.55 (0.15–1.99)	0.36
Flexibility	8.2 (5/61)	4.0 (2/50)	4.6 (3/65)	1.54 (0.33–7.26)	0.59	0.79 (0.10–6.02)	0.82	0.41 (0.07–2.29)	0.31
Emergent meta-cognition	14.8 (9/61)	10.0 (5/50)	15.4 (10/65)	0.56 (0.18–1.73)	0.31	0.42 (0.11–1.56)	0.20	0.61 (0.18–2.08)	0.43
Global executive	14.8 (9/61)	10.0 (5/50)	6.2 (4/65)	1.98 (0.54–7.28)	0.31	1.60 (0.36–7.19)	0.54	0.59 (0.18–1.96)	0.39
CBCL syndrome scales (T score ≥64) (≥18 mo)									
Internalizing	7.7 (5/65)	3.7 (2/54)	3.9 (3/76)	1.61 (0.34–7.70)	0.55	0.68 (0.09–5.07)	0.70	0.45 (0.08–2.46)	0.36
Externalizing	9.2 (6/65)	5.6 (3/54)	2.6 (2/76)	2.80 (0.50–15.65)	0.24	1.52 (0.22–10.44)	0.67	0.50 (0.12–2.15)	0.35
Total composite	10.8 (7/65)	5.6 (3/54)	2.6 (2/76)	4.02 (0.77–20.99)	0.10	1.38 (0.18–10.83)	0.76	0.41 (0.10–1.75)	0.23
CBCL DSM-oriented scales (T score ≥70) (≥18 mo)									
Affective problems	10.8 (7/65)	3.6 (2/55)	0.0 (0/76)	NC		NC		0.28 (0.06–1.44)	0.13
Anxiety problems	6.2 (4/65)	1.8 (1/55)	1.3 (1/76)	5.14 (0.52–50.50)	0.16	1.83 (0.10–34.69)	0.69	0.58 (0.03–2.59)	0.26
Pervasive developmental	3.1 (2/65)	3.6 (2/55)	2.6 (2/76)	0.98 (0.11–8.88)	0.99	2.00 (0.25–15.85)	0.51	1.05 (0.14–8.04)	0.96
ADHD	3.1 (2/65)	0.0 (0/55)	0.0 (0/73)	NC		NC		NC	
Oppositional defiant	7.7 (5/65)	5.5 (3/55)	1.3 (1/76)	5.93 (0.65–54.27)	0.12	4.23 (0.37–47.89)	0.24	0.60 (0.13–2.71)	0.51

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; aOR = adjusted odds ratio; Bayley-III = Bayley Scales for Infant and Toddler Development, Third Edition; BRIEF-P = Behavior Rating Inventory of Executive Function, Preschool Version; CBCL = Child Behavior Checklist–Preschool; CI = confidence interval; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; FS = febrile seizure; NC = not calculated as n = 0 in at least 1 comparison group; NVP = non–vaccine-proximate; VP = vaccine-proximate.
n Is the number below cutoff levels/number of age-appropriate participants for the assessment.
[a] Adjusted for socioeconomic status.

infancy and continue into adolescence,[49,50] and hence, younger children are at greater risk of impairments. In children with a history of brain insult who were assessed at 10 to 16 years of age, children with an early insult occurring before 3 years of age had more severe and global executive deficits compared to children with brain insults occurring at a later age.[51] Therefore, it is possible that certain cognitive impairments associated with FS may not appear until later in childhood. A follow-up assessment of our unique cohort during late childhood, differentiating cases with VP-FS and from cases with NVP-FS, would

Table 6 Multiple linear regression analysis for variables predicting Bayley-III cognitive scores for all participants with FS (n = 131[a])

Variable	*B* Value	SE *B*	β Value	*t* Value	*p* Value
SES (maternal education)	1.618	0.787	0.182	2.055	0.04
Age at FS (<12 vs ≥12 mo)	0.163	2.217	0.007	0.074	0.94
FS group (VP-FS vs NVP-FS)	1.106	2.008	0.051	0.551	0.58
FS type (complex vs simple)	−1.209	2.163	−0.052	−0.559	0.58
No. of subsequent seizures	−0.088	0.286	−0.028	−0.308	0.76

Abbreviations: Bayley-III = Bayley Scales for Infant and Toddler Development, Third Edition; FS = febrile seizure, NVP = non–vaccine proximate; SES = socioeconomic status; VP = vaccine-proximate.
R^2 = 0.038, adjusted R^2 = 0.000, $F_{5,130}$ = 0.999, p = 0.42.
[a] One case with VP-FS did not complete the Bayley-III assessment.

be valuable in providing more robust longitudinal data on developmental and behavioral outcomes.

This study demonstrates favorable results for the developmental and behavioral outcomes of children after VP-FS. Having a VP-FS did not significantly affect cognitive function 12 to 24 months after the initial FS compared to children with NVP-FS or controls, providing reassurance to clinicians and parents on the developmental outcomes of a well-recognized, albeit relatively uncommon, adverse event after immunization. Measles-containing vaccines are the vaccines most commonly associated with FS. At a time when there is a global resurgence of measles, our findings are particularly important in reassuring parents and providers about the safety of vaccines and in enhancing immunization provider and public knowledge of and confidence in the benefit-to-risk profile of vaccination.

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Appendix Authors

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Lucy Deng, MBBS	National Centre for Immunisation Research and Surveillance, The Children's Hospital at Westmead, Sydney	Conducted the data analyses and drafted the manuscript, performed statistical analysis, reviewed and revised the manuscript
Nicholas Wood, PhD	National Centre for Immunisation Research and Surveillance, The Children's Hospital at Westmead, Sydney, Australia	Conceptualized and designed the study, coordinated and supervised the project, contributed to the interpretation of the results, reviewed and revised the manuscript
Kristine Macartney, MD	National Centre for Immunisation Research and Surveillance, The Children's Hospital at Westmead, Sydney, Australia	Contributed to the interpretation of the results, reviewed and revised the manuscript
Michael Gold, MD	Department Paediatrics, Women's and Children's Hospital, Adelaide, Australia	Contributed to the interpretation of the results, reviewed and revised the manuscript
Nigel Crawford, PhD	Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, Australia	Contributed to the interpretation of the results, reviewed and revised the manuscript
Jim Buttery, PhD	Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, Australia	Contributed to the interpretation of the results, reviewed and revised the manuscript
Peter Richmond, MBBS	Wesfarmer's Centre of Vaccines and Infectious Disease, Telethon Kids Institute, West Perth, Australia	Contributed to the interpretation of the results, reviewed and revised the manuscript

Continued

Appendix *(continued)*

Name	Location	Contribution
Belinda Barton, PhD	Children's Hospital Education Research Institute and Kids Neuroscience Centre, The Children's Hospital at Westmead, Sydney, Australia	Assisted the design and coordination of the study, assisted in the data analyses, supervised the interpretation of the results and writing of the manuscript, performed statistical analysis, reviewed and revised the manuscript

References

1. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993;34:592–596.
2. Barlow WE, Davis RL, Glasser JW, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med 2001;345:656–661.
3. Gold MS, Effler P, Kelly H, Richmond PC, Buttery JP. Febrile convulsions after 2010 seasonal trivalent influenza vaccine: implications for vaccine safety surveillance in Australia. Med J Aust 2010;193:492–493.
4. Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. 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;30:2024–2031.
5. Macartney KK, Gidding HF, Trinh L, et al. Febrile seizures following measles and varicella vaccines in young children in Australia. Vaccine 2015;33:1412–1417.
6. Tickner S, Leman PJ, Woodcock A. Factors underlying suboptimal childhood immunisation. Vaccine 2006;24:7030–7036.
7. Leaffer EB, Hinton VJ, Hesdorffer DC. Longitudinal assessment of skill development in children with first febrile seizure. Epilepsy Behav 2013;28:83–87.
8. Visser AM, Jaddoe VW, Ghassabian A, et al. Febrile seizures and behavioural and cognitive outcomes in preschool children: the Generation R study. Dev Med Child Neurol 2012;54:1006–1011.
9. Ellenberg JH, Nelson KB. Febrile seizures and later intellectual performance. Arch Neurol 1978;35:17–21.
10. Chang YC, Guo NW, Huang CC, Wang ST, Tsai JJ. Neurocognitive attention and behavior outcome of school-age children with a history of febrile convulsions: a population study. Epilepsia 2000;41:412–420.
11. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. N Engl J Med 1998;338:1723–1728.
12. Hackett R, Hackett L, Bhakta P. Febrile seizures in a South Indian district: incidence and associations. Dev Med Child Neurol 1997;39:380–384.
13. Chang YC, Guo NW, Wang ST, Huang CC, Tsai JJ. Working memory of school-aged children with a history of febrile convulsions: a population study. Neurology 2001;57:37–42.
14. Kolfen W, Pehle K, Konig S. Is the long-term outcome of children following febrile convulsions favorable? Dev Med Child Neurol 1998;40:667–671.
15. Weiss EF, Masur D, Shinnar S, et al. Cognitive functioning one month and one year following febrile status epilepticus. Epilepsy Behav 2016;64:283–288.
16. Bertelsen EN, Larsen JT, Petersen L, Christensen J, Dalsgaard S. Childhood epilepsy, febrile seizures, and subsequent risk of ADHD. Pediatrics 2016;138:e20154654.
17. 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;263:1641–1645.
18. World Health Organization. International Classification of Diseases (ICD) Information Sheet. 2018. Available at: who.int/classifications/icd/factsheet/en/. Accessed April 20, 2019.
19. Zurynski Y, McIntyre P, Booy R, Elliott EJ, Group PI. Paediatric active enhanced disease surveillance: a new surveillance system for Australia. J Paediatr Child Health 2013;49:588–594.
20. Deng L, Gidding H, Macartney K, et al. Postvaccination febrile seizure severity and outcome. Pediatrics 2019;143:e20182120 .
21. Hull B, Dey A, Campbell-Llyod S, Frank B, McIntyre P. NSW Annual Immunisation Coverage Report, 2014. Commun Dis Intell Q Rep 2017;41:E68–E90.
22. Bonhoeffer J, Menkes J, Gold MS, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004;22:557–562.
23. Rowhani-Rahbar A, Klein NP, Dekker CL, et al. Biologically plausible and evidence-based risk intervals in immunization safety research. Vaccine 2012;31:271–277.
24. Sun Y, Christensen J, Hviid A, et al. Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type B. JAMA 2012;307:823–831.
25. Macartney K, Gidding HF, Trinh L, et al. Evaluation of combination measles-mumps-rubella-varicella vaccine introduction in Australia. JAMA Pediatr 2017;171:992–998.
26. Bayley N. Bayley Scales of Infant and Toddler Development, 3rd Edition: Technical Manual. San Antonio: Harcourt Assessment; 2006.
27. Woodcock RW, McGrew KS, Mather N. Woodcock-Johnson III Tests of Achievement. Itasca: Riverside Publishing; 2001.
28. Albers CA, Grieve AJ. Test review. In: Bayley N. Bayley Scales of Infant and Toddler Development–Third Edition. San Antonio: Harcourt Assessment.
29. Gioia GA, Espy KA, Isquith PK. BRIEF-P: Behavior Rating Inventory of Executive Function–Preschool Version. Lutz: Psychological Assessment Resources; 2003.
30. Sherman EBB. behavior rating inventory of executive function – preschool version (BRIEF-P): test review and clinical guidelines for use. Child Neuropsychol 2010;16:503–519.
31. Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms & Profiles. Burlington: University of Vermont: Research Center for Children, Youth, & Families; 2001.
32. Damiano JA, Deng L, Li W. SCN1A Variants in Vaccine-Related Febrile Seizures: A Prospective Study. Ann Neurol 2020 Feb;87:281–288.
33. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–191.
34. Cohen J. Statistical Power Analysis for the behavioral Sciences, 2nd ed. Hillsdale: Lawrence Erlbaum; 1988.
35. Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. J Exp Psychol Gen 2012;141:2–18.
36. Bartels M, van Beijsterveldt CEM, Boomsma DI. Breastfeeding, maternal education and cognitive function: a prospective study in twins. Behav Genet 2009;39:616–622.
37. Patra K, Greene MM, Patel AL, Meier P. Maternal education level predicts cognitive, language, and motor outcome in preterm infants in the second year of life. Am J Perinatol 2016;33:738–744.
38. Hillemeier MM, Morgan PL, Farkas G, Maczuga SA. Perinatal and socioeconomic risk factors for variable and persistent cognitive delay at 24 and 48 months of age in a national sample. Matern Child Health J 2011;15:1001–1010.
39. Smith JA, Wallace SJ. Febrile convulsions: intellectual progress in relation to anticonvulsant therapy and to recurrence of fits. Arch Dis Child 1982;57:104–107.
40. Mardell-Czudnowski C, Goldenberg DS. Developmental Indicators for the Assessment of Learning. 3rd ed. Circle Pines: American Guidance Service; 1998.
41. Touwen BCL. Examination of the Child with Minor Neurological Dysfunction. 2nd ed. Heinemann: Lippincott for Spastics International Medical Publications; 1979.
42. Bradley RH, Corwyn RF. Socioeconomic status and child development. Annu Rev Psychol 2002;53:371–399.
43. Richels CG, Johnson KN, Walden TA, Conture EG. The relation of socioeconomic status and parent education on the vocabulary and language skills of children who do and do not stutter. J Commun Disord 2013;46:361–374.
44. Turkheimer E, Haley A, Waldron M, D'Onofrio B, Gottesman II. Socioeconomic status modifies heritability of IQ in young children. Psychol Sci 2003;14:623–628.
45. Bayley N. Bayley Scales of Infant and Toddler Development. 3rd ed: Administration Manual. San Antonio: Harcourt; 2006.
46. Australian Bureau of Statistics. Gender Indicators, Australia. Table 5: Attainment of a Bachelor Degree or Above by Age, 2001 to 2015 (A)(b), Data Cube: Excel Spreadsheet, cat. no. 41250DS0002. 2016. Available at: abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/4125.0Feb%202016?OpenDocument. Accessed November 18, 2018.
47. Johnson MH. Sensitive periods in functional brain development: problems and prospects. Dev Psychobiol 2005;46:287–292.
48. Thomas MSC, Johnson MH. New advances in understanding sensitive periods in brain development. Curr Dir Psychol Sci 2008;17:1–5.
49. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. Brain 2011;134:2197–2221.
50. Crowe LM, Catroppa C, Babl FE, Rosenfeld JV, Anderson V. Timing of traumatic brain injury in childhood and intellectual outcome. J Pediatr Psychol 2012;37:745–754.
51. Anderson V, Spencer-Smith M, Coleman L, et al. Children's executive functions: are they poorer after very early brain insult. Neuropsychologia 2010;48:2041–2050.

2.6 Translating research into practice (published manuscript)

Following the publication of my research findings as three separate papers in different high impact specialty journals, I felt it was important to synthesise the findings into an accessible and practical resource for clinicians who are at the coalface of managing children with VP-FSs and addressing their parents' concerns. I therefore wrote a peer-reviewed narrative review summarising the research leading up to my PhD and my research findings on VP-FS, with illustrative case examples of how to approach children with different vaccine-proximate seizures using the evidence available. The review article, published in the *Australian Journal of General Practice*, is intended as a clinical resource for general practitioners who are the first point of call for families seeking advice about their child's subsequent vaccinations after having an AEFI.

Seizures following vaccination in children: risks, outcomes and management of subsequent revaccination.

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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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References

1. Guidelines for epidemiologic studies on epilepsy. Commission on epidemiology and prognosis, international league against epilepsy. Epilepsia 1993;34(4):592–96. doi: 10.1111/j.1528-1157.1993.tb00433.x.
2. Offringa M, Bossuyt PM, Lubsen J, et al. Risk factors for seizure recurrence in children with febrile seizures: A pooled analysis of individual patient data from five studies. J Pediatr 1994;124(4):574–84. doi: 10.1016/s0022-3476(05)83136-1.
3. Barlow WE, Davis RL, Glasser JW, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med 2001;345(9):656–61. doi: 10.1056/NEJMoa003077.
4. Sun Y, Christensen J, Hviid A, et al. Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and haemophilus influenzae type B. JAMA 2012;307(8):823–31. doi: 10.1001/jama.2012.165.
5. Macartney K, Gidding HF, Trinh L, et al. Evaluation of combination measles-mumps-rubella-varicella vaccine introduction in Australia. JAMA Pediatr 2017;171(10):992–98. doi: 10.1001/jamapediatrics.2017.1965.
6. Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics 2010;126(1):e1–e8. doi: 10.1542/peds.2010-0665.
7. Macartney KK, Gidding HF, Trinh L, et al. Febrile seizures following measles and varicella vaccines in young children in Australia. Vaccine 2015;33(11):1412–17. doi: 10.1016/j.vaccine.2014.10.071.
8. Deng L, Gidding H, Macartney K, et al. Postvaccination febrile seizure severity and outcome. Pediatrics 2019;143(5)e20182120. doi: 10.1542/peds.2018-2120.
9. Farrington P, Rush M, Colville A. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. Lancet 1995;345(8949):567–69. doi: 10.1016/s0140-6736(95)90471-9.
10. Miller E, Andrews N, Stowe J, Grant A, Waight P, Taylor B. Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom. Am J Epidemiol 2007;165(6):704–09. doi: 10.1093/aje/kwk045.
11. 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(6):645–50. doi: 10.1016/j.vaccine.2013.12.011.
12. Klein NP, Lewis E, Baxter R, et al. Measles-containing vaccines and febrile seizures in children age 4 to 6 years. Pediatrics 2012;129(5):809–14. doi: 10.1542/peds.2011-3198.
13. Andrews N, Stowe J, Wise L, Miller E. Post-licensure comparison of the safety profile of diphtheria/tetanus/whole cell pertussis/haemophilus influenza type b vaccine and a 5-in-1 diphtheria/tetanus/acellular pertussis/haemophilus influenzae type b/polio vaccine in the United Kingdom. Vaccine 2010;28(44):7215–20. doi: 10.1016/j.vaccine.2010.08.062.
14. Huang WT, Gargiullo PM, Broder KR, et al. Lack of association between acellular pertussis vaccine and seizures in early childhood. Pediatrics 2010;126(2):263–9. doi: 10.1542/peds.2009-1496.
15. Armstrong PK, Dowse GK, Effler PV, 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. doi: 10.1136/bmjopen-2010-000016.
16. Hambidge SJ, Glanz JM, France EK, et al. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. JAMA 2006;296(16):1990–97. doi: 10.1001/jama.296.16.1990.
17. Li R, Stewart B, McNeil MM, et al. Post licensure surveillance of influenza vaccines in the vaccine safety datalink in the 2013–2014 and 2014–2015 seasons. Pharmacoepidemiology Drug Saf 2016;25(8):928–34. doi: 10.1002/pds.3996.
18. Pillsbury A, Quinn H, Cashman P, Leeb A, Macartney K. Active SMS-based influenza vaccine safety surveillance in Australian children. Vaccine 2017;35(51):7101-06. doi: 10.1016/j.vaccine.2017.10.091.
19. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. N Engl J Med 1976;295(19):1029–33. doi: 10.1056/NEJM197611042951901.
20. Berg AT, Shinnar S. Complex febrile seizures. Epilepsia 1996;37(2):126–33. doi: 10.1111/j.1528-1157.1996.tb00003.x.
21. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med 1987;316(9):493–98. doi: 10.1056/NEJM198702263160901.
22. Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. I – Prevalence and recurrence in the first five years of life. Br Med J (Clin Res Ed) 1985;290(6478):1307–10. doi: 10.1136/bmj.290.6478.1307.

23. Tartof SY, Tseng HF, Liu IL, et al. Inpatient admission for febrile seizure and subsequent outcomes do not differ in children with vaccine-associated versus non-vaccine associated febrile seizures. Vaccine 2014;32(48):6408–14. doi: 10.1016/j.vaccine.2014.09.055.
24. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. N Engl J Med 1998;338(24):1723–28. doi: 10.1056/NEJM199806113382403.
25. Chang YC, Guo NW, Huang CC, Wang ST, Tsai JJ. Neurocognitive attention and behavior outcome of school-age children with a history of febrile convulsions: A population study. Epilepsia 2000;41(4):412–20. doi: 10.1111/j.1528-1157.2000.tb00182.x.
26. Deng L, Wood N, Macartney K, et al. Developmental outcomes following vaccine–proximate febrile seizures in children. Neurology 2020;10.1212/WNL.0000000000009876. doi: 10.1212/WNL.0000000000009876.
27. von Spiczak S, Helbig I, Drechsel-Baeuerle U, et al. A retrospective population-based study on seizures related to childhood vaccination. Epilepsia 2011;52(8):1506–12. doi: 10.1111/j.1528-1167.2011.03134.x.
28. Berkovic SF, Harkin L, McMahon JM, et al. De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: A retrospective study. Lancet Neurology 2006;5(6):488–92. doi: 10.1016/S1474-4422(06)70446-X.
29. McIntosh AM, McMahon J, Dibbens LM, et al. Effects of vaccination on onset and outcome of Dravet syndrome: A retrospective study. Lancet Neurol 2010;9(6):592–98. doi: 10.1016/S1474-4422(10)70107-1.
30. Verbeek NE, van der Maas NA, Jansen FE, van Kempen MJA, Lindhout D, Brilstra EH. Prevalence of SCN1A-related Dravet syndrome among children reported with seizures following vaccination: A population-based ten-year cohort study. PloS One 2013;8(6):e65758. doi: 10.1371/journal.pone.0065758.
31. Damiano JA, Deng L, Li W, et al. SCN1A Variants in vaccine-related febrile seizures: A prospective study. Ann Neurol 2020;87(2):281–88. doi: 10.1002/ana.25650.
32. Depienne C, Trouillard O, Saint-Martin C, et al. Spectrum of SCN1A gene mutations associated with Dravet syndrome: Analysis of 333 patients. J M Genet 2009;46(3):183–91. doi: 10.1136/jmg.2008.062323.
33. Korff C, Laux L, Kelley K, Goldstein J, Koh S, Nordli D Jr. Dravet syndrome (severe myoclonic epilepsy in infancy): A retrospective study of 16 patients. J Child Neurol 2007;22(2):185–94. doi: 10.1177/0883073807300294.
34. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001;68(6):1327–32. doi: 10.1086/320609.
35. Harkin LA, McMahon JM, Iona X, et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 2007;130(Pt 3):843–52. doi: 10.1093/brain/awm002.
36. Mulley JC, Scheffer IE, Petrou S, Dibbens LM, Berkovic SF, Harkin LA. SCN1A mutations and epilepsy. Human Mutat 2005;25(6):535–42. doi: 10.1002/humu.20178.
37. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infants (Dravet syndrome). In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, editors. Epileptic syndromes in infancy, childhood and adolescence. 3rd edn. Montrouge, FR: John Libbey Eurotext, 2002; p. 89–113.
38. Nabbout R, Chemaly N, Chipaux M, et al. Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. Orphanet J Rare Dis 2013;8:176. doi: 10.1186/1750-1172-8-176.
39. Wakai S, Ito N, Sueoka H, Kawamoto Y, Hayasaka H, Chiba S. Severe myoclonic epilepsy in infancy and carbamazepine. Eur J Pediatr 1996;155(8):724. doi: 10.1007/BF01957165.

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2.7 Key findings

In this chapter, I explored the clinical severity, developmental outcomes and genetic risk of VP-FS compared to NVP-FS through two prospective studies across three original research publications and a clinical practice publication. My key findings from these studies were as follows:

1. VP-FSs were not clinically different to NVP-FSs. The majority were brief seizures (<15 minutes) with no seizure recurrence in the acute period, no prolonged hospitalisation (<1 day) and not requiring antiepileptic medication on discharge.
2. The majority of VP-FSs were following the first dose of measles-containing vaccine.
3. Pathogenic *SCN1A* variants occurred in young infants (<12 months of age) presenting with prolonged VP-FS.
4. VP-FS was not associated with increased risk of developmental or behavioural problems in young children at 12–24 months after the initial FS when compared to children with NVP-FS or children with no seizure history.

From these findings, I draw the following recommendations:

1. Parents and providers can be reassured that the clinical and developmental outcomes of children who experience a VP-FS are no different to children who have an NVP-FS or healthy controls. Children who have a VP-FS should therefore continue to be vaccinated, as would a child who had an NVP-FS.
2. Young infants (aged <12 months) presenting with prolonged VP-FS should be recommended for screening of genetic epilepsies, especially *SCN1A* variants, to allow for early diagnosis and appropriate seizure management for these children, including for their subsequent vaccinations.

This chapter addresses the knowledge gaps on the clinical severity, developmental outcomes and genetic risk of VP-FS with reassuring findings. It identified an increased risk for an underlying severe genetic epilepsy in children presenting with prolonged FS. Therefore, I will examine the more severe form of seizures, status epilepticus, following vaccination in the next chapter.

Chapter 3 Status epilepticus following vaccination

3.1 Introduction

In **Chapter 2**, I showed that the clinical and developmental outcomes following VP-FSs were usually brief and self-resolving, which was reassuring. However, at the start of my PhD candidature, I was involved in a case of VP-SE that resulted in hypoxic ischaemic encephalopathy and subsequent death in a previously well infant. The case and subsequent vaccination management of the child's sibling is described in **Section 3.2** as a published case study (Paper 5). While reviewing the case and as the clinician managing the younger sibling's vaccinations, I discovered a knowledge gap in the literature on the risk and clinical outcomes of VP-SE.

Historical cohort studies and case series have reported on VP-SE following DTP-containing vaccine(152) and as first seizure presentations in children with Dravet syndrome.(175, 177, 180) However, unlike VP-FS, population-level data on the proportion of SE that is vaccine-proximate, details on the clinical severity of VP-SE compared to NVP-SE, SE recurrence rate, and the impact on vaccination uptake following VP-SE is not known.

Through two retrospective studies, this chapter aims to address the following knowledge gaps:

1. The proportion of first SE that are vaccine proximate and the impact of SE on subsequent vaccination uptake.
2. Clinical severity and outcome differences between VP-SE and NVP-SE.

To determine the proportion of first SE in children that are vaccine proximate, and to compare clinical severity of and subsequent vaccination coverage following VP-SE to NVP-SE, I undertook a retrospective population-based cohort study linking birth records for a cohort of 1.4 million Australian children to hospital admissions and vaccination history. The study is presented in **Section 3.3** as a manuscript under review (Paper 6). The study protocol can be found in **Appendix 2**. I wrote the protocol as an amendment of an existing protocol titled "Linkage of the Australian Childhood Immunisation Register (ACIR) and state-based registers to evaluate and inform Australia's immunisation program". I sought ethics amendment approvals from the Australian Institute of Health and Welfare, NSW Population and Health Services Research Ethics Committee, Aboriginal Health and Medical Research Council of NSW, Western Australian Department of Health Human Research

Ethics Committee, and Western Australian Aboriginal Health Ethics Committee for the use of an existing population-based linked dataset for my analysis.

To supplement hospital administrative data from the population-based cohort study, which was limited in case history and follow-up data, I undertook a multi-centre 5-year retrospective cohort study of first SE admissions in children aged ≤24 months to compare in further detail the clinical differences and seizure outcomes of VP-SE and NVP-SE 12 months following the initial SE. This study is presented in **Section 3.4**. The study protocol can be found in **Appendix 3**.

3.2 Case study (published manuscript)

Vaccination management in an asymptomatic child with a novel *SCN1A* variant and family history of status epilepticus following vaccination: a case report on a potential new direction in personalised medicine.

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Short communication

Vaccination management in an asymptomatic child with a novel *SCN1A* variant and family history of status epilepticus following vaccination: A case report on a potential new direction in personalised medicine

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ABSTRACT

Purpose: *SCN1A* variants cause a spectrum of epilepsy syndromes from Dravet Syndrome, a severe epileptic encephalopathy of early infancy to the milder disorder of genetic epilepsy with febrile seizures plus (GEFS+). These genetic epilepsies are associated with increased risk of poor outcome including complications of status epilepticus and early mortality. Individualised management of young children known to be at increased risk should be considered, such as around vaccination management.

Methods: We describe two siblings with a novel pathogenic *SCN1A* variant, their management and clinical outcomes following routine childhood vaccinations.

Results: The index case who had a family history of epilepsy of unknown genetic aetiology, died from hypoxic ischemic encephalopathy following his 12-month vaccinations, in the context of status epilepticus and enterovirus 71 infection. The sibling of the index case with the same *SCN1A* variant was subsequently managed with prophylactic regular sodium valproate and additional clobazam post vaccination to reduce the risk of seizure. She has successfully completed the childhood immunisations to 18 months with no seizures and normal neurodevelopmental progress.

Conclusion: As the aetiology of genetic epilepsies is increasingly known in early childhood, opportunities to personalise care, minimise risks and optimise outcomes are changing. Further research is needed on the risks and benefits of symptomatic and preventative management of seizures around vaccinations in young children with genetic epilepsies.

1. Introduction

Pathogenic variants in *SCN1A*, a sodium channel alpha-1 subunit gene, cause a range of epilepsy syndromes from generalised epilepsy with febrile seizures plus (GEFS+) to the more severe developmental and epileptic encephalopathy, Dravet Syndrome. [1] Approximately 80 % of children with Dravet syndrome have a *SCN1A* variant, of which 95 % are de novo variants. [2] Those with familial variants often have the milder phenotype of GEFS + and generally follow an autosomal dominant inheritance pattern with some showing reduced penetrance [3].

Vaccinations have been implicated in triggering an earlier onset of seizures in children with underlying genetic epilepsy, including *SCN1A*-related Dravet syndrome. [4] Here, we report of two siblings with a

Abbreviations: SCN1A, sodium channel alpha-1 subunit gene; GEFS+, generalised epilepsy with febrile seizures plus; FS, febrile seizure; DTPa-Hib-HepB-IPV, diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, hepatitis B and inactivated polio combination vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; Hib-MenC, Haemophilus influenzae type b and meningococcal C conjugate vaccine; MMR, measles-mumps-rubella vaccine; CSF, cerebrospinal fluid; CT, computer tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiogram; SUDEP, sudden unexpected death in epilepsy; 4vMenCV, quadrivalent (A, C, W, Y) meningococcal conjugate vaccine; DTPa, diphtheria, tetanus and acellular pertussis combination vaccine; HiB, Haemophilus influenzae type b vaccine; VZV, varicella zoster virus vaccine; CNS, central nervous system

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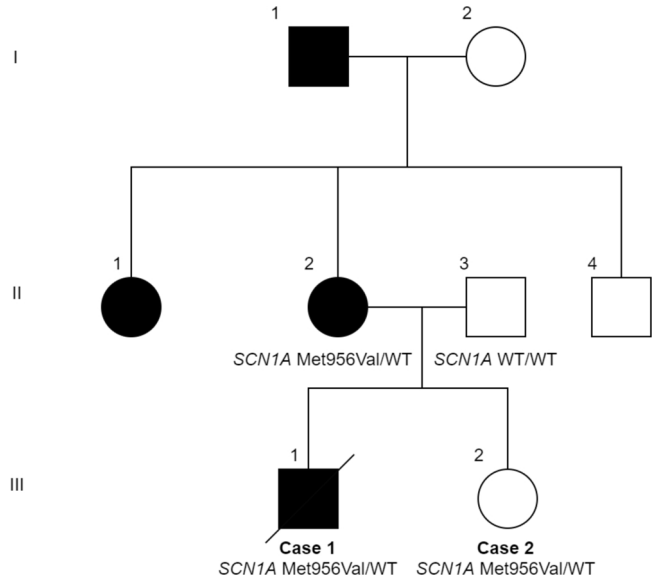

Fig. 1. Pedigree of family.

novel *SCN1A* variant, their clinical management and outcomes, with focus on their vaccinations.

2. Case 1

The first patient (index case, III:1 in Figure) was a 12-month-old boy, born at full-term via spontaneous vaginal delivery to non-consanguineous Caucasian parents (first pregnancy via in-vitro fertilisation).

His mother (II:2) had epilepsy from infancy, with her first febrile seizure (FS) before 12 months old. She progressed to have both febrile and afebrile bilateral tonic clonic seizures, but no focal seizures or status epilepticus. Her seizures were managed with sodium valproate only. Seizure frequency decreased from once every two months from infancy to puberty, to being seizure free for 4 years before ceasing medication for 5 years before the patient's birth. There was no significant neurodevelopmental impact from the seizures, and she completed high school studies with no assistance. There was a history of epilepsy in her older sister (II:1) and her father's family (I:1). No family members had prolonged seizures or developmental concerns. (Fig. 1).

The patient was a healthy infant with normal growth and development and no significant medical history aside from omphalitis as a neonate. He received his first three sets of infant vaccinations (DTPa-Hib-HepB-IPV, PCV13 and rotavirus vaccines at 6 weeks and 4 months and DTPa-Hib-HepB-IPV and PCV13 at 6 months) with no adverse events following immunisation.

At 12 months old, he had a mild febrile illness with rhinorrhoea lasting 1–2 weeks and had been afebrile for 3–4 days at the time of Hib-MenC and MMR vaccinations. Approximately 27 h later, his first seizure occurred. The child's mother saw him sitting up in bed on the baby video monitor, and went into the room to find him staring, unresponsive with lip smacking, followed by bilateral tonic clonic movements. Fever to 38.5 °C was recorded on arrival to emergency. Four doses of midazolam were given before status epilepticus terminated at approximately 40 min. He went into cardiopulmonary arrest during intubation and had 40 min of down time before return of spontaneous circulation on an adrenalin infusion. A loading dose of levetiracetam (30 mg/kg) was given and he was transferred to paediatric intensive care unit on morphine and adrenaline infusion. Antibiotics were commenced, CSF collection was deferred. CT brain showed severe global hypoxic ischemic brain injury with cerebral oedema. The admission was complicated by pulmonary oedema, secondary pneumonia, diabetes insipidus, hyperglycaemia, hyperthermia and hypertension. EEG showed electrocerebral silence, and MRI re-demonstrated extensive changes with cerebellar tonsillar herniation and absence of flow in the intracranial arteries on MRA consistent with brain death; medical support was withdrawn, and he died.

Autopsy found severe cerebral oedema with diffuse hypoxic ischemic encephalopathy changes and cerebellar tonsillar herniation. There was also extensive bronchopneumonia. Enterovirus 71 was found on tracheal and rectal swab. There were no signs of meningitis or encephalitis on neuropathological exam of brain and spinal cord.

Genomic testing was not performed at the time of autopsy. Instead, the mother was referred for genetic review during her subsequent pregnancy (Case 2). Whole exome sequencing was arranged on a stored liver-derived DNA sample from Case 1, focussing on a panel of SUDEP (sudden unexpected death in epilepsy), long QT syndrome and hypoventilation-associated genes.

The detected heterozygous missense variant in *SCN1A* (NM_001165963.1: c.2866A > G;p.(Met956Val)) was novel and classified as likely pathogenic by American College of Medical Genetics guidelines (Class 4: PM2, PM5, PP2, PP3). [5] While this was a novel amino acid change, other pathogenic missense changes affecting the same residue, including p.Met956Thr, have been reported where in vitro studies demonstrate reduced cell surface *SCN1A* expression, highlighting the functional importance of this particular highly conserved methionine. [6,7] The absence of variants in this position in population databases including Genome Aggregation Database (gnomAD) [8] and in silico predictions support this missense variant as being likely pathogenic. This variant was also subsequently found in the mother.

3. Case 2

The second patient (III:2), is the younger sister of the index case, born 12 months after the index case's death. Given the history of vaccine-proximate status epilepticus in Case 1, though genetic results were unknown then, she was reviewed by an immunisation specialist and a neurologist prior to her vaccinations. She was admitted for 6-week and 4-month vaccinations (DTPa-HiB-IPV-HepB, PCV13 and rotavirus vaccine) and given prophylactic paracetamol. There were no adverse events.

She was also reviewed by clinical genetics soon after birth. The parents were counselled on predictive genetic testing for the *SCN1A* variant given her 50 % inheritance risk from her mother, identified when Case 2 was 5 months old, and genetic testing was performed with consent. She was found to also harbour the same variant. After careful consideration and consultation with neurology colleagues, she was commenced on prophylactic sodium valproate (20 mg/kg/day) to reduce the risk of seizures, with no side effects reported. In addition, prophylactic paracetamol and clobazam (0.3 mg/kg/day) was given following her 6-, 12- and 18-month vaccinations for the period where a fever post-vaccination was expected (2 days following inactivated vaccine; 14 days following live-attenuated vaccine). Inactivated vaccines (4vMenCV, PCV13 at 12 months and DTPa, HiB at 18 months) were given separate to live-attenuated vaccines (MMR and VZV respectively) to reduce any added risk of FS in concomitant vaccine administration. Currently, at 18 months' old, she has remained seizure free with normal development on prophylactic valproate, with weaning off medication planned from age 2 years.

4. Discussion

Knowledge of the genetic aetiology of epilepsy syndromes offers potential to inform risk stratification and personalised patient care in early childhood, including immunisation management. We report a novel missense *SCN1A* variant in a 12-month-old child who suffered a catastrophic outcome from status epilepticus with cardiac arrest

following vaccination, in the context of recent febrile illness likely associated with enterovirus 71. A subsequent asymptomatic sibling was identified with the same variant, raising the question of optimal management in this case.

Multiple factors may have contributed to the death of Case 1 including vaccination, status epilepticus, pathogenic *SCN1A* variant and enterovirus infection. Although it is not possible to predict an individual's phenotype based on their genotype alone, the pattern in this family is more consistent with GEFS + syndrome, and missense variants more commonly occur with the milder GEFS + phenotype. [1]

Post-vaccination seizures occur in a small number of individuals and are well documented in children with Dravet syndrome. [4]] *SCN1A* variants predispose individuals, particularly those with Dravet syndrome, to status epilepticus and to an increased risk of SUDEP. [9] Optimal acute management of status epilepticus is essential, with emphasis on timely and appropriate emergent benzodiazepine treatment (2 adequate doses) followed promptly by second line medication, as per best practice guidelines [10].

Enterovirus 71 infection can cause FSs, aseptic meningitis, and encephalitis following a prodromal illness as in Case 1 and does not typically have evidence of cerebritis at autopsy. [11,12] The presence of CNS infection was unclear due to lack of CSF sampling in this acutely ill infant. In this case, where cardiac arrest followed status epilepticus, enterovirus 71 also predisposes to pulmonary oedema and myocarditis, with young children more severely affected [12]. This underscores the importance of deferring vaccination in children with an acute febrile illness.

Genetic testing in this case had important ethical and counselling implications. Pursuing extended genetic testing at autopsy would have provided the family timely information for reproductive planning, including pre-implantation genetic diagnosis with in-vitro fertilisation. As massively parallel sequencing and genetic diagnosis becomes more prevalent in childhood epilepsy, issues arise about predictive testing for asymptomatic siblings and parents, and optimal evidence-based management for asymptomatic individuals carrying pathogenic variants.

Pre-symptomatic treatment is not our standard management of FSs or risk of seizures in families with genetic epilepsy, as antiepileptic medications may be associated with side effects including on neurodevelopment and cognition. Risk of seizures and poor outcome in Case 2 was considered high given the significant family history, previous infant death, and familial *SCN1A* variant.

Valproic acid and clobazam are considered first line medications in Dravet syndrome with treatment aimed at avoidance of status epilepticus and its impact on neurodevelopment, and are rational choices for epilepsy management in GEFS+. [13] Given the tragic outcome of status epilepticus in the index case, the parents were terrified by the risk of any potential seizure triggers, including febrile illnesses, for Case 2. Therefore, prophylactic treatment with a single first line antiepileptic medication with close monitoring for potential side effects was recommended to reduce the risk of seizure and was provided safely.

Intermittent clobazam use has also been shown to be effective compared to placebo in preventing FSs in children, [14] and was therefore prescribed in addition in the period following vaccination where FS risk is highest. Strategies to reduce seizure triggers in children with Dravet syndrome, recommended by expert consensus panel, include the use of prophylactic antipyretics with vaccination and illness, and prophylactic benzodiazepines with febrile illnesses [13]. While avoidance of or selective immunisation is not recommended in children with epilepsy or epileptic encephalopathy, there are no guidelines on risk management around vaccination of these patients [13,15]. Important principles include deferring vaccination until febrile illness has fully resolved, considering administering vaccines separately, educating families about seizure appearances and first aid, ensuring optimal emergency seizure management, and considering the potential risks and benefits of prophylactic antiepileptic treatment in selected high risk cases.

These cases highlight the challenges of managing young children with genetic epilepsies, including asymptomatic infants with novel pathogenic variants. A conservative approach using antiepileptic medication (daily monotherapy with additional clobazam during a period where fever was likely following vaccination) and prophylactic antipyretics was associated with absence of seizures or significant complications in the second child. The extent to which pre-symptomatic management should be considered in other cases must be carefully assessed on an individual basis. There is not currently adequate evidence to recommend this approach for all children.

5. Conclusion

This is the first report of this novel pathogenic *SCN1A* variant associated with status epilepticus, viral infection and infant death following vaccination. We have described an approach to personalised management around vaccination of an asymptomatic younger sibling with the same variant. Establishing genetic aetiology as early as possible in familial epilepsies has the potential to change management and outcomes for affected children. In future, through cooperative international efforts using well-designed natural history and treatment trials, it should be possible to predict risks and benefits of pre-symptomatic treatment with greater certainty in similar cases, with a view to optimising personalised management of vaccination for children with genetic epilepsies.

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Declaration of Competing Interest

The authors have no conflict of interest to declare.

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References

[1] Zuberi SM, Brunklaus A, Birch R, Reavey E, Duncan J, Forbes GH. Genotype-phenotype associations in SCN1A-related epilepsies. Neurology 2011;76(7):594–600.
[2] Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001;68(6):1327–32.
[3] Zhang YH, Burgess R, Malone JP, et al. Genetic epilepsy with febrile seizures plus: refining the spectrum. Neurology 2017;89(12):1210–9.
[4] McIntosh AM, McMahon J, Dibbens LM, et al. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. Lancet Neurol 2010;9(6):592–8.
[5] Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405–24.
[6] Pippucci T, Licchetta L, Baldassari S, et al. Epilepsy with auditory features: a heterogeneous clinico-molecular disease. Neurol Genet 2015;1(1):e5.
[7] Bechi G, Rusconi R, Cestele S, Striano P, Franceschetti S, Mantegazza M. Rescuable folding defective NaV1.1 (SCN1A) mutants in epilepsy: properties, occurrence, and novel rescuing strategy with peptides targeted to the endoplasmic reticulum. Neurobiol Dis 2015;75:100–14.
[8] Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature 2016;536(7616):285–91.
[9] Cooper MS, McIntosh A, Crompton DE, et al. Mortality in dravet syndrome. Epilepsy Res 2016;128:43–7.
[10] Abend NS, Loddenkemper T. Management of pediatric status epilepticus. Curr Treat Options Neurol 2014;16(7):301.
[11] McMinn P, Stratov I, Nagarajan L, Davis S. Neurological manifestations of enterovirus 71 infection in children during an outbreak of hand, foot, and mouth disease in Western Australia. Clin Infect Dis 2001;32(2):236–42.
[12] Ooi MH, Wong SC, Lewthwaite P, Cardosa MJ, Solomon T. Clinical features, diagnosis, and management of enterovirus 71. Lancet Neurol 2010;9(11):1097–105.

[13] Wirrell EC, Laux L, Donner E, et al. Optimizing the diagnosis and management of dravet syndrome: recommendations from a North American consensus panel. Pediatr Neurol 2017;68:18–34. e13.
[14] Bajaj AS, Bajaj BK, Purib V, Tayal G. Intermittent clobazam in febrile seizures: an Indian experience. J Pediatr Neurol 2005;3:19–23.
[15] Pruna D, Balestri P, Zamponi N, et al. Epilepsy and vaccinations: Italian guidelines. Epilepsia 2013;54(Suppl 7):13–22.

3.3 Epidemiology (manuscript under review)

Clinical outcomes and risk of status epilepticus following vaccination in children: a retrospective, population-based, record-linked cohort study.

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Status epilepticus outcomes among vaccinated and unvaccinated children: a population-based study

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Conflict of Interest
Dr Gill has received a speaker honorarium from BioMarin and served as an investigator for Zogenix. There are no other interests from the authors which might be perceived as posing a conflict or bias.

Author contribution statement
Dr Deng, A/Profs Gidding and Wood conceptualised and designed the study. Dr Deng did the analysis and drafted the initial manuscript. A/Prof Gidding provided advice on data cleaning and analysis. Prof Macartney, A/Profs Wood and Gidding, Drs Gill and Fathima provided clinical and epidemiological advice and assisted with the interpretation and presentation of the results. All authors reviewed and revised the manuscript and approved the submitted final manuscript.

Abbreviations

AEFI: adverse event following immunisation
DTPa: diphtheria-tetanus-acellular pertussis containing
FS: febrile seizure
Hib-MenC: Haemophilus influenza B and meningococcal C conjugate vaccine
ICD: International Classification of Diseases
ICU: intensive care unit
MCV: measles containing vaccine
MMR: measles-mumps-rubella
NSW: New South Wales
NVP-SE: non-vaccine proximate status epilepticus
SE: status-epilepticus
VP-SE: vaccine-proximate status epilepticus
WA: Western Australia

What this paper adds

- Vaccine-proximate status epilepticus accounted for 3.6% of all first status epilepticus episodes
- Vaccine-proximate status epilepticus most frequently followed dose-1 measles-containing-vaccine (16 of 31 cases)
- Vaccine-proximate cases were younger and had longer hospital stays than non-proximate cases
- Recurrence rates were similar in vaccine-proximate and non-vaccine-proximate status epilepticus cases
- Subsequent vaccine uptake decreased in both vaccine-proximate and non-proximate cases

Abstract

Aim

To determine the proportion of first status epilepticus (SE) cases that are vaccine-proximate (VP-) and compare clinical outcomes to non-vaccine-proximate (NVP-) cases.

Methods

Birth records for 1,440,807 Australian children born in 1998–2012, were probabilistically linked to hospitalisations, deaths and vaccination history available to 2013. First SE coded hospitalisations were categorised as VP-SE or NVP-SE; clinical severity and post-SE vaccination coverage were compared. SE rates were calculated.

Results

Of 867 first SE cases (7.9 per 100,000 person-years), 31 (3.6%) were VP-SE; 16 followed dose-1 measles vaccine (1.2 SE per 100,000 doses). Compared with NVP-SE, VP-SE cases were younger (1.0 vs 2.6 years, $P<0.0001$), had longer hospitalisations (4 vs 3 days, $P=0.005$), and higher coinfection rates (35.8% vs 19.9%, $P=0.42$). Controlling for age, intensive care unit (ICU) admission had a stronger association with coinfection (aOR 2.41 (95%CI 1.71-3.40)) than having VP-SE (aOR 1.45 (0.68-3.11)). Groups had similar SE recurrence rates at 12-months (12.9% VP vs 16.9% NVP, $P=0.56$) and reduced vaccine uptake following initial SE (from 93.5% to 56.3%).

Interpretation

Proportionally few SE cases were VP-SE, with higher ICU admission rates mostly explained by younger age and higher coinfection rates. Vaccination plans are needed to improve vaccine uptake following SE.

Introduction

Status epilepticus (SE) is a neurologic emergency associated with significant morbidity and mortality.[1] Population studies on SE have shown that the incidence of SE is highest under 12 months of age at 50-150/100,000 person-years.[2-4]

While most childhood vaccinations are given when SE incidence is highest, few studies have examined vaccine-proximate status epilepticus (VP-SE). The British National Childhood Encephalopathy Study identified 2 SE cases occurring within 7 days following diphtheria-tetanus-acellular-pertussis (DTPa) vaccine in children aged 2 to 35 months.[5] A German Adverse Event Following Immunisation (AEFI) database from 2006-2008 reported 21 SE cases,[6] although no details of the vaccine or seizure timing were provided. VP-SE as the first seizure presentation in children with Dravet syndrome has also been previously reported.[7,8] These studies describe VP-SE cases, but do not provide population-level data on what proportion of all SE are VP-SE. To our knowledge, there are also no studies comparing VP-SE to SE due to other causes (non-vaccine proximate SE; NVP-SE) in terms of clinical severity, SE recurrence, or vaccination coverage following the initial SE episode.

We used linked health and immunisation data from a 15-year birth cohort across two Australian states to determine the overall incidence of SE, the proportion which are VP-SE, the differences in clinical severity between VP-SE and NVP-SE cases and their subsequent vaccination uptake.

Methods

Data sources and study cohort

This retrospective population-based cohort study included children born in two Australian states (approximately 42% of Australia's population combined):[9] Western Australia (WA) from 1 January 1998 to 31 December 2012 and New South Wales (NSW) from 1 July 2001 to 31 Dec 2012. As

previously described,[9,10] birth records for these children were probabilistically linked (using name, date of birth, residential address and sex) to hospitalisation, death and vaccination records, available until 31 December 2013. Linkage accuracy was reported to be >99%.[9]

The cohort was restricted to all live-born births with both a perinatal (WA Midwives' Notification System and NSW Perinatal Data Collection) and birth registration (WA Birth Register and NSW Registry of Births) record, which included 97.5% of all live births during these periods.[9] Perinatal data included maternal and child demographic and birth details. Socioeconomic disadvantage was measured by the Socio-Economic Indexes for Areas (SEIFA), calculated using information from five-yearly census data on the mother's residential area's socioeconomic characteristics at the time of birth, grouped into three categories (0-25, 25-75, 76-100) with the lowest centile being the most disadvantaged.[11] Aboriginal and Torres Strait Islander (hereafter respectfully referred to as Indigenous) status was determined using an established algorithm based on all of the linked databases except deaths.[9,12]

SE hospitalisations were identified from linked hospitalisation records using International Classification of Diseases (ICD)[13] Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision, Australian Modification (ICD-10-AM) diagnosis code for SE (345.2 and 345.3 in ICD-9-CM and G41.X in ICD-10-AM) in either primary/principal or secondary/additional diagnosis codes. For SE cases from multiparity pregnancies where more than one child had a SE, only the first live-born child of that pregnancy was included to minimise potential of correlation (Appendix A).

Ethics approvals were obtained from respective state Aboriginal ethics committees, state and Commonwealth health departments, and the Australian Institute of Health and Welfare Ethics Committee.

Case definition and outcome measures

The first SE hospitalisation record for each child was categorised into VP-SE and NVP-SE. Based on previous studies on the timing of fever onset and FS following specific vaccines,[14] VP-SE was defined as a SE hospitalisation where the admission date was 0-2 days following receipt of an inactivated vaccine, 5-14 days following a live-attenuated vaccine or 0-14 days following a combination of inactivated and live-attenuated vaccines. A SE hospitalisation outside of this period was categorised as an NVP-SE (Appendix A). Vaccine exposures, including vaccination date and type, were obtained by linkage of the cohort to the Australian Childhood Immunisation Register, a national population based register for all vaccines administered to children <7 years of age.[15]

The first SE hospitalisation record was used to identify length of stay, intensive care unit (ICU) admission and presence of concomitant infection diagnoses using ICD codes. ICD codes from prior admissions were used to identify history of medical conditions that increase the risk of seizures (including cerebral palsy, perinatal intracranial haemorrhage, hydrocephalus or other intracranial pathology), and ICD codes from prior and subsequent admissions were used to identify seizures of any kind. A full list of ICD codes used is provided in Appendix B.

Statistical analyses

The overall and age-specific incidence rate per 100,000 person-years of first SE hospitalisation by Indigenous status was calculated using person-time from birth to first SE hospitalisation, death or end of study period (31st December, 2013) whichever was earliest, partitioned into age groups as displayed in Figure 1.

To examine the rate of SE following vaccination, we focussed on dose-1 measles-mumps-rubella vaccine (MMR), as this vaccine accounted for the highest proportion of the VP-SE in our analysis and also enabled comparison to Klein *et al*.'s population-based study on FS rates following MMR

vaccination.[16] Two measures were calculated: (1) the proportion of children given dose-1 MMR between 11 and 23 months of age who had their first SE 0-14 days following vaccination and (2) the incidence rate of first SE following dose-1 MMR vaccination, calculated by dividing the number of SE occurring between 0-14 days and 7-10 days following vaccination by the sum of the corresponding amount of person-time (14 or 4 days, respectively).

Sociodemographic, birth, past medical conditions and first SE hospitalisation details and vaccination coverage before and after the first SE were compared between VP-SE and NVP-SE. For pre-SE vaccination coverage, a case was considered age-eligible for vaccination if they were scheduled to receive a vaccine according to the government funded schedule at the time,[17] prior to their first SE. For post-SE vaccination coverage, a case was considered eligible for a vaccine if they were scheduled to receive a funded vaccine from the time of discharge following their first SE to the end of the study period. A sub-analysis comparing first VP-SE and NVP-SE hospitalisations in children with no previous seizure hospitalisations was performed. Groups were compared using the Chi-squared test for categorical data, independent t-tests for parametric continuous data and Mann-Whitney U test for non-parametric continuous data.

Univariable and multivariable logistic regression was undertaken to examine the association between ICU admission and type of first SE (VP vs. NVP), age at SE (categorised into six groups) and evidence of a concomitant infection and to determine if type of SE was an independent predictor of ICU admission. *P* values <0.05 were considered statistically significant.

All analyses were conducted using SAS v9.2 (SAS Institute Inc. Cary, North Carolina).

Results

Incidence of status epilepticus

Among 1,440,807 children born in the study period, 1,390 SE hospitalisations were identified (Appendix A). Of these, 867 (63.4%) were first SE hospitalisations over 10,974,684 person-years; an overall incidence of 7.9 per 100,000 person-years (95%CI 7.5-8.5) or 1 first SE for every 12,659 children. The highest incidence was in children aged <2 years at 14.7 per 100,000 person-years (Figure 1A). Among infants, the peak was in 12-17-month-olds at 19.2 per 100,000 person-years, then progressively declined with increasing age (Figure 1B). The overall SE incidence for Indigenous children was double that of non-Indigenous children (16.5 per 100,000 person-years (95%CI 13.4-20.4) versus 7.5 per 100,000 person-years (95%CI 7.0-8.1)) with rates consistently higher across all ages in children under 12 years (Figure 1A).

Vaccine-proximate status epilepticus

There were 31 VP-SE (3.6%) out of 867 first SE cases; 17 (54.8%) were following measles-mumps-rubella (MMR) vaccine, 7 (22.6%) following DTPa containing vaccines, 5 (16.1%) following monovalent varicella vaccine and two (6.5%) following concomitant Hepatitis B and oral polio vaccination.

Of the 17 VP-SE following MMR vaccine, 16 were following dose-1 and one following dose 2. The timing of first SE hospitalisations relative to dose-1 MMR vaccine is shown in Appendix C. Fifteen of the 16 cases received Haemophilus influenzae type b and meningococcal C conjugate vaccine (HiB-MenC) concomitantly.

In the cohort, 1,331,303 children were vaccinated with dose-1 MMR between the ages of 11 and 23 months, equating to 1.2 SE per 100,000 first doses of MMR given. The incidence rate of VP-SE following dose-1 MMR vaccine was 0.31 SE per 1,000 person-years 0-14 days following vaccination and 0.75 SE per 1,000 person-years for 7-10 days following vaccination.

There were no significant differences detected between VP-SE and NVP-SE groups in sociodemographic or perinatal factors (Table 1). The proportion of first VP-SE cases who were recorded as Indigenous was lower than in the NVP-SE group, though the difference was not significant (3.2% vs 10.4%, *P*=0.19). Comparing VP-SE to NVP-SE hospitalisations, VP-SE cases were younger (median [interquartile range] 1.0 [0.4-1.1] vs. 2.2 [1.2-4.1] years, *P*<0.0001), had longer lengths of hospital stay (4 [3-8] vs. 3 [2-6] days, *P*=0.005) and were more likely to be admitted to ICU (51.6% vs 34.4%, *P*=0.049; Table 2). There was a higher proportion of VP-SE cases with a coinfection diagnosis compared to NVP-SE but the difference was not statistically significant (35.8% vs. 19.9%, *P*=0.42). The case fatality rate was similar between the groups (3.2% VP-SE vs 1.7% NVP-SE, *P*=0.42), as was SE recurrence within 12 months of the initial SE (12.9% VP-SE vs. 16.9% NVP-SE, *P*=0.56).

A larger proportion of children with NVP-SE had a prior neurological condition (22.0% vs 6.5%, *P*=0.038). Half of all children had at least one seizure-related hospitalisation before their first SE, with no difference in proportion between the groups. When these children were excluded, VP-SE cases were still younger (1.0 [1.0-1.1] vs. 1.6 [0.9-3.3] years, *P*=0.008), had longer hospitalisation (5 [4-20] vs. 3 [2-6] days, *P*=0.006) and were more likely to require ICU admission (68.8% vs. 40.9%, *P*=0.027). In this subset, the proportion of VP-SE cases with a coinfection diagnosis was significantly higher than for the NVP-SE group (43.8% vs. 21.7%, *P*=0.038).

Both univariate and multivariate analyses found age and presence of infection as predictors of ICU admission but not SE type (VP vs. NVP; Table 3). While VP-SE was associated with ICU admission, the association was not statistically significant, especially after adjusting for other variables.

Vaccination uptake

The proportion of children who had a least one vaccination prior to their first SE was >90% in both groups and not significantly different (Table 2). The proportion who had vaccinations post-SE decreased in both groups, though it was higher in following VP-SE compared to NVP-SE (64.5% vs 56.0%, *P*=0.003). In the subset of children with no seizure-related hospitalisation prior to their first SE, both groups had similarly high vaccination coverage pre-SE. However, VP-SE cases had significantly lower vaccination coverage post-SE compared to NVP-SE cases in this subset (62.5% vs 85.0%, *P*=0.017). Vaccination coverage following NVP-SE in children with a seizure history was significantly lower than in children with no seizure history (76.3% (212/278) vs 85.0% (256/301), *P*=0.007). Vaccination coverage following VP-SE was similar in those with and without a seizure history (62.5% (10/16) vs 66.7% (10/15), *P*=0.81).

Discussion

To our knowledge, this is the first population-based study to compare VP-SE and NVP-SE outcomes internationally, and measure SE rates in Australian children. This study found that the overall incidence of SE in Australian children was low, at 1 SE for every 12,659 children, with incidence two-fold higher in Indigenous children compared to non-Indigenous children. VP-SE accounted for only 3.6% of first SE cases. When examining SE following MMR vaccination, the vaccine most frequently associated with SE, VP-SE rate was considerably lower than the VP-FS rate following MMR vaccination reported by Klein *et al*.[16] (0.75 SE vs 26.3 FS per 1,000 person years). There was an association between VP-SE and ICU admission, largely related to the younger age and higher coinfection rates in this group. There was no difference in case fatality rate or in SE recurrence within 12 months between VP and NVP-SE. Importantly, vaccination uptake decreased in both groups following first SE, highlighting the need to ensure safe and timely vaccinations in this population.

While reported SE incidence rates vary widely, our rate was lower than many other countries.[2-4,18-20] The incidence found in our study (7.9/100,000 person-years for 0-16 years) was closest to that reported from studies in California[18] (7.5/100,000 person-years for 0-4 years and 2.6/100,000 for 5-19 years from 1991-1998) and Taiwan[19] (10.2 SE/100,000 person-years for 0-4 years and 2.3/100,000 for 5-19 years from 2000-2011) which, like our study, relied on ICD-coded hospitalisation data. Other studies where medical record reviews were used for case identification reported higher incidence rates. While there was a likely higher case ascertainment, these studies were smaller in size which may explain the significant variability in reported rates. In the earliest epidemiological study of SE in children,[2] the incidence for children <14 years was reported as 24.1/100,000 person-years in Minnesota, USA. In North London[4] it was 17-23/100,000 person-years, in French-speaking Switzerland[20] it was 38.7/100,000 in children 0-4 years and 10.9/100,000 person-years in 5-14 years, whilst in Japan it was 42.0/100,000 person-years in children <15 years.[21] The age distribution of SE in our study was comparable to previous studies, all reporting the highest incidence in <2 year olds. However, we found incidence peaked in 12-17 month-olds, while three previous studies[2-4] reported peaks in <12 month-olds and one study in 12-23 month-olds.[21]

We identified a higher SE incidence in Indigenous children compared to non-Indigenous children aged <12 years that has not previously been reported. Variation in SE incidence by ethnicity has, however been previously identified, with incidence in non-Caucasian Americans being double that of Caucasian Americans.[3] Chin *et al*.[22] also found that socioeconomic deprivation and Asian ethnicity (defined as Indian, Pakistani, Bangladeshi and other Asian) independently increased the risk of both convulsive SE. .There was a higher proportion of Indigenous children in the more disadvantaged socioeconomic group compared to non-Indigenous children in our study (Appendix C) which could have also contributed to the higher SE incidence in Indigenous children. Our study

did not aim to examine the aetiology of the SE, so we could not determine if the difference in incidence was due to underlying risk factors or susceptibility to SE in Indigenous children.

To our knowledge, this is the first study to describe the frequency of VP-SE at a population level. We identified 31 first VP-SE cases over the 16-year study period in a cohort with 1.4 million births, using a strict biologically plausible definition for VP-SE. This rate was lower than the 21 SE events over 2 years reported from Germany's AEFI database in children <6 years,[6] although their definition of VP-SE was unclear and the study relied on spontaneous reporting by healthcare providers.

We found VP-SE most frequently followed MMR vaccine, which is consistent with the vaccine's known association with FS.[14] However, the proportion of SE following MMR vaccination was very low (1.2 SE per 100,000 first MMR doses). This proportion is 20 times lower than the proportion of FS following MMR reported in a comparable Australian cohort[23] (24 FS per 100,000 first MMR doses). Similarly, our incidence rate of VP-SE in children aged 11-23 months, 7-10 days following dose-1 MMR vaccine (0.75 SE per 1,000 person-years) was 35 times lower than the reported rate of VP-FS following the same vaccine (26.4 FS per 1,000 person-years) by Klein *et al*.[16] Our study did not aim to measure the association between SE and receipt of specific vaccines. However, compared to the rate of FS reported by Klein for the same risk window and age group, the rate of SE we report here is reassuringly low and consistent with the majority of VP-FS being brief seizures that do not progress to SE.

We believe this is also the first study to compare children with VP-SE to children with NVP-SE. We found the proportion of past seizures in both groups comparable with Shinnar *et al*.'s[24] study that found 41% of children had an unprovoked afebrile seizure before their first SE compared to 35% in both groups in our study. We saw a lower proportion of VP-SE children with an existing

neurological condition compared to the NVP-SE group (6.5% vs 22.0%), both lower than the 38% reported by Maytal *et al*,[25] though the neurological conditions included in Maytal's study were not specified. The lower proportion of children with an existing neurological condition in the VP-SE group is likely related to the younger age at presentation. The case fatality rate in both groups was comparable to 2.3-3.6% reported in previous paediatric cohorts.[3,4,19,25] Similarly, SE recurrence was not significantly different between the groups and the same as reported in Chin *et al*.'s study[4] of 16% over the same follow-up period.

We found a non-statistically significant association between ICU admission and VP-SE after adjustment for age and concomitant infection (aOR 1.45 (0.68-3.11)). The VP-SE group had a higher proportion with co-infection than the NVP-SE group and, together with their younger age, this explained much of the association between ICU admission and VP-SE. The younger age in VP-SE cases is likely due to childhood vaccinations being given mostly in children ≤18-months-old and especially receipt of dose-1 MMR vaccine at 12 months. However, as there were only 31 VP-SE cases in our study, a larger study is needed to examine whether there is an independent association between ICU admission and VP-SE.

Finally, we found uptake of vaccines scheduled following their first SE was lower than uptake pre-SE. While there are no studies examining vaccination coverage in children with seizures specifically, our finding adds to the limited evidence that children with neurological conditions are less likely to be fully immunised and are at increased risk of delayed vaccinations compared to children without such conditions.[26,27] Physicians have also reported a lower likelihood of vaccinating these children.[28] One survey study identified "concerns about how the vaccine would affect my child" as a major barrier to vaccination for parents of children with neurological conditions.[29] It is also possible that children with poorly controlled seizure disorders do not get vaccinated due to competing medical priorities. In children with no prior seizure history, the larger

reduction in vaccination coverage following first VP-SE compared to NVP-SE is likely a reflection of parental concern regarding vaccine safety as vaccination would be considered the child's trigger of their first ever seizure. Our study highlights a vaccination coverage gap in children who are likely at increased risk of complications from vaccine-preventable diseases such as influenza. Further studies to understand the barriers in maintaining high coverage for this cohort would be beneficial.

The study's strengths include the large denominator population assembled through linked datasets, including all hospitalisations to determine the incidence of SE. The ability to link individual vaccination encounters has allowed SE hospitalisations to be classified into VP and NVP for comparison and to determine the impact of SE on vaccination rates.

Limitations related to assembly of the cohort have been described in detail previously.[9] As our cohort is based on births, there may be some unobserved loss to follow-up from children moving interstate or overseas that may have affected the reported SE incidence and vaccination coverage post-SE but this is unlikely to differ between VP and NVP-SE. Our study is also limited by the use of ICD-coded data only to identify SE cases. While the ICD-code for SE is likely to be specific, hospitalisations where an alternate similar diagnosis, such as FS or seizure, was coded may have led to an under ascertainment of cases. To our knowledge, there are no ICD validation studies on SE to determine the degree of under ascertainment and this is also likely to vary geographically. We did not have access to medical records to confirm the SE diagnosis or to determine the underlying aetiology of SE. Similarly, there may also be an under ascertainment of concomitant infection diagnoses using ICD-coded data. We only included hospitalisations and not emergency department only SE presentations. However, unlike FS, as SE is a life-threatening condition with significant morbidity and mortality, children presenting with their first SE are most likely to be hospitalised for investigation and management.

In conclusion, parents and immunisation providers should be reassured that the risk of SE following vaccination is low. The lower uptake of vaccination following SE warrants increased attention by clinicians to provide subsequent safe and timely vaccinations to this vulnerable population.

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References

1. Glauser T, Shinnar S, Gloss D, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy currents.* 2016;16(1):48-61.
2. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. *Neurology.* 1998;50(3):735-741.
3. DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology.* 1996;46(4):1029-1035.
4. Chin RF, Neville BG, Peckham C, et al. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. *Lancet (London, England).* 2006;368(9531):222-229.
5. Miller D, Wadsworth J, Ross E. Severe neurological illness: further analyses of the British National Childhood Encephalopathy Study. *The Tokai journal of experimental and clinical medicine.* 1988;13 Suppl:145-155.
6. von Spiczak S, Helbig I, Drechsel-Baeuerle U, et al. A retrospective population-based study on seizures related to childhood vaccination. *Epilepsia.* 2011;52(8):1506-1512.
7. McIntosh AM, McMahon J, Dibbens LM, et al. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. *Lancet Neurology.* 2010;9(6):592-598.
8. Verbeek NE, van der Maas NA, Jansen FE, van Kempen MJ, Lindhout D, Brilstra EH. Prevalence of SCN1A-related dravet syndrome among children reported with seizures following vaccination: a population-based ten-year cohort study. *PloS one.* 2013;8(6):e65758.
9. Gidding H, McCallum L, Fathima P, et al. Probabilistic linkage of national immunisation and state-based health records for a cohort of 1.9 million births to evaluate Australia's childhood immunisation program *International Journal of Population Data Science.* 2017;2(1):1-13.
10. Moore HC, Guiver T, Woollacott A, de Klerk N, Gidding HF. Establishing a process for conducting cross-jurisdictional record linkage in Australia. *Aust N Z J Public Health.* 2016;40(2):159-164.
11. Australian Bureau of Statistics. Socio-Economic Indexes for Areas. 2018; https://www.abs.gov.au/websitedbs/censushome.nsf/home/seifa.
12. Christensen D, Davis G, Draper G, et al. Evidence for the use of an algorithm in resolving inconsistent and missing Indigenous status in administrative data collections. *Australian Journal of Social Issues.* 2014;49(4):423-443.
13. World Health Organisation. International Classification of Diseases (ICD) Information Sheet. 2018; https://www.who.int/classifications/icd/factsheet/en/.
14. Deng L, Gidding H, Macartney K, et al. Postvaccination Febrile Seizure Severity and Outcome. *Pediatrics.* 2019;143(5).
15. Hull BP, Deeks SL, McIntyre PB. The Australian Childhood Immunisation Register-A model for universal immunisation registers? *Vaccine.* 2009;27(37):5054-5060.
16. Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics.* 2010;126(1):e1-8.
17. National Centre for Immunisation Research and Surveillance. History of immunisation in Australia. 2020; http://ncirs.org.au/health-professionals/history-immunisation-australia. Accessed 1 Jul 2020.
18. Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive status epilepticus in California. *Neurology.* 2002;58(7):1070-1076.
19. Ong CT, Sheu SM, Tsai CF, Wong YS, Chen SC. Age-dependent sex difference of the incidence and mortality of status epilepticus: a twelve year nationwide population-based cohort study in Taiwan. *PLoS ONE [Electronic Resource].* 2015;10(3):e0122350.

20. Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). *Neurology.* 2000;55(5):693-697.
21. Nishiyama I, Ohtsuka Y, Tsuda T, et al. An epidemiological study of children with status epilepticus in Okayama, Japan: incidence, etiologies, and outcomes. *Epilepsy research.* 2011;96(1-2):89-95.
22. Chin RF, Neville BG, Peckham C, et al. Socioeconomic deprivation independent of ethnicity increases status epilepticus risk. *Epilepsia.* 2009;50(5):1022-1029.
23. Macartney KK, Gidding HF, Trinh L, et al. Febrile seizures following measles and varicella vaccines in young children in Australia. *Vaccine.* 2015;33(11):1412-1417.
24. Shinnar S, Pellock JM, Moshe SL, et al. In whom does status epilepticus occur: age-related differences in children. *Epilepsia.* 1997;38(8):907-914.
25. Maytal J, Shinnar S, Moshe SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. *Pediatrics.* 1989;83(3):323-331.
26. Tillmann BU, Tillmann HC, Heininger U, Lütschg J, Weber P. Acceptance and timeliness of standard vaccination in children with chronic neurological deficits in north-western Switzerland. *Eur J Pediatr.* 2005;164(5):320-325.
27. Pandolfi E, Carloni E, Marino MG, et al. Immunization coverage and timeliness of vaccination in Italian children with chronic diseases. *Vaccine.* 2012;30(34):5172-5178.
28. Campbell JR, Szilagyi PG, Rodewald LE, Winter NL, Humiston SG, Roghmann KJ. Intent to immunize among pediatric and family medicine residents. *Archives of pediatrics & adolescent medicine.* 1994;148(9):926-929.
29. Smith M, Peacock G, Uyeki TM, Moore C. Influenza vaccination in children with neurologic or neurodevelopmental disorders. *Vaccine.* 2015;33(20):2322-2327.

Figure 1. Incidence of first status epilepticus hospitalisation by age and Indigenous status, 1998-2013

Table 1: Sociodemographic characteristics and perinatal history of study participants by first status epilepticus type

Table 2: Seizure details and vaccination coverage by first status epilepticus type and history of prior seizures

Table 3: Association between intensive care unit admission and status epilepticus type (vaccine proximate versus non-vaccine proximate), concomitant infection and age at SE

Appendix A: Flowchart of study cohort

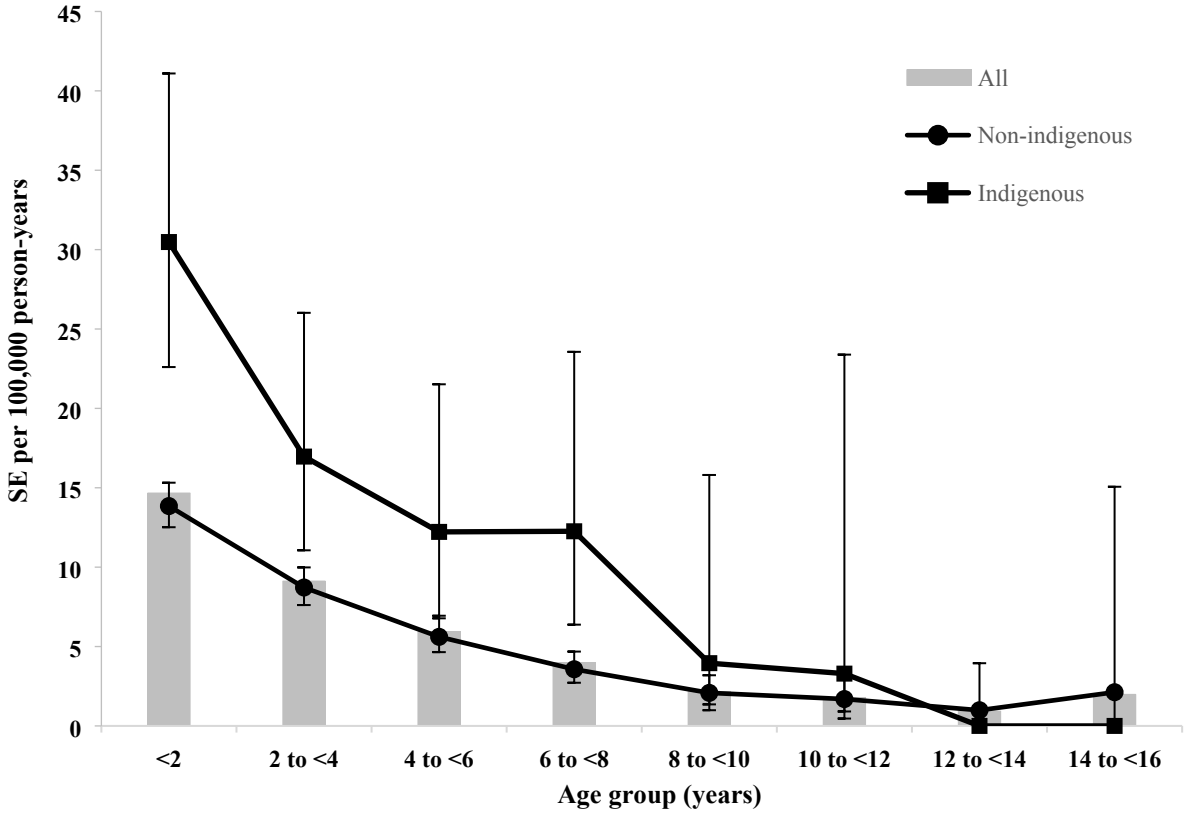
Appendix B: International Classification of Diseases (ICD) codes for conditions of interest

Appendix C: Rate of status epilepticus post measles-mumps-rubella (MMR) vaccination in 11 to <24-month-olds

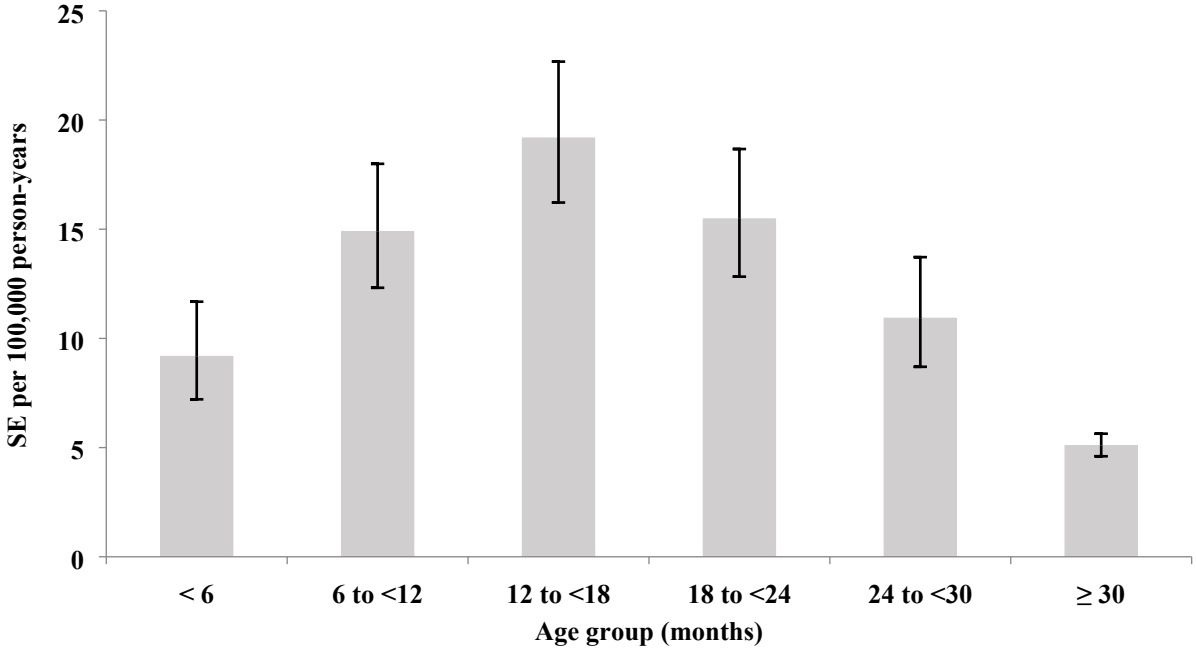
Appendix D: Distribution of Indigenous and non-Indigenous children by Socio-Economic Indexes for Areas (SEIFA)

Figure 1: Incidence of first status epilepticus hospitalisation by age and Indigenous status, 1998-2013

(A) Incidence of first status epilepticus by age in years and Indigenous status to 16 years old



(B) Incidence of first status epilepticus hospitalisation by age in months



Age range for WA cohort=0-16 years, NSW=0-13 years
SE=status epilepticus

Table 1: Sociodemographic characteristics and perinatal history of study participants by first status epilepticus type

	All cases n (%)	NVP-SE n (%)	VP-SE n (%)	P*
n	867	836 (96·4%)	31 (3·6%)	
Sex (male)	459 (50·9%)	443 (50·9%)	16 (51·6%)	0·95
Indigenous	88 (10·1%)	87 (10·4%)	1 (3·2%)	0·19
Birthweight (grams) mean, SD	3176·5, 762·0	3171·1, 761·5	3321·6, 772·1	0·34
≥4500	33 (3·8%)	33 (3·9%)	0 (0·0%)	
3500-4499	98 (11·3%)	93 (11·1%)	5 (16·1%)	
2500-3499	428 (49·4%)	413 (49·4%)	15 (48·4%)	
<2500	308 (35·5%)	297 (35·5%)	11 (35·5%)	
Gestational age (weeks)				
≥37	760 (87·7%)	733 (87·7%)	27 (87·1%)	0·49
32-36	98 (11·3%)	94 (11·2%)	4 (12·9%)	
≤31	36 (4·2%)	36 (4·3%)	0 (0·0%)	
Apgar score at 5 minutes				
7-10	812 (93·7%)	782 (93·5%)	30 (96·8%)	0·47
≤6	55 (6·3%)	54 (6·5%)	1 (3·2%)	
Maternal age (years) mean, SD	29·4, 6·1	29·4, 6·2	30·0, 5·1	0·64
SEIFA				
76-100 most advantaged	170 (19·6%)	164 (19·6%)	6 (19·4%)	0·50
26-75	395 (45·6%)	378 (45·2%)	17 (54·8%)	
0-25 least advantaged	272 (31·4%)	265 (31·7%)	7 (22·6%)	
Unknown	30 (3·5%)	29 (3·5%)	1 (3·2%)	

NVP-SE=non-vaccine proximate status epilepticus, SD=standard deviation, SEIFA=Socio-Economic Indexes for Areas with lowest centiles being the most disadvantaged, VP-SE=vaccine proximate status epilepticus
*Chi-square test for categorical data, independent t-test for parametric continuous data (birthweight and maternal age) and Mann-Whitney U test for non-parametric continuous data comparing VP-SE and NVP-SE group

Table 2: Seizure details and vaccination coverage by first status epilepticus type and history of prior seizures

		All first SE cases			First SE cases with no history of seizures prior to first SE		
	All	**NVP-SE**	**VP-SE**	**P***	**NVP-SE**	**VP-SE**	**P***
n	867	836	31		401	16	
Age at first SE (years) median [IQR]	2.1 [1·1-4·0]	2.2 [1·2-4·1]	1.0 [0·4-1·1]	<0·0001	1·6 [0·9-3·3]	1·0 [1·0-1·1]	0·008
Past admission history							
Any seizure	450 (51·9%)	435 (52·0%)	15 (48·4%)	0·69	0 (0·0%)	0 (0.0%)	
Febrile seizure	80 (9·2%)	80 (9·6%)	0 (0·0%)				
Other seizure	306 (35·3%)	295 (35·3%)	11 (35·5%)				
Both	64 (7·4%)	60 (7·2%)	4 (12·9%)				
Neurological condition*	186 (21·5%)	184 (22·0%)	2 (6·5%)	0·038	37 (9·2%)	0 (0.0%)	0·20
Admission details							
LOS (days) median [IQR]	3 [2-6]	3 [2-6]	4 [3-8]	0·005	3 [2-6]	5 [4-20]	0·006
ICU	304 (35·1%)	288 (34·4%)	16 (51·6%)	0·049	164 (40·9%)	11 (68·8%)	0·027
Death	15 (1·7%)	14 (1·7%)	1 (3·2%)	0·52	8 (2·0%)	1 (6·3%)	0·25
Infection	174 (20·1%)	166 (19·9%)	8 (35·8%)	0·42	87 (21·7%)	7 (43·8%)	0·038
SE recurrence in subsequent 12 months	145 (16·7%)	141 (16·9%)	4 (12·9%)	0·56	48 (12·0%)	1 (6·3%)	0·49
Vaccination coverage							
Any vaccine pre-SE	790/845 (93·5%)	762/814 (93·6%)	28/31 (90·3%)	0·47	351/379 (92·6%)	15/16 (93 ·8%)	0·86
Any vaccine post-SE	488/610 (56·3%)	468/579 (56·0%)	20/31 (64·5%)	0·003	256/301 (85·0%)	10/16 (62·5%)	0·017

ICU=intensive care unit, IQR=interquartile range, LOS=length of stay, NVP-SE=non-vaccine proximate status epilepticus, SE=status epilepticus, VP-SE=vaccine proximate status epilepticus

*Chi-square for categorical data and Mann-Whitney U test for non-parametric continuous data

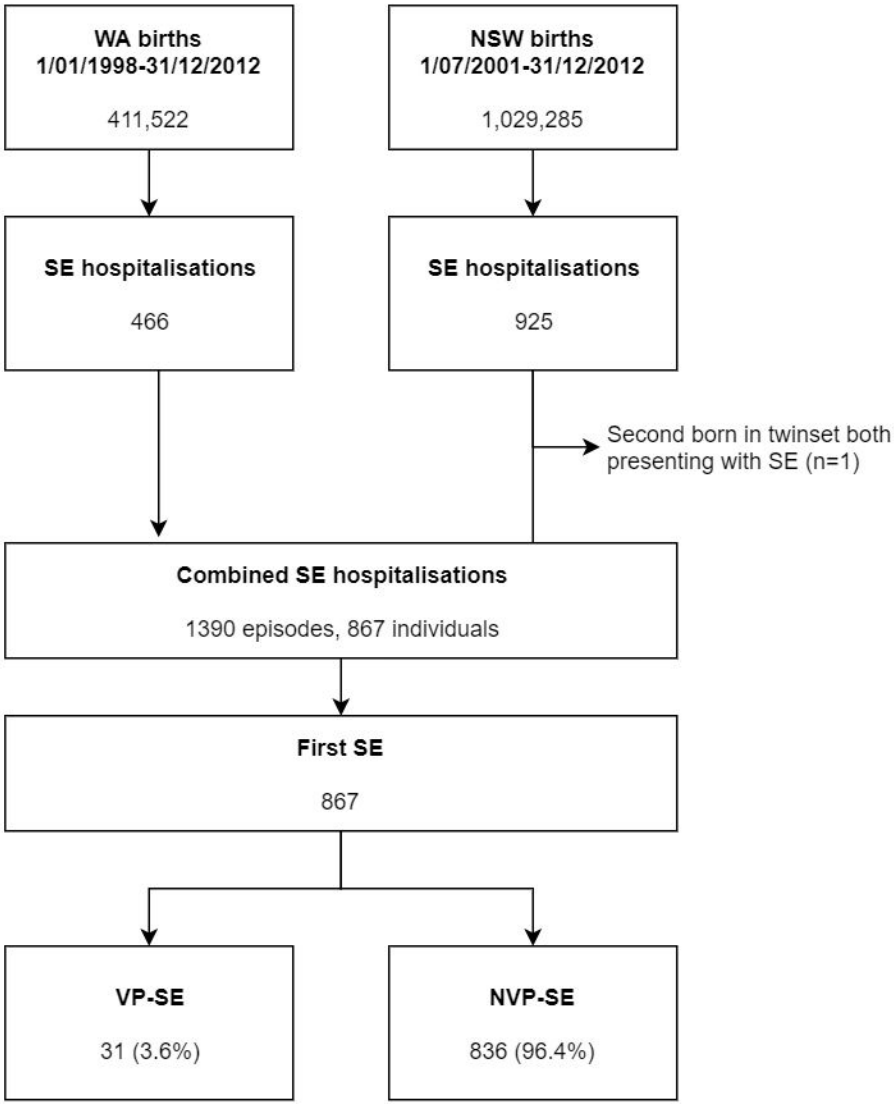
**Neurological conditions include cerebral palsy, perinatal intracranial haemorrhage, intracranial pathology and hydrocephalus

Table 3: Association between intensive care unit admission and status epilepticus type (vaccine proximate versus non-vaccine proximate), concomitant infection and age at SE

	Total SE cases	ICU admissions	Univariate OR (95% CI)	P	Multivariate aOR (95% CI)	P
VP-SE	31	16 (51·6%)	2·03 (0·99-4·16)	0.054	1·45 (0·68-3·11)	0·34
Infection	174	91 (52·3%)	2·47 (1·76-3·47)	<0.0001	2·41 (1·71-3·40)	<0·0001
Age						
0 - 5 months	66	38 (57·6%)	1	0.0003		0·0025
6 - 11 months	107	28 (26·2%)	0·26 (0·14-0·50)		0·27 (0·14-0·53)	
12 - 17 months	137	54 (39·4%)	0·48 (0·26-0·87)		0·46 (0·25-0·85)	
18 - 23 months	109	44 (40·4%)	0·50 (0·27-0·93)		0·51 (0·27-0·95)	
24 - 35 months	145	47 (32·4%)	0·35 (0·19-0·64)		0·38 (0·21-0·70)	
≥ 36 months	303	93 (30·7%)	0·33 (0·19-0·56)		0·36 (0·20-0·63)	

aOR=adjusted odds ratio, OR=odds ratio, SE=status epilepticus, VP-SE=vaccine proximate status epilepticus

Appendix A: Flowchart of study cohort

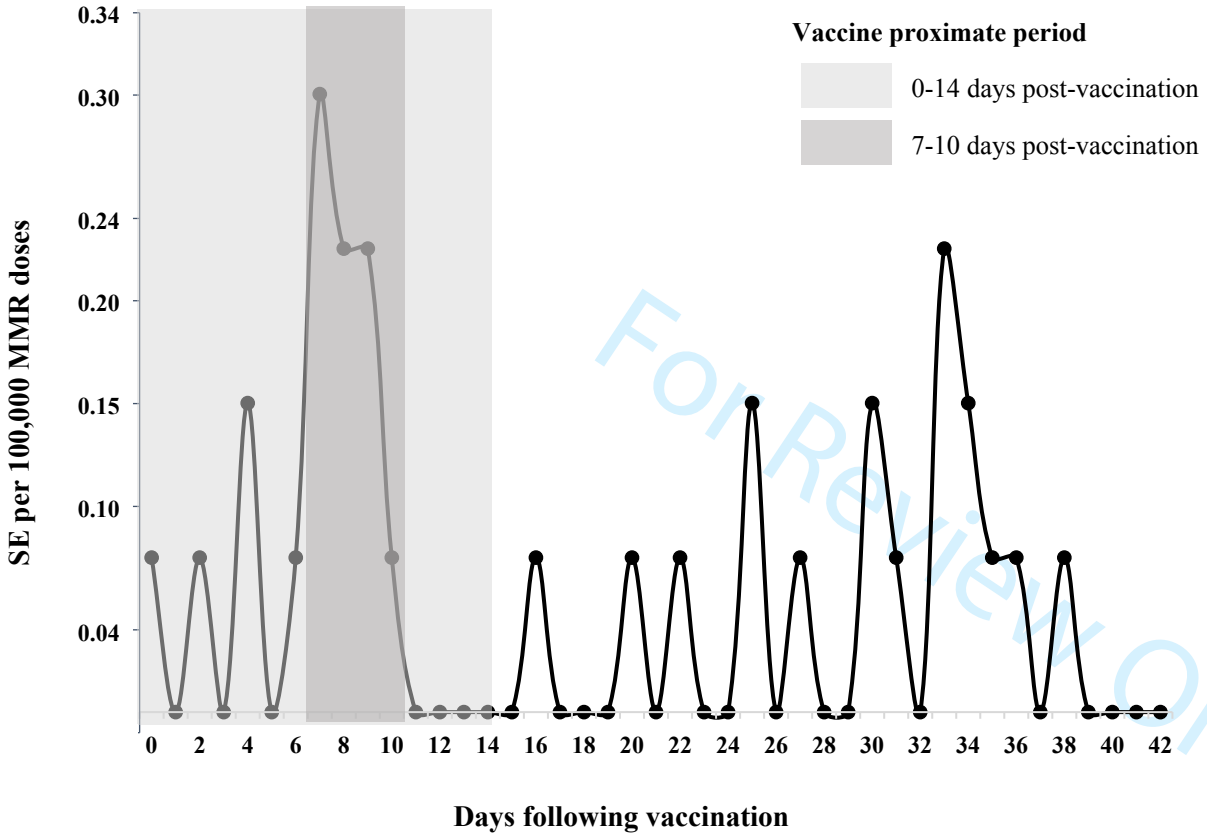


WA=Western Australia, NSW=New South Wales, SE=status epilepticus, VP=vaccine proximate, NVP=non-vaccine proximate

Appendix B: International Classification of Diseases (ICD) codes for conditions of interest

Condition	ICD-9-CM	ICD-10-AM
Infection	000-139 Infectious and parasitic diseases	A00-B99 Certain infectious and parasitic diseases
Status epilepticus	345.2 Petit mal 345.3 Grand mal	G41.X Status epilepticus
Seizures/epilepsy	345.X Epilepsy multiple causes 333.2 Myoclonus 780.39 Convulsion, not otherwise specified	G40.X Epilepsy F80.3 Landau-Kleffner syndrome R56.8 Convulsions, not otherwise specified
Febrile seizures	780.31 Febrile convulsion (simple) 780.32 Febrile convulsion (complex)	R56.0 Febrile convulsions
Cerebral palsy	343.X Infantile cerebral palsy	G80.X Cerebral palsy
Perinatal/neonatal intracranial pathology	767.0 Birth trauma – subdural haemorrhage, subarachnoid haemorrhage 772.1-2 Neonatal intraventricular haemorrhage	P10 Intracranial haemorrhage from birth P11 Other central nervous system injuries from birth P52 Intracranial haemorrhage of foetus and newborn
Hydrocephalus	742.3 Congenital hydrocephalus 741.0 Spina bifida with hydrocephalus 771.2 Hydrocephalus from toxoplasmosis 331.3 Communicating hydrocephalus (secondary to normal pressure hydrocephalus) 331.4 Obstructive hydrocephalus (acquired)	Q03 Congenital hydrocephalus Q04 Other congenital malformation of brain Q05.0-Q05.4 spina bifida with hydrocephalus Q07.0 Arnold Chiari syndrome G91 Hydrocephalus (non-acquired) G94.0/G94.1/G94.2 Hydrocephalus acquired
Other intracranial pathology	430-438 Cerebrovascular disease – subarachnoid haemorrhage, intracranial haemorrhage not otherwise specified, stenosis, occlusion, transient ischemic attack	I61-69 Cerebrovascular disease – subarachnoid haemorrhage, intracranial haemorrhage not otherwise specified, stenosis, occlusion, transient ischemic attack G93 Other disorders of brain G94.8 Other specified disorders of brain in diseases classified elsewhere G96 Other disorders of central nervous system

Appendix C: Rate of status epilepticus post measles-mumps-rubella (MMR) vaccination in 11 to <24-month-olds



SE=status epilepticus, MMR=measles, mumps, rubella

Appendix D: Distribution of Indigenous and non-Indigenous children by SEIFA

SEIFA	Indigenous n (%)	Non-indigenous n (%)
76-100 most advantaged	4 (4·5%)	166 (21·3%)
26-75	26 (29·5%)	369 (47·4%)
0-25 least advantaged	53 (60·2%)	219 (28·1%)
Unknown	5 (5·7%)	25 (3·2%)

SEIFA=Socio-Economic Indexes for Areas with lowest centile being the most disadvantaged

3.4 Clinical outcomes

3.4.1 Introduction

In the retrospective population-based record-linked cohort study in **Section 3.3**, first VP-SE cases accounted for 3.6% of all first SE in children aged <16 years, most frequently following the first dose of MMR vaccine. First VP-SE cases were found to be younger than NVP-SE cases, had longer hospitalisation and were more likely to require ICU admission, though ICU admission was more strongly associated with younger age at SE and presence of a coinfection than having a VP-SE. While the record-linked study was able to identify the proportion of first SE that was VP-SE at a population level and describe SE hospitalisations based on administrative hospital data, detailed clinical data and subsequent neurological outcomes were not available.

I therefore conducted a retrospective cohort study of children aged ≤24 months, the age group in which most of the vaccines on the Australian National Immunisation Program are given, to validate the record-linked SE hospitalisation data and to further elucidate clinical outcomes following VP-SE, including subsequent epilepsy diagnosis.

3.4.2 Methods

Study population

Children aged ≤24 months presenting with SE to one of five tertiary paediatric hospitals (The Royal Children's Hospital Melbourne; The Children's Hospital at Westmead, Sydney; John Hunter Hospital, Newcastle; Queensland Children's Hospital, Brisbane; and Perth Children's Hospital) between January 2013 and December 2017 were identified by searching medical records for primary and additional diagnoses of SE using International Classification of Diseases (ICD) Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision, Australian Modification (ICD-10-AM) diagnosis codes for SE (345.2 and 345.3 in ICD-9-CM and G41.X in ICD-10-AM).(188) Medical records of each SE hospitalisation were reviewed to confirm that the SE event satisfied the ILAE definition.(90) Children presenting with their first SE were included in the study, and those with no vaccination record on the

Australian Immunisation Register, a national population-based register of all vaccines administered,(189) were excluded.

Patient age, sex, medical history prior to their first SE presentation, clinical features of their first SE presentation, seizure recurrence and admissions in the subsequent 12 months, and genetic testing results were obtained from medical records. Receipt of vaccines was verified for all cases by using data from the Australian Immunisation Register.(189)

Case definition and outcome measures

First SE cases were categorised into VP-SE and NVP-SE based on previous studies on the timing of when fever peaks and when FSs occur following specific vaccines.(155) A VP-SE was defined as an SE episode that occurred 0–2 days after receipt of an inactivated vaccine, 5–14 days after a live attenuated vaccine, or 0–14 days after a combination of inactivated and live attenuated vaccines. An SE episode outside these periods was considered an NVP-SE.

The primary outcome measures were hospital length of stay, ICU admission, seizure recurrence within 24 hours of the initial SE and requirement for antiepileptic medication on discharge, which together define SE severity. The secondary outcome measures were clinical outcomes 12 months following the initial SE, specifically subsequent seizure admissions, epilepsy diagnosis and vaccination uptake.

Data analysis

Patient demographics, medical history, and primary and secondary outcome measures for VP-SE and NVP-SE groups were compared using the Chi-squared test for categorical data, independent t-tests for parametric continuous data and Mann-Whitney U test for non-parametric continuous data. VP-SE cases with previous seizures were compared with VP-SE cases without previous seizures. Statistical significance was defined as $P<0.05$. Statistical analyses were conducted using Stata 16 (StataCorp, College Station, TX).

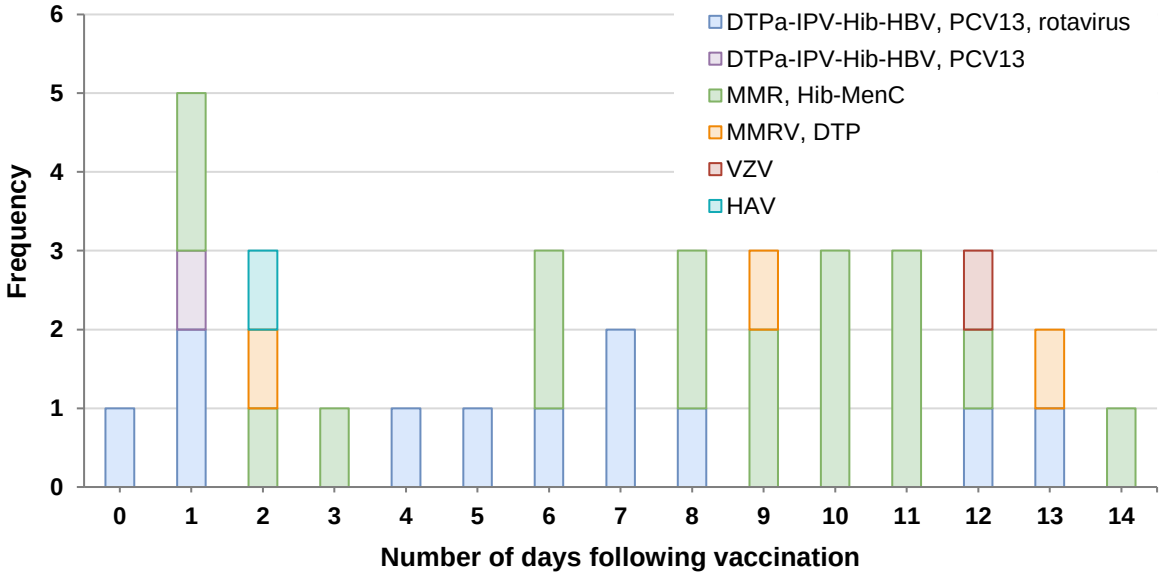
This study was approved by Sydney Children's Hospitals Network Human Research Ethics Committee (2019/ETH05430).

3.4.3 Results

There were 366 SE admissions in children aged ≤24 months across five Australian paediatric hospitals between January 2013 and December 2017. Of these, 99 were repeat SE admissions and 22 did not have an Australian Immunisation Register record, leaving 245 first SE admissions with immunisation records. Of the 245 first SE cases, 35 (14.3%) were VP-SE and 210 (85.7%) were NVP-SE.

Of the 35 VP-SE cases, 21 (60.0%) were following a measles-containing vaccine (18 dose-1 MMR in combination with Hib-MenC, and 3 MMRV), 12 (34.3%) were following DTPa-IPV-Hib-HBV (11 in combination with PCV13 and rotavirus vaccine, and 1 with PCV13 only), 1 was following hepatitis A vaccine, and 1 was following varicella-zoster vaccine. The timing of each VP-SE following vaccination is displayed in Figure 3.1.

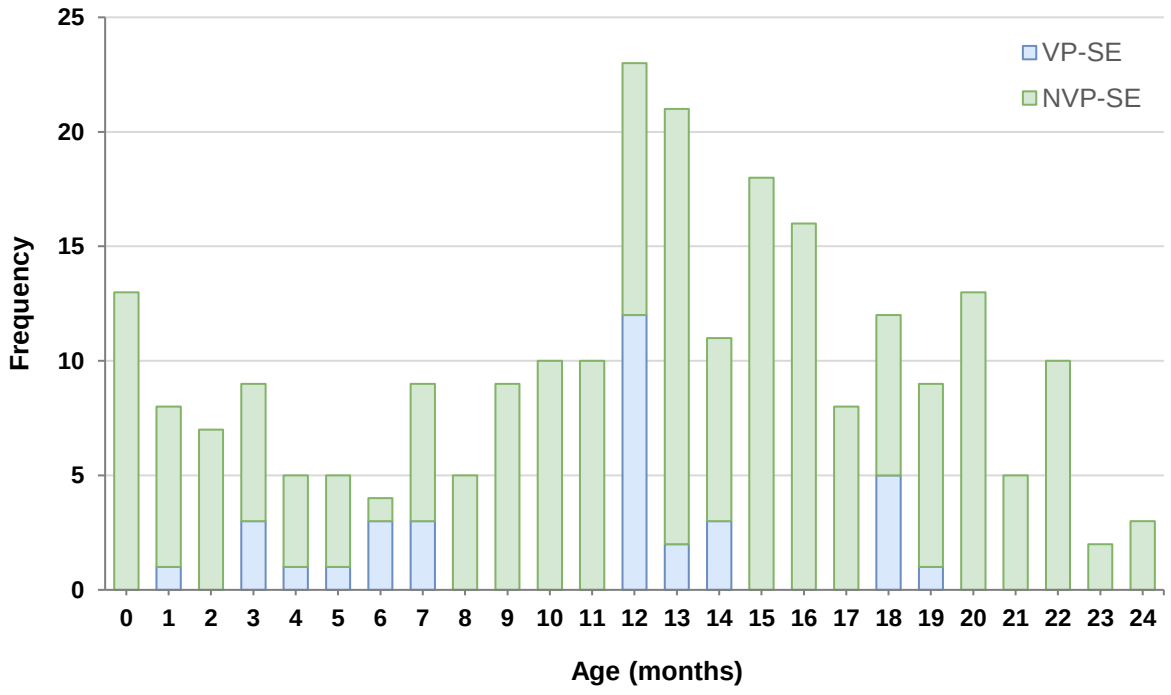
Figure 3.1 Timing of vaccine-proximate status epilepticus following vaccination



DTP=diphtheria-tetanus-pertussis, DTPa-IPV-Hib-HBV=diphtheria-tetanus-acellular pertussis, inactivated polio, *Haemophilus influenzae* type b and hepatitis B combination vaccine, HAV=hepatitis A vaccine, Hib-MenC=combined *H. influenzae* type b and meningococcal C conjugate vaccine, MMR=measles-mumps-rubella vaccine, MMRV=measles-mumps-rubella-varicella vaccine, PCV13=13-valent pneumococcal conjugate vaccine, VZV=varicella-zoster vaccine

Comparing children with first VP-SE to those with NVP-SE, there was no difference in their age at first SE, with the highest frequency in children aged 12–13 months in both groups (Figure 3.2). There was also no difference in the proportion of children with previous seizures or an underlying neurological condition (Table 3.1). Both groups had a similar distribution of seizure features, proportion of febrile SE and infections isolated. In terms of seizure severity, there was no difference between children with VP-SE and NVP-SE in their length of hospital stay, proportion requiring ICU admission, seizure recurrence within 24 hours of the initial SE or requirement for antiepileptic medications on discharge. Deaths following SE were low in both groups (2 following VP-SE and 1 following NVP-SE), but the difference in proportion was significant (5.7% for VP-SE vs 0.5% for NVP-SE, *P*=0.01). At 12 months following the initial SE, there was no difference between groups in the proportion of cases with epilepsy diagnosis, recurrent SE or other seizure admission. There were 2 subsequent deaths following VP-SE and 3 deaths following NVP-SE groups during this follow-up period (5.7% for VP-SE vs 1.4% for NVP-SE, *P*=0.03).

Figure 3.2 First status epilepticus cases by age and type (vaccine-proximate vs non-vaccine-proximate)



NVP-SE=non-vaccine-proximate status epilepticus, VP-SE=vaccine-proximate status epilepticus

Amongst the 35 children with VP-SE, 12 (34.3%) had a seizure prior to their first SE (Table 3.2). When comparing VP-SE cases with a previous seizure to VP-SE cases without, those without a

history of seizures had longer lengths of stay (median [interquartile range] 4 [2–8] vs 1.5 [1.5–3] days, *P*=0.02) with a larger proportion requiring ICU admission (73.9% vs 41.7%, *P*=0.06). However, VP-SE cases with previous seizures were more likely to be diagnosed with epilepsy (66.7% vs 30.4%, *P*=0.04), and have further seizure admissions (58.3% vs 21.7%, *P*=0.03) and further ICU admissions (41.7% vs 0.0%, *P*=0.001) in the follow-up period. Five VP-SE cases had a pathogenic variant identified on genetic testing (Table 3.1): three *SCN1A* variants (Dravet syndrome), one 22q11 deletion (DiGeorge syndrome) and one PTPN11 variant (Noonan syndrome). There was no difference in the proportion with genetic epilepsy between children with VP-SE with and without previous seizures (Table 3.2) or between children with VP-SE and those with NVP-SE (Table 3.1).

Table 3.1 Clinical history and seizure details of first status epilepticus (vaccine-proximate vs non-vaccine-proximate)

Details	**Total SE** ***n* (%)**	**NVP-SE** ***n* (%)**	**VP-SE** ***n* (%)**	***P***
N	245	210	35	
Male	120 (49.0%)	97 (46.2%)	23 (65.7%)	0.03
Age, months; median [IQR]	13.5 [8.8–17.3]	13.5 [8.8–17.3]	12.5 [6.4–14.1]	0.13
Medical history				
Any previous seizures	73 (29.8%)	61 (29.0%)	12 (34.3%)	0.53
Febrile	49 (20.0%)	41 (19.5%)	8 (22.9%)	0.65
Afebrile	43 (17.6%)	37 (17.6%)	6 (17.1%)	0.94
Neurological condition	52 (21.2%)	44 (21.0%)	8 (22.9%)	0.80
First SE details				
Febrile	130 (53.1%)	115 (54.8%)	15 (42.9%)	0.19
Features				
Generalised tonic-clonic	190 (77.6%)	164 (78.1%)	26 (74.3%)	
Myoclonic	6 (2.4%)	5 (2.4%)	1 (2.9%)	
Absence	10 (4.1%)	6 (2.9%)	4 (11.4%)	
Atonic	2 (0.8%)	2 (1.0%)	0 (0.0%)	
Hemiclonic	3 (0.8%)	2 (1.0%)	1 (2.9%)	
Focal	56 (22.9%)	42 (20.0%)	14 (40.0%)	
Spasms	1 (0.4%)	1 (0.5%)	0 (0.0%)	
Tonic	13 (5.3%)	10 (4.8%)	3 (8.6%)	
Seizure recurrence within 24 h	74 (30.2%)	63 (30.0%)	11 (31.4%)	0.73

Details	Total SE *n* (%)	NVP-SE *n* (%)	VP-SE *n* (%)	*P*
Admission details				
LOS days, median [IQR]	3 [2–7]	3 [2–8]	3 [2–6]	0.50
ICU admission	167 (68.2%)	145 (69.0%)	22 (62.9%)	0.42
Death	3 (1.2%)	1 (0.5%)	2 (5.7%)	0.01
AED on discharge	165 (67.3%)	139 (66.2%)	26 (74.3%)	0.34
Benzodiazepines only	55 (22.4%)	44 (21.0%)	11 (31.4%)	
Single regular AED	64 (26.1%)	55 (26.2%)	9 (25.7%)	
Multiple regular AED	46 (18.8%)	40 (19.0%)	6 (17.1%)	
Investigation details				
Infection (*n* positive/*n* done)	108/223 (48.4%)	91/193 (47.2%)	17/30 (56.7%)	0.33
Blood culture	19/213 (8.9%)	17/185 (9.2%)	2/28 (7.1%)	
Urine culture	7/153 (4.6%)	4/138 (2.9%)	3/15 (20.0%)	
NPA	75/152 (49.3%)	62/131 (47.3%)	13/21 (61.9%)	
LP	21/125 (16.8%)	19/111 (17.1%)	2/14 (14.3%)	
Neurological investigations (*n* abnormal/*n* done)	106/203 (52.2%)	90/172 (52.3%)	16/31 (56.7%)	0.94
EEG	65/136 (47.8%)	57/116 (49.1%)	8/20 (40.0%)	
CT	36/127 (28.3%)	32/109 (29.4%)	4/18 (22.2%)	
MRI	67/98 (68.4%)	55/80 (68.8%)	12/18 (66.7%)	
Genetic (*n* abnormal/*n* done)	34/51 (66.7%)	29/41 (70.7%)	5/10 (50.0%)	0.21
SCN1A	16	13	3	
SCN2A/*SCN8A*	1	1	0	
Other	17	15	2	
VOUS/no abnormality	17	12	5	
12-month follow-up				
Epilepsy diagnosis	84 (34.3%)	69 (32.9%)	15 (42.9%)	0.25
Dravet	16 (6.5%)	14 (6.7%)	2 (5.7%)	0.83
Subsequent seizure admissions	86 (35.1%)	74 (35.2%)	12 (34.3%)	0.88
SE	15 (6.1%)	12 (5.7%)	3 (8.6%)	0.51
ICU admissions	26 (10.6%)	21 (10.0%)	5 (14.3%)	0.46
Subsequent vaccination	224 (91.4%)	193 (91.9%)	31 (88.6%)	0.39
Death	5 (2.0%)	3 (1.4%)	2 (5.7%)	0.03

AED=antiepileptic drug, CT=computed tomography, EEG=electroencephalogram, ICU=intensive care unit, IQR=interquartile range, LOS=length of stay, LP=lumbar puncture, MRI= magnetic resonance imaging,

NPA=nasopharyngeal aspirate, NVP-SE=non-vaccine-proximate status epilepticus, SE=status epilepticus, VOUS=variant of unknown significance, VP-SE=vaccine-proximate status epilepticus

Table 3.2 Clinical history and seizure details of first vaccine-proximate status epilepticus (with vs without previous seizure)

Details	No previous seizure	Previous seizure	*P*
N	23	12	
Male	17 (73.9%)	6 (50.0%)	0.16
Age, months; median [IQR]	12.3 [5.8–12.9]	12.2 [12.4–16.7]	0.05
First SE details			
Febrile	12 (52.2%)	3 (25.0%)	0.12
Seizure recurrence within 24 h	9 (39.1%)	2 (16.7%)	0.22
Admission details			
LOS days, median [IQR]	4 [2–8]	1.5 [1.5–3]	0.02
ICU admission	17 (73.9%)	5 (41.7%)	0.06
Death	1 (4.3%)	1 (8.3%)	0.63
AED on discharge	16 (69.6%)	10 (83.3%)	0.38
Investigation details			
Infection isolated	12 (52.2%)	5 (41.7%)	0.56
Genetic (*n* abnormal/*n* done)	5 (21.7%)	5 (41.7%)	0.22
SCN1A/*SCN2A*	1 (4.3%)	2 (16.7%)	0.77
Other	1 (4.3%)	1 (8.3%)	
VOUS/no abnormality	3 (13.0%)	2 (16.7%)	
12-month follow-up			
Epilepsy diagnosis	7 (30.4%)	8 (66.7%)	0.04
SCN1A variant	1 (4.3%)	2 (16.7%)	0.22
Subsequent seizure admissions	5 (21.7%)	7 (58.3%)	0.03
ICU admissions	0 (0.0%)	5 (41.7%)	0.001
Subsequent vaccination	21 (91.3%)	10 (83.3%)	0.48

AED=antiepileptic drug, ICU=intensive care unit, IQR=interquartile range, LOS=length of stay, SE=status epilepticus, VOUS=variant of unknown significance

There were two deaths following VP-SE, both with an underlying genetic epilepsy. The first case was a 12-month-old with hypoxic ischaemic encephalopathy following prolonged SE on the day of MMR and Hib-MenC vaccination, who had a post-mortem diagnosis of a pathogenic *SCN1A* variant. This was the same case described in the case report in **Section 3.2**. The second case was a 12-month-old with known epileptic encephalopathy and Noonan's syndrome who presented with SE 12 days following MMR and Hib-MenC vaccination, and died 12 days later.

Of the surviving 33 VP-SE cases, 31 (93.9%) had another vaccination. Vaccination uptake was similar in VP-SE cases with and without previous seizures. Two cases (6.5%) had a seizure recurrence on subsequent vaccination. One case was a child with Dravet syndrome who had seizures following two other vaccination encounters (the first following 12-month Hib-MenC and MMR vaccination, and the second following influenza vaccination). The other case was a child with idiopathic generalised epilepsy who had a seizure following MMRV and chose not to have further vaccinations.

3.4.4 Discussion

This study provides a comprehensive comparison of clinical severity and outcomes between VP-SE and NVP-SE in children aged ≤24 months, the age at which children receive the majority of their childhood vaccinations.

By examining a narrower age group in whom vaccine exposure is concentrated, I identified a higher proportion of first VP-SE compared to the proportion of first VP-SE in children aged ≤16 years reported in the population-based data linkage study. As there are five vaccination schedule points in the first 24 months of life and only an additional three vaccination schedules points from 2–16 years old, the exposure period as a proportion of the total time is higher in this cohort and is likely to account for the increased proportion of VP-SE compared to the data linkage study. Consistent with previous studies on SE in this age group (children aged ≤24 months), approximately half of all SE were febrile SE, and approximately half of both VP-SE and NVP-SE groups had a laboratory-confirmed infection.(94, 96) There was no difference in age at the time of first VP-SE or NVP-SE in this cohort. This suggests that the higher proportion of VP-SE in the younger age group previously identified in the population-based data linkage study with a wider age group (<16 years) was a function of the age at which vaccines are given rather than a risk factor for VP-SE. VP-SE most commonly followed dose-1 of MMR vaccine, matching the data linkage study findings and the known risk of FS following MMR vaccination.(154, 155) Reassuringly, hospital length of stay, the proportion requiring ICU admission, seizure recurrence within the first 24 hours of the initial SE and requirement for antiepileptic medications on discharge were similar between the groups. While this is in contrast to the data linkage study, which found VP-SE cases had longer hospitalisations and higher ICU admission rates, the difference is likely associated with the age range of children in each study cohort.

Through detailed medical record review, this retrospective cohort study was able to examine clinical outcomes in the 12 months following a child's initial SE, which was not possible using record-linked administrative hospitalisation data. We found no difference between VP-SE and NVP-SE groups in the proportion of children who had further seizure hospitalisations or ICU admissions, or who develop epilepsy. I was also able to compare outcomes of VP-SE cases with and without a history of seizures prior to their first SE. Children with seizures prior to their first VP-SE were more likely to have further

seizure hospitalisations and ICU admissions, and be diagnosed with epilepsy, compared to children with no seizures prior to their first VP-SE. This suggests that the risk of ongoing seizures is a result of the child's underlying epilepsy diagnosis rather than the VP-SE itself.

In this small cohort, 2 (6.5%) out of 31 VP-SE cases had VP-SE recurrence. This is comparable to the large population-based study in the Netherlands(180) that found 4.2% of 1,269 children who had a vaccine-proximate seizure in the first 2 years of life had another seizure following revaccination, though the study did not differentiate seizure type. In contrast to the data linkage study, there was a high vaccination uptake in the 12 months following SE. This is likely due to the shorter follow-up period in this study compared to the data linkage study, which limited both the number of vaccinations due and time for seizure recurrence to occur and possibly impact vaccination decisions.

The strength in this study lies in the ability to collect detailed clinical data, seizure history and seizure progression through medical record review, which was not possible using administrative hospitalisation data only. The study, however, is limited by its small sample size with recruitment limited to tertiary paediatric hospitals. While it may not reflect all SE presentations in this age group, it is likely to capture the more severe cases and may be more representative of the whole of Australia than the data linkage study, which relied on a birth cohort of children from two Australian states only.

3.4.5 Section summary and conclusion

This retrospective cohort study confirmed that VP-SE most commonly follows dose-1 of MMR vaccine. Reassuringly, clinical severity was no different between VP-SE and NVP-SE in children aged ≤24 months. In children with VP-SE, seizure progression and subsequent epilepsy diagnosis was associated with having seizures prior to their first VP-SE and repeat seizure on revaccination was rare. This is reassuring data for immunisation providers who are counselling parents with children who have experienced a VP-SE. Children with a history of previous or ongoing seizures should have close neurological follow-up, as a proportion will develop epilepsy and their subsequent seizure control may impact their future vaccination uptake and outcomes.

3.5 Key findings

In this chapter, I presented the first ever studies to my knowledge on the relative proportions, clinical severity and outcomes of VP-SE compared to NVP-SE in children <16 years of age, through a case report, a retrospective population-based record-linked study and a retrospective cohort study on VP-SE. The key findings from these studies were as follows:

1. VP-SE is rare, accounting for 3.6% of all first SE in children aged <16 years and 14.3% in children aged ≤24 months.
2. VP-SE most commonly followed dose-1 of MMR, with an incidence rate of 0.75 SE per 1,000 person-years in the 7–10 days following vaccination, a rate 35 times lower than that of VP-FS following dose-1 of MMR for the same risk window.
3. After accounting for age, there was no difference in clinical severity between VP-SE and NVP-SE.
4. Children who had seizures prior to their VP-SE were more likely to have ongoing seizures and subsequent epilepsy diagnosis.
5. VP-SE, when associated with an underlying genetic epilepsy, can result in significant morbidity and occasionally mortality.
6. Children with underlying genetic predisposition to epilepsy can be safely vaccinated with prophylactic antiepileptic medication and benzodiazepine.
7. Vaccination uptake following initial SE of any type (both VP and NVP) was high in the first 12 months but decreased with time.

From these findings, I draw the following recommendations:

1. Parents and providers can be reassured that VP-SE is rare.
2. Children who have had an SE episode, in particular VP-SE, should be reviewed by a neurologist and immunisation specialist to investigate for an underlying genetic epilepsy, and to provide a safe and timely vaccination plan to maintain high vaccination coverage in this population.

Chapter 3 builds on findings from **Chapter 2** that vaccine-proximate seizures are rare. Reassuringly, the more severe form of seizure, SE, is rarer than FS, and its clinical outcome is dependent on the presence of underlying genetic epilepsy. What remained unclear in both VP-FS and VP-SE cases outlined in **Chapters 2** and **3** is the risk of seizure recurrence on revaccination, factors associated with this risk of seizure recurrence, and ways to minimise the risk of seizure recurrence on

revaccination. **Chapter 4**, therefore, examines revaccination practices and outcomes to address this knowledge gap.

Chapter 4 Revaccination following vaccine-proximate seizures

4.1 Introduction

In **Chapters 2** and **3**, I described the clinical severity of and outcomes following VP-FS and VP-SE. I demonstrated that VP-FS and VP-SE were rare AEFIs in children, with clinical outcomes comparable to NVP-FS and NVP-SE, respectively. As with children with epilepsy or seizures from another cause, children with vaccine-proximate seizures (VPSs) are recommended to continue subsequent vaccinations, though little is known about the outcomes of revaccination in these children.

The only published population-based study on VPS recurrence in children found an overall risk of 4.2% in children who have experienced a previous VPS.(180) The study identified children with Dravet syndrome were at highest risk of VPS recurrence. However, it did not describe the vaccination management of these children or the clinical outcomes of the recurrent VPSs.

This chapter follows on from the exploration of clinical outcomes of the initial VPS in previous chapters, to explore the management and outcomes of revaccination in children following their initial VPS, addressing the final two aims of my thesis.

I sought to augment the existing population-based data on VPS recurrence with a more detailed clinical review of vaccination management and outcomes by conducting a retrospective cohort study on children with a history of VPS who presented to Specialist Immunisation Clinics in Australia for vaccination. Based on the knowledge of risk differences from previous chapters, I examined VPS recurrence risk and factors affecting this in two separate cohorts: children whose first seizure was a VPS and children with Dravet syndrome.

4.2 Methods

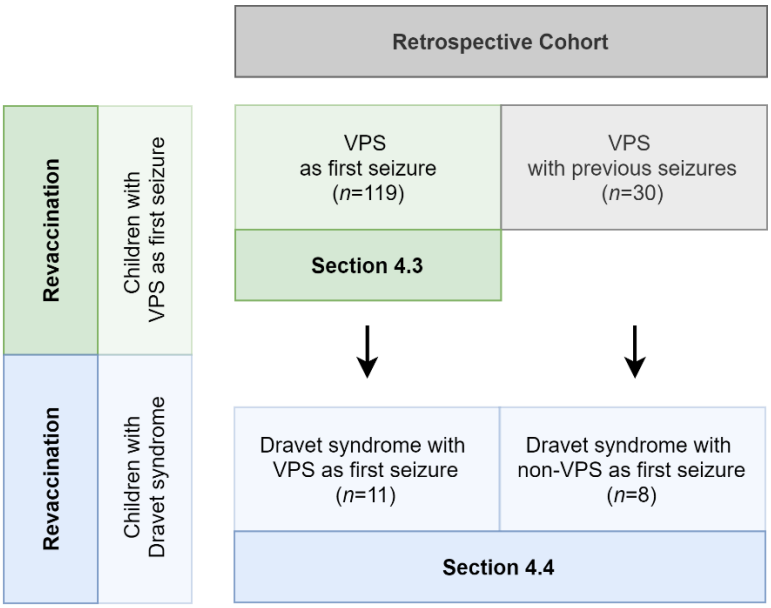
Specialist Immunisation Clinics at tertiary paediatric hospitals provide specialised medical assessment and management of children with AEFIs, and, where appropriate, arrange for vaccination of these children either in the clinic, in a day stay unit or as a hospital inpatient. Children with VPSs are often referred to these clinics for review prior to their next vaccination. I therefore reviewed 119 children with a history of VPS who presented to a Specialist Immunisation Clinic at one of four Australian tertiary paediatric hospitals (The Royal Children's Hospital Melbourne; The Children's Hospital at Westmead, Sydney; Women's and Children's Hospital, Adelaide; and Perth Children's Hospital) between January 2013 and December 2017 in a retrospective cohort study, to examine their revaccination management and outcomes.

The study protocol can be found in **Appendix 3**. I wrote the study protocol, sought ethical approval as the coordinating principal investigator, and sought site-specific approvals and research collaborative agreements for each participating site. **Sections 4.3** and **4.4** describe subgroups of this retrospective cohort study.

Section 4.3 examines children whose first seizure was a VPS and their vaccination outcomes on their first presentation at a Specialist Immunisation Clinic. The study is presented as a published manuscript (Paper 7). From Section 4.3, VPS recurrence was found to occur most frequently in children *SCN1A*-associated Dravet syndrome. **Section 4.4**, therefore, focuses on children diagnosed with Dravet syndrome who were reviewed in a Specialist Immunisation Clinic for vaccination, and describes each of their vaccination encounters and outcomes.

Included cases for both chapters and case overlap between the chapters are outlined in Figure 4.1.

Figure 4.1 Study cohorts for Sections 4.3 and 4.4



VPS=vaccine-proximate seizure

4.3 Revaccination outcomes of children with vaccine-proximate seizures (published manuscript)

Revaccination outcomes of children with vaccine proximate seizures.

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Revaccination outcomes of children with vaccine proximate seizures

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ABSTRACT

Background: Seizures, whether febrile or afebrile, occurring within 14 days following vaccination can be considered as vaccine proximate seizures (VPSs). While the attributable risk and clinical severity of first febrile VPS is well known, the risk and clinical outcomes of VPS recurrence is less well defined.
Methods: We conducted a retrospective review of revaccination management and outcomes in children who experienced a VPS as their first seizure seen in Australian Specialist Immunisation Clinics between 2013 and 2017. Vaccination outcomes were compared between children who had a VPS as their only seizure (VPS only) and children who had further non-vaccine proximate seizures following their initial VPS (VPS+) prior to review at the clinic.
Results: We identified 119 children with a VPS as their first seizure, of which 61 (51%) went on to have other seizures (VPS+). Children with VPS+ were more likely to present at a younger age (6.2 vs 12.5 months, $P = 0.03$), with afebrile seizures (42.6% vs 15.5%, $P = 0.002$) compared to VPS only children. VPS recurrence on revaccination was uncommon in both groups, but more common in VPS+ children (12.5% vs 2.4%, $P = 0.07$). Having an epilepsy diagnosis, specifically Dravet syndrome, was associated with VPS recurrence ($P < 0.001$). Of the four children with Dravet syndrome who had VPS recurrence, all had status epilepticus following revaccination.
Conclusion: In children who presented with a single VPS as their only seizure, VPS recurrence on revaccination was uncommon. Children who had multiple non-vaccine proximate seizures following their initial VPS (VPS+) were more likely to present with afebrile VPS, at a younger age and have a VPS recurrence with vaccination. In these children, particularly those aged < 12 months, assessment and investigation for diagnosis of Dravet syndrome should be considered and additional precautions for revaccination undertaken as they are at highest risk of VPS recurrence.

1. Introduction

Seizures, defined by the Brighton Collaboration as a witnessed sudden loss of consciousness with generalised, tonic, clonic, tonic-clonic or atonic motor manifestations [1], are a rare but known serious adverse event following immunisation (AEFI) [2]. A seizure occurring within 14 days of a vaccine can be considered a vaccine proximate seizure (VPS) [3,4], of which febrile seizures (FSs) are the most common form. There is a well-defined two-fold risk of a vaccine proximate FS 5–14 days following a first dose

Abbreviations: AEFI, adverse event following immunisation; AFS, afebrile seizure; DTaP-Hib-HepB-IPV, diphtheria-tetanus-acellular pertussis, *Haemophilus influenzae* type b, hepatitis B, and inactivated polio combination vaccine; FS, febrile seizure; Hib-MenC, *Haemophilus influenzae* type b and meningococcal C conjugate vaccine; MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; PCV13, 13-valent pneumococcal conjugate vaccine; SE, status epilepticus; SIC, Specialist Immunisation Clinic; VPS, vaccine proximate seizure.

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measles containing vaccine [5–8], and an association with previous whole cell pertussis vaccines [6] and influenza vaccines [9,10] with FSs 0–2 days following vaccination, though less is known about the risk of other seizure types following vaccination [2]. Vaccine proximate FSs have not been shown to be associated with an increased risk of FS recurrence [11] and children with epilepsy are not found to be at increased risk of medically attended seizure following immunisation [12]. However, the risk of recurrent seizures with further vaccination has not been well studied, with only one previous population-based Dutch study [13] examining the risk of both febrile and afebrile VPS following revaccination. The study identified a 4.2% risk of VPS recurrence in children under 2 years of age with a previous VPS, and those with Dravet syndrome were found to be at highest risk. The study, however, did not describe the management or clinical outcomes of the reported VPS recurrence. Furthermore, whole-cell pertussis vaccines were mostly used during the study's 10-year period and therefore may not be representative of VPS risk with current vaccine schedules in high income countries where predominantly acellular pertussis vaccines are used.

As having a VPS is not a contraindication to further vaccination [14], we conducted a retrospective review of vaccination outcomes for children whose first seizure was a VPS and who presented to Specialist Immunisation Clinics (SIC) in Australia for revaccination. We aimed to use this data to better inform parents and clinicians on the risk factors affecting VPS recurrence and to tailor revaccination management for these children to ensure safe and timely vaccination.

2. Methods

A five-year retrospective audit was conducted on all children aged < 18 years presenting to a SIC at one of four public tertiary paediatric hospitals, across four states in Australia between January 2013 and December 2017 with a history of VPS as their first seizure. SICs provide specialised medical assessment and management advice on AEFIs and where appropriate arrange for vaccination of these children either in the clinic, day stay unit or as a hospital inpatient. A VPS was defined as a seizure of any kind (febrile or afebrile) within 14 days of a vaccination encounter.

Potential VPS cases were identified by searching clinic databases at each hospital for the keywords seizure, convulsion, status epilepticus and epilepsy as the presenting problem or diagnosis and their medical records were reviewed. Cases were included if their first seizure fulfilled the Brighton Collaboration definition [1] and was within 14 days of a vaccination encounter recorded on the Australian Immunisation Register [15]. Medical records of included cases were used to obtain their demographics, VPS details, seizure history including epilepsy diagnoses, revaccination management and VPS recurrence on revaccination following review at the SIC. Revaccination management were classified as (1) vaccinated, where a vaccination was administered within 1 month of SIC review, or (2) deferred, where a vaccination was not administered within 1 month of SIC review with reasons for deferral detailed.

First VPS cases were further categorised into (1) VPS only, defined as children who had no further seizures following their initial VPS at the time of SIC review and (2) VPS+, defined as children who had further non-vaccine proximate seizures following their initial VPS at the time of SIC review. Initial and recurrent VPSs were categorised into febrile seizure (FS: seizure lasting < 30 min with a documented temperature of $\geq$ 38 °C, afebrile seizure (AFS: seizure lasting < 30 min with no documented temperature of $\geq$ 38 °C) and status epilepticus (SE: seizure lasting $\geq$ 30 min or multiple seizures with no return to normal level of consciousness for $\geq$ 30 min). The primary outcome measure was VPS recurrence on revaccination.

2.1. Statistical analysis

Demographics, clinical details of the initial VPS, revaccination management and outcomes following SIC review were compared between children with VPS only and children with VPS+. Clinical details of the initial VPS, subsequent seizure history from initial VPS to the time of SIC review, vaccination plan on review and subsequent immunisation coverage were also compared by revaccination outcome (with and without VPS recurrence). Chi-squared test was used for categorical data and Mann-Whitney *U* test for non-parametric continuous data. Statistical significance was defined as $P < 0.05$. Statistical analyses were conducted using Stata 16 (StataCorp LLC. College Station, TX).

This study was approved by Sydney Children's Hospital Network Human Research Ethics Committee (2019/ETH05430).

3. Results

We identified 158 children presenting to a SIC between 1 January 2013 and 31 December 2017 with a history of any seizure. Of these, 119 (75.3%) had a VPS as their first seizure and 39 were excluded, including 9 with epilepsy with no VPS and 30 who had a seizure prior to their documented VPS (Appendix A).

Of the 119 children with VPS as their first ever seizure, 58 (48.7%) had no further seizures (VPS only) and 61 (51.3%) had further seizures (VPS+) at the time of SIC review. In relation to their first VPS, children with VPS+ were younger compared to children with VPS only (median 6.2 [interquartile range IQR 4.2–12.3] vs 12.5 [IQR 6.5–14.4] months old, $P = 0.03$; Table 1) and were more likely to have an AFS (42.6% vs 15.5%, $P = 0.002$) compared to VPS only children.

Amongst the 58 children with VPS only, 30 (51.7%) were following a measles containing vaccine, 0–11 days (median 6.5 [IQR 1–9]) following vaccination, which included 1 (3.3%) following measles-mumps-rubella (MMR) alone, 25 (83.3%) following MMR with Haemophilus influenzae type b and meningococcal C conjugate (Hib-MenC) and 4 (13.3%) following measles-mumps-rubella-varicella (MMRV). In contrast, of the 61 children with VPS+, 42 (68.9%) were following the combination vaccine diphtheria-tetanus-acellular pertussis, *Haemophilus influenzae* type b, hepatitis B, and inactivated polio (DTaP-Hib-HepB-IPV), 0–2 days (median 1 [IQR 0–2]) post vaccination, which included 1 (2.4%) given alone, 6 (14.3%) in combination with 13-valent pneumococcal conjugate vaccine (PCV13) only and 35 (83.3%) with PCV13 and rotavirus vaccine.

The time from the initial VPS to the time of clinic review for revaccination were similar between the groups (5.9 [IQR 2.9–10.1] months for VPS only vs. 6.3 [IQR 3.1–21.5] months for VPS +, $P = 0.78$; Table 2). At the time of clinic review, 45.9% of children with VPS+ had been diagnosed with epilepsy. Of 119 children, 83 (69.7%) children were vaccinated following clinic review with a similar proportion vaccinated in VPS only and VPS+ groups (74.1% vs 65.6%, $P = 0.31$). Children with VPS only were more likely to be vaccinated in clinic (83.7% vs 60.0%, $P = 0.02$) and fewer received pre-medication with their vaccinations, including paracetamol (14.0% vs 37.5%, $P = 0.03$).

Of the 83 children who proceeded with further vaccination following clinic review, 6 (7.2%) had a VPS recurrence. Children in the VPS only group were less likely to have VPS recurrence on revaccination. There was one child in the VPS only group compared to five children in the VPS+ group who had another VPS on revaccination, though the difference between the two groups was not statistically significant (2.4% vs. 12.5%, $P = 0.07$). For the child in the VPS only

Table 1
Clinical history and seizure details of children presenting to Specialist Immunisation Clinics (SICs) whose first seizure was a vaccine-proximate seizure (VPS); a comparison of children in whom there were no further seizures (VPS only) with children who have had subsequent seizures following their initial VPS (VPS+).

Details	VPS only	VPS+	*P*
N (n = 119)	58 (48.7%)	61 (51.3%)	
Sex (male)	32 (55.2%)	28 (45.9%)	0.31
First VPS			
Age, median months [IQR]	12.5 [6.5–14.4]	6.2 [4.2–12.3]	0.03
0–5 months	10 (17.2%)	27 (44.3%)	
6–11 months	11 (19.0%)	16 (26.3%)	
12–17 months	26 (44.8%)	10 (16.4%)	
≥18 months	11 (19.0%)	8 (13.1%)	
Vaccine involved			
Inactivated only	16 (27.6%)	9 (14.8%)	0.22
Live only*	4 (6.9%)	4 (6.6%)	
Combination	38 (65.5%)	48 (78.7%)	
Seizure type			
Afebrile seizure	9 (15.5%)	26 (42.6%)	0.003
Febrile seizure	40 (69.0%)	25 (40.9%)	
Status epilepticus	9 (15.5%)	10 (16.4%)	
Seizure history at the time of first SIC review			
Seizure frequency	N/A		
Multiple/week		17 (27.9%)	
Multiple/month		11 (18.0%)	
<1/month		33 (54.1%)	
Any non-vaccine proximate status epilepticus	N/A	15 (24.8%)	
Any ICU admissions	N/A	9 (14.8%)	
Regular antiseizure medicine use	1 (1.7%)	24 (39.3%)	
Epilepsy diagnosis	N/A	28 (45.9%)	

N/A = not applicable, VPS = vaccine proximate seizure as first seizure, VPS+= vaccine proximate seizure as first seizure with further non-vaccine proximate seizures, IQR = interquartile range, ICU = intensive care unit, SIC = Specialist Immunisation Clinic.
* Live vaccines only in both VPS only and VPS+ groups included 2 MMR and 2 MMRV vaccination encounters.

Table 2
Revaccination management and outcome of children presenting to Specialist Immunisation Clinics with a vaccine-proximate seizure (VPS) as their first ever seizure, comparing children with (VPS+) and without (VPS only) subsequent seizures following their initial VPS.

Details	VPS only	VPS+	P
N	58	61	
Time from first VPS to clinic review, median months [IQR]	5.9 [2.9–10.1]	6.3 [3.1–21.5]	0.78
Vaccinated	43 (74.1%)	40 (65.6%)	0.31
Vaccination location			
Clinic	36/43 (83.7%)	24/40 (60.0%)	0.03
Day stay unit	4/43 (9.3%)	5/40 (12.5%)	
Inpatient	3/43 (7.0%)	11/40 (27.5%)	
Pre-medication used			
Anti-pyretics	6/43 (14.0%)	14/40 (37.5%)	0.03
Benzodiazepine	0/43 (0.0%)	2/40 (5.0%)	NC
Increased regular antiseizure medication	0/43 (0.0%)	2/40 (5.0%)	NC
Re-vaccination VPS	1/43 (2.3%)	5/40 (12.5%)	0.07
Deferred	15 (25.9%)	21 (34.4%)	0.31
Deferral reason			
Documented immunity on serological testing	9/15 (60.0%)	4/21 (34.4%)	NC
Additional investigations	1/15 (6.7%)	5/21 (19.0%)	
Vaccine hesitancy	4/15 (26.7%)	8/21 (38.1%)	
Unstable epilepsy	0/15 (0.0%)	1/21 (4.8%)	
Acutely unwell	1/15 (6.7%)	3/21 (14.3%)	
Subsequent vaccination			
Any further vaccinations	37 (63.8%)	40 (65.6%)	0.84
Up to date with vaccinations	51 (87.9%)	43 (70.5%)	0.02

NC= not calculated, VPS only = vaccine proximate seizure as first seizure, VPS+= vaccine proximate seizure as first seizure with further non-vaccine proximate seizures.

group who had VPS on revaccination (Case 1; Table 3), their initial VPS was an episode of SE one day following MMR and Hib-MenC vaccination at 12 months of age and no further seizures before review. For this child, VPS recurrence occurred following monovalent varicella zoster virus (VZV) vaccination at 18 months of age, where they had a 15-minute FS 6 days after vaccination. The case was admitted to hospital for observation but did not require any treatment for the seizure. In the five VPS+ cases who experienced VPS on revaccination (Case 2–6; Table 3), all had their initial VPS following their 4-month DTaP-Hib-HepB-IPV, PCV13 and rotavirus vaccination, which included 1 FS, 2 AFS and 2 SE. On revaccination, four of the five cases (Case 2–5) had SE requiring midazolam for termination and hospitalisation and one was admitted to the intensive care unit. All four of these cases had Dravet syndrome, though the diagnosis was only known in one case (Case 5) at the time of their second VPS as the others were diagnosed at 10–12 months of age. Case 6 was a child with generalised epilepsy who had a brief self-resolving afebrile focal seizure 2 days following DTP-IPV and VZV vaccination that did not require any acute management.

Comparing children by revaccination outcome, children who had another VPS on revaccination were more likely to have had SE as their initial VPS (50.0% vs 13.0%, $P = 0.03$; Table 4). Whereas children with no VPS recurrence were more likely to have had a FS as their initial VPS (59.7% vs 16.6%, $P = 0.03$). Having a diagnosis of epilepsy, and specifically Dravet syndrome, were the only factors associated with revaccination VPS ($P < 0.001$). Children with VPS recurrence were less likely to be up to date their vaccinations (50.0% vs 90.9%, $P < 0.001$).

In children whose vaccinations were deferred (25.9% of VPS only and 34.4% of VPS+ cases), documented immunity (positive MMR antibodies) was the most common deferral reason in children with VPS only, while vaccine hesitancy was most common in children with VPS+ (Table 2). Children with VPS only were more likely to be up to date with their vaccinations compared to children with VPS+ (87.9% vs. 70.5%, $P = 0.02$; Table 2).

4. Discussion

This is the first study, to our knowledge, to describe in detail VPS recurrence in children who experienced a VPS as their first seizure. Children who present to clinic with a VPS as their first and only seizure (VPS only) were older (median 12.5 months) and more likely to experience a FS compared to the children who went on to have further non-vaccine proximate seizures following their initial VPS (VPS+). Children in the VPS+ group were younger (median 6.2 months) and more likely to experience SE as their first seizure. In addition, the VPS+ cohort were more likely to have another VPS on revaccination, with the majority being in children with Dravet syndrome and importantly were less likely to be up to date with their vaccinations. Our findings suggest that children aged ≥ 12 months with a single febrile VPS as their only seizure are most likely to be able to proceed safely with routine vaccinations as an outpatient in the community, whilst children

Table 3
Case details of children with vaccine proximate seizure on revaccination.

	Group	Initial VPS		Seizure frequency	Epilepsy diagnosis	Revaccination				Revaccination VPS				
		Age (months)	Seizure type			Age (months)	Vaccines	Setting	Medication	Seizure type	Onset	Duration (minutes)	Management	Setting
1	VPS only	12	SE	N/A	None	18	VZV	Clinic	Nil	FS	Day 6	15	Self-resolved	Hospitalised
2	VPS+	4	SE	Multiple/ month	Dravet syndrome	6	DTPa-IPV-Hib-HBV	Clinic	Nil	SE	16 hours	>30	Midazolam ASM commencement	Hospitalised
3	VPS+	4	AFS	<1/month	Dravet syndrome	7	DTPa-IPV-Hib-HBV PCV13	Inpatient	Paracetamol Regular ASM	SE	14hrs hours	>30	Midazolam ASM adjustment	ICU
4	VPS+	4	FS	Multiple/ month	Dravet syndrome	8	DTPa-IPV-Hib-HBV PCV13	DSU	Paracetamol	SE	30 hours	>30	Midazolam ASM commencement	Hospitalised
5	VPS+	4	SE	<1/month	Dravet syndrome	24	DTPa MenACWY MMR	Clinic	Regular ASM	SE	Day 11	>30	Midazolam ASM adjustment	Hospitalised
6	VPS+	4	AFS	Multiple/ week	Generalised epilepsy	32	DTPa-IPV VZV	Inpatient	Paracetamol Regular ASM	AFS	48 hours	<5	Self-resolved	Managed at home

ASM = antiseizure medicine, AFS = afebrile seizure, DTPa = diphtheria-tetanus-acellular pertussis vaccine, DTPa-IPV = diphtheria-tetanus-acellular pertussis and inactivated polio vaccine, DTPa-IPV-Hib-HBV = diphtheria-tetanus-acellular pertussis, inactivated polio, *H influenzae* type b and Hepatitis B combination vaccine, DSU = day stay unit, FS = febrile seizure SE = status epilepticus, ICU = intensive care unit, N/A = not applicable, PCV13 = 13-valent pneumococcal conjugate vaccine, VPS only = vaccine proximate seizure as first seizure, VPS+ = vaccine proximate seizure as first seizure with further non-vaccine proximate seizures, VZV = varicella zoster virus.

who present with an initial VPS aged < 12 months, followed by further seizures are more likely to experience a recurrence and should be assessed in a specialised immunisation clinic for a tailored revaccination plan.

4.1. VPS only

In our study, VPS only cases were mostly FSs following dose-1 MMR vaccine at 12 months of age, consistent with MMR vaccination being the most common cause of FS following vaccination. [11] Previous studies have reported a 20–30% FS recurrence rate in children with vaccine proximate FS,[4,11] similar to that in children with non-vaccine proximate FS. However, none have examined FS recurrence on revaccination specifically and in particular following receipt of a vaccine with the same antigens linked to their first VPS such as dose-2 of a measles containing vaccine. Verbeek *et al.*'s [13] population based 10-year cohort study found 4.2% VPS recurrence in 1,269 children who had a VPS in the first 2 years of life, but did not differentiate VPS seizure type or vaccines involved. Our study found a higher overall VPS recurrence at 7.2%, though we did not include children who had a seizure prior to their initial VPS. Our study adds to Verbeek *et al.*'s by describing VPS recurrence in detail. We found no VPS recurrence in children with a single vaccine proximate simple FS. Our single case in the VPS only group who had a VPS recurrence on revaccination was in a child whose first VPS was SE. This is reassuring data suggesting that the risk of VPS recurrence following a single vaccine proximate FS is low and these children can be safely revaccinated in the general practice or community setting. In children due dose-2 MMR, vaccination should be recommended with no serological testing, to ensure longer immune protection.

4.2. VPS+

We found children who went on to develop further seizures following their initial VPS (children with VPS+) were younger at the time of their first VPS, at the 4- or 6- month vaccination, compared to at the 12-month vaccination for VPS only cases. This is consistent with previous studies where children with Dravet syndrome were found to be younger at their VPS presentation, compared to the peak incidence of FS in second year of life for the general population [16–19]. Amongst children with Dravet syndrome, those whose first seizure was vaccine proximate were also younger than those whose first seizure was not vaccine proximate [19,20], suggestive that vaccination may unmask an earlier onset of this underlying genetic epilepsy.

There was a higher proportion of VPS recurrence in children with VPS+ compared to children with VPS only, with diagnoses of epilepsy and Dravet syndrome being the only significant factors associated with VPS recurrence between the groups. While a study from Nova Scotia identified 6 in 80 (7.5%) children aged < 7 years with epilepsy had a VPS, the study found no increased relative risk of seizures 14 days following vaccination compared to 21–83 days post-vaccination [12]. Case 6 in our study is consistent with this where the self-resolving afebrile focal seizure 2-days following revaccination was in the context of a seizure baseline of multiple focal seizures per week and therefore within the expected seizure frequency for the case.

Our study found that a subsequent diagnosis of Dravet syndrome was significantly associated with VPS recurrence, with four out of five children with VPS+ and VPS recurrence diagnosed with this rare severe genetic epilepsy. This is consistent with Verbeek *et al.*'s population study which found children with Dravet syndrome were more likely to have VPS recurrence than those without [13]. In a separate cohort study, Verbeek *et al.* [19] also found 69% (11/16) of children with Dravet syndrome whose first seizure was

Table 4
Revaccination management of children presenting to Specialist Immunisation Clinic with a vaccine-proximate seizure (VPS) as their first ever seizure by VPS recurrence.

Details	All vaccinated	No VPS recurrence	VPS recurrence	P
N	83	77	6	
Time since VPS	5.6 [2.7–12.3]	5.9 [2.8–12.0]	6.5 [2.4–17.5]	0.92
Age at vaccination	17.9 [9.8–32.7]	18.0 [11.6–36.9]	10.6 [6.9–30.3]	0.32
VPS				
Category				
VPS only	43 (51.8%)	42 (54.5%)	1 (16.7%)	0.07
VPS+	40 (48.2%)	35 (45.5%)	5 (83.3%)	
Type				
Afebrile seizure	23 (27.7%)	21 (27.3%)	2 (33.3%)	0.03
Febrile seizure	47 (56.6%)	46 (59.7%)	1 (16.7%)	
Status epilepticus	13 (15.7%)	10 (13.0%)	3 (50%)	
Seizure history				
Epilepsy[a]	19 (22.9%)	14 (18.2%)	5 (83.3%)	<0.001
Dravet syndrome[b]	7 (8.4%)	3 (3.9%)	4 (66.7%)	<0.001
Frequency[c]				
Multiple/week	11/40 (27.5%)	10/35 (28.6%)	1/5 (20.0%)	0.51
Multiple/month	8/40 (20.0%)	6/35 (17.1%)	2/5 (40.0%)	
<1/month	21/40 (52.5%)	19/35 (54.3%)	2/5 (40.0%)	
Vaccination plan				
Clinic/GP	60 (72.3%)	57 (74.0%)	3 (50.0%)	0.43
Day stay unit	9 (10.8%)	8 (10.4%)	1 (16.7%)	
Inpatient	14 (16.9%)	12 (15.6%)	2 (33.3%)	
Pre-medication used				
Anti-pyretics	19 (22.9%)	16 (20.8%)	3 (50.0%)	0.10
Benzodiazepine	2 (2.4%)	2 (2.6%)	0 (0%)	0.69
Increased regular antiseizure medicine	2 (2.4%)	2 (2.6%)	0 (0%)	0.69
Subsequent vaccinations	69 (83.1%)	63 (81.8%)	6 (100.0%)	0.25
Further vaccination	56 (67.5%)	53 (68.8%)	3 (50.0%)	0.12
Up to date with vaccinations	73 (88.0%)	70 (90.9%)	3 (50.0%)	<0.001

VPS = vaccine proximate seizure, VPS+= vaccine proximate seizure with subsequent seizures.
[a] Diagnosed at time of clinic review.
[b] Diagnosed at any time, including after clinic review.
[c] In VPS only.

vaccine proximate had a VPS recurrence. Neither studies, however, examined VPS severity and outcomes in these children.

In our study, all four cases of Dravet syndrome had SE on revaccination. Whilst these children are known to have prolonged seizures [21] and have SE following vaccination as the first seizure presentations of Dravet syndrome [16,20], this is the first study to identify SE on revaccination. As SE can lead to significant neurologic morbidity [22], particularly in children with Dravet syndrome who are already at risk of neurodevelopmental decline, our study suggests precautions to reduce VPS risk should be considered in this population. While there is no specific management plan recommended for vaccinating children with Dravet syndrome, the use of prophylactic benzodiazepine such as clobazam is recommended by an expert consensus panel for children with Dravet syndrome to reduce seizure risk during febrile illnesses [23]. This, together with hospital admission for close post-vaccination monitoring and prompt emergency seizure management, should be considered when vaccinating children with Dravet syndrome.

We found all four Dravet syndrome cases with VPS recurrence presented with their first VPS at 4 months of age, consistent with previous reports of vaccine-associated Dravet syndrome onset [16,20]. While children who presented for vaccination at their next vaccination schedule point at 6 months had no yet being diagnosed with Dravet syndrome, all had multiple seizures in 2–3 month period between their initial VPS and clinic review. Given this, vaccination of infants with VPS+ and seizure onset aged < 12 months should be treated as possible Dravet syndrome cases and the same precautions should be considered to reduce VPS risk. Genetic testing, especially for *SCN1A* variants, for these children should be initiated early to help guide management.

Unsurprisingly, we found children with recurrent VPS were less likely to be up to date with their vaccinations. While children with neurological conditions have previously been reported to have lower vaccination coverage than the general population [24,25], particularly in children with Dravet syndrome [26], our study shows VPS recurrence can further impact on vaccination coverage. Our study findings highlight the need for development of a revaccination management protocol for children with severe genetic epilepsies such as Dravet syndrome to ensure safe and timely vaccinations in this population at risk of serious AEFIs.

Finally, a proportion of children in the study deferred their vaccinations. In children with VPS only, the most common reason for vaccination deferral was documented immunity on serological testing. While there is no increased risk of FS following dose-2 MMR vaccination at a population level [5], the risk of FS recurrence following dose-2 MMR vaccination in a child who had a FS with dose-1 MMR, based on existing literature is unclear. Our study found an absence of VPS recurrence with dose-2 MMR vaccination even in children who had a FS following dose-1 MMR. This should encourage clinicians to proceed with dose-2 MMR vaccination without serological testing. In children with VPS+, the most common reason for delay in vaccination was vaccine hesitancy which is in line with a survey study that identified "concerns about how the vaccine would affect my child" as a major barrier to vaccination for parents of children with neurological conditions [27]. Studies like ours that contribute to a better understanding on the risk of VPS recurrence will hopefully reduce the proportion of children with VPS who defer vaccination.

The study's strengths include our ability to collect detailed information on clinical features on both the initial and subsequent seizures through medical record review. We were also able to verify vaccination details using a national immunisation register. It is, however, limited by the small sample size and therefore not pow-

ered to detect smaller but possibly clinically significant differences between groups. Finally, while our multicentre study allowed us to capture children from around Australia, we only reviewed those who were referred to and had access to a SIC at a tertiary paediatric hospital, missing children with VPS that might have been managed at other secondary hospitals or in the community by paediatricians or general practitioners.

5. Conclusion

This study found that VPS recurrence was more likely in children who presented with their first VPS aged < 12 months and had subsequent non-vaccine proximate seizures prior to their next scheduled vaccination. These children were more likely to be diagnosed with epilepsy, particularly Dravet syndrome. Infants presenting with VPS as their first seizure at < 12 months and with ongoing seizures should be referred for early investigation of an underlying genetic epilepsy. Additional precautions should be considered when vaccinating children with or suspected to have Dravet syndrome, who are at highest risk of VPS recurrence and significant neurological sequalae.

CRediT authorship contribution statement

Lucy Deng: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - original draft, Project administration. **Margie Danchin:** Conceptualization, Methodology, Writing - review & editing. **Georgina Lewis:** Investigation, Writing - review & editing. **Abigail Cheung:** Investigation, Writing - review & editing. **Anita J. Campbell:** Investigation, Writing - review & editing. **Ushma Wadia:** Investigation, Writing - review & editing. **Krist Ewe:** Investigation, Writing - review & editing. **Nicholas Wood:** Conceptualization, Methodology, Writing - review & editing, Supervision.

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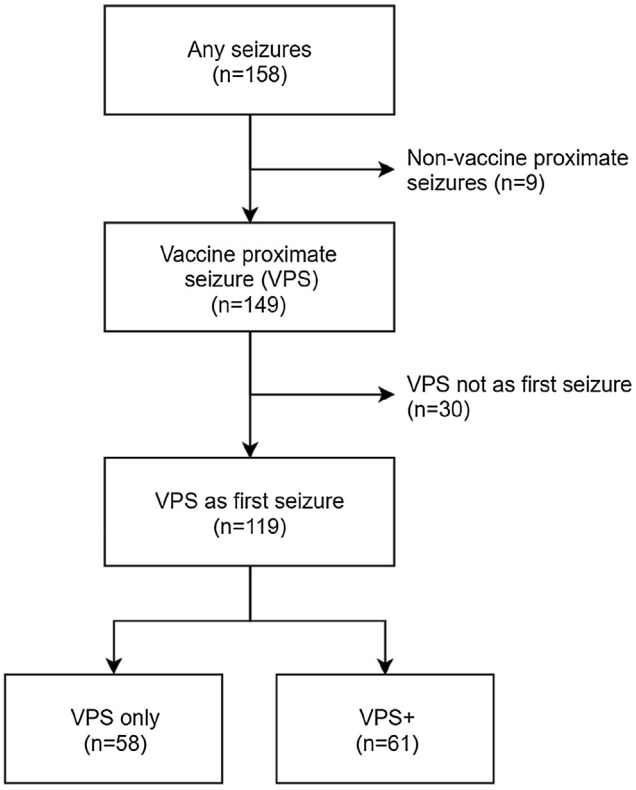
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Participant recruitment



VPS = vaccine proximate seizure; any seizure occurring within 14 days of a vaccine.
VPS only = single VPS as first and only seizure at time of clinic review.
VPS+=VPS as first seizure followed one or more non-vaccine proximate seizures at the time of clinic review.

References

[1] Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004;22(5–6):557–62.
[2] von Spiczak S, Helbig I, Drechsel-Baeuerle U, Muhle H, van Baalen A, van Kempen MJ, et al. A retrospective population-based study on seizures related to childhood vaccination. Epilepsia 2011;52(8):1506–12.
[3] Tartof SY, Tseng HF, Liu AL, Qian L, Sy LS, Hechter RC, et al. Exploring the risk factors for vaccine-associated and non-vaccine associated febrile seizures in a large pediatric cohort. Vaccine 2014;32(22):2574–81.
[4] Tartof SY, Tseng HF, Liu IL, Qian L, Sy LS, Hechter RC, et al. Inpatient admission for febrile seizure and subsequent outcomes do not differ in children with vaccine-associated versus non-vaccine associated febrile seizures. Vaccine 2014;32(48):6408–14.
[5] Macartney KK, Gidding HF, Trinh L, Wang H, McRae J, Crawford N, et al. Febrile seizures following measles and varicella vaccines in young children in Australia. Vaccine 2015;33(11):1412–7.
[6] Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. New Engl J Med 2001;345(9):656–61.
[7] Gold MS, Effler P, Kelly H, Richmond PC, Buttery JP. Febrile convulsions after 2010 seasonal trivalent influenza vaccine: implications for vaccine safety surveillance in Australia. Med J Australia 2010;193(9):492–3.
[8] Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. 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):2024–31.
[9] 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.
[10] Hambidge SJ, Glanz JM, France EK, McClure D, Xu S, Yamasaki K, et al. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. JAMA 2006;296(16):1990–7.
[11] Deng L, Gidding H, Macartney K, Crawford N, Buttery J, Gold M, et al. Postvaccination febrile seizure severity and outcome. Pediatrics 2019;143(5).
[12] Top KA, Brna P, Ye L, Smith B. Risk of seizures after immunization in children with epilepsy: a risk interval analysis. BMC Pediatrics 2018;18(1):134.
[13] Verbeek NE, van der Maas NA, Jansen FE, van Kempen MJ, Lindhout D, Brilstra EH. Prevalence of SCN1A-related dravet syndrome among children reported with seizures following vaccination: a population-based ten-year cohort study. PLoS ONE 2013;8(6):e65758.
[14] Pruna D, Balestri P, Zamponi N, Grosso S, Gobbi G, Romeo A, et al. Epilepsy and vaccinations: Italian guidelines. Epilepsia 2013;54(Suppl 7):13–22.
[15] Hull BP, Deeks SL, McIntyre PB. The Australian childhood immunisation register-A model for universal immunisation registers?. Vaccine 2009;27(37):5054–60.
[16] Berkovic SF, Harkin L, McMahon JM, Pelekanos 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(6):488–92.
[17] 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(1):175–8.
[18] Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain 2012;135(Pt 8):2329–36.
[19] Verbeek NE, van der Maas NA, Sonsma AC, Ippel E, Vermeer-de Bondt PE, Hagebeuk E, et al. Effect of vaccinations on seizure risk and disease course in Dravet syndrome. Neurology 2015;85(7):596–603.
[20] 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(6):592–8.
[21] Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infants (Dravet syndrome). In: Roger J, Bureau M, Dravet C, Genton P, Tassinari C, Wolf P, editors. Epileptic Syndromes in Infancy, Childhood and Adolescence. London: John Libbey Eurotext; 2005. p. 89–113.
[22] Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American epilepsy society. Epilepsy Curr 2016;16(1):48–61.
[23] Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, et al. Optimizing the diagnosis and management of dravet syndrome: recommendations from a North American consensus panel. Pediatr Neurol 2017;68. 18–34.e3.
[24] Tillmann BU, Tillmann HC, Heininger U, Lütschg J, Weber P. Acceptance and timeliness of standard vaccination in children with chronic neurological deficits in north-western Switzerland. Eur J Pediatr 2005;164(5):320–5.
[25] Pandolfi E, Carloni E, Marino MG, Ciofi degli Atti ML, Gesualdo F, Romano M, et al. Immunization coverage and timeliness of vaccination in Italian children with chronic diseases. Vaccine 2012;30(34):5172–8.
[26] Tanabe T, Awaya 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 = Brain and Development 2004;36(4):318–23.
[27] Smith M, Peacock G, Uyeki TM, Moore C. Influenza vaccination in children with neurologic or neurodevelopmental disorders. Vaccine 2015;33(20):2322–7.

4.4 Revaccination outcomes of children with Dravet syndrome

4.4.1 Introduction

In **Section 4.3**, there were 6 (7.2%) VPS recurrences out of 83 children who had another vaccination following their initial VPS. Of those, 4 (67%) had a diagnosis of Dravet syndrome and all 4 children unfortunately had VP-SE with their next vaccination encounter.

VPSs, including SE, have been reported in children with Dravet syndrome and have been implicated in triggering an earlier onset of the epileptic syndrome in children genetically destined to develop the condition.(175, 177) McIntosh et al.(177) found no evidence that children whose first seizure was vaccine proximate had different clinical or developmental outcomes to those whose first seizure was not vaccine proximate, and therefore vaccination should not be withheld. Children with epilepsy, including Dravet syndrome, are recommended to continue vaccination following diagnosis,(139) though there is little evidence on the risk of seizure recurrence with subsequent vaccinations. A Dutch study found that 4 out of 15 (26.7%) children with *SCN1A*-related Dravet syndrome <2 years old had another seizure with subsequent vaccinations, though all followed whole-cell pertussis vaccines, and the study did not describe the management or clinical outcomes of the reported VPS recurrences.(180)

Strategies to minimise the risk of seizure triggers in children with Dravet syndrome, recommended by expert panel consensus, include the use of prophylactic benzodiazepines with febrile illnesses and prophylactic antipyretics with vaccination and illness.(190) However, management of vaccination in these children varies and can be clinician dependent.

I therefore aimed to describe the vaccination management and outcomes of children with Dravet syndrome presenting to Specialist Immunisation Clinics in Australia from 2013 to 2017, during which no established vaccination protocols were routinely used for children with Dravet syndrome.

4.4.2 Methods

Children with Dravet syndrome who presented to a Specialist Immunisation Clinic at one of four Australian tertiary paediatric hospitals (The Royal Children's Hospital Melbourne; The Children's Hospital at Westmead, Sydney; Women's and Children's Hospital, Adelaide; and Perth Children's Hospital) between January 2013 and December 2017 were included in the study. Potential cases were identified by searching clinic databases at each hospital for the keywords seizure, convulsion, status epilepticus, epilepsy and Dravet syndrome as the clinic-presenting problem or diagnosis. Children for whom a diagnosis of Dravet syndrome, confirmed by a paediatric neurologist, was identified on review of their medical records were included. Results of any genetic molecular analysis of DNA extracted from cases' venous blood samples were obtained from medical records.

Clinical details on each case's first VPS (defined as a seizure within 14 days of receiving a vaccine), including age, vaccine(s) given, seizure type and description using ILAE definitions(191, 192), and whether it was their first ever seizure, were obtained through medical record review. Management and outcomes of subsequent vaccination encounters including vaccine(s) given, setting they were given in, medications used, and details of VPS following revaccination including timing of onset, seizure type and management were also obtained through medical record review. Receipt of immunisations was verified for all cases using data from the Australian Immunisation Register.(189)

Age, vaccine type, vaccination setting, and medication used for subsequent vaccination encounters were compared between cases who had VPS recurrence on revaccination and cases who did not, and between cases who received prophylactic benzodiazepine and cases who did not. The Chi-squared test was used for categorical data and Mann-Whitney U test for non-parametric continuous data. Statistical significance was defined as $P<0.05$. Odds ratios were calculated for VPS recurrence with prophylactic benzodiazepine as the exposure of interest. Statistical analyses were conducted using Stata 16 (StataCorp, College Station, TX).

This study was approved by Sydney Children's Hospitals Network Human Research Ethics Committee (2019/ETH05430).

4.4.3 Results

Nineteen children with Dravet syndrome, all with a history of VPS, presented to a Specialist Immunisation Clinic between 1 January 2013 and 31 December 2017 for further vaccination. Of the 19 cases, 18 had a *SCN1A* variant and 1 had 11p14.1 deletion. The cases were aged 4–19 months at their first VPS (mean 6.0 months [interquartile range 4.3–6.9]), with 16 (84%) cases following DTPa-IPV-Hib-HBV, PCV13, +/− rotavirus vaccines at either 4 months or 6 months of age (Table 4.1). FSs were the most common VPS presentation (*n*=8, 42%), followed by SE (*n*=7, 37%; 3 afebrile SE, 4 febrile SE). There were 11 (58%) cases where VPS was their first ever seizure.

Seventeen (90%) of the 19 children had further vaccinations, though only 6 (32%) were up to date for age with their vaccination according to the Australian Immunisation Program schedule at the end of the study period (Table 4.1). Eleven (58%) had another VPS on revaccination. There were 12 VPS recurrences in 47 subsequent vaccination encounters (26% recurrence, with an average 2.8 vaccination encounters/child) in the 11 children (Table 4.2); 5 followed inactivated vaccines, 2 followed live attenuated vaccines, and 5 followed a combination of both inactivated and live attenuated vaccines. There were 7 (58%) afebrile SE and 5 (42%) afebrile seizures. There was no difference in proportion of VPS recurrence by age at time of revaccination or by vaccination setting (outpatient department, day stay admission, hospital admission). Half occurred within the first 48 hours of vaccination. In terms of seizure management, 2 were managed a home, 2 had emergency department presentations only, and 6 were hospitalised with 2 requiring ICU admission.

Table 4.1 Details of the first vaccine-proximate seizure and subsequent vaccination outcome in children with Dravet syndrome presenting to a Specialist Immunisation Clinic

Details	***n* (%)**
N	19
Male	10 (53%)
First vaccine-proximate seizure	
Age, months; median [IQR]	6.0 [4.3–6.9]
4–5 months (dose-2 DTPa-IPV-Hib-HBV, PCV13, rotavirus)	10 (53%)
6–7 months (dose-3 DTPa-IPV-Hib-HBV, PCV13, +/− rotavirus)*	6 (32%)
12–13 months (dose-1 MMR; Hib, MenC)	2 (11%)
19 months (VZV)	1 (5%)
Seizure type	
Afebrile seizure	4 (21%)
Febrile seizure	8 (42%)
Status epilepticus	3 (16%)
Febrile status epilepticus	4 (21%)
Seizure description	
Focal	2 (11%)
Hemiclonic	2 (11%)
Myoclonic	1 (5%)
Generalised tonic-clonic	14 (74%)
VPS as first ever seizure	11 (58%)
Revaccination	
Further vaccinations following initial VPS	17 (90%)
Revaccination seizure	11 (58%)**
Vaccinations up to date	6 (32%)

*3 with rotavirus vaccine, 3 without

**1 case had 2 VPS recurrences

DTPa-IPV-Hib-HBV=diphtheria-tetanus-acellular pertussis, inactivated polio, *Haemophilus influenzae* type b and hepatitis B combination vaccine, Hib=*H. influenzae* type b vaccine, IQR=interquartile range, PCV13=13-valent pneumococcal conjugate vaccine, MenC=meningococcal C vaccine, MMR=measles-mumps-rubella vaccine, VPS=vaccine-proximate seizure, VZV=varicella-zoster vaccine

Table 4.2 Vaccination management of each vaccination encounter, by revaccination outcome

Details	All vaccinations	Revaccination outcome		
		No VPS	VPS	*P*
N	47	35	12	
Age, months; median [IQR]	17 [12–48]	20 [12–50]	12 [7–25]	0.11
Vaccine type				
Inactivated only	25 (53%)	20 (57%)	5 (42%)	0.45
Live attenuated only	9 (19%)	7 (20%)	2 (17%)	
Combination	13 (28%)	8 (23%)	5 (42%)	
Vaccination setting				
Outpatient (clinic/GP)	24 (51%)	16 (46%)	8 (67%)	0.36
Day stay unit	3 (6%)	2 (6%)	1 (8%)	
Inpatient	20 (43%)	17 (49%)	3 (25%)	
Medication use				
Regular AED	44 (94%)	33 (84%)	11 (92%)	0.75
Prophylactic clobazam/ clonazepam	26 (55%)	25 (71%)	1 (8%)	<0.001
Seizure onset post vaccination (days)				
0–2 (0–48 hours)			6 (50%)	
3–4 (48–96 hours)			3 (25%)	
5–7			1 (8%)	
8–14			2 (17%)	
Seizure type				
Afebrile seizure			5 (42%)	
Status epilepticus			7 (58%)	
Management				
Home			2 (17%)	
ED presentation			2 (17%)	
Hospitalisation			6 (50%)	
ICU			2 (17%)	

AED=antiepileptic drug, ED=emergency department, GP=general practice, ICU=intensive care unit, IQR=interquartile range, VPS=vaccine-proximate seizure

The majority of children (*n*=44 encounters, 94%) were on regular antiepileptic medication at the time of revaccination. There was no difference in the proportion of children with VPS recurrence who were on AED compared to the proportion of children without VPS who were on AED. Additional prophylactic benzodiazepine (either clobazam or clonazepam) was used in 26 (55%) vaccination encounters. Benzodiazepine was given for 48 hours following inactivated vaccines and 14 days following live attenuated vaccines. The proportion of prophylactic benzodiazepine use was significantly higher in children who did not have VPS recurrence compared to children who did (71% vs 8%, *P*<0.001). Only 1/26 (4%) vaccination encounter with prophylactic benzodiazepine had a VPS recurrence compared to 11/21 (52%) encounters without prophylactic benzodiazepine (OR 0.036 [95%CI 0.004–0.320], *P*<0.001). The VPS recurrence in the single case who had prophylactic benzodiazepine was in a 25-month-old who had a brief self-resolving afebrile seizure 56 hours following their MMRV vaccination that did not require treatment. There was no difference in the age, vaccine type, vaccination setting or use of regular AEDs in children who were given prophylactic benzodiazepine compared to children who were not (Table 4.3). Details of each case's initial VPS and subsequent revaccination management and outcomes are shown in Table 4.4.

Table 4.3 Vaccination management of each vaccination encounter, by use of prophylactic benzodiazepine

Details	All vaccination encounters	No benzodiazepine	Benzodiazepine	*P*
N	47	21	26	
Age, months; median [IQR]	17 [12–48]	12 [7–21]	23 [15–50]	0.21
Vaccine type				
Inactivated only	25 (53%)	11 (52%)	14 (54%)	0.63
Live attenuated only	9 (19%)	3 (14%)	6 (23%)	
Combination	13 (28%)	7 (33%)	6 (23%)	
Vaccination setting				
Outpatient (clinic/GP)	24 (51%)	16 (76%)	8 (31%)	0.008
Day stay unit	3 (6%)	1 (5%)	2 (8%)	
Inpatient	20 (43%)	4 (19%)	16 (62%)	
Regular AED use	44 (94%)	19 (90%)	25 (96%)	0.43
Revaccination VPS				
N	12	11 (52%)	1 (4%)	<0.001
Seizure onset post vaccination (days)				
0–2 (0–48 hours)	6 (50%)	6 (55%)	0	0.35
3–4 (48–96 hours)	3 (25%)	2 (18%)	1 (100%)	
5–7	1 (8%)	1 (9%)	0	
8–14	2 (17%)	2 (18%)	0	
Seizure type				
Afebrile seizure	5 (42%)	4 (36%)	1 (100%)	0.22
Status epilepticus	7 (58%)	7 (64%)	0	
Management				
Home	2 (17%)	1 (9%)	1 (100%)	0.14
ED presentation	2 (17%)	2 (18%)	0	
Hospitalisation	6 (50%)	6 (55%)	0	
ICU	2 (17%)	2 (18%)	0	

AED=antiepileptic drug, ED=emergency department, GP=general practice, ICU=intensive care unit, IQR=interquartile range, VPS=vaccine-proximate seizure

Table 4.4 Details of the first vaccine-proximate seizure of children with Dravet syndrome and their subsequent revaccination management and outcome

	VPS					Revaccination management					Revaccination seizure			
Case	Age (mo)	First seizure	Vaccine	Seizure type		Age (mo)	Vaccine	Regular AED	Clobazam/ Clonazepam	Setting	VPS?	Onset	Seizure type	Management
1	4	Y	DTPa-IPV-Hib-HBV	AFS	GTCS	6	PCV13	Y	N	Clinic	N			
			PCV13			7	Hexa	Y	N	Clinic	N			
			Rota			52	MenACWY	Y	Y	Inpatient	N			
						58	MMR	Y	Y	Clinic	N			
						62	MMRV	Y	Y	Clinic	N			
2	4	Y	DTPa-IPV-Hib-HBV	AFS	Hemiclonic	7	Hexa, PCV13	Y	N	DSU	Y	30 h	AFS	Hospitalised
			PCV13											
			Rota											
3	4	Y	DTPa-IPV-Hib-HBV	FS	Focal	6	Hexa, PCV13, Rota	N	N	GP	N			
			PCV13			24	DTPa, MenACWY, MMR	Y	N	Clinic	Y	Day 11	SE	Hospitalised
			Rota											
4	4	Y	DTPa-IPV-Hib-HBV	FS	GTCS	Parental decision to have no further vaccinations								
			PCV13											
			Rota											
5	4	Y	DTPa-IPV-Hib-HBV	SE	GTCS	7	Hexa, PCV13, Rota	Y	N	Inpatient	Y	14 h	SE	ICU
			PCV13			12	Hib-MenC, Influenza	Y	Y	Inpatient	N			
			Rota			21	Influenza	Y	Y	Clinic	N			
						45	DTPa-IPV, Influenza	Y	Y	Clinic	N			
6	4	Y		FSE	GTCS	6	Hexa	Y	N	Clinic	Y	16 h	SE	Hospitalised

	VPS					Revaccination management						Revaccination seizure			
Case	Age (mo)	First seizure	Vaccine	Seizure type		Age (mo)	Vaccine	Regular AED	Clobazam/ Clonazepam	Setting	VPS?	Onset	Seizure type	Management
			DTPa-IPV-Hib-HBV			8	PCV13	N	Y	Inpatient	N			
						13	Hib-MenC	Y	Y	Inpatient	N			
			PCV13			15	MMR	Y	Y	Clinic	N			
			Rota											
7	4	Y	DTPa-IPV-Hib-HBV	FSE	GTCS	6	Hexa, PCV13	Y	N	Clinic	N			
						12	MMR, Hib-MenC	Y	N	Clinic	Y	D7	SE	ED
			PCV13			21	MMRV	Y	N	Inpatient	N			
			Rota			24	Influenza	Y	N	Inpatient	Y	22 h	SE	ICU
						54	DTPa-IPV	Y	Y	Inpatient	N			
8	5	Y	DTPa-IPV-Hib-HBV	FSE	GTCS	9	Hexa, PCV13	Y	Y	Inpatient	N			
						50	DTPa-IPV, MenACWY	Y	Y	Inpatient	N			
			PCV13			50	MMR, Hib-MenC	Y	Y	Inpatient	N			
			Rota											
9	5	N	DTPa-IPV-Hib-HBV	FSE	GTCS	7	Hexa, PCV13	Y	N	Inpatient	Y	72 h	AFS	Hospitalised
						50	MenACWY, DTPa-IPV	Y	Y	Inpatient	N			
			PCV13			50	MMR, Hib	Y	Y	Inpatient	N			
			Rota											
10	5	N	DTPa-IPV-Hib-HBV	SE	GTCS	12	Hexa, PCV13	Y	Y	Inpatient	N			
						12	MMR, Hib-MenC	Y	Y	Inpatient	N			
			PCV13			20	MMRV, DTPa	Y	Y	Inpatient	N			
			Rota			25	Influenza	Y	Y	Inpatient	N			
11	6	Y		FS	GTCS	12	Hib-MenC	Y	N	Clinic	N			
						17	MMR	Y	Y	Clinic	N			

	VPS					Revaccination management						Revaccination seizure			
Case	Age (mo)	First seizure	Vaccine	Seizure type		Age (mo)	Vaccine	Regular AED	Clobazam/ Clonazepam	Setting	VPS?	Onset	Seizure type	Management
			DTPa-IPV-Hib-HBV PCV13			20 25	DTPa MMRV	Y Y	Y Y	Clinic Clinic	N Y	56 h	AFS	Self-resolved
12	6	Y	DTPa-IPV-Hib-HBV PCV13	AFS	Hemiclonic	13 14 25	Hib-MenC MMR VZV	Y Y Y	N N N	Clinic Clinic Clinic	N N Y	D14	AFS	Midazolam at home
13	6	Y	DTPa-IPV-Hib-HBV PCV13 Rota	AFS	GTCS	7	Hexa, PCV13	N	N	GP	Y	13 h	SE	Hospitalised
14	6	N	DTPa-IPV-Hib-HBV PCV13 Rota	FS	Focal	12 52	MMR, Hib-MenC DTPa-IPV, VZV	Y Y	N Y	Clinic Inpatient	N N			
15	6	N	DTPa-IPV-Hib-HBV PCV13 Rota	FS	GTCS	12 48	MMR, Hib-MenC VZV, DTPa-IPV	Y Y	N Y	GP Inpatient	Y N	24 h	AFS	ED
16	7	N	DTPa-IPV-Hib-HBV PCV7	SE	GTCS	51	MMR, Hib-MenC	Y	N	Clinic	Y	72 h	SE	Hospitalised
17	12	N	Hib-MenC	FS	GTCS	No further vaccines due to poor seizure control								

	VPS					Revaccination management					Revaccination seizure			
Case	Age (mo)	First seizure	Vaccine	Seizure type		Age (mo)	Vaccine	Regular AED	Clobazam/ Clonazepam	Setting	VPS?	Onset	Seizure type	Management
			MMR											
18	13	N	Hib MenC MMR	FS	Myoclonic	17 19	VZV Influenza	Y Y	Y Y	DSU DSU	N N			
19*	19	N	VZV	FS	GTCS	57	DTPa-IPV	Y	N	Clinic	N			

*11p14.1 deletion

AED=antiepileptic drug, AFS=afebrile seizure, DSU=day stay unit, DTPa=diphtheria-tetanus-acellular pertussis vaccine, DTPa-IPV=diphtheria-tetanus-acellular pertussis and inactivated polio combination vaccine, ED=emergency department presentation, FS=febrile seizure, FSE=febrile status epilepticus, GP=general practice, GTCS=generalised tonic-clonic seizure, DTPa-IPV-Hib-HBV=diphtheria-tetanus-acellular pertussis, inactivated polio, *Haemophilus influenzae* type b and hepatitis B combination vaccine, Hib= *H. influenzae* type b vaccine, Hib-MenC=combined *H. influenzae* type b and meningococcal C conjugate vaccine, ICU=intensive care unit, MMR=measles-mumps-rubella vaccine, MMRV=measles-mumps-rubella-varicella vaccine, MenACWY=meningococcal A, C, W and Y vaccine, PCV7=7-valent pneumococcal conjugate vaccine, MenC=meningococcal C vaccine, PCV13=13-valent pneumococcal conjugate vaccine, Rota=rotavirus vaccine, SE=status epilepticus, VPS=vaccine-proximate seizure, VZV=varicella-zoster vaccine

4.4.4 Discussion

This retrospective review of vaccination management in children with Dravet syndrome identified a significant protective association between the use of prophylactic benzodiazepine (clobazam or clonazepam) and VPS recurrence on revaccination. The odds of having a VPS was 96% lower with prophylactic benzodiazepine than without prophylactic benzodiazepine.

Clobazam, together with valproic acid, is considered a first-line antiepileptic in children with Dravet syndrome.(190) Intermittent clobazam use during a febrile illness has been shown to be effective in preventing FSs in children, and is frequently recommended for children with Dravet syndrome during febrile illnesses based on expert panel consensus with Class IV evidence (case reports).(55, 190, 193) It is therefore consistent that the use of prophylactic benzodiazepine, such as clobazam, for the period where a fever is likely to occur following vaccination could decrease the risk of an FS or febrile SE. In 2019, the use of prophylactic benzodiazepine for vaccination was adopted by The Royal Children's Hospital Melbourne in their revaccination protocol for children with Dravet syndrome based on expert consensus.(194) This study is the first to provide evidence to support this guideline.

This study also found that 7 out of 11 (63%) children who had VPS recurrence in the absence of prophylactic benzodiazepine had SE. Given the priority in seizure management of children with Dravet syndrome involves the avoidance of SE and its impact on neurodevelopment and quality of life, the use of prophylactic benzodiazepine should strongly be considered for preventing these occurrences following vaccination.

VPS recurred following both inactivated and live attenuated vaccines and up to 14 days following vaccination. The timing of the VPS recurrence was consistent with the known timing of fever onset after specific vaccines, and this should be considered when determining the duration of prophylactic benzodiazepine therapy.(137, 140-142, 154) In children in the study cohort who received prophylactic benzodiazepine, it was given for 48 hours following inactivated vaccine(s) and for 14 days following measles-containing or varicella vaccine(s). Tolerability to side effects from benzodiazepine use needs to be weighed up against the risk of not vaccinating or VPS recurrence.

Half of the children (9/18) who continued vaccination had at least another vaccination encounter aged <12 months before they were diagnosed with Dravet syndrome. Amongst these children, 50% had a VPS recurrence, none of whom had prophylactic benzodiazepine. It is therefore important for children who present with VPS in infancy (<12 months old) to be referred for early neurological review and investigation for genetic epilepsies. Prophylactic benzodiazepine for vaccination should be considered in children where a diagnosis of Dravet syndrome is suspected, even prior to confirmatory genetic testing. This will assist in children getting on-time vaccinations, to ensure they are provided with adequate protection against vaccine-preventable diseases while minimising the risk of a seizure, in particular SE, following vaccination.

This study was limited in the number of cases. However, despite the small number of cases and vaccination encounters, a statistically significant association between the use of prophylactic benzodiazepine and reduction in VPS recurrence was found. The use of benzodiazepine in each vaccination encounter was clinician determined and therefore subject to selection bias. A prospective study examining the outcomes and potential side effects of a revaccination protocol established from this study's findings should be considered to validate the study findings.

4.4.5 Section conclusion

This retrospective review identified that prophylactic benzodiazepine use for the period where a fever following vaccination is most likely to occur is protective against VPS recurrence and therefore should be considered for all children with suspected or confirmed Dravet syndrome to prevent VPSs, particularly SE.

4.5 Key findings

In this chapter, I examined revaccination management and outcomes of children with a history of VPS who presented to a Specialist Immunisation Clinic over 5 years in two separate cohorts: children whose first seizure was a VPS and children with Dravet syndrome. The key findings from these studies were as follows:

1. Approximately 25–30% of children deferred their vaccination following a VPS. Having positive MMR antibodies was the most common reason in children with a single VPS and no other seizures (VPS only), and parental anxiety was the most common reason for children with multiple non-vaccine-related seizures following their first VPS (VPS+).
2. Children with VPS only were less likely to have another VPS on revaccination compared to children with VPS+, regardless of vaccination location and prophylactic medication used.
3. Children with VPS recurrence were more likely to have an underlying genetic epilepsy, in particular, Dravet syndrome.
4. In children with Dravet syndrome, VPS recurrence decreased with the use of prophylactic benzodiazepine with vaccination.

From these findings, I draw the following recommendations:

1. Children with a single VPS with no further seizures have a low risk of seizure recurrence with revaccination and can therefore be safely revaccinated in the community by general practitioners with no added precautions following clinical review.
2. Children with VPS and other non-vaccine-proximate seizures require clinical review and consideration for investigation for underlying genetic epilepsy.
3. The use of prophylactic benzodiazepine for vaccination should be considered in children with suspected or confirmed Dravet syndrome to reduce the risk of revaccination VPS.

Chapter 4 addresses the risk of seizure recurrence on revaccination in children with a previous VPS. It builds on findings on the clinical severity and outcomes following VP-FS and VP-SE provided in **Chapters 2** and **3**, to assist clinicians in counselling parents on not only the risk and outcomes of the initial VPS, but also on the risk and outcomes of subsequent vaccinations. The next (concluding)

chapter summarises my thesis findings and next steps in advancing the knowledge on severe neurological adverse events and other serious adverse events following immunisation.

Chapter 5 Conclusion and future research

5.1 Key findings and insights

In Chapter 1, following a review of existing literature, I outlined the key unknowns about seizures occurring after vaccination (which formed the basis of my thesis chapters), the relevance of these gaps in the knowledge about vaccine safety and clinical management for policymakers and providers, and the studies I undertook to fill these knowledge gaps (Table 1.4). Table 5.1 summarises the findings from my thesis for each respective knowledge gap first outlined in Table 1.4.

Table 5.1 Knowledge gap and thesis findings

Knowledge gap	Thesis findings
Clinical severity of VPSs	VP-FS was not more severe than NVP-FS VP-SE was not more severe than NVP-SE
Genetic risk for VPS	Pathogenic *SCN1A* variants occurred in young infants (aged <12 months) presenting with prolonged VP-FS
Developmental outcome following VPS	Children with VP-FS had no increased risk of developmental or behavioural problems compared to children with NVP-FS or no seizure history
Vaccination coverage following VPS	Vaccination coverage following initial SE decreased with time, placing children at risk of vaccine-preventable diseases
Risk of VPS recurrence	VPS recurred in children whose first VPS occurred at <12 months old and who had further non-vaccine-related seizures following their initial VPS
Factors that reduce risk of VPS recurrence	Prophylactic benzodiazepine reduced the risk of VPS recurrence in children with suspected or confirmed Dravet syndrome

NVP-FS=non-vaccine-proximate febrile seizure, NVP-SE=non-vaccine-proximate status epilepticus, SE=status epilepticus, VP-FS=vaccine-proximate febrile seizure, VP-SE=vaccine-proximate status epilepticus, VPS=vaccine-proximate seizure

Relating to **febrile seizures** following vaccination, I demonstrated that there was no difference in clinical severity between VP-FS and NVP-FS through a multi-site prospective cohort study. A subsequent prospective case-control study found that VP-FS was not associated with increased risk of developmental or behavioural problems in young children at 12–24 months after the initial FS, when compared to children with NVP-FS or children with no seizure history. Pathogenic *SCN1A*

variants were found to occur in young infants (aged <12 months) presenting with prolonged VP-FS, prompting a recommendation that children aged <12 months presenting with VPS should have early neurological review and genetic testing, as outlined in my published clinical practice article for general practitioners.

Relating to **status epilepticus** following vaccination, through a population-based cohort study using linked data I found VP-SE was rare overall, and most commonly occurred after dose-1 of MMR vaccine, with an incidence rate 35 times lower than that of VP-FS following dose-1 of MMR vaccine. Similar to my findings on FS, detailed clinical review of individual cases showed no apparent difference in clinical severity, by risk of ICU admission, between VP-SE and NVP-SE after adjusting for age in this population-based cohort study. I then confirmed this in a retrospective cohort study examining medical records of children presenting with SE to tertiary paediatric hospitals in Australia. Notably, seizure progression and subsequent epilepsy diagnosis in children with VP-SE was associated with having seizures prior to their first VP-SE rather than the initial VP-SE itself. This allows us to reassure parents that even if their child had a prolonged seizure following vaccination, their child's risk of further seizures is dependent on their underlying risk of epilepsy rather than the vaccination encounter itself. However, I found vaccination coverage following the initial SE decreased with time, regardless of whether the SE followed vaccination or not, suggesting that parents and/or immunisation providers have concerns about the impact of subsequent vaccinations. This highlights the need for prompt neurological review, investigation if a genetic epilepsy is suspected, and the provision of additional immunisation clinical support, such as through specialist immunisation services, to ensure safe and timely vaccination in these children.

Finally, relating to **revaccination**, through a retrospective clinical review of children with VPS presenting to Specialist Immunisation Clinics for assessment for revaccination, I found the risk of VPS recurrence to be low in children who have had no further seizures following their initial VPS. In contrast, I found VPS recurred in children who had multiple non-vaccine-related seizures prior to their next vaccination and whose first VPS occurred at <12 months old. These children were more likely to have an underlying genetic epilepsy, in particular, Dravet syndrome. VPS recurrence in these children decreased with the use of prophylactic benzodiazepine with vaccination, confirming the current

recommendation for its use based on expert consensus. As a clinician working both as an emergency paediatrician and immunisation specialist, these research findings have been useful in both counselling parents of children who present to the emergency department with potentially life-threatening seizures and later when discussing revaccination plans in my Specialist Immunisation Clinic. My research findings provide the first empirical evidence to support local clinical practice guidelines (which are currently not consistently or widely applied due to absence of evidence) on the use of prophylactic benzodiazepine in children with suspected or confirmed genetic epileptic encephalopathies such as Dravet syndrome, to ensure safe and on-time vaccinations.

At an individual level, my thesis has provided empirical evidence for clinicians and immunisation providers to counsel parents with concerns on vaccine safety, particularly on the risk and outcomes following VPS, and better guide their decision-making on vaccine uptake. Clinicians can also more confidently manage children with VPS and their subsequent vaccinations based on the child's risk profile, down to the level of the individual's genotype.

At the clinical practice level, my thesis findings provide guidance for general practitioners to triage children with VPS for specialist input. My findings also strengthen existing clinical practice guidelines on revaccination for immunisation specialists, which have previously been based on expert consensus. This will allow for wider and more consistent use of these clinical guidelines to achieve safe revaccination of children most vulnerable to further neurological sequalae from potentially vaccine-preventable infectious diseases.

At a policy level, my findings on both background SE rates and VP-SE rates at a population level support existing vaccination policy, but also highlight gaps in vaccination coverage that require attention.

Finally, at the pharmacovigilance level, my research has shown the success of a multi-pronged approach in improving vaccine safety science by using different research methodologies to achieve a holistic picture on risk, and immediate and longer-term outcomes of AEFIs, at both the individual and population level. The multi-disciplinary collaboration forged through the research studies that formed

my thesis have also set up a network of specialists – paediatricians, infectious disease specialists, neurologists, geneticists, developmental psychologists, epidemiologists and others – whose expertise is integral to vaccine safety science and can be drawn upon for many years to come.

5.2 Future research

My PhD journey started with a need to address key knowledge gaps to improve the understanding of the safety profile of vaccines in children, in particular, associations with severe acute neurological adverse events, which was brought to light following a specific vaccine safety signal. My thesis findings contribute to global vaccine safety knowledge, which is critical to strengthen provider and consumer confidence in an era when the incidence of vaccine-preventable diseases is declining with successful vaccination programs, public focus has shifted to vaccine safety, and vaccine hesitancy has become one of the top 10 threats to global health identified by the World Health Organization (WHO).(195) My PhD journey ends in the midst of a pandemic, as multiple vaccines, novel both in target antigen and vaccine platform used,(196) and for which the rare serious and long-term safety profile is unknown, are being rolled out to a global population spanning the whole of life. More critical than ever before is the ongoing understanding and minimising of serious AEFIs to maintain public trust and confidence in vaccine safety.

Through my PhD, I have not only identified research areas for post-doctoral studies in vaccine safety science specific to vaccine-proximate seizures in children but also developed a set of skills and a framework for setting up a robust vaccine safety investigation system that can detect and respond to any vaccine safety concerns. There are already emerging areas for research on the pathogenesis, and individual and epidemiological of risk of anaphylaxis or severe allergic reaction(197) , myocarditis and pericarditis(198) following vaccination with the mRNA-based COVID-19 vaccines and thrombosis with thrombocytopenia syndrome following vaccination with adenovirus-vectored vaccines COVID-19 vaccines.(199) Through a comprehensive vaccine safety surveillance system using mechanisms outlined below, I hope my future work will contribute to the first strategic priority outlined by the WHO Immunisation Agenda 2030(200), to sustain trust and therefore vaccination uptake for COVID-19 vaccines and any new vaccines on the horizon.

5.2.1 Linked data for rare serious adverse events surveillance

Population-based studies using linked health and immunisation records in Australia, led by the Australian Childhood Immunisation Register Investigation Team,(201) have been used to examine

vaccination coverage and vaccine effectiveness. My study on SE incidence is the first study in Australia on AEFI using the same linked dataset, and has shown the potential to monitor for serious adverse events that result in hospitalisation using routinely collected health data.

Population-based surveillance using linked health data is particularly important for new vaccines with novel vaccine platforms and adjuvants (such as in emerging COVID-19 vaccines) that may have the potential for unexpected and/or delayed AEFIs. For example, the association between narcolepsy and the 2009 H1N1 pandemic influenza vaccine was first confirmed and quantified using linked population health data in Finland.(202) Linked population-based data also allows AEFI monitoring of at-risk populations, including those with underlying medical conditions, specific age groups, pregnant women and others, where clinical trial safety data may be lacking, but vaccination is warranted or even a priority due to the potential benefits. This paradox is exemplified in the emergency approval and rollout of COVID-19 vaccine programs in the context of the current pandemic, in which the greatest morbidity and mortality is seen in the elderly and those with complex underlying medical conditions, yet they had no or limited inclusion in randomised controlled clinical trials.

Australia is one of only a handful of countries with health and vaccination registries that are inclusive of the whole population. Population health data in Australia is available from birth and death registries; perinatal, hospitalisation and emergency department datasets; the Medicare Benefits Schedule; the Pharmaceutical Benefits Scheme; and the National Notifiable Diseases Surveillance System. Data from the Australian Immunisation Register comprises vaccination records for the whole of life and includes vaccine brands. Linking population health and immunisation register data can assist in differentiating vaccine safety profiles by brand. It also allows population-based rates of AEFIs and adverse events of special interest (AESIs), such as myocarditis, pericarditis, Guillain-Barré syndrome, encephalitis, myelitis and others as identified by the Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC) Project for COVID-19 vaccines,(203) to be estimated by vaccination status to measure the magnitude of association between an AEFI and a specific vaccine and brand.

As novel COVID-19 vaccines are being rolled out, the immediate research priority should be using linked data to identify expected levels (background rates) of AEFIs and AESIs prior to the introduction

of these vaccines, as identified by the ACCESS (vACCine covid-19 monitoring readinESS) project(204) led by the Vaccine Monitoring Collaboration for Europe.(205) Then rates of AEFIs after the introduction of new vaccines can be contextualised as a way of signal confirmation for rare, late-onset and unexpected AEFIs, and magnitude of association can be measured once a signal has been confirmed. This methodology has already been implemented in Denmark and Norway to calculate observed compared to expected rates of thromboembolic events following vaccination with Oxford-AstraZeneca ChAdOx1-S vaccine(206) and rates of myocarditis following vaccination with mRNA COVID-19 vaccines.(198)

5.2.2 Adversomics

The risk of serious adverse events following vaccination at a population level may be different to the risk at an individual level, depending on an individual's immunological response and genetic makeup. This has long been known to apply to the world of medicines and therapeutics. This emerging science, the immunogenetics and immunogenomics of vaccine adverse events at the individual and population level, respectively, as defined by Poland et al.(207) as "adversomics".

The application of adversomics was demonstrated in this thesis in the examination of VP-SE in children subsequently diagnosed with an underlying genetic epilepsy compared to presentations of simple VP-FS in those who did not have this underlying condition. This work builds on the association between a vaccine-associated epileptic encephalopathy and an underlying genetic variant in the *SCN1A* gene that was first reported by our collaborators Berkovic et al.(175) Another example of the use of adversomics is the discovery of the genotypic association between an increased risk of narcolepsy and receipt of the 2009 H1N1 pandemic influenza vaccine that was first identified using linked population health data. An increased antibody response to the vaccine viral nucleoprotein was observed to be associated with the HLA-DQB1*06:02 risk allele for narcolepsy.(208, 209)

This thesis demonstrated that early identification of underlying genetic variants allows for tailored vaccination plans to ensure safe vaccination of these individuals. Future adversomics research, through the establishment of biobanks for AEFIs, with accompanying clinical details, within the

existing national network of Specialist Immunisation Clinics and through jurisdictional collaborations, could possibly lead to improved individualisation of vaccination management for even safer outcomes.

5.2.3 Revaccination protocol development through Specialist Immunisation Clinic networks

The review of existing management practices for subsequent vaccinations following serious AEFIs and their longer-term clinical outcomes was only possible in this thesis through collaborative work undertaken via an established network of Specialist Immunisation Clinics in Australia, the Adverse Event Following Immunisation Clinical Assessment Network (AEFI-CAN), where case identification and detailed clinical information was readily available.

Future research should focus on developing a clinical protocol for revaccination following VPS based on my thesis findings; the dissemination and use of this protocol through AEFI-CAN in Australia and, potentially, through other immunisation clinical networks globally; validation of the protocol through a prospective study; and finally, endorsement of the protocol based on findings of validation studies by international expert groups such as ILAE. The same methodology should be used to harmonise clinical practice guidelines for other serious AEFIs. Assessment and revaccination protocols should be developed both nationally through AEFI-CAN and also through international collaborations through the International Network of Special Immunisation Services, including the US Clinical Immunization Safety Assessment network. Prospective routine collation of revaccination outcomes using standardised case report forms within such networks can be analysed periodically to develop best practices that are evidence based, and to provide individualised care that can be based on phenotypic and genotypic profile.

The expansion of such clinical networks to adult services would enable clinical follow up and revaccination management and outcomes in the older population to be captured. Immunisation programs are continually expanding to encompass whole of life. Examples include live attenuated shingles (zoster) vaccine for the older population and now multiple novel COVID-19 vaccines for all adults. It is therefore important to set up similar safety monitoring mechanisms for all populations who are recommended a vaccination.

5.2.4 A programmatic approach

AEFI surveillance and investigation at the population level using linked data, together with genomics, clinical management and follow-up data at the individual level, should be part of the national vaccine safety surveillance system to inform both immunisation programmatic policies and individualised patient care.

I am fortunate to have already had the opportunity to contribute to and incorporate many of the AEFI surveillance and investigation methodologies outlined in this section into the expansion and enhancement of Australia's vaccine safety surveillance program, AusVaxSafety, for COVID-19 vaccine surveillance, in conjunction with the Therapeutic Goods Administration and Australian Government Department of Health. This will see the AusVaxSafety program expand from the well-established active surveillance system(148, 210-214) that solicits AEFIs in the days following vaccination, to include surveillance, investigation and follow-up of serious, unexpected and late-onset AEFIs and AESIs through hospital surveillance and data linkage studies. A new national program of research has been established to prospectively collect long-term clinical and psychological outcome data in those with serious AEFIs including thrombosis with thrombocytopenia syndrome and myocarditis. This together with proposed data linkage studies will also contribute to the Global COVID Vaccine Safety Project led by the Global Vaccine Data Network. I hope to continue to apply my skills and research knowledge acquired through this thesis as the clinical lead in AusVaxSafety to further enhance and strengthen Australia's vaccine safety system.

References

1. World Health Organization. Module 3: Adverse events following immunisation. In: Expanded Programme on Immunisation DoI, Vaccines and Biologicals, editor. Vaccine safety bascis learning manual. Geneva, Switzerland: WHO Document Production Services; 2013.
2. Chen RT, Shimabukuro TT, Martin DB, Zuber PL, Weibel DM, Sturkenboom M. Enhancing vaccine safety capacity globally: A lifecycle perspective. Vaccine. 2015;33 Suppl 4(0 4):D46-54.
3. Stokes B. Ministerial review into the public health response into the adverse events to the seasonal influenza vaccine: final report to the Minister for Health. Perth, Australia: Department of Health; 2010.
4. Gold MS, Effler P, Kelly H, Richmond PC, Buttery JP. Febrile convulsions after 2010 seasonal trivalent influenza vaccine: implications for vaccine safety surveillance in Australia. Med J Aust. 2010;193(9):492-3.
5. Department of Health and Human Services, Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices: summary report, August 5, 2010. Atlanta, GA: CDC; 2010.
6. Therapeutic Goods Administration. Overview of vaccine regulation and safety monitoring and investigation into adverse events following 2010 seasonal influenza vaccination in young children. Canberra, Australia: Australian Government Department of Health and Ageing; 2010.
7. Blyth CC, Richmond PC, Jacoby P, Thornton P, Regan A, Robins C, et al. The impact of pandemic A(H1N1)pdm09 influenza and vaccine-associated adverse events on parental attitudes and influenza vaccine uptake in young children. Vaccine. 2014;32(32):4075-81.
8. Smith M, Peacock G, Uyeki TM, Moore C. Influenza vaccination in children with neurologic or neurodevelopmental disorders. Vaccine. 2015;33(20):2322-7.
9. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470-2.
10. Nickels KC, Zaccariello MJ, Hamiwka LD, Wirrell EC. Cognitive and neurodevelopmental comorbidities in paediatric epilepsy. Nat Rev Neurol. 2016;12(8):465-76.
11. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia. 1993;34(4):592-6.
12. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. N Engl J Med. 1976;295(19):1029-33.
13. Berg AT, Shinnar S. Unprovoked seizures in children with febrile seizures: short-term outcome. Neurology. 1996;47(2):562-8.
14. Berg AT, Shinnar S. Complex febrile seizures. Epilepsia. 1996;37(2):126-33.
15. Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. I – Prevalence and recurrence in the first five years of life. BMJ (Clin Res Ed). 1985;290(6478):1307-10.
16. Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. Pediatrics. 1978;61(5):720-7.
17. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med. 1987;316(9):493-8.
18. Hauser WA. The prevalence and incidence of convulsive disorders in children. Epilepsia. 1994;35 Suppl 2:S1-6.
19. Offringa M, Bossuyt PM, Lubsen J, Ellenberg JH, Nelson KB, Knudsen FU, et al. Risk factors for seizure recurrence in children with febrile seizures: a pooled analysis of individual patient data from five studies. J Pediatr. 1994;124(4):574-84.
20. Offringa M, Hazebroek-Kampschreur AA, Derksen-Lubsen G. Prevalence of febrile seizures in Dutch school children. Paediatr Perinat Epidemiol. 1991;5(2):181-8.
21. Johnston MV. Seizures in childhood. In: Kliegman RM, editor. Nelson's textbook of paediatrics. 18th ed. Philadelphia, PA: Elsevier Saunders; 2006.

22. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures, American Academy of Pediatrics. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics. 2008;121(6):1281-6.
23. Van der Berg BJ, Yerushalmy J. Studies on convulsive disorders in young children. I. Incidence of febrile and nonfebrile convulsions by age and other factors. Pediatr Res. 1969;3(4):298-304.
24. Okubo Y, Handa A. National trend survey of hospitalized patients with febrile seizure in the United States. Seizure. 2017;50:160-5.
25. Manfredini R, Vergine G, Boari B, Faggioli R, Borgna-Pignatti C. Circadian and seasonal variation of first febrile seizures. J Pediatr. 2004;145(6):838-9.
26. Millichap JJ, Millichap JG. Diurnal and seasonal occurrence of febrile seizures. Pediatr Neurol Briefs. 2015;29(4):29.
27. Chiu SS, Tse CY, Lau YL, Peiris M. Influenza A infection is an important cause of febrile seizures. Pediatrics. 2001;108(4):E63.
28. Chung B, Wong V. Relationship between five common viruses and febrile seizure in children. Arch Dis Child. 2007;92(7):589-93.
29. Polkinghorne BG, Muscatello DJ, Macintyre CR, Lawrence GL, Middleton PM, Torvaldsen S. Relationship between the population incidence of febrile convulsions in young children in Sydney, Australia and seasonal epidemics of influenza and respiratory syncytial virus, 2003–2010: a time series analysis. BMC Infect Dis. 2011;11:291.
30. Millichap JG, Millichap JJ. Role of viral infections in the etiology of febrile seizures. Pediatr Neurol. 2006;35(3):165-72.
31. Hall CB, Long CE, Schnabel KC, Caserta MT, McIntyre KM, Costanzo MA, et al. Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. N Engl J Med. 1994;331(7):432-8.
32. Bertolani MF, Portolani M, Marotti F, Sabbattini AM, Chiossi C, Bandieri MR, et al. A study of childhood febrile convulsions with particular reference to HHV-6 infection: pathogenic considerations. Childs Nerv Syst. 1996;12(9):534-9.
33. Epstein LG, Shinnar S, Hesdorffer DC, Nordli DR, Hamidullah A, Benn EK, et al. Human herpesvirus 6 and 7 in febrile status epilepticus: the FEBSTAT study. Epilepsia. 2012;53(9):1481-8.
34. Shinnar S. Febrile seizures and mesial temporal sclerosis. Epilepsy Curr. 2003;3(4):115-8.
35. Verity CM, Golding J. Risk of epilepsy after febrile convulsions: a national cohort study. BMJ. 1991;303(6814):1373-6.
36. Greenberg DA, Holmes GL. The genetics of febrile seizures. In: Baram TZ, Shinnar S, editors. Febrile seizures. San Diego, CA: Academic Press; 2002. p. 249-61.
37. Berg AT, Shinnar S, Darefsky AS, Holford TR, Shapiro ED, Salomon ME, et al. Predictors of recurrent febrile seizures. a prospective cohort study. Arch Pediatr Adolesc Med. 1997;151(4):371-8.
38. Audenaert D, Schwartz E, Claeys KG, Claes L, Deprez L, Suls A, et al. A novel GABRG2 mutation associated with febrile seizures. Neurology. 2006;67(4):687-90.
39. Wallace RH, Scheffer IE, Barnett S, Richards M, Dibbens L, Desai RR, et al. Neuronal sodium-channel alpha1-subunit mutations in generalized epilepsy with febrile seizures plus. Am J Hum Genet. 2001;68(4):859-65.
40. Schubert J, Siekierska A, Langlois M, May P, Huneau C, Becker F, et al. Mutations in STX1B, encoding a presynaptic protein, cause fever-associated epilepsy syndromes. Nat Genet. 2014;46(12):1327-32.
41. Zhang YH, Burgess R, Malone JP, Glubb GC, Helbig KL, Vadlamudi L, et al. Genetic epilepsy with febrile seizures plus: refining the spectrum. Neurology. 2017;89(12):1210-9.
42. Scheffer IE, Berkovic SF. Generalized epilepsy with febrile seizures plus: a genetic disorder with heterogeneous clinical phenotypes. Brain. 1997;120(Pt 3):479-90.
43. Singh R, Scheffer IE, Crossland K, Berkovic SF. Generalized epilepsy with febrile seizures plus: a common childhood-onset genetic epilepsy syndrome. Ann Neurol. 1999;45(1):75-81.

44. Bethune P, Gordon K, Dooley J, Camfield C, Camfield P. Which child will have a febrile seizure? Am J Dis Child. 1993;147(1):35-9.
45. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures, American Academy of Pediatrics. Clinical practice guideline – Febrile seizures: guideline for the neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics. 2011;127(2):389-94.
46. Frantzen E, Lennox-Buchthal M, Nygaard A. Longitudinal EEG and clinical study of children with febrile convulsions. Electroencephalogr Clin Neurophysiol. 1968;24(3):197-212.
47. Thorn I. The significance of electroencephalography in febrile convulsions. In: Akimoto H, Kazamatsuri H, Seino M, Ward A, editors. Advances in epileptology: 13th International Epilepsy Symposium. New York, NY: Raven Press; 1982. p. 93-5.
48. Harden C. Findings from the FEBSTAT study: can observations after a provoked seizure occurrence have broad implications for epileptogenesis? Epilepsy Curr. 2013;13(3):143-5.
49. Schnaiderman D, Lahat E, Sheefer T, Aladjem M. Antipyretic effectiveness of acetaminophen in febrile seizures: ongoing prophylaxis versus sporadic usage. Eur J Pediatr. 1993;152(9):747-9.
50. Uhari M, Rantala H, Vainionpaa L, Kurttila R. Effect of acetaminophen and of low intermittent doses of diazepam on prevention of recurrences of febrile seizures. J Pediatr. 1995;126(6):991-5.
51. Murata S, Okasora K, Tanabe T, Ogino M, Yamazaki S, Oba C, et al. Acetaminophen and febrile seizure recurrences during the same fever episode. Pediatrics. 2018;142(5):e20181009.
52. Offringa M, Newton R, Cozijnsen MA, Nevitt SJ. Prophylactic drug management for febrile seizures in children. Cochrane Database Syst Rev. 2017;(2):CD003031.
53. Verrotti A, Latini G, di Corcia G, Giannuzzi R, Salladini C, Trotta D, et al. Intermittent oral diazepam prophylaxis in febrile convulsions: its effectiveness for febrile seizure recurrence. Europ J Paediatr Neurol. 2004;8(3):131-4.
54. Rosman NP, Colton T, Labazzo J, Gilbert PL, Gardella NB, Kaye EM, et al. A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. N Engl J Med. 1993;329(2):79-84.
55. Bajaj AS, Bajaj BK, Purib V, Tayal G. Intermittent clobazam in febrile seizures: an Indian experience. J Pediatr Neurol. 2005;3(1):19-23.
56. Shinnar S, Glauser TA. Febrile seizures. J Child Neurol. 2002;17 Suppl 1:S44-52.
57. Uemura N, Okumura A, Negoro T, Watanabe K. Clinical features of benign convulsions with mild gastroenteritis. Brain Dev. 2002;24(8):745-9.
58. Pavlidou E, Tzitiridou M, Kontopoulos E, Panteliadis CP. Which factors determine febrile seizure recurrence? A prospective study. Brain Dev. 2008;30(1):7-13.
59. Hesdorffer DC, Benn EK, Bagiella E, Nordli D, Pellock J, Hinton V, et al. Distribution of febrile seizure duration and associations with development. Ann Neurol. 2011;70(1):93-100.
60. Shinnar S, Bello JA, Chan S, Hesdorffer DC, Lewis DV, Macfall J, et al. MRI abnormalities following febrile status epilepticus in children: the FEBSTAT study. Neurology. 2012;79(9):871-7.
61. Vestergaard M, Pedersen CB, Sidenius P, Olsen J, Christensen J. The long-term risk of epilepsy after febrile seizures in susceptible subgroups. Am J Epidemiol. 2007;165(8):911-8.
62. Chung S. Febrile seizures. Korean journal of pediatrics. 2014;57(9):384-95.
63. Leaffer EB, Hinton VJ, Hesdorffer DC. Longitudinal assessment of skill development in children with first febrile seizure. Epilepsy Behav. 2013;28(1):83-7.
64. Visser AM, Jaddoe VW, Ghassabian A, Schenk JJ, Verhulst FC, Hofman A, et al. Febrile seizures and behavioural and cognitive outcomes in preschool children: the Generation R study. Dev Med Child Neurol. 2012;54(11):1006-11.
65. Chang YC, Guo NW, Huang CC, Wang ST, Tsai JJ. Neurocognitive attention and behavior outcome of school-age children with a history of febrile convulsions: a population study. Epilepsia. 2000;41(4):412-20.
66. Ellenberg JH, Nelson KB. Febrile seizures and later intellectual performance. Arch Neurol. 1978;35(1):17-21.

67. Hackett R, Hackett L, Bhakta P. Febrile seizures in a south Indian district: incidence and associations. Dev Med Child Neurol. 1997;39(6):380-4.

68. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. N Engl J Med. 1998;338(24):1723-8.

69. Scott RC, King MD, Gadian DG, Neville BG, Connelly A. Hippocampal abnormalities after prolonged febrile convulsion: a longitudinal MRI study. Brain. 2003;126(Pt 11):2551-7.

70. Sokol DK, Demyer WE, Edwards-Brown M, Sanders S, Garg B. From swelling to sclerosis: acute change in mesial hippocampus after prolonged febrile seizure. Seizure. 2003;12(4):237-40.

71. Byeon JH, Kim GH, Kim JY, Sun W, Kim H, Eun BL. Cognitive dysfunction and hippocampal damage induced by hypoxic-ischemic brain injury and prolonged febrile convulsions in immature rats. J Korean Neurosurg Soc. 2015;58(1):22-9.

72. Cooper JM, Gadian DG, Jentschke S, Goldman A, Munoz M, Pitts G, et al. Neonatal hypoxia, hippocampal atrophy, and memory impairment: evidence of a causal sequence. Cereb Cortex. 2015;25(6):1469-76.

73. Chang YC, Guo NW, Wang ST, Huang CC, Tsai JJ. Working memory of school-aged children with a history of febrile convulsions: a population study. Neurology. 2001;57(1):37-42.

74. Smith JA, Wallace SJ. Febrile convulsions: intellectual progress in relation to anticonvulsant therapy and to recurrence of fits. Arch Dis Child. 1982;57(2):104-7.

75. Norgaard M, Ehrenstein V, Mahon BE, Nielsen GL, Rothman KJ, Sorensen HT. Febrile seizures and cognitive function in young adult life: a prevalence study in Danish conscripts. J Pediatr. 2009;155(3):404-9.

76. Kolfen W, Pehle K, Konig S. Is the long-term outcome of children following febrile convulsions favorable? Dev Med Child Neurol. 1998;40(10):667-71.

77. Weiss EF, Masur D, Shinnar S, Hesdorffer DC, Hinton VJ, Bonner M, et al. Cognitive functioning one month and one year following febrile status epilepticus. Epilepsy Behav. 2016;64(Pt A):283-8.

78. Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain. 2012;135(Pt 8):2329-36.

79. Hurst DL. Epidemiology of severe myoclonic epilepsy of infancy. Epilepsia. 1990;31(4):397-400.

80. Depienne C, Trouillard O, Saint-Martin C, Gourfinkel-An I, Bouteiller D, Carpentier W, et al. Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients. J Med Genet. 2009;46(3):183-91.

81. Korff C, Laux L, Kelley K, Goldstein J, Koh S, Nordli D, Jr. Dravet syndrome (severe myoclonic epilepsy in infancy): a retrospective study of 16 patients. J Child Neurol. 2007;22(2):185-94.

82. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet. 2001;68(6):1327-32.

83. Harkin LA, McMahon JM, Iona X, Dibbens L, Pelekanos JT, Zuberi SM, et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain. 2007;130(Pt 3):843-52.

84. Mulley JC, Scheffer IE, Petrou S, Dibbens LM, Berkovic SF, Harkin LA. SCN1A mutations and epilepsy. Hum Mutat. 2005;25(6):535-42.

85. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infants (Dravet syndrome). In: Roger J, Bureau M, Dravet C, Genton P, Tassinari C, Wolf P, editors. Epileptic syndromes in infancy, childhood and adolescence. 3rd ed. London, England: John Libbey Eurotext; 2005. p. 89-113.

86. Nabbout R, Chemaly N, Chipaux M, Barcia G, Bouis C, Dubouch C, et al. Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. Orphanet J Rare Dis. 2013;8:176.

87. Wakai S, Ito N, Sueoka H, Kawamoto Y, Hayasaka H, Chiba S. Severe myoclonic epilepsy in infancy and carbamazepine. Eur J Pediatr. 1996;155(8):724.

88. Guerrini R, Dravet C, Genton P, Belmonte A, Kaminska A, Dulac O. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. Epilepsia. 1998;39(5):508-12.
89. Meldrum BS, Horton RW. Physiology of status epilepticus in primates. Arch Neurol. 1973;28(1):1-9.
90. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus – report of the ILAE task force on classification of status epilepticus. Epilepsia. 2015;56(10):1515-23.
91. Gastaut H. Classification of status epilepticus. Adv Neurol. 1983;34:15-35.
92. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. Neurology. 1998;50(3):735-41.
93. Maytal J, Shinnar S, Moshe SL, Alvarez LA. Low morbidity and mortality of status epilepticus in children. Pediatrics. 1989;83(3):323-31.
94. DeLorenzo RJ, Hauser WA, Towne AR, Boggs JG, Pellock JM, Penberthy L, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology. 1996;46(4):1029-35.
95. DeLorenzo RJ, Towne AR, Pellock JM, Ko D. Status epilepticus in children, adults, and the elderly. Epilepsia. 1992;33 Suppl 4:S15-25.
96. Shinnar S, Pellock JM, Moshe SL, Maytal J, O'Dell C, Driscoll SM, et al. In whom does status epilepticus occur: age-related differences in children. Epilepsia. 1997;38(8):907-14.
97. Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). Neurology. 2000;55(5):693-7.
98. Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC, et al. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet. 2006;368(9531):222-9.
99. Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive status epilepticus in California. Neurology. 2002;58(7):1070-6.
100. Ong CT, Sheu SM, Tsai CF, Wong YS, Chen SC. Age-dependent sex difference of the incidence and mortality of status epilepticus: a twelve year nationwide population-based cohort study in Taiwan. PLoS One. 2015;10(3):e0122350.
101. Nishiyama I, Ohtsuka Y, Tsuda T, Kobayashi K, Inoue H, Narahara K, et al. An epidemiological study of children with status epilepticus in Okayama, Japan: incidence, etiologies, and outcomes. Epilepsy Res. 2011;96(1-2):89-95.
102. Knake S, Rosenow F, Vescovi M, Oertel WH, Mueller HH, Wirbatz A, et al. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia. 2001;42(6):714-8.
103. Lv RJ, Wang Q, Cui T, Zhu F, Shao XQ. Status epilepticus-related etiology, incidence and mortality: A meta-analysis. Epilepsy Res. 2017;136:12-7.
104. Logroscino G, Hesdorffer DC, Cascino GD, Annegers JF, Bagiella E, Hauser WA. Long-term mortality after a first episode of status epilepticus. Neurology. 2002;58(4):537-41.
105. National Institute for Health and Care Excellence. Epilepsies: diagnosis and management. London, England: NICE; 2018.
106. Agency for Clinical Innovation. Infants and children – acute management of seizures. In: Health N, editor. Sydney, Australia: NSW Health; 2018.
107. Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? Ann Neurol. 2001;49(5):659-64.
108. Ashrafi MR, Khosroshahi N, Karimi P, Malamiri RA, Bavarian B, Zarch AV, et al. Efficacy and usability of buccal midazolam in controlling acute prolonged convulsive seizures in children. Europ J Paediatr Neurol. 2010;14(5):434-8.
109. McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. Lancet. 2005;366(9481):205-10.

110. Mpimbaza A, Ndeezi G, Staedke S, Rosenthal PJ, Byarugaba J. Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. Pediatrics. 2008;121(1):e58-64.
111. Chamberlain JM, Okada P, Holsti M, Mahajan P, Brown KM, Vance C, et al. Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. JAMA. 2014;311(16):1652-60.
112. Reiter PD, Huff AD, Knupp KG, Valuck RJ. Intravenous levetiracetam in the management of acute seizures in children. Pediatr Neurol. 2010;43(2):117-21.
113. Gallentine WB, Hunnicutt AS, Husain AM. Levetiracetam in children with refractory status epilepticus. Epilepsy Behav. 2009;14(1):215-8.
114. Kim JS, Lee JH, Ryu HW, Lim BC, Hwang H, Chae JH, et al. Effectiveness of intravenous levetiracetam as an adjunctive treatment in pediatric refractory status epilepticus. Pediatr Emerg Care. 2014;30(8):525-8.
115. Isguder R, Guzel O, Ceylan G, Yilmaz U, Agin H. A comparison of intravenous levetiracetam and valproate for the treatment of refractory status epilepticus in children. J Child Neurol. 2016;31(9):1120-6.
116. Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. Lancet. 2019;393(10186):2135-45.
117. Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet. 2019;393(10186):2125-34.
118. Dunn DW. Status epilepticus in children: etiology, clinical features, and outcome. J Child Neurol. 1988;3(3):167-73.
119. Aicardi J, Chevrie JJ. Convulsive status epilepticus in infants and children: a study of 239 cases. Epilepsia. 1970;11(2):187-97.
120. Cavazzuti GB, Ferrari P, Lalla M. Follow-up study of 482 cases with convulsive disorders in the first year of life. Dev Med Child Neurol. 1984;26(4):425-37.
121. Shinnar S, Maytal J, Krasnoff L, Moshe SL. Recurrent status epilepticus in children. Ann Neurol. 1992;31(6):598-604.
122. Neville BG, Chin RF, Scott RC. Childhood convulsive status epilepticus: epidemiology, management and outcome. Acta Neurol Scand Suppl. 2007;186:21-4.
123. Besli GE, Saltik S, Erguven M, Bulut O, Abul MH. Status epilepticus in children: causes, clinical features and short-term outcome. Pediatr Int. 2010;52(5):749-53.
124. Hauser WA. Status epilepticus: epidemiologic considerations. Neurology. 1990;40(5 Suppl 2):9-13.
125. Hauser WA, Anderson VE, Loewenson RB, McRoberts SM. Seizure recurrence after a first unprovoked seizure. N Engl J Med. 1982;307(9):522-8.
126. Shinnar S, Berg AT, Moshe SL, O'Dell C, Alemany M, Newstein D, et al. The risk of seizure recurrence after a first unprovoked afebrile seizure in childhood: an extended follow-up. Pediatrics. 1996;98(2 Pt 1):216-25.
127. Yoong M, Martinos MM, Chin RF, Clark CA, Scott RC. Hippocampal volume loss following childhood convulsive status epilepticus is not limited to prolonged febrile seizures. Epilepsia. 2013;54(12):2108-15.
128. Yoong M, Seunarine K, Martinos M, Chin RF, Clark CA, Scott RC. Prolonged febrile seizures cause reversible reductions in white matter integrity. Neuroimage Clin. 2013;3:515-21.
129. Martinos MM, Yoong M, Patil S, Chong WK, Mardari R, Chin RF, et al. Early developmental outcomes in children following convulsive status epilepticus: a longitudinal study. Epilepsia. 2013;54(6):1012-9.
130. Raspall-Chaure M, Chin RFM, Neville BG, Bedford H, Scott RC. The epidemiology of convulsive status epilepticus in children: a critical review. Epilepsia. 2007;48(9):1652-63.

131. Martinos MM, Pujar S, Gillberg C, Cortina-Borja M, Neville BGR, De Haan M, et al. Long-term behavioural outcomes after paediatric convulsive status epilepticus: a population-based cohort study. Dev Med Child Neurol. 2018;60(4):409-16.
132. Reilly C, Atkinson P, Das KB, Chin RF, Aylett SE, Burch V, et al. Features of autism spectrum disorder (ASD) in childhood epilepsy: a population-based study. Epilepsy Behav. 2015;42:86-92.
133. Reilly C, Atkinson P, Das KB, Chin RFM, Aylett SE, Burch V, et al. Parent- and teacher-reported symptoms of ADHD in school-aged children with active epilepsy: a population-based study. J Atten Disord. 2017;21(11):887-97.
134. Sundelin HE, Larsson H, Lichtenstein P, Almqvist C, Hultman CM, Tomson T, et al. Autism and epilepsy: a population-based nationwide cohort study. Neurology. 2016;87(2):192-7.
135. Bonhoeffer J, Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004;22(5-6):557-62.
136. Marcy MS, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004;22(5-6):551-6.
137. Macartney K, Gidding HF, Trinh L, Wang H, Dey A, Hull B, et al. Evaluation of combination measles-mumps-rubella-varicella vaccine introduction in Australia. JAMA Pediatr. 2017;171(10):992-8.
138. Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics. 2010;126(1):e1-8.
139. Australian Technical Advisory Group on Immunisation (ATAGI). Australian immunisation handbook [online] Canberra, Australia: Australian Government Department of Health; 2018 [cited 2021 10 February]. Available from: https://immunisationhandbook.health.gov.au.
140. Rowhani-Rahbar A, Klein NP, Dekker CL, Edwards KM, Marchant CD, Vellozzi C, et al. Biologically plausible and evidence-based risk intervals in immunization safety research. Vaccine. 2012;31(1):271-7.
141. Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med. 2001;345(9):656-61.
142. Sun Y, Christensen J, Hviid A, Li J, Vedsted P, Olsen J, et al. Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type B. JAMA. 2012;307(8):823-31.
143. Farrington P, Rush M, Miller E, Pugh S, Colville A, Flower A, et al. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. Lancet. 1995;345(8949):567-9.
144. Andrews N, Stowe J, Wise L, Miller E. Post-licensure comparison of the safety profile of diphtheria/tetanus/whole cell pertussis/Haemophilus influenza type b vaccine and a 5-in-1 diphtheria/tetanus/acellular pertussis/Haemophilus influenza type b/polio vaccine in the United Kingdom. Vaccine. 2010;28(44):7215-20.
145. Huang WT, Gargiullo PM, Broder KR, Weintraub ES, Iskander JK, Klein NP, et al. Lack of association between acellular pertussis vaccine and seizures in early childhood. Pediatrics. 2010;126(2):263-9.
146. Hambidge SJ, Glanz JM, France EK, McClure D, Xu S, Yamasaki K, et al. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. JAMA. 2006;296(16):1990-7.
147. 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.
148. Pillsbury A, Quinn H, Cashman P, Leeb A, Macartney K. Active SMS-based influenza vaccine safety surveillance in Australian children. Vaccine. 2017;35(51):7101-6.
149. Miller E, Andrews N, Stowe J, Grant A, Waight P, Taylor B. Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom. Am J Epidemiol. 2007;165(6):704-9.

150. 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(6):645-50.

151. Klein NP, Lewis E, Baxter R, Weintraub E, Glanz J, Naleway A, et al. Measles-containing vaccines and febrile seizures in children age 4 to 6 years. Pediatrics. 2012;129(5):809-14.

152. Miller D, Wadsworth J, Ross E. Severe neurological illness: further analyses of the British National Childhood Encephalopathy Study. Tokai J Exp Clin Med. 1988;13 Suppl:145-55.

153. Institute of Medicine (US) Committee. Adverse effects of pertussis and rubella vaccines: a report of the committee to review the adverse consequences of pertussis and rubella vaccines. Howson CP, Howe CJ, Fineberg HV, editors. Washington, DC: National Academies Press (US); 1991.

154. Macartney KK, Gidding HF, Trinh L, Wang H, McRae J, Crawford N, et al. Febrile seizures following measles and varicella vaccines in young children in Australia. Vaccine. 2015;33(11):1412-7.

155. Deng L, Gidding H, Macartney K, Crawford N, Buttery J, Gold M, et al. Postvaccination febrile seizure severity and outcome. Pediatrics. 2019;143(5):e20182120.

156. Griffin MR, Ray WA, Mortimer EA, Fenichel GM, Schaffner W. Risk of seizures after measles-mumps-rubella immunization. Pediatrics. 1991;88(5):881-5.

157. 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.

158. Petousis-Harris H, Poole T, Turner N, Reynolds G. Febrile events including convulsions following the administration of four brands of 2010 and 2011 inactivated seasonal influenza vaccine in NZ infants and children: the importance of routine active safety surveillance. Vaccine. 2012;30(33):4945-52.

159. Maraskovsky E, Rockman S, Dyson A, Koernig S, Becher D, Morelli AB, et al. Scientific investigations into febrile reactions observed in the paediatric population following vaccination with a 2010 southern hemisphere trivalent influenza vaccine. Vaccine. 2012;30(51):7400-6.

160. Kelly HA, Skowronski DM, De Serres G, Effler PV. Adverse events associated with 2010 CSL and other inactivated influenza vaccines. Med J Aust. 2011;195(6):318-20.

161. Rockman S, Becher D, Dyson A, Koernig S, Morelli AB, Barnden M, et al. Role of viral RNA and lipid in the adverse events associated with the 2010 southern hemisphere trivalent influenza vaccine. Vaccine. 2014;32(30):3869-76.

162. Blyth CC, Currie AJ, Wiertsema SP, Conway N, Kirkham LA, Fuery A, et al. Trivalent influenza vaccine and febrile adverse events in Australia, 2010: clinical features and potential mechanisms. Vaccine. 2011;29(32):5107-13.

163. Rockman S, Dyson A, Koernig S, Becher D, Ng M, Morelli AB, et al. Evaluation of the bioactivity of influenza vaccine strains in vitro suggests that the introduction of new strains in the 2010 southern hemisphere trivalent influenza vaccine is associated with adverse events. Vaccine. 2014;32(30):3861-8.

164. Leroy Z, Broder K, Menschik D, Shimabukuro T, Martin D. Febrile seizures after 2010-2011 influenza vaccine in young children, United States: a vaccine safety signal from the vaccine adverse event reporting system. Vaccine. 2012;30(11):2020-3.

165. Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. 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):2024-31.

166. Li R, Stewart B, McNeil MM, Duffy J, Nelson J, Kawai AT, et al. Post licensure surveillance of influenza vaccines in the Vaccine Safety Datalink in the 2013–2014 and 2014–2015 seasons. Pharmacoepidemiol Drug Saf. 2016;25(8):928-34.

167. Kawai AT, Martin D, Kulldorff M, Li L, Cole DV, McMahill-Walraven CN, et al. Febrile seizures after 2010–2011 trivalent inactivated influenza vaccine. Pediatrics. 2015;136(4):e848-55.

168. Tartof SY, Tseng HF, Liu AL, Qian L, Sy LS, Hechter RC, et al. Exploring the risk factors for vaccine-associated and non-vaccine associated febrile seizures in a large pediatric cohort. Vaccine. 2014;32(22):2574-81.

169. Tartof SY, Tseng HF, Liu IL, Qian L, Sy LS, Hechter RC, et al. Inpatient admission for febrile seizure and subsequent outcomes do not differ in children with vaccine-associated versus non-vaccine associated febrile seizures. Vaccine. 2014;32(48):6408-14.

170. Black FL, Hierholzer W, Woodall JP, Pinhiero F. Intensified reactions to measles vaccine in unexposed populations of American Indians. J Infect Dis. 1971;124(3):306-17.

171. Stanley SL, Jr., Frey SE, Taillon-Miller P, Guo J, Miller RD, Koboldt DC, et al. The immunogenetics of smallpox vaccination. J Infect Dis. 2007;196(2):212-9.

172. Schlachter K, Gruber-Sedlmayr U, Stogmann E, Lausecker M, Hotzy C, Balzar J, et al. A splice site variant in the sodium channel gene SCN1A confers risk of febrile seizures. Neurology. 2009;72(11):974-8.

173. Petrovski S, Scheffer IE, Sisodiya SM, O'Brien TJ, Berkovic SF. Lack of replication of association between SCN1A SNP and febrile seizures. Neurology. 2009;73(22):1928-30.

174. Feenstra B, Pasternak 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(12):1274-82.

175. Berkovic SF, Harkin L, McMahon JM, Pelekanos 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(6):488-92.

176. Reyes IS, Hsieh DT, Laux LC, Wilfong AA. Alleged cases of vaccine encephalopathy rediagnosed years later as Dravet syndrome. Pediatrics. 2011;128(3):e699-702.

177. 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(6):592-8.

178. 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(1):175-8.

179. Verbeek NE, van der Maas NA, Sonsma AC, Ippel E, Vermeer-de Bondt PE, Hagebeuk E, et al. Effect of vaccinations on seizure risk and disease course in Dravet syndrome. Neurology. 2015;85(7):596-603.

180. Verbeek NE, van der Maas NA, Jansen FE, van Kempen MJ, Lindhout D, Brilstra EH. Prevalence of SCN1A-related Dravet syndrome among children reported with seizures following vaccination: a population-based ten-year cohort study. PLoS One. 2013;8(6):e65758.

181. Miller DL, Ross EM, Alderslade R, Bellman MH, Rawson NS. Pertussis immunisation and serious acute neurological illness in children. British medical journal (Clinical research ed). 1981;282(6276):1595-9.

182. von Spiczak S, Helbig I, Drechsel-Baeuerle U, Muhle H, van Baalen A, van Kempen MJ, et al. A retrospective population-based study on seizures related to childhood vaccination. Epilepsia. 2011;52(8):1506-12.

183. Zamponi N, Passamonti C, Petrelli C, Veggiotti P, Baldassari C, Verrotti A, et al. Vaccination and occurrence of seizures in SCN1A mutation-positive patients: a multicenter Italian study. Pediatr Neurol. 2014;50(3):228-32.

184. Tillmann BU, Tillmann HC, Heininger U, Lütschg J, Weber P. Acceptance and timeliness of standard vaccination in children with chronic neurological deficits in north-western Switzerland. Eur J Pediatr. 2005;164(5):320-5.

185. Pandolfi E, Carloni E, Marino MG, Ciofi degli Atti ML, Gesualdo F, Romano M, et al. Immunization coverage and timeliness of vaccination in Italian children with chronic diseases. Vaccine. 2012;30(34):5172-8.

186. Campbell JR, Szilagyi PG, Rodewald LE, Winter NL, Humiston SG, Roghmann KJ. Intent to immunize among pediatric and family medicine residents. Arch Pediatr Adolesc Med. 1994;148(9):926-9.

187. Zurynski Y, McIntyre P, Booy R, Elliott EJ, PAEDS Investigators Group. Paediatric Active Enhanced Disease Surveillance: a new surveillance system for Australia. J Paediatr Child Health. 2013;49(7):588-94.

188. World Health Organisation. International Classification of Diseases (ICD) information sheet [online] Geneva, Switzerland: WHO; 2018 [cited 2021 23 April]. Available from: https://www.who.int/classifications/icd/factsheet/en/.

189. Hull BP, Deeks SL, McIntyre PB. The Australian Childhood Immunisation Register – a model for universal immunisation registers? Vaccine. 2009;27(37):5054-60.

190. Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American consensus panel. Pediatr Neurol. 2017;68:18-34.e3.

191. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522-30.

192. Rossetti AO, Trinka E, Stahli C, Novy J. New ILAE versus previous clinical status epilepticus semiologic classification: Analysis of a hospital-based cohort. Epilepsia. 2016;57(7):1036-41.

193. Wirrell EC. Treatment of Dravet Syndrome. Can J Neurol Sci. 2016;43 Suppl 3:S13-8.

194. RCH Immunisation and Neurology Team. Protocol for immunisation of children with Dravet syndrome or other vaccine-proximate seizures [online] Melbourne, Australia: The Royal Children's Hospital Melbourne; 2019 [cited 2021 23 April]. Available from: https://mvec.mcri.edu.au/wp-content/uploads/2020/03/Protocol-for-immunisation-of-children-with-Dravet-syndrome-or-other-vaccine-proximate-seizures.pdf.

195. World Health Organisation. Ten threats to global health in 2019 Geneva, Switzerland: WHO; 2019 [cited 2021 23 April]. Available from: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019.

196. Krammer F. SARS-CoV-2 vaccines in development. Nature. 2020;586(7830):516-27.

197. Shimabukuro T, Nair N. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine. JAMA. 2021;325(8):780-1.

198. Bozkurt B, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. Circulation. 2021;144(6):471-84.

199. World Health Organisation. Global Advisory Committee on Vaccine Safety (GACVS) review of latest evidence of rare adverse blood coagulation events with AstraZeneca COVID-19 Vaccine (Vaxzevria and Covishield) Geneva, Switzerland2021 [cited 2021 1 May]. Available from: https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield).

200. World Health Organisation. Immunisation Agenda 2030: a global strategy to leave no one behind. Geneva, Switzerland; 2020.

201. Gidding H, McCallum L, Fathima P, Snelling T, Liu B, de Klerk N, et al. Probabilistic linkage of national immunisation and state-based health records for a cohort of 1.9 million births to evaluate Australia's childhood immunisation program. Int J Popul Data Sci. 2017;2(1):1-13.

202. Nohynek H, Jokinen J, Partinen M, Vaarala O, Kirjavainen T, Sundman J, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLoS One. 2012;7(3):e33536.

203. Law B. SO2-D2.1.2 Priority list of COVID-19 adverse events of special interest: quarterly update December 2020. Decatur, GA; 2020.

204. Dodd C, Willame C, Sturkenboom M. Feasibility analysis of a European infrastructure for COVID-19 vaccine monitoring: background rates of adverse events of special interest. London, England; 2020.

205. Sturkenboom M, Bahri P, Chiucchiuini A, Grove Krause T, Hahné S, Khromava A, et al. Why we need more collaboration in Europe to enhance post-marketing surveillance of vaccines. Vaccine. 2020;38 Suppl 2:B1-7.

206. Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021;373:n1114.

207. Poland GA, Ovsyannikova IG, Jacobson RM. Adversomics: the emerging field of vaccine adverse event immunogenetics. Pediatr Infect Dis J. 2009;28(5):431-2.

208. Hor H, Kutalik Z, Dauvilliers Y, Valsesia A, Lammers GJ, Donjacour CE, et al. Genome-wide association study identifies new HLA class II haplotypes strongly protective against narcolepsy. Nat Genet. 2010;42(9):786-9.

209. Vaarala O, Vuorela A, Partinen M, Baumann M, Freitag TL, Meri S, et al. Antigenic differences between AS03 adjuvanted influenza A (H1N1) pandemic vaccines: implications for Pandemrix-associated narcolepsy risk. PLoS One. 2014;9(12):e114361.

210. Pillsbury AJ, Glover C, Jacoby P, Quinn HE, Fathima P, Cashman P, et al. Active surveillance of 2017 seasonal influenza vaccine safety: an observational cohort study of individuals aged 6 months and older in Australia. BMJ Open. 2018;8(10):e023263.

211. Pillsbury AJ, Fathima P, Quinn HE, Cashman P, Blyth CC, Leeb A, et al. Comparative Postmarket Safety Profile of Adjuvanted and High-Dose Influenza Vaccines in Individuals 65 Years or Older. JAMA Netw Open. 2020;3(5):e204079.

212. Pillsbury A, Cashman P, Leeb A, Regan A, Westphal D, Snelling T, et al. Real-time safety surveillance of seasonal influenza vaccines in children, Australia, 2015. Euro Surveill. 2015;20(43):pii=30050.

213. Jacoby P, Glover C, Damon C, Fathima P, Pillsbury A, Durrheim D, et al. Timeliness of signal detection for adverse events following influenza vaccination in young children: a simulation case study. BMJ Open. 2020;10(2):e031851.

214. Glover C, Crawford N, Leeb A, Wood N, Macartney K. Active SMS-based surveillance of adverse events following immunisation with influenza and pertussis-containing vaccines in Australian pregnant women using AusVaxSafety. Vaccine. 2020;38(31):4892-900.

Appendices

Appendix 1. Research protocol for Sections 2.4 and 2.5

Febrile seizures following vaccination in children: What is the long-term clinical and developmental outcome?

PROTOCOL

Febrile seizures following vaccination in children: What is the long-term clinical and developmental outcome?

Protocol Number: **FS2013**

Version: 5
Date: 15/09/2015

Author/s:
Dr Nicholas Wood

Sponsor/s:
Not applicable

Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

FS 2013 Protocol Update	
Version 1	11th April 2014
Version 2	30th May 2014
Version 3	13th June 2014
Version 4	14th October 2014
Version 5	15th September 2015

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1. Glossary of Abbreviations & Terms

Abbreviation	Description (using lay language)
PVFS	Post febrile seizure
AFS	Afebrile seizure
Febrile	With fever
Afebrile	Without fever
AEFI	Adverse event following immunisation
FS	Febrile seizure

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4. Funding and Resources

4.1 Source/s of Funding

NHMRC project grant APP1049557: $672,384.96 over 3 years from 2013-2015 inclusive. Budget allocation by year of grant

Year	Year 1	Year 2	Year 3
TOTAL	$313,509.50	$193,564.61	$165,310.86

5. Introduction/Background Information

5.1 Lay Summary

Severe acute neurological adverse events following immunisation (AEFI), such as febrile seizures (FS), are dramatic, likely to result in medical consultation, impact on both parent and provider confidence in the safety of vaccines and may have implications for further vaccinations of the child and other family members, such as siblings. The aim of this study is to comprehensively categorise and describe the clinical and revaccination outcomes of children who have experienced a FS post vaccination and determine if there are any genetic markers (principally variants in the sodium channel gene mutation *SCN1A*) predisposing to

FS. Three groups of children aged between 12 and 42 months will be enrolled in this study. The groups are as follows; Group 1 (n=100) - FS occurring within 48 hours of an inactivated vaccine and 5-14 days of a live attenuated vaccine, defined as post vaccine febrile seizures (PVFS), Group 2 (n=100) - FS with no recent receipt of a vaccine and a control Group 3 (n=100) with no history of FS or afebrile seizure (AFS) and no first degree relative with FS or AFS.

All participants will be assessed during a face-to-face follow up visit at approximately 1 year after their FS (Groups 1 and 2) and provide information on their clinical history, ongoing seizures, recurrence with re-vaccination and family history of FS or epilepsy. Children in Group 3 will be assessed at approximately the same mean age as those in Group 1 and 2. All participants will have a detailed clinical assessment undertaken by a clinician or clinical research fellow using a standardised proforma. All children will then have their cognitive, motor and language development assessed using a standardised tool that will be administered by personnel suitably trained in administering Bayleys-III assessments. Parents will also complete a questionnaire to obtain information about their child's social-emotional and adaptive behaviour. Finally, children will be asked to have a venous blood or saliva sample for analysis of genes linked with FS and epilepsy. Results of genetic testing and all other outcome measures will be compared across groups. The results of this study, in particular long term outcomes, are extremely important for parents and healthcare providers, and may contributed to changes in immunisation policy and practice. Studies of this nature are essential to maintain public confidence in vaccines.

5.2 INTRODUCTION

Severe acute neurological adverse events following immunisation (AEFI), such as febrile seizures (FS), are dramatic, likely to result in medical consultation, impact on both parent and provider confidence in the safety of vaccines and may have implications for further vaccinations of the child and possibly other family members, such as siblings. This was clearly illustrated in April 2010, when the Chief Health Officer of Australia suspended the use of seasonal trivalent influenza vaccine (TIV) in children under 5 years old due to an unexpected and alarming increased rate of fever and FS post TIV. (1) A subsequent national investigation found an increased risk of FS following one specific brand of TIV (Fluvax® CSL Biotherapies, Australia) of 4.4 per 1000 doses in children <5 years of age (10), well above the background rate of <1 in 1000 vaccinees.(2) This unprecedented vaccine safety issue in Australia had significant implications on perceptions of vaccine safety from both public and professional perspectives, initiated coroners and parliamentary inquiries (Stokes Ministerial Review and Horvath Review), and altered guidelines for vaccine use and surveillance both within Australia and internationally.(3-5) In particular, the 2010 FS experience highlighted the urgent need for new methods of active vaccine safety surveillance to estimate the risk of acute severe neurological events following vaccination in children and further research on long-term clinical and developmental outcomes of such events.

Importantly, new vaccines added to the National Immunisation Program (NIP) for all Australian children, pneumococcal conjugate 13 vaccine (PCV13) in 2011 and a combination measles-mumps-rubella-varicella vaccine (MMRV) in 2013 have been associated with an increased risk of fever and FS in certain circumstances.(6) For PCV13 a warning about PVFS has been issued by governmental authorities, such as the US Food and Drugs Authority

(FDA), to providers.(7) In addition, a novel meningococcal B vaccine now registered and available for use in Australia has been associated with high rates of fever (> 38ºC in 80% of vaccine recipients) in infants in clinical trials, such that prophylactic anti-pyretics are recommended to reduce the rate of fever in children and parents specifically warned of the potential for this adverse event. (8) Given the 2010 experience with TIV in Australia, combined with current and future use of vaccines with a high potential to cause fever and FS underpins the importance of this research to inform risks and anticipated outcomes for Australian parents, healthcare providers and policy makers.

This study will comprehensively categorise and describe the clinical and revaccination outcomes of children who have experienced a PVFS and determine if there are any genetic markers (principally variants in the sodium channel gene mutation *SCN1A*) predisposing to PVFS. The results of this study, in particular long term outcomes, are extremely important for parents and healthcare providers and are key to maintaining public confidence in vaccines.

5.3 BACKGROUND INFORMATION.

Acute neurological adverse events following vaccination

Common expected AEFIs include injection site reactions and fever. Seizures are a rarer AEFI but are well documented and can occur following any vaccine, at any age. They are categorised into febrile seizures (FS) or afebrile seizures (AFS). Seizures occurring within 48 hours of an inactivated vaccine, such as diphtheria-tetanus-acellular pertussis (DTPa) or influenza vaccine, or within 5-14 days of a live attenuated vaccine, such as MMR or varicella, are biologically plausible causal associations and considered to be possibly related to the vaccine if no alternate aetiology is found. Such seizures are referred to as post vaccine febrile seizures (PVFS). Seizures with onset occurring beyond these time periods are usually considered to be unrelated to vaccination. PVFS are more common than AFS after vaccination, however most studies combine data for both FS and AFS, making a separate assessment of relative risks difficult.

Concerns about vaccination causing chronic neurological events such as multiple sclerosis and autism remain unsupported by evidence, despite multiple large scale epidemiological investigations.(9) In contrast, despite FS being more common and associated with vaccination, there is very limited information on the risk factors, clinical outcome and recurrence of FS with further vaccination. Importantly, no studies have examined genetic markers in children who have had PVFS.

Febrile seizures following vaccination: FS usually occur in children aged 6 months to 6 years, peaking in the second year of life and are triggered by a sudden rise in temperature. Post vaccination fever is common after live attenuated vaccines (MMR, varicella), usually occurring 5-14 days post vaccination. Fever and FS also follow certain inactivated vaccines, within 48 hours, particularly whole cell pertussis containing vaccines (DTPw) and seasonal trivalent influenza vaccine (TIV). The current NIP commences at birth (hepatitis B vaccine), followed by 3 doses of an acellular pertussis combination vaccine (with tetanus, diphtheria, polio, *Hib* and hepatitis B), PCV13 and rotavirus vaccine (RV) at 6 weeks, 4 and 6 months of age. At 12 months of age measles, mumps, rubella (MMR), *Haemophilus influenzae* type b (Hib) and meningococcal C (MenC) are given followed by a MMR-varicella combination

(MMRV) vaccine at 18 months of age. Fever >38°C within 48 hours post vaccination is common, occurring in 20% of infants after pertussis containing combination vaccines.(10) High fever >39°C post live attenuated vaccines, such as MMR, usually occurs 5-12 days post vaccination and is also common occurring in 5-15% of children.(10) Fever within the first 24 hours of influenza vaccine appears to be common (10-20%), particularly after the first dose in pre-school aged vaccine-naive subjects. (11,12) This period of vaccination overlaps a similar period of high frequency for FS in children in the general population. The cumulative incidence of FS in children between the ages of 6 months and 5 years is 2-5%, with a peak incidence between 14–18 months of age. FS are most commonly associated with viral infections, however, as vaccines can cause fever it is biologically plausible that in some children vaccines may induce FS.(13-15)

Rates of febrile seizure post DTP and MMR vaccination: The vaccine attributable rate of FS following DTPw is estimated at 1 per 2250 vaccinees and for MMR vaccine 1 per 3030 vaccinees.(16) Due to high rates of fever, FS, and rare reports of encephalopathy, DTPw was replaced by an acellular pertussis containing vaccine (DTPa) in many developed country vaccine schedules, including Australia. DTPa vaccine has lower rates of fever, however FS still occur with reported rates of 1 per 20000 vaccinees.(17,18) Rates of FS following PCV13, RV, Hib and MenC vaccines are less well documented. In January 2012 the US Federal Drugs Administration (FDA) issued a warning about a potential increase in risk for febrile seizure (0-1 day following vaccination) with concomitant use of PCV13 and TIV in children aged 12 to 23 months with an estimated rate of 1 per 2222 vaccinees.(7,19)

Rates of seizure following influenza vaccine and the 2010 experience in Australia: Fever and FS have been reported in temporal association with seasonal TIV. Seasonal TIV is different to other routinely administered vaccines as its composition can change annually to match the circulating influenza virus strains. As a result there may be adjustments in the manufacturing process potentially leading to an altered vaccine safety profile which is not detected because large scale clinical trials are not performed each year prior to vaccine release in the community. In Australia, following the pandemic of 2009 H1N1 influenza, the Southern hemisphere 2010 TIV was the first seasonal vaccine to contain the pandemic strain A/California/7/2009 (H1N1), in addition to A/Perth/16/2009 (H3N2) and B/Brisbane/60/2008 influenza viruses. On the 23rd April 2010 the Chief Medical Officer (CMO) of Australia suspended the use of seasonal TIV in children 5 years of age and under. (1) This was a direct result of a safety signal detected in WA children where there was an increase in numbers of children presenting to emergency departments with high fever and FS following TIV.(20) Subsequent investigations calculated the rate of FS post one specific brand of TIV Fluvax®/Fluvax Junior® (CSL) at 4.4 per 1000 doses (10), while no FS were reported following another brand Influvac® (Solvay).(21) In the United States, where influenza vaccination of young children has been recommended for 8 years, data from passive surveillance systems (Vaccine Adverse Events Report System and US Vaccine Safety Datalink), estimate rates of TIV-related FS in children 6 months to 3 years of 1 per 6250 in the 7 day period post TIV administration. (2,11,12)

Seizures post vaccination: Longer term outcomes

Epidemiological clinical studies indicate that the majority of children with a history of FS

have normal intelligence, academic achievement and behaviour. (22,23) However, a small proportion of children appear to be at an increased risk for potential hippocampal damage and cognitive impairment - these include children who had FS during the first year of life, those with prior neurodevelopmental problems, pre-natal and perinatal events. (22,24,25) There is NO data on the long-term outcome, seizure prevalence, recurrence risk in children who have had PVFSs currently in use in Australia.

FS occur following both live attenuated and inactivated vaccines. Importantly, this study will address the lack of available information on long-term clinical, neuro-developmental outcomes and recurrence rate (with revaccination) in children who experienced a PVFS.

What is known about genetic markers in children with seizures and FS?

Host/genetic factors are likely to contribute to the occurrence of neurological AEFIs in some predisposed children; however, these factors are not well defined or characterised. Most FS are simple (<15 minutes in duration) and comprise generalised convulsions. A proportion have a syndrome known as FS plus (FS+) in which FS fall outside the age range of 6 months to 6 years.(26) FS+ forms part of the familial epilepsy syndrome called Genetic epilepsy with febrile seizures plus (GEFS+) where at least two family members have phenotypes that fit within the GEFS+ spectrum. The spectrum of epilepsies in GEFS+ is wide, varying from simple FS to severe epileptic encephalopathies, including Dravet syndrome.

Molecular studies in FS syndromes have largely focussed on families manifesting dominant inheritance patterns and a number of chromosomal linkages have been described. Mutations in ion (sodium, potassium and GABA) and non ion channel genes have also been found in association with seizures. There are a cluster of voltage-gated sodium channel genes including *SCN1A* and *SCN2A* which encode different sodium channel subunits. However the only validated gene discoveries in these families belong to the GEFS+ spectrum and here mutations in sodium channels (largely *SCN1A*, but also *SCN1B, SCN8A*, and *SCN2A*) and rarely GABA receptor subunits (*GABRG2*) have been implicated (27). An association of *SCN1A* and susceptibility to FS was reported by Schlacter et al, who found a specific *SCN1A* polymorphism occurs more commonly in adult epilepsy patients with a history of FS compared to both non epileptic controls and adult epilepsy patients with no history of FS, as well as a significant association of *SCN1A* presence in children with FS compared to population controls.(28) In contrast, an Australian study by Petrovski et al, did not confirm this finding in adults.(29) Further study is needed to identify the real relevance of this genetic marker in the susceptibility to FS and to identify additional causative genes. Mutations in the *SCN1A* gene have also been associated with a severe AFS disorder of infancy known as Dravet syndrome. Infants with Dravet syndrome have their onset of seizures around 4-6 months old, during the period in which infant vaccines are administered, fever is known to be a trigger factor and approximately 70-80% have the *SCN1A* mutation.(30,31) Of the candidate genetic mutations associated with seizures, *SCN1A* mutations are associated with severe epilepsy syndromes in >85% of cases, linked to susceptibility for FS and less frequently with other types of focal and generalised seizures.(32)

In a landmark study 2006 Berkovic and Scheffer reported for the first time an association

between *SCN1A* genetic mutation and children with an alleged "vaccine encephalopathy", who had seizures and developmental delay with onset post vaccination in infancy.(33) Of 14 cases with "vaccine encephalopathy", 12 had the typical clinical picture of Dravet syndrome on expert review and 11 of 14 (79%) cases had the *SCN1A* mutation. The same Australian group has further studied the onset of Dravet syndrome and its relationship to vaccination in 40 cases.(34) Cases whom had onset of seizure on the day of or after vaccination were significantly younger, by 8 weeks, than cases with onset > 2 days after vaccination. The authors conclude that vaccination may trigger earlier onset of Dravet syndrome in those genetically predisposed with the *SCN1A* mutation.(34) Reyes et al report 5 cases of alleged "vaccine encephalopathy" re-diagnosed years later as Dravet syndrome with *SCN1A* mutation, of note FS within 24 hours of vaccination were the first seizure event in 3 cases.(35) Despite the small sample size and retrospective data collection, these findings suggests a possible gene-environment interaction and highlights the need for further studies in infants who have seizures post vaccinations incorporating genetic studies with comprehensive neuro-developmental outcomes.

Little is known about the genetic markers in children who have had seizures with onset close in time to vaccination. The most likely gene mutation, based on previous small studies, is the *SCN1A* mutation although it is clear there are other unidentified genes involved in causing FS. This study, using the internationally recognised expertise of the Epilepsy Research Centre, Melbourne will investigate these genetic mutations in children with onset of febrile seizure following vaccination.

6. STUDY OBJECTIVES

6.1 RESEARCH QUESTION

What is the long-term clinical and developmental outcome of children who had a febrile seizure post vaccination?

6.2 PRIMARY OBJECTIVE

To determine the long-term clinical, cognitive, behavioural and neurological outcome of children who have experienced a post vaccine febrile seizure.

6.3 SECONDARY OBJECTIVES

To describe the risk of recurrence of a FS following revaccination in children who previously had PVFS

To determine the presence of specific genetic markers (principally variants in the sodium channel gene mutation *SCN1A*) in children with PVFS.

6.4 HYPOTHESES

The following hypotheses underpin the study objectives and design:

1. Risk factors for a PVFS include administration of a live attenuated vaccine (with or without a killed vaccine), age 6 months to 2 years and a family history of FS.

2. The majority of children who have experienced a PVFS (in the absence of pre-existing neurological illness) will have normal clinical, cognitive, behavioural and neurological outcome when reviewed at least 1 year after the event.

3. The risk of recurrent FS following revaccination with any vaccines in children who have had PVFS is <10%.

4. The proportion of children with;

    a. a single PVFS and *SCN1A* variants is NO different to that observed in healthy Australian children who have not had a PVFS.

    b. recurrent FS and *SCN1A* variants (+/- developmental abnormality) is higher than that observed in healthy Australian children who have not had a PVFS.

6.5 Outcome Measures

- Long-term clinical outcome of children with PVFS:

    1. Clinical and medical history

    2. Cognitive, behavioural and development

- Genetic mutations in sodium channel genes, principally prevalence of genetic mutations of sodium channel (*SCN1A*) gene in patients with PVFS in comparison with AFS and control participants.

7. Study Design

7.1 Study Design and Schedule

This is a prospective case control study involving 3 groups of children (n=300):
Group 1: Vaccine proximate FS group (PVFS) (n=100)
Group 2: Vaccine distant FS group (n=100)
Group 3: Healthy controls with no history of FS (n=100)
All groups will be assessed between 12-42 months of age.

7.2 Study type and design schedule

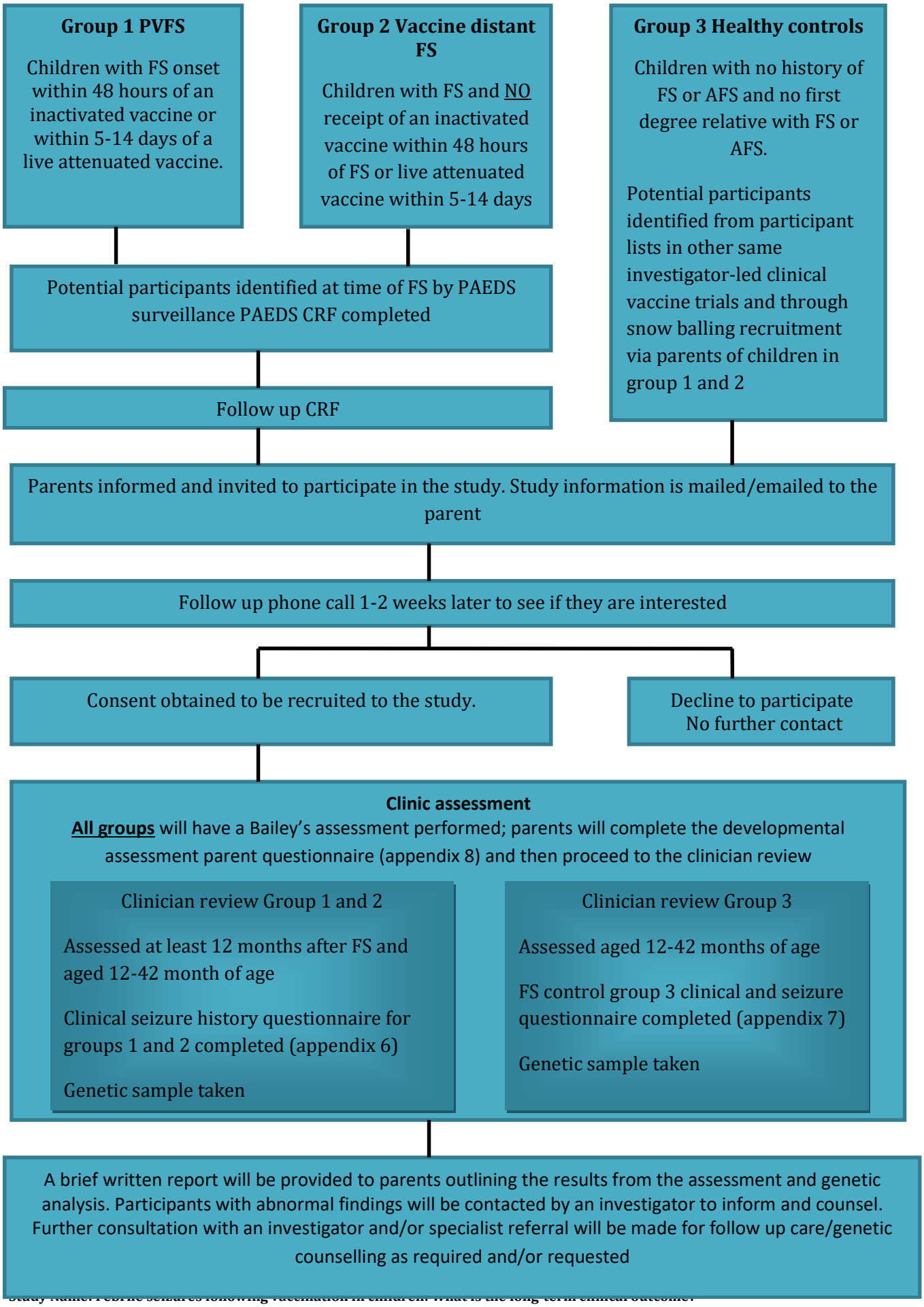
The study design is detailed in Figure 1, on page 12. Details on participant recruitment are included in section 7.4.

7.3 Randomisation

This study is not randomised. Psychologists performing and scoring the cognitive/developmental assessments will be blinded to group allocations.

Laboratory staff performing the genetic analysis will be blinded to group allocations.

Figure 1


Group 1 PVFS
Children with FS onset within 48 hours of an inactivated vaccine or within 5-14 days of a live attenuated vaccine.
Group 2 Vaccine distant FS
Children with FS and NO receipt of an inactivated vaccine within 48 hours of FS or live attenuated vaccine within 5-14 days
Group 3 Healthy controls
Children with no history of FS or AFS and no first degree relative with FS or AFS.
Potential participants identified from participant lists in other same investigator-led clinical vaccine trials and through snow balling recruitment via parents of children in group 1 and 2
Potential participants identified at time of FS by PAEDS surveillance PAEDS CRF completed
Follow up CRF
Parents informed and invited to participate in the study. Study information is mailed/emailed to the parent
Follow up phone call 1-2 weeks later to see if they are interested
Consent obtained to be recruited to the study.
Decline to participate
No further contact
Clinic assessment
All groups will have a Bailey's assessment performed; parents will complete the developmental assessment parent questionnaire (appendix 8) and then proceed to the clinician review
Clinician review Group 1 and 2
Assessed at least 12 months after FS and aged 12-42 month of age
Clinical seizure history questionnaire for groups 1 and 2 completed (appendix 6)
Genetic sample taken
Clinician review Group 3
Assessed aged 12-42 months of age
FS control group 3 clinical and seizure questionnaire completed (appendix 7)
Genetic sample taken
A brief written report will be provided to parents outlining the results from the assessment and genetic analysis. Participants with abnormal findings will be contacted by an investigator to inform and counsel. Further consultation with an investigator and/or specialist referral will be made for follow up care/genetic counselling as required and/or requested

7.4 STUDY METHODOLOGY

Study procedures and clinical assessment:

1. *Enrolment and consent of children*: Parents of eligible children will be approached at each site by investigators and other study staff. The study explained and signed consent obtained (Consent form all age groups Appendix 3). See also study population in section 8.

2. *6 month follow up call*: Parents of participants in groups 1 and 2 are contacted for a brief phone call to assess recurrence of seizures and further vaccination (Follow up CRF Appendix 5). Group 3 will not receive a follow up call.
   An appointment will be made for the parent and child to attend the hospital for the following clinic assessments.

3. *Clinic assessment*:

   - *Clinical questionnaires*

   A clinician or clinical research fellow using a standardised proforma will perform a semi-structured follow up interview. FS study groups 1 and 2 will have a clinical seizure history questionnaire for groups 1 and 2 (appendix 6) completed and FS study control group 3 using the clinical and seizure questionnaire (appendix 7). Data to be collected include: clinical description of seizure/s e.g. age at event, length of seizure (Groups 1 and 2 only), vaccination history, medical illness, prenatal and perinatal history, hospitalisations, medications, ongoing seizures, and recurrence with re-vaccination and family history of FS or epilepsy.

   - *Genetic analysis:*

   Participants will receive pre-testing counselling at the clinical assessment on what is involved and the implications abnormal results may have prior to tests being undertaken. Following consent their child's blood sample to be taken via venepuncture (2-4ml as appropriate for the child's age and size, in EDTA tubes). This will be taken at the time of the clinical assessment. Saliva sampling using an oral swab (Oragene DNA, OG-575 for Assisted Collection kit) will be offered to those who refuse venepuncture. Blood samples are preferred over saliva as blood provides more DNA and the DNA is of better quality.. Samples will be labelled with a unique study code at the time they are taken and transported to the relevant laboratory department at the participating site and stored as per their guidelines prior to transport to the testing laboratory.

   Molecular analysis will be done on genomic DNA extracted from patients' venous blood samples or from saliva samples when venepuncture is refused. All 26 exons of SCN1A will be PCR amplified with flanking intronic primers using standard PCR conditions. Sequencing from independent PCR products in both directions will be performed on an ABI 3700 sequencer (Applied Biosystems, CA, USA). Numbering of *SCN1A* mutations will be taken from the start codon ATG of the full-length *SCN1A* mRNA sequence (Genbank accession number AB093548). Mutations will be divided into missense mutations or others from which markedly abnormal protein was predicted, including truncation, frame shift, and splice site mutations. At the time of providing the child's sample, parents of participants will be asked if they agree to store DNA samples for future testing of new genetic mutations as they become identified (consent form, all age groups Appendix 3). Future testing of DNA samples if undertaken will require an ethics amendment and re-consent of parents prior to testing.

Results and interpretation of the genetic analysis will be included in a brief report mailed to the parents. Participants who are found to have *SCN1A* mutations will be contacted by a study investigator, informed and counseled. Further consultation with an investigator will be offered and specialist referral will be made for follow up care/genetic counselling as required and/or requested by the participant.

- *Developmental assessment, parental questionnaires and family background*:
Parents will be interviewed to complete the developmental assessment parent questionnaire the trained research assistant/psychologist (appendix 8*)* to collect demographic data to enable socio-economic status (SES) to be determined using the Australian National University scale 4 (ANU-4). Information regarding the child's and family background e.g. child's first language and other potential risk factors for poor development e.g. family history of learning disabilities will be obtained using a semi-structured questionnaire.

A developmental assessment will be performed by suitably trained and qualified person who will be blinded to group status. All children will be 12 months to 42 months of age when assessed. Children will be assessed using the Bayley Scales for Infant and Toddler Development (3rd ed'n). The Bayley-III consists of the three administered scales: cognitive, language and motor scale and a short questionnaire that is completed by the parent/caregiver to assess social-emotional behaviour and adaptive functioning. In children ≥ 2 years, pre-academic skills and behaviour will be assessed using the following subtests from the Woodcock-Johnson Tests of Achievement – Third Edition (WJ-III): letter-word identification, understanding directions, and applied problems. Parents will also complete the i) Child Behaviour Checklist – Preschool (children ≥ 1.5 years); ii) Behavior Rating Inventory of Executive Function–Preschool Version to assess executive functioning (children > 2 years); and iv) the MacArthur-Bates Communicative Development Inventory to assess children's (> 8mths old) expressive language and communication skills. The child's assessment will take 1-2 hours to complete depending upon the age of the child.

A brief written report will be provided by mail to parents outlining the results of the assessment. Participants with abnormal findings will be contacted by an investigator to inform and counsel. Further consultation with an investigator and/or specialist referral will be made for follow up care as required.

Children will be excluded from the developmental assessment if they have pre-existing diagnosis of developmental delay, intellectual impairment, hearing or visual problems (see exclusion criteria 8.3). This is because such a pre-existing condition would likely lead to reduced performance in the developmental assessment. They will not however be excluded from the genetic analysis.

8. STUDY POPULATION

8.1 RECRUITMENT PROCEDURE

Groups 1 and 2 (history of FS): Participants for potential inclusion in groups 1 and 2 (100 in each respectively) will be recruited from 3 sources:

1. *PAEDS Surveillance*

Since May 1st 2013 FS cases have been identified in real time from emergency department visits and hospitalisations at five participating major tertiary paediatric hospitals participating in the Paediatric Active Enhanced Disease Surveillance (PAEDS) surveillance system (SCHN ethics approval #2007-009 and subsequently HREC-13-SCHN-402). This surveillance is funded by the Australian Government Department of Health. Of the five PAEDS hospitals, four are study sites for this study application. As at February 28th 2014 across all 5 PAEDS sites, 1211 FS have been identified with 66 children meeting inclusion criteria for PVFS and 1145 children meeting inclusion criteria for non-vaccine proximate FS. Cases identified through PAEDS will be approached to be recruited to this study. This is feasible as lead investigators Wood and Macartney are also investigators on PAEDS at CHW and other lead investigators on this study are PAEDS members at the other hospital sites.

From May 1st 2013 to December 2013 once identified, PAEDS research nurses have been contacting parents of children with a FS, either in person whilst the child is in hospital or via telephone within 1-2 weeks after discharge. Parental consent obtained and interviews conducted to confirm the cases as a FS. As part of the previous ethics approval for PAEDS surveillance (#2007-009) parents of FS cases also consented to a follow up phone call 6 and (if necessary) at 12 months after the initial FS to assess for recurrence of seizures and further vaccination. Under this new study, at the planned 12 month follow up phone call FS cases meeting inclusion criteria for groups 1 and 2 will be informed about this study and invited to participate in the follow up study by undertaking the clinical, developmental and genetic assessment shown in Figure 1.

From 1st July 2014 all PVFS (and if necessary non-vaccine proximate FS) cases identified through PAEDS who are potentially eligible for this study, will be contacted by research nurses at the time of their initial FS to inform them of this study and obtain consent. Once participants have consented they will also have a follow up phone call 6 months after the initial FS.

All participants in FS groups 1 and 2 will have a clinical assessment at least 12months post their first (or only) FS and aged 12-42 months old.

2. *Immunisation Adverse Event Clinics*

Immunisation adverse events clinics are held routinely (weekly or fortnightly) at all the PAEDS hospitals. These clinics review and manage children with neurological AEFI and investigators can prospectively enroll eligible children with PVFS. Parents will be informed about the study by the investigator at the clinic visit and invited to participate in the follow up study.

3. *SAEFVIC*

In Victoria, in addition to the above methods, recruitment will be augmented through the Serious Adverse Events following Vaccination in the Community (SAEFVIC) service. SAEFVIC is responsible for recording and follow-up of all AEFI reports in Victoria. At the point of notification to this service clinical staff will be able to inform parents of those who meet the inclusion criteria about the study and invite them to participate.

Those who were sent study information will receive one follow-up 1-2 weeks later call to see if they are interested in participating.

FS groups 1 and 2 who experienced their FS aged < 2 years of age will be invited to participate in this study at least 12months after the occurrence of their first FS and aged 12-42 months old

Group 3 Healthy controls: Healthy control children aged 12 months to 42 months old will be approached by study staff, informed about the study and invited to participate.

Group 3 participants will include children identified from the following sources by investigator Wood and who have active participation in current clinical vaccine trials:

a) Multicentre NHMRC project grant (570756) clinical vaccine trial. This vaccine trial has been conducted in the same sites as FS children will be recruited (Sydney, Melbourne, Perth, Adelaide) and includes 440 participants.
b) Alternate pertussis vaccine schedule study – funded by the Foundation for Children.

Children enrolled in these clinical vaccine trials have received all routine vaccines on the national immunisation program, documented vaccine history/dates and have regular medical follow up (as part of the study protocol).

Participants will also be recruited:

- Using snow balling recruitment method. Parents of children in groups 1 and 2 will be asked if they are willing to pass on an information sheet to a family friend who has a child approximately the same age. Families interested in having their child participate in the study can contact the study investigators by phoning or returning a reply paid slip with their contact details (Group 3 study information sheet Appendix 2).

- Through an advertisement (appendix 9) placed in local newspapers, childcare centers, hospital notices and websites and on-line through facility social media accounts.

8.2 INCLUSION CRITERIA

The following inclusion criteria will pertain to each group:

Group 1: Vaccine proximate FS
Children with FS onset within 48 hours of an inactivated vaccine or within 5-14 days of a live attenuated vaccine , at least 12 months has elapsed since onset of (first or only) FS and aged less than 42 months old.

Case definition: For the purpose of this study a PVFS will be defined as;

- A seizure that fulfills the Brighton Collaboration case definition for a seizure[36]
- Occurs within 48 hours of an inactivated vaccine and/or 5-14 days of a live attenuated vaccine
- Is associated with documented fever (>38°C) either by a parent and/or health provider

Group 2: Vaccine distant FS
Children with FS and **NO** receipt of an inactivated vaccine within 48 hours of FS or live attenuated vaccine within 5-14 days AND at least 12 months has elapsed since onset of (first or only) FS, aged less than 42 months old. Children in group 2 will be aged matched (with a window of 2 months either side) to children in group 1.

Group 3: Healthy controls

Children aged 12 months to 42 months old with no history of FS or AFS and no first degree relative with FS or AFS. Children in group 3 will be age matched (with a window of 2 months either side) with group 1 at the time of the developmental assessment.

8.3 Exclusion Criteria

Children who are older than 42 months of age.

Children whose parents are not fluent in the English will be excluded since many of the standardised questionnaires used to assess the child's functioning are in English.

Healthy control children (group 3) will be excluded from the developmental and genetic testing assessment if they have pre-existing diagnosis of developmental delay, intellectual disability, medical and/or genetic condition or injury that may affect cognition e.g. head injury, Down syndrome, born pre-term i.e. <37 weeks etc.

All children who have a hearing or visual impairment and/or are not learning and/or speak the English language will be excluded from the developmental assessment.

8.4 Consent

The study will be explained to parents, with the explanation accompanied by a copy of the study information sheet for groups 1 and 2 who have had a FS (Groups 1 and 2 study information sheet Appendix 1), and for group 3 with no seizure history (Group 3 study information sheet Appendix 2). Parents will be informed that participation is voluntary and they may withdraw from the study at any time. Parents indicating interest in the study will have opportunity to discuss the study with the researchers and family members, their medical advisers or other persons of their choosing.

A follow-up phone call from the study staff will be made 1-2 weeks later to see if they are interested in participating.

Signed consent will be obtained (Consent form all groups Appendix 3). Only those providing written consent will be recruited to the study. No further contact will be made to parents who refuse consent. Written consent can be obtained at the time of the consultation or returned in a reply paid envelope.

Parents will be informed that they can elect not to participate in the genetic analysis and proceed with the clinical and developmental assessments only. Parents have the option of ticking one or both options on the consent form.

9. Participant Safety and Withdrawal

9.1 Risk Management and Safety

There is no compromise to patient safety in this study. Developmental assessments will be undertaken by staff trained in administering the standardised tests/assessments. Blood tests will be performed by staff trained in paediatric venepuncture.

Results from the genetic analysis and developmental assessment will be included in a brief report mailed to the parents. Participants who are found to have *SCN1A* mutations and/or abnormal developmental assessment will be contacted by a study investigator, informed and counseled. Further consultation in person with an investigator will be offered and specialist

referral will be made for follow up care/genetic counselling as required and/or requested by the participant.

9.2 Adverse Event Reporting

All children identified as PVFS will be reported to the appropriate state authorities in line with the AEFI reporting requirements in each respective State's Public Health Act.

9.3 Handling of Withdrawals

Participants may choose to withdraw from the study at any time and without reason and without any consequence to the standard of care provided by the facility for other conditions unrelated to this study. At the time of withdrawal, parents will be asked if they request any or all of the collected data to be removed from the study analysis. All specified data will be removed; otherwise it will continue to be included in the study analysis.

Results from any developmental assessment and genetic analysis that may have been taken prior to withdrawal will be informed to the parent/guardian in writing when available. Appropriate referral for follow-up will be made.

10. Statistical Methods

10.1 Sample Size Estimation & Justification

Over the study duration (3 years) 300 subjects in total will be enrolled according to the following: Group 1 PVFS (n=100), Group 2 vaccine distant FS (n=100), Group 3 healthy controls (n=100).

10.2 Power Calculations

The planned sample size is sufficient to detect genetic mutations in *SCN1A* gene of significant difference from population control data. The frequency of *SCN1A* mutations in Dravet syndrome is >70%. The frequency in simple febrile seizures is quite low and has never been systematically measured but probably ~ 1% or less. The frequency in controls of truncation mutations is zero and for suspicious missense variants it is difficult to estimate because knowledge of known polymorphisms is growing but suspected to be <0.1%. A clinically meaningful result in this study would be the discovery of any truncation variants and a frequency of missense variants of >5% which will be detectable with our sample size.

Developmental standard scores for subscale of the Bayley III will be compared between the three groups using one-way ANOVAs. With 100 subjects in each group, power will be high (power = 88%, $\alpha = 0.05$) to detect a small effect size (0.2) (SPSS Sample Power).

10.3 Statistical Methods

Genotyping: Allelic and genotypic differences between groups will be compared using Pearson χ^2 and the Armitage trend test.

Developmental assessment data: Developmental assessment score for each scale of the Bayley-III will be compared between the three groups using one-way ANOVAs with post-hoc testing conducted using Tukey's HSD. The same analysis will also be conducted for standard scores obtained from parental questionnaires. The frequency of scores in the abnormal/clinical range for each measure will also be reported for each group.

Multiple linear regression will be conducted to identify potential risk factors (e.g. age at seizure, number of seizures) associated with cognitive impairment.

Finally, logistic regression will be conducted on developmental, clinical and genetic factors combined, to examine whether developmental delay is associated with PVFS, after adjustment for genotypic differences and other risk factors for severe outcomes following FS.

11. STORAGE OF BLOOD AND TISSUE SAMPLES

11.1 SAMPLES STORAGE AND CONSENT FOR FUTURE USE OF SAMPLES

Blood samples (2-4ml as appropriate for the child's age and size, in EDTA tubes) or Saliva using Oragene DNA (OG-575) kits will be taken at the time of the clinical assessment. Samples will be labelled with a unique study identification code, transported to the relevant laboratory department at the participating site and stored as per their guidelines prior to transport to the testing laboratory. All samples sent for genetic testing will be labelled with a unique study number with no patient identifiers.

Genetic testing will be undertaken by the Epilepsy Research group in Melbourne. All samples taken will be batched and transported via a medical courier for testing.

Consent will only be obtained for genetic testing specific to this study, as outlined in the participant information sheet.

12. DATA SECURITY & HANDLING

12.1 RECORD STORAGE

All identifiable paper records (Case report forms, consent forms and assessment pro forma) will be stored in a locked cabinet at each study location. Identifiable data will be accessible by site investigators and study staff at each site. Each participant will be assigned a unique study code. De-identified data from each site containing only the unique study code will be sent to the main study location at CHW using a password protected electronic file for data analysis

Electronic records (results) will be kept on a de-identified password protected database. De-identified data will be collated centrally for data analysis.

Laboratory staff will not have access to identifying information. Results of the genetic analysis will be reported to investigators by study code. Only the investigators at each participant's site have access to identifying information and are able to re-identify participants to include findings in the parent report and data analysis or in the event of a participant's death.
All paper and electronic records will be kept until the youngest applicant is 25 years of age.

12.2 CONFIDENTIALITY AND SECURITY

As above

12.3 ANCILLARY DATA

Not applicable

13. APPENDIX

List of Attachments included:

Appendix	Document Name	Version Number	Date
1	Groups 1 and 2 study information Sheet	5	15.09.2015
2	Group 3 study information Sheet	3	09.01.2014
3	Consent form (all groups)	3	13.06.2014
4	PAEDS Febrile Seizure CRF	2	28.04.2014
5	Follow up CRF	1	08.04.2014
6	Clinical seizure history questionnaire for groups 1 and 2	2	12.08.2014
7	FS control group clinical and seizure questionnaire	1	12.08.2014
8	Developmental assessment parent questionnaire	3	14.01.2014
9	Study advertisement	1	15.07.2015

14. REFERENCES

1. Australian Government Department of Health and Ageing, Therapeutic Goods Administration. Departmental Media Releases 23 April 2010: Seasonal Flu Vaccine and young children. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-yr10-dept-dept230410.htm
2. Australian Government Department of Health and Ageing, Therapeutic Goods Administration. Overview of vaccine regulation and safety monitoring and investigation into adverse events following 2010 seasonal influenza vaccination in young children. 8 October 2010. Available from: http://www.tga.gov.au/alerts/medicines/vaccine-overview.htm
3. Stokes B. Ministerial Review into the Public Health Response into the Adverse Events to the Seasonal Influenza Vaccine: Final Report to the Minister for Health. Department of Health, Western Australia 2010
4. Gold M, Effler P, Kelly H et al. Febrile convulsions after 2010 seasonal trivalent influenza vaccine: implications for vaccine safety surveillance in Australia. *Med J Aust* 2010 193 :492-3
5. Advisory Committee on Immunization Practices (ACIP). Summary Report. August 5, 2010. Department of Health and Human Services. Centers for Disease Control and Prevention. http://www.cdc.gov/vaccines/recs/acip/downloads/min-aug10.pdf
6. Department of Health and Ageing. Strengthening immunisation for children. http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/factsheet-strengthening-immunisation Accessed 20th February 2014
7. FDA Advisory warning. http:// www.medscape.com/viewarticle/757814 Accessed 1st March 2014

8. Gossger N, Snape M, Yu L et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules. *JAMA* 2012; 307: 573-582
9. Immunisation myths and realities. Australian Government Department of Health and Ageing, 2008.
10. National Health and Medical Research Council. The Australian immunisation handbook. 10th ed. Canberra: Australian Government Department of Health and Ageing, 2013
11. Hambidge S, Glanz J, France E et al. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. *JAMA* 2006; 296:1990-1997.
12. Fiore A, Shay D, Broder K et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009.[Erratum appears in MMWR Recomm Rep. 2009 Aug 21;58(32):896-7]. *MMWR Recomm Rep* 2009; 58(RR-8): 1-52
13. Verity C, Butler N, Golding J. Febrile convulsions in a national cohort followed up from birth. Incidence, prevalence and recurrence in the first five years of life.*Br. Med. J. (Clin. Res. Ed)* 1985; 290: 1307-1310
14. Van den Berg B, Yerushalmy J. Studies on convulsive disorders in young children. I. Incidence of febrile and nonfebrile convulsions by age and other factors. *Pediatric Research* 1969; 3: 298-30
15. Johnston MV. Seizures in Childhood. In: Kliegman RM, ed. Nelson's Textbook of Pediarics, 18th edition, Philadelphia, Elsevier Saunders, 2006
16. Farrington P, Pugh S, Colville A et al. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet* 1995;345:567-569
17. Jackson L, Carste B, Malais D et al. 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* 2001; 21: 781-785
18. Sun Y, Christensen J, Hviid A et al. Risk of Febrile Seizures and Epilepsy After Vaccination With Diphtheria, Tetanus, Acellular Pertussis, Inactivated Poliovirus, and Haemophilus Influenzae Type b. *JAMA*. 2012;307:823-831
19. Tse A, Tseng H, Greene S et al. 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: 2024-2031
20. Horvath J. Review of the management of adverse events associated with Panvax and Fluvax. Australian Government Department of Health and Ageing 2011
21. Wood N, Menzies R, Gold M et al. Febrile seizures following influenza vaccine in Australian children in 2010; a self controlled case series analysis. Accepted abstract. Public Health Association Australia Immunisation Conference 2012.
22. Verity C, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. *N Engl J Med.* 1998; 338: 1723-8
23. Chang Y, Guo N, Huang C et al. Neurocognitive attention and behavior outcome of school-age children with a history of febrile convulsions: a population study. *Epilepsia* 2000; 41: 412-20.
24. Patrick S, Berg A, Spencer S. EEG and seizure outcome after epilepsy surgery. *Epilepsia* 1995; 36: 236-40
25. Chang Y, Guo N, Wang S et al. Working memory of school-aged children with a history of febrile convulsions: a population study. *Neurology* 2001; 57: 37-42
26. Scheffer I, Berkovic S. Generalised epilepsy with febrile seizures plus: A genetic disorder with heterogeneous clinical phenotypes. *Brain* 1997; 12: 479-490
27. Deprez L, Jansen A, De Jonghe P. Genetics of epilepsy syndromes starting in the first year of life. *Neurology* 2009; 72: 273-281
28. Schlacter K, Gruber-Seldymar U, Stogmann E et al. A splice site variant in the sodium channel gene SCN1A confers risk of febrile seizures. *Neurology* 2009; 72: 974-978
29. Petrowksi S, Scheffer I, Sisodiya S et al. Lack of replication of association between SCN1A SNP and febrile seizures. Neurology 2009; 73: 1928-1930

30. Gambardella A, Marin C. Clinical spectrum of SCN1A mutations. *Epilepsia* 2009; 50 (suppl 5): 20-23
31. Escayg A, Goldin A. Sodium channel SCN1A and epilepsy: Mutations and mechanisms. *Epilepsia* 2010; 51: 1650-1658
32. Morse R. Dravet syndrome: Inroads into understanding the epileptic encephalopathies. J. *Pediatrics* 2011; 158: 354-359
33. Berkovic S, Harkin L, McMahon J et al. De novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. *Lancet Neurol.* 2006; 5: 488-492
34. McIntosh A, McMahon J, Dibbens L et al. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. *Lancet Neurol*. 2010;9:592-598
35. Reyes I, Hsieh D, Laux L et al. Alleged cases of vaccine encephalopathy rediagnosed years later as Dravet syndrome. *Pediatrics* 2011; 128: e699-e702
36. Bonhoeffer J, Menkes J, Gold M et al. Generalised convulsive seizure as an adverse event following immunisation: case definition and guidelines for data collection, analysis and presentation. *Vaccine* 2004; 22: 557-562

Appendix 2. Research protocol for Section 3.3

Linkage of Australian Immunisation Register and state-based registers to evaluate severe acute neurological events following immunisation

PROTOCOL

Linkage of Australian Immunisation Register and state based registers to evaluate severe acute neurological events following immunisation

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Version 7

Date: 19/12/2018

Author/s:

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A/Prof Heather Gidding

A/Prof Nicholas Wood

Abbreviations

FS: febrile seizure

VP-FS: vaccine proximate febrile seizure

NVP-FS: non vaccine proximate febrile seizure

SE: status epilepticus

VP-SE: vaccine proximate status epilepticus

NVP-SE: non vaccine proximate status epilepticus

DTP: diphtheria tetanus pertussis

AEFI: Adverse Event Following Immunisation

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2. Funding and resources

This study will be funded by the National Centre for Immunisation Research and Surveillance.

3. Project summary

Febrile seizure (FS) is a known adverse event following immunisation, with specific attributable risks for different vaccines including a two-fold increase following measles containing vaccine. Few studies, however, have examined whether vaccine-proximate febrile seizure (VP-FS) have a different risk profile, clinical outcome and recurrence rate compared to non-vaccine proximate febrile seizures (NVP-FS).

More recently, prolonged seizures have also been associated with vaccination, especially in those with an underlying genetic risk of epilepsy. Mutations in sodium channel genes, mostly in the SCN1A gene, have been found in association with prolonged seizures following vaccination.(1) Unlike FS, the risk of status epilepticus (SE), defined as a continuous seizure lasting for more than 30 minutes or repeat seizures with no return to normal level of consciousness within 30 minutes, following vaccination is unknown. There are no data on the proportion of SE episodes that are vaccine-proximate or the rate of SE per vaccination episode for each vaccine combination. It is also not known if these children continue to have subsequent seizures and develop epilepsy and whether they continue to have their routine vaccinations in a timely manner.

This study aims to identify the proportion of FS and SE that are vaccine proximate, the proportion with a concomitant infection, their severity by comparing their length of stay, risk of recurrence and impact on subsequent vaccinations.

4. Background / Rationale

Febrile seizure (FS) risk following vaccination within a defined period after vaccination when a fever peaks is well recognised.(2-5) For example, measles containing vaccines are associated with a 2-3 fold risk increase of FS 5-12 days following vaccine(5), while whole cell pertussis vaccines and influenza vaccines in combination with pneumococcal vaccines are associated with an increased rate of FS within 48 hours following vaccination(2, 4).

While data to define the attributable risk of vaccine-proximate febrile seizure (VP-FS) is becoming increasingly available, only two previous studies,(6, 7) of the same cohort of 3348 US children aged 6 months to 3 years over an 8 year period, directly compared VP-FS to non-vaccine proximate (NVP-FS). In the first study, children with a first VP-FS were more likely to be female, younger, have a lower birth weight, a lower Apgar score at 1 minute and a higher chance of FS recurrence compared to NVP-FS children.(6) The second study showed no difference in risk of hospitalisation for first FS.(7)

These studies have not been replicated elsewhere and it is unclear if the risk factors identified for VP-FS or risk difference for hospitalisation between VP-FS and NVP-FS are the same in other populations. There is also no study on whether children who have VP-FS continue to have their routine vaccinations in a timely manner.

More recently, afebrile seizures and prolonged seizures have also been reported following vaccinations. Prolonged seizures, specifically status epilepticus (SE) where the seizure lasts for more than 30 minutes or there are repeat seizures with no return to

normal level of consciousness within 30 minutes, are a medical emergency and can be life threatening. A retrospective study in Germany over 3 years identified 8.5% (21/247) of seizures following vaccination were SE.(8) In a landmark Australian study, Dravet syndrome, a form of severe epilepsy resulting from a mutation in the sodium channel gene SCN1A was associated with post-vaccination seizures in the first year of life, especially within 48 hours of diphtheria-tetanus-pertussis (DTP) vaccination. The study described 14 cases of first seizures following vaccination, of which 9 were afebrile seizures and 6 were status epilepticus.(1) Similar findings were reported in a subsequent retrospective study in the Netherlands of 1269 children with seizures following vaccination where 15 SCN1A-associated Dravet syndrome cases were identified, with similar proportion of afebrile seizures and status epilepticus (9 and 6 respectively) compared to the Australian study.(9)

Currently, there are no Australian data on the number of children with vaccine proximate SE (VP-SE), the proportion of all SE that are vaccine proximate or the relative risk of SE following vaccination. It is also not known if these children are more likely to have subsequent seizures and develop epilepsy. Their risk of SE with subsequent vaccination is also unknown, as is whether they have their routine vaccinations in a timely manner.

Children with a history of seizures following vaccination will often be referred to an Adverse Event Following Immunisation (AEFI) Clinic for review and management of further vaccination. Understanding the outcomes and natural progression of these children will be useful in counselling parents and managing these children with their subsequent vaccinations.

5. Study objectives

5.1 Primary objective

To determine the proportion of FS or SE emergency presentations and hospitalisations that are vaccine proximate. A FS or SE would be considered vaccine-proximate if it occurred on day 0-2 following receipt of an inactivated vaccine, day 5-14 following a live-attenuated vaccine, or day 0-14 following a combination of inactivated and live-attenuated vaccines.

5.2 Secondary objectives

Relating to both FS and SE:

a) To determine the proportion of FS or SE per vaccination episode for each vaccine combination
b) To compare the proportion of VP-FS and VP-SE with an infectious disease diagnosis to proportion of NVP-FS and NVP-FS with an infectious disease diagnosis
c) To compare the length of stay (LOS) between VP-FS and VP-SE to NVP-FS and non-vaccine proximate SE (NVP-SE) hospitalisations as an indication of clinical severity
d) To report the number of VP-FS and VP-SE related deaths compared to the number of NVP-FS and NVP-SE deaths
e) To determine if children who have VP-FS/VP-SE continue to have on time vaccinations

f) To determine the FS and SE recurrence rate in those with VP-FS/VP-SE compared to NVP-FS/NVP-SE

5.3 Hypotheses

We hypothesise that

a) Children who present with VP-SE account for a small proportion of all SE
b) SE recurrence rates in VP-SE and NVP-SE are comparable
c) Children who have VP-SE are less likely to have on time vaccinations compared to children who have NVP-SE and children with no history of SE
d) Children who present with VP-FS account for a small proportion of all FS
e) FS recurrence rates in VP-FS and NVP-FS are comparable
f) Children who have VP-FS continue to have on time vaccinations compared to children who have NVP-FS and children with no history of FS

6. Study design

6.1 Type of study

This is a retrospective population-based cohort study using existing de-identified, individually linked records from multiple state-based administration datasets (Midwife data collection, birth registry), National Death Index and the Australian Immunisation Register that forms a part of a larger data linkage study.

6.2 Study population

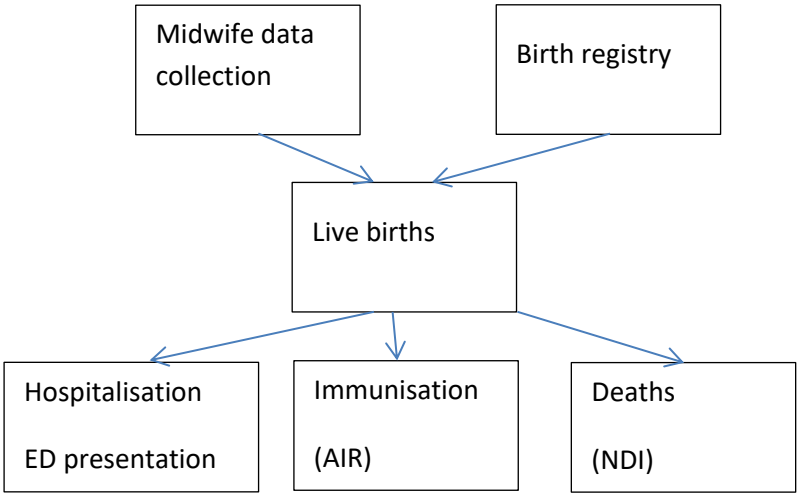
The study cohort will include all live births from 1996 to 2012 in Western Australia (WA) and from mid-2001 to 2013 in New South Wales (NSW) (approximately 28,000 and 86,000births per year respectively and at least 95% of all live births) recorded on the Registry of Births.

The birth cohort identified from the Registry (which includes full name of the baby) has been linked to the midwives data collections in each state to include additional demographic and other information about each child's mother and the birth details of the child.

7. Study methods

The study involves using an existing linked dataset as outlined in the original study protocol) to examine severe acute neurological events, specifically seizures, following immunisation.

Data linkage flow chart



Data sources

As outlined in the original study protocol:

- Midwives' data collection
- Birth register
- Hospitalisations
- ED presentations
- AIR
- NDI

Jurisdiction	Name of data collection	Part of MLK*	Start year†
WA	Midwives' Notification System	Y	1996-2012
WA	Birth Register	Y	1996-2012
WA	Hospital Morbidity Database System	Y	1996-2013
WA	Emergency Department Data Collection	Y	2002-2013
NSW	NSW Perinatal Data Collection (PDC)	Y	1996-2012
NSW	NSW Registry of Births	Y	1996-2012
NSW	NSW Admitted Patient Data Collection	Y	July 2001-2013
NSW	NSW Emergency Department Data Collection (EDDC)	Y	2005-2013
C'wealth	Australian Childhood Immunisation Register	N/A	1996-2013
C'wealth	National Death Index (NDI)	N/A	1996-2013

* Forms part of the Master Linkage Key (MLK) held by the CHeReL (NSW datasets) or WA Data Linkage System (WADLS) core datasets.
† Data will be requested from the start year until the most recent year available

Case identification

Patients with febrile seizures or status epilepticus will be identified using ICD-10-AM-coded discharge data with the following codes for hospitalisations in NSW and WA:

- G41 Status epilepticus

- R56.0 Febrile seizure

Additional febrile seizure and status epilepticus encounters will be identified through coded ED presentations in Emergency Department Data Collection (NSW) and Emergency Department Information System (WA) datasets.

Infectious disease diagnosis identification

An infectious disease diagnosis will be identified using ICD-10-AM-coded discharge data (for secondary diagnoses) with the following codes for hospitalisations in NSW and WA:

- A00-B99 Certain infectious and parasitic diseases

Variables required from linked datasets

- Date of birth
- Region
- Sex
- Aboriginality
- Maternal age
- Socioeconomic status (SES)
- Birth weight
- Gestational age
- Apgar score
- Risk group (history of previous hospitalisation for seizures ICD-10-AM G40.X)
- Vaccines received
- Vaccination date
- Length of stay for above coded hospitalisations
- Date of Death and ICD code

8. Data analysis

Data will be analysed using SAS within SURE, the Secure Unified Research Environment.

- Demographic data (age at seizure, sex, Indigenous status, maternal age, SES, birth weight, gestational age, Apgar scores, history of seizures or neurological disorders) on VP-FS vs NVP-FS and VP-SE vs NVP-SE patients will be compared using Pearson's Chi square test or Fisher's exact test for categorical values, as appropriate, and the Mann-Whitney U test for non-parametric continuous values.
- To determine if we need to look at both ED presentations and hospital admissions data, we will use the WA dataset (which has ED data for the whole state unlike NSW) to, determine the proportion of children who have an ED presentation coded for SE or FS who do not proceed to be hospitalised with a ICD-10-AM code G41 for SE, ICD-9 345.3 for SE, or R56 for FS
- Calculate the proportion of FS and SE that are vaccine proximate
- Calculate the proportion of vaccinations that are associated with a FS and SE. For each vaccine combination, this will be obtained by dividing the number of VP-FS and VP-SE by the number of children vaccinated
- Self-controlled case series method will be used to calculate the relative risk of FS and SE following each dose and vaccination type

- Calculate the proportion of VP-FS and NVP-FS with an infectious disease diagnosis
- Calculate the proportion of VP-SE and NVP-SE with an infectious disease diagnosis
- LOS for VP-FS and VP-SE compared to NVP-FS and NVP-SE will be compared using the Mann-Whitney U test or if appropriate LOS will be categorised and compared using Pearson's Chi square test
- Subsequent vaccination outcomes in children following VP-FS and VP-SE will be examined by calculating the proportion of VP-FS and VP-SE cases who continue to receive vaccinations following their initial seizure by calculating the proportion who had completed their 12 month and 48 month vaccinations at 13 months and 49 months old respectively. This will be compared to children in the dataset with no VP-FS or VP-SE or no history of FS/SE.
- Determine the proportion of VP-FS/VP-SE cases who have FS/SE recurrence with subsequent vaccinations

9. Ethical considerations

9.1 Participant recruitment and consent

There is no direct participant recruitment for this study as it relies on de-identified linked datasets with information already collected by population-based health administration registries.

No consent is obtained for this study as it is not feasible due to the size of the cohort and absence of up to date contact details for all subjects in the cohort.

9.2 Likely benefits of the project for the participants, institution and/or community

Information gained from this study will provide new and important information concerning the outcomes of children presenting with seizures following vaccination. This can be used to counsel parents and providers of the risks of both FS and SE following vaccination and recurrence rate with re-vaccination to help guide advice on subsequent vaccination of this population.

9.3 Actual or potential risk associated with the project

There are minimal risks associated for the population investigated in this study. Only aggregated de-identified data will be exported from Secure Unified Research Environment (SURE) for reporting or publication via a secure Curated Gateway, which includes a log of all data transfers (allowing auditing by the SURE team). Furthermore, the AIHW and then a senior study investigator will review all outgoing data to ensure the risk of disclosure is minimised prior to release from the Curated Gateway.

10. Data security and handling

All researchers will undertake Secure Unified Research Environment (SURE) training before accessing the de-identified linked data. This training involves learning about the legal and ethical responsibilities of a researcher, information security, and statistical disclosure control. Each researcher will sign a confidentiality agreement and also undertake not to attempt to re-identify study participants.

Access to the de-identified linked datasets by researchers will be via the SURE. The de-identified data available through SURE is stored at a high security data centre and not on the researchers' computer. The SURE access process will also include checks on the

end users computing environment to ensure that the computer has a firewall and up-to date antivirus software and patches for their operating system. Access to the SURE virtual research project workspace and individual researcher computing environments is over encrypted internet connections and requires multiple authentication steps. Even though multiple researchers will have access to this project workspace there will be no cross project access. Only researchers that are named on the ethically approved research project, have undertaken SURE training (see above), and signed a deed outlining the terms and conditions of using SURE will be provided with access. Whilst using SURE, the researcher will not be able to access the internet, email, print or copy data to a USB memory stick or other removable media. There will be no paper forms.

Aggregated data extracted from SURE via a secure Curated Gateway will be stored on a computer network system maintained by the National Centre for Immunisation Research and Surveillance (NCIRS). The system is secured by user names and passwords and only the study investigators will have access to this extracted aggregated data and other research documents.

11. Dissemination and reporting of study results

Analysis will be published in a peer reviewed journal and at conference presentations. It will be used to determine the need for future prospective studies in this area.

12. References

1. Berkovic SF, Harkin L, McMahon JM, Pelekanos JT, Zuberi SM, Wirrell EC, et al. De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. Lancet Neurology. 2006;5(6):488-92.
2. Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. The New England journal of medicine. 2001;345(9):656-61.
3. Gold MS, Effler P, Kelly H, Richmond PC, Buttery JP. Febrile convulsions after 2010 seasonal trivalent influenza vaccine: implications for vaccine safety surveillance in Australia. The Medical journal of Australia. 2010;193(9):492-3.
4. Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. 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):2024-31.
5. Macartney KK, Gidding HF, Trinh L, Wang H, McRae J, Crawford N, et al. Febrile seizures following measles and varicella vaccines in young children in Australia. Vaccine. 2015;33(11):1412-7.
6. Tartof SY, Tseng HF, Liu AL, Qian L, Sy LS, Hechter RC, et al. Exploring the risk factors for vaccine-associated and non-vaccine associated febrile seizures in a large pediatric cohort. Vaccine. 2014;32(22):2574-81.
7. Tartof SY, Tseng HF, Liu IL, Qian L, Sy LS, Hechter RC, et al. Inpatient admission for febrile seizure and subsequent outcomes do not differ in children with vaccine-associated versus non-vaccine associated febrile seizures. Vaccine. 2014;32(48):6408-14.
8. von Spiczak S, Helbig I, Drechsel-Baeuerle U, Muhle H, van Baalen A, van Kempen MJ, et al. A retrospective population-based study on seizures related to childhood vaccination. Epilepsia. 2011;52(8):1506-12.
9. Verbeek NE, van der Maas NA, Jansen FE, van Kempen MJ, Lindhout D, Brilstra EH. Prevalence of SCN1A-related dravet syndrome among children reported with seizures following vaccination: a population-based ten-year cohort study. PloS one. 2013;8(6):e65758.

Appendix 3. Research protocol for Sections 3.4, 4.3 and 4.4

Characterising clinical presentation and outcomes of children presenting with seizures following vaccination

PROTOCOL

Characterising clinical presentation and outcomes of children presenting with seizures following vaccination

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Version 6

Date: 01/04/2019

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Dr Margie Danchin

A/Prof Nicholas Wood

Dr Lucy Deng

Sponsor/s:

Nil

1. Investigator at facilities

1.1 Study location

The study will be conducted across six sites:

- Sydney Children's Hospital Network, Sydney
- Royal Children's Hospital, Melbourne
- Women's and Children Hospital, Adelaide
- Queensland Children's Hospital, Brisbane
- Perth Children's Hospital (previously Prince Margaret Hospital for Children), Perth
- John Hunter Hospital, Newcastle

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2. Funding and resources

This study will be funded by the National Centre for Immunisation Research and Surveillance.

3. Introduction and background

Febrile seizure risk following vaccination within a defined period after vaccination when a fever peaks is well recognised.(1-4) For example, measles containing vaccines is associated with a 2-3 fold risk increase of FS 5-12 days following vaccine(4), while whole cell pertussis vaccines and influenza vaccines in combination with pneumococcal vaccines is associated with increased rate of FS within 48 hours following vaccination(1, 3). Epidemiological studies show that most children with a history of FS develop normally (5, 6).

Only recently, however, have afebrile seizures and prolonged seizures been reported following vaccinations. In a landmark Australian study, SCN1A-associated Dravet syndrome was associated with post-vaccination seizures in the first year of life, especially within 48 hours of DTP vaccination. The study described 14 cases of first seizures following vaccination, of which 9 were afebrile seizures and 6 were status epilepticus.(7)

A subsequent large retrospective study in the Netherlands identified that SCN1A-associated Dravet syndrome accounted for 2.5% of reported seizures following vaccination in the first year of life and 1.2% of children presenting with seizures following vaccination in the 2 years of life.(8) The study identified 15 cases, with similar proportion of afebrile seizures and status epilepticus (9 and 6 respectively) compared to the Australian study.

While Dravet syndrome is rare, it is a severe form of infantile onset epilepsy that can progress to refractory seizures and developmental delay.(7, 9, 10) Early diagnosis of children with Dravet syndrome can assist in their management, especially when planning for future vaccinations.

Currently, there is no Australian data on the proportion of children presenting with status epilepticus who get genetic testing or are subsequently diagnosed with Dravet syndrome or another genetic epilepsy. It is also not known if these children continue to have their routine vaccinations in a timely manner.

Children with a known seizure disorder or a history of seizures following vaccination will often be referred to an Adverse Event Following Immunisation (AEFI) Clinic at a tertiary paediatric hospital for review and management of further vaccination. Current re-vaccination management for this group of children varies across Australia and re-vaccination outcomes have not been described.

4. Study objectives

4.1 Primary objective

To determine the proportion of children who present with status epilepticus following vaccination with Dravet syndrome or another genetic epilepsy.

4.2 Secondary objectives

a) To describe the clinical differences (seizure time post vaccination/type/duration and vaccine given; length of stay; PICU admission; antiepileptic use, death) between vaccine-proximate status epilepticus (VP-SE) and non-vaccine proximate status epilepticus (NVP-SE) cases
b) To determine the risk of SE following vaccination
c) To determine if subsequent vaccinations have been given
d) To determine if subsequent vaccinations have been given on time
e) To identify the risk of seizure recurrence on revaccination
f) To describe the revaccination management of children with a history of seizures in different paediatric hospitals in Australia

4.3 Hypotheses

We hypothesis that

a) There are no clinical differences between VP-SE and NVP-SE cases
b) The proportion of children who present with status epilepticus following vaccination who have Dravet syndrome is higher than background rate
c) There is no increased risk of SE following vaccination
d) The proportion of children who present with seizures following vaccination diagnosed with another genetic epilepsy is no different to the background rate
e) There is a higher proportion of delayed vaccinations
f) The rate of seizure recurrence with revaccination is low
g) Children with Dravet syndrome require added precautions to be safely be vaccinated
h) Children with other epilepsy syndromes can be safely vaccinated if their seizure disorder is stable, with no added precautions needed

5. Study design

5.1 Inclusion and exclusion criteria

Part 1

Inclusion: Children, aged 24 months and under, presenting to a study site hospital with status epilepticus between January 2013 to December 2017.
Exclusion: Children older than 24 months

Part 2

Inclusion: Children who present to an Adverse Event Following Immunisation (AEFI) Clinic at a study site with either a previously diagnosed seizure disorder or previous seizure/status epilepticus within 14 days of a vaccination
Exclusion: Children who have had a single seizure episode but no diagnosed seizure disorder or who have had febrile seizures outside of 14 days of vaccination

6. Study methods

This is a retrospective medical record audit.

Case identification – part 1

Patients with seizures following vaccination will be identified using ICD-coded discharge data with the following codes:

- G41 Status epilepticus

for hospitalisations between 1 January 2013 to 31 December 2017.

Case identification – part 2

Patients with history of seizures presenting at AEFI Clinics will be identified through existing clinic database search for “seizure” between 1 January 2013 to 31 December 2017.

Medical record review

Eligible cases and their medical record numbers (MRN) will be identified using the abovementioned case identification method. Using the MRN, electronic medical record will be accessed at each site.

Data will be collected on patient age, sex, clinical features of initial seizure presentation, seizure recurrence in subsequent 12 months, any genetic or developmental assessments performed, revaccination attempts and outcomes.

Immunisation history

Where available the patient’s date of birth, name and Medicare number will be used to access the Australian Immunisation Register to record the patient’s vaccine history, particularly the vaccination around the time of seizure.

7. Participant safety

7.1 Likely benefits of the project for the participants, institution and/or community

Information gained from this study will provide new and important information concerning the outcomes of children presenting with seizures following vaccination. There will be no direct benefit to a child or their parent for us reviewing their medical record.

7.2 Actual or potential risk associated with the project

There are minimal risks associated with taking this study. As mentioned we are asking for permission to examine the medical records of children who have had a seizure and review their vaccine history on the Australian Immunisation register. There is no direct contact with parents. Review of a vaccine history of any patient admitted to a hospital is considered to be part of routine clinical practice.

We acknowledge the collection of identifiable data using case report forms can pose a risk to the participants’ privacy and therefore have put in measures to hold the data confidentially and securely at all times as outlined in Section 10: Data security and handling. All data analysed and presented will be de-identified form.

8. Study outcomes

8.1 Primary outcome

Proportion of children presenting with status epilepticus following vaccination diagnosed with Dravet syndrome or another genetic epilepsy

8.2 Secondary outcomes

Part 1

a) Clinical differences (seizure time post vaccination/type/duration and vaccine given; length of stay, PICU admission, antiepileptic use, death) between VP-SE and NVP-SE
b) Risk of SE following vaccination
c) Proportion of children with status epilepticus following vaccination who get genetic testing
d) Proportion of children with seizure recurrence in subsequent 12 months
e) Proportion of children who received subsequent vaccines
f) Timeliness of subsequent vaccination
g) Proportion of seizure recurrence following revaccination

Part 2

a) Proportion of seizure recurrence following re-vaccination
b) Description of vaccine(s) administered in recurrent seizures
c) Description of revaccination protocols used by different AEFI clinics
d) Correlation between potential risk factors (type of genetic epilepsy, seizure free period before vaccination, regular antiepileptics, additional antiepileptics used prophylactically) and seizure recurrence with revaccination

9. Data analysis

Data will be analysed with either SPSS or STATA. Descriptive statistics will be used to describe the cohort. Differences in proportions will be compared using Pearson's Chi square test. Relative incidence of SE following vaccination will be determined using self-control case series method.

10. Data security and handling

All identifiable records will be stored on paper based case report forms in a secure area (locked filing cabinet in a secure building) at each study location. Identifiable data will be accessible by site investigators and study staff at each site only.

De-identified data from each site will be sent to the main study location at The Children's Hospital at Westmead using a password protected electronic file via electronic mail (email) for data analysis. The password protected email will be sent from an organisational email address from each site to the organisational email of the coordinating site (The Children's Hospital at Westmead). The email and all electronic data will be saved and stored on a computer network system maintained by the National Centre for Immunisation Research and Surveillance (NCIRS), on The Children's Hospital at Westmead computer network server. The system is secured by user names and passwords. Once the email is saved on the network server, it will be deleted from the organisational email inbox to ensure the only copy stored is on the password protected network server.

All records will be kept for 15 years after the date of publication or termination of the study and deleted at the end of this period, as per Sydney Children's Hospital Network requirements. The data will be disposed of by secure destruction methods such as shredding of paper data and erasure of computer generated data.

11. HREC approval

This protocol will be reviewed by the Sydney Children's Hospital Network HREC. Site specific assessment (SSA) for each site will be obtained prior to the commencement of the study.

12. Dissemination and reporting of study results

De-identified data and analysis will be published in a peer reviewed journal and at conference presentations. It will be used to determine the need for a prospective study.

13. References

1. Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. The New England journal of medicine. 2001;345(9):656-61.
2. Gold MS, Effler P, Kelly H, Richmond PC, Buttery JP. Febrile convulsions after 2010 seasonal trivalent influenza vaccine: implications for vaccine safety surveillance in Australia. The Medical journal of Australia. 2010;193(9):492-3.
3. Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. 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):2024-31.
4. Macartney KK, Gidding HF, Trinh L, Wang H, McRae J, Crawford N, et al. Febrile seizures following measles and varicella vaccines in young children in Australia. Vaccine. 2015;33(11):1412-7.
5. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. The New England journal of medicine. 1998;338(24):1723-8.
6. Chang YC, Guo NW, Huang CC, Wang ST, Tsai JJ. Neurocognitive attention and behavior outcome of school-age children with a history of febrile convulsions: a population study. Epilepsia. 2000;41(4):412-20.
7. Berkovic SF, Harkin L, McMahon JM, Pelekanos JT, Zuberi SM, Wirrell EC, et al. De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. Lancet Neurology. 2006;5(6):488-92.
8. Verbeek NE, van der Maas NA, Jansen FE, van Kempen MJ, Lindhout D, Brilstra EH. Prevalence of SCN1A-related dravet syndrome among children reported with seizures following vaccination: a population-based ten-year cohort study. PloS one. 2013;8(6):e65758.
9. Reyes IS, Hsieh DT, Laux LC, Wilfong AA. Alleged cases of vaccine encephalopathy rediagnosed years later as Dravet syndrome. Pediatrics. 2011;128(3):e699-702.
10. 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. The Lancet Neurology. 2010;9(6):592-8.

Case Report Form 1

Characterising clinical presentation and outcomes of children presenting with status epilepticus following vaccination

PATIENT DETAILS

1. First 2 letters of first name ☐☐
2. First 2 letters of second name ☐☐
3. Date of birth ☐☐/☐☐/☐☐
4. Sex M☐ F☐
5. Site
   - ☐ CHW
   - ☐ JHH
   - ☐ RCH
   - ☐ QCH
   - ☐ WCH
   - ☐ PCH

SEIZURE PRESENTATION

6. Date of admission ☐☐/☐☐/☐☐
7. Date of discharge ☐☐/☐☐/☐☐
8. Date of most proximate vaccine ☐☐/☐☐/☐☐
9. Vaccine given
   - ☐ DTP-HepB-IPV-HiB
   - ☐ DTP-IPV
   - ☐ DTP
   - ☐ Rotavirus
   - ☐ PCV13
   - ☐ PCV7
   - ☐ 23vPPV
   - ☐ HiB
   - ☐ MenACWY
   - ☐ MenB
   - ☐ MenC
   - ☐ HiB-MenC
   - ☐ MMR
   - ☐ MMRV
   - ☐ VZV
   - ☐ HepA

☐ HepB

☐ Typhoid

☐ Influenza

☐ Other

10. Was seizure within 14 days of vaccination? Y ☐ N ☐

VACCINE PROXIMATE SEIZURES

Continue if Question 9 = Y

11. Duration of seizure < 5min☐ 5-10min☐ 10-15min☐ 15-30min☐ >30min☐

12. Description of seizure

☐ GTCS

☐ GCS

☐ GC (uncertain if tonic-clonic or clonic)

☐ Myoclonic

☐ Absences

☐ Atonic

☐ Complex partial

☐ Hemiclonic

☐ Focal

☐ Spasms

☐ Tonic

13. Febrile around time of seizure Y ☐ N ☐ If yes, specify temp (°C): _____

14. Investigations

☐ Blood culture If yes, specify result: _____

☐ Urine culture If yes, specify result: _____

☐ NPA If yes, specify result: _____

☐ LP If yes, specify result: _____

☐ EEG If yes, specify result: _____

☐ CT If yes, specify result: _____

☐ MRI If yes, specify result: _____

☐ Genetic testing If yes, specify result: _____

15. Recurrence within 24 hours of initial Y ☐ N ☐

16. Length of stay in hospital (days) _____

17. Death? Y ☐ N ☐ If yes, specify date: _____

18. PICU admission? Y ☐ N ☐

19. Use of antiepileptics in hospital Y ☐ N ☐ If yes, specify AED: _____
20. Other medications used Y ☐ N ☐ If yes, specify: _____
21. Discharged on antiepileptics Y ☐ N ☐ If yes, specify AED: _____
22. Previous seizures? Y ☐ N ☐ If yes, febrile ☐ afebrile ☐ both ☐
23. Pre-existing neurological condition? Y ☐ N ☐ If yes, specify: _____

FOLLOW UP

24. Genetic testing Y ☐ N ☐ If yes, specify test date/outcome: _____
25. Epilepsy diagnosis Y ☐ N ☐ If yes, specify: _____
26. Subsequent seizure admissions Y ☐ N ☐ If yes, specify number: _____
27. Subsequent PICU admissions Y ☐ N ☐ If yes, specify number: _____
28. Subsequent vaccination Y ☐ N ☐
29. If yes, specify:

    Date: _____ Vaccine(s):_____ Subsequent seizure Y ☐ N ☐ DK ☐

    Date: _____ Vaccine(s):_____ Subsequent seizure Y ☐ N ☐ DK ☐

    Date: _____ Vaccine(s):_____ Subsequent seizure Y ☐ N ☐ DK ☐

    Date: _____ Vaccine(s):_____ Subsequent seizure Y ☐ N ☐ DK ☐

Case Report Form 2

AEFI Clinic Revaccination outcomes of children with history of seizures – Initial consultation

PATIENT DETAILS

1. First 2 letters of first name ☐☐
2. First 2 letters of second name ☐☐
3. Date of birth ☐☐/☐☐/☐☐
4. Sex M☐ F☐
5. Postcode of family ☐☐☐☐
6. Birth weight (grams) _____
7. Gestational age (weeks) _____
8. Past medical history _____
9. Site
   - ☐ CHW
   - ☐ JHH
   - ☐ RCH
   - ☐ LCCH
   - ☐ WCH
   - ☐ PCH

RECRUITMENT PROCESS

10. Eligibility criteria
    - ☐ Seizure disorder AND / OR
    - ☐ Vaccine proximate seizure (< 14 days post vaccination)
11. Patient eligible Y☐ N☐

VACCINE PROXIMATE SEIZURE

12. Did they have a seizure within 14 days of any vaccination? Y☐ N☐
13. Date of seizure ☐☐/☐☐/☐☐
14. Date of vaccination ☐☐/☐☐/☐☐
15. Vaccine given
    - ☐ DTP-HepB-IPV-HiB
    - ☐ DTP-IPV
    - ☐ DTP
    - ☐ Rotavirus
    - ☐ PCV13
    - ☐ PCV7
    - ☐ 23vPPV

☐ HiB

☐ MenACWY

☐ MenB

☐ MenC

☐ HiB-MenC

☐ MMR

☐ MMRV

☐ HepA

☐ HepB

☐ Typhoid

☐ Influenza

☐ Other

16. Verified on AIR? Y ☐ N ☐

17. Duration of seizure < 5min☐ 5-10min☐ 10-15min☐ 15-30min☐ >30min☐

18. Description of seizure ☐ GTCS

☐ GCS

☐ GC (uncertain if tonic-clonic or clonic)

☐ Myoclonic

☐ Absences

☐ Atonic

☐ Complex partial

☐ Hemiclonic

☐ Focal

☐ Spasms

☐ Tonic

19. Febrile around time of seizure Y ☐ N ☐ If yes, specify temp (°C): _____

20. Recurrence within 24 hours of initial Y ☐ N ☐

21. Length of stay in hospital (days) _____

22. PICU admission? Y ☐ N ☐

23. Use of antiepileptics in hospital Y ☐ N ☐ If yes, specify AED: _____

24. Other medications used Y ☐ N ☐ If yes, specify: _____

25. Discharged on antiepileptics Y ☐ N ☐ If yes, specify AED: _____

SEIZURE PROGRESSION / DETAILS OF DIAGNOSED SEIZURE DISORDER

Please complete the following using only clinical data available at the time of review in AEFI Clinic

26. Date first seizure ☐☐ /☐☐ /☐☐

27. Seizure recurrence since first Y ☐ N ☐

If yes, specify number: < 5 ☐ 5 -10 ☐ >10 ☐

28. Seizure frequency Multiple/week ☐ Weekly ☐ Fortnight ☐ Monthly ☐

Fewer than monthly ☐ Fewer than once every 6 month ☐

29. Seizure type(s) – select multiple

☐ GTCS

☐ GCS

☐ GC (uncertain if tonic-clonic or clonic)

☐ Myoclonic

☐ Absences

☐ Atonic

☐ Complex partial

☐ Hemiclonic

☐ Focal

☐ Spasms

☐ Tonic

30. Status epilepticus Y ☐ N ☐ If yes, specify number: _____

31. PICU admissions Y ☐ N ☐ If yes, specify number: _____

32. Current antiepileptic use Y ☐ N ☐ If yes, specify: _____

33. Previous antiepileptic use Y ☐ N ☐ If yes, specify: _____

34. Developmental concerns

Language Y ☐ N ☐

Gross motor Y ☐ N ☐

Fine moor Y ☐ N ☐

Social Y ☐ N ☐

35. Developmental testing Y ☐ N ☐ If yes, specify result: _____

Please complete the following question using <u>clinical data from any time</u>

36. Genetic testing Y ☐ N ☐

If yes, specify test date and result: _____

37. Epilepsy diagnosis Y ☐ N ☐

If yes, specify diagnosis: _____

RE-VACCINATION MANAGEMENT

38. Clinic date ☐☐/☐☐/☐☐
39. Vaccine(s) due _____
40. Vaccination plan
    - ☐ Fully vaccinated in clinic
    - ☐ Partially vaccinated in clinic (separating vaccines)
    - ☐ Vaccinated in day stay unit
    - ☐ Vaccinated as inpatient, specify LOS: _____
    - ☐ Vaccinate deferred, specify reason: _____
    - ☐ Other, specify: _____
41. Vaccination date ☐☐/☐☐/☐☐
42. Vaccine(s) given _____
43. Prophylactic PIVC insertion Y ☐ N ☐
44. Pre-medications use
    - ☐ Paracetamol
    - ☐ Clonazepam
    - ☐ Other antiepileptics, specify: _____
    - ☐ Other, specify: _____
45. Medical exemption given Y ☐ N ☐ If yes, specify: _____
46. Seizure post vaccination Y ☐ N ☐
    a) If yes, specify timing (hours) _____
    b) If yes, specify seizure duration < 5min☐ 5-10min☐ 10-15min☐ 15-30min☐ >30min☐
    c) If yes, describe seizure
        - ☐ GTCS
        - ☐ GCS
        - ☐ GC (uncertain if tonic-clonic or clonic)
        - ☐ Myoclonic
        - ☐ Absences
        - ☐ Atonic
        - ☐ Complex partial
        - ☐ Hemiclonic
        - ☐ Focal
        - ☐ Spasms
        - ☐ Tonic
    d) If yes, specify management _____

47. Subsequent vaccinations as per AIR record
    Date: _____ Vaccine(s):_____

Date: _____ Vaccine(s):_____

Date: _____ Vaccine(s):_____

Date: _____ Vaccine(s):_____

Case Report Form 3

AEFI Clinic Revaccination outcomes of children with history of seizures – Follow up

PATIENT DETAILS

1. First 2 letters of first name ☐☐
2. First 2 letters of second name ☐☐
3. Date of birth ☐☐ /☐☐ /☐☐
4. Does this relate a follow up visit? Y ☐ Proceed with this CRF
   N ☐ Please complete Case Report Form 2

SEIZURE PROGRESSION / DETAILS OF DIAGNOSED SEIZURE DISORDER

Please complete the following using only clinical data available at the time of review in AEFI Clinic

5. Clinic date ☐☐ /☐☐ /☐☐
6. Seizures since last review Y ☐ N ☐ If yes, specify number: _____

Only complete Q7-9 in relation to seizures since last review if you answered Yes in Q6

7. Seizure frequency Multiple/week☐ Weekly☐ Fortnight☐ Monthly☐
   Fewer than monthly ☐ Fewer than once every 6 month ☐

   Seizure type(s) – select multiple
   - ☐ GTCS
   - ☐ GCS
   - ☐ GC (uncertain if tonic-clonic or clonic)
   - ☐ Myoclonic
   - ☐ Absences
   - ☐ Atonic
   - ☐ Complex partial
   - ☐ Hemiclonic
   - ☐ Focal
   - ☐ Spasms
   - ☐ Tonic
8. Status epilepticus Y ☐ N ☐ If yes, specify number: _____
9. PICU admissions Y ☐ N ☐ If yes, specify number: _____
10. Current antiepileptic use Y ☐ N ☐ If yes, specify: _____
11. Previous antiepileptic use Y ☐ N ☐ If yes, specify: _____
12. Developmental concerns
    - Language Y ☐ N ☐
    - Gross motor Y ☐ N ☐
    - Fine moor Y ☐ N ☐

Social Y ☐ N ☐

13. Developmental testing Y ☐ N ☐ If yes, specify result: _____

RE-VACCINATION MANAGEMENT

14. Vaccine(s) due _____

15. Vaccination plan
- ☐ Fully vaccinated in clinic
- ☐ Partially vaccinated in clinic (separating vaccines)
- ☐ Vaccinated in day stay unit
- ☐ Vaccinated as inpatient, specify LOS: _____
- ☐ Vaccinate deferred, specify reason: _____
- ☐ Other, specify: _____

16. Vaccination date ☐☐ /☐☐ /☐☐

17. Vaccine(s) given _____

18. Prophylactic PIVC insertion Y ☐ N ☐

19. Pre-medications use
- ☐ Paracetamol
- ☐ Clonazepam
- ☐ Other antiepileptics, specify: _____
- ☐ Other, specify: _____

20. Medical exemption given Y ☐ N ☐ If yes, specify: _____

21. Seizure post vaccination Y ☐ N ☐

e) If yes, specify timing (hours) _____

f) If yes, specify seizure duration < 5min☐ 5-10min☐ 10-15min☐ 15-30min☐ >30min☐

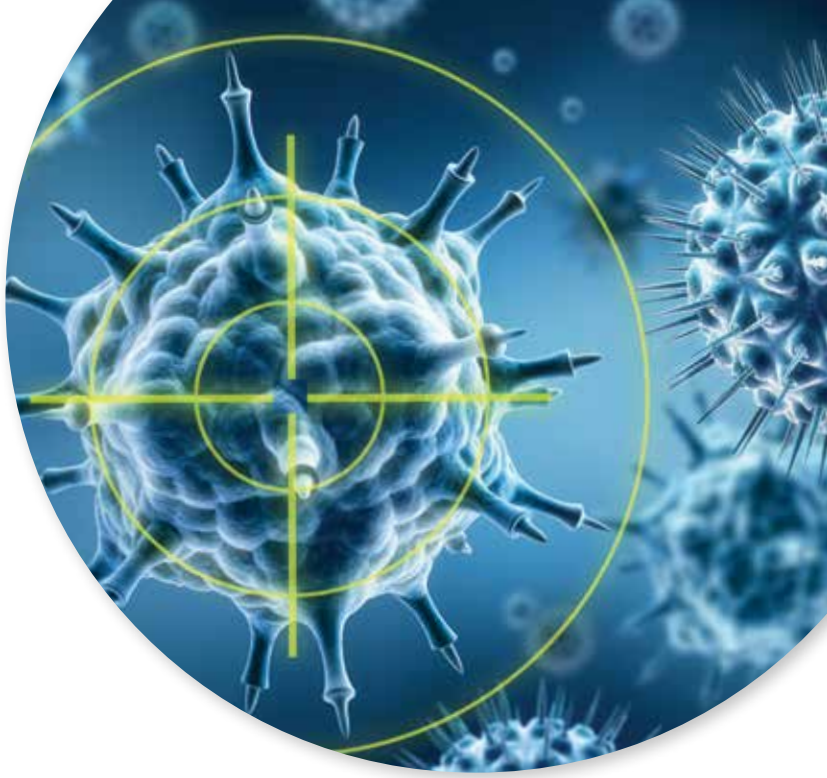
g) If yes, describe seizure
- ☐ GTCS
- ☐ GCS
- ☐ GC (uncertain if tonic-clonic or clonic)
- ☐ Myoclonic
- ☐ Absences
- ☐ Atonic
- ☐ Complex partial
- ☐ Hemiclonic
- ☐ Focal
- ☐ Spasms
- ☐ Tonic

h) If yes, specify management _____

Appendix 4. Publications arising from other research during my thesis

I co-authored the following publications not directly related to my thesis during my PhD candidature:

1. Koirala A, **Deng L**, Wood N. Keeping up with vaccinations: what's new, what's available and who to ask for help. Medicine Today. 2019;20(10):59-66.
2. **Deng L**, Mazzocato P, Saravanos G, Leder K, Britton PN. A high proportion of interseasonal childhood influenza cases in 2019 were travel related. Public Health Research & Practice. 2020;30(2):e3022012. doi:10.17061/phrp3022012
3. Macartney K, Quinn HE, Pillsbury AJ, Koirala A, **Deng L**, Winkler N, et al. Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study. The Lancet Child & Adolescent Health. 2020;4(11):807-16. doi:10.1016/S2352-4642(20)30251-0
4. **Deng L**, Barton B, Lorenzo J, Rashid H, Dastouri F, Booy R. Longer term outcomes following serogroup B invasive meningococcal disease. Journal of Paediatrics and Child Health. 2021. doi: 10.1111/jpc.15350



Keeping up with vaccinations

What's new, what's available and who to ask for help

ARCHANA KOIRALA MBChB, MIPH; **LUCY DENG** MB BS, MIPH
NICHOLAS WOOD MB BS, MPH, PhD

Vaccination is crucial in maintaining individual and population health. Australia's National Immunisation Program has been active since 1997 and is regularly updated as new vaccines, technology and surveillance data become available. It is therefore important that GPs have access to the most up-to-date information and resources to best advise patients, especially more vulnerable groups including children, older people, pregnant women and Aboriginal and Torres Strait Islander people.

MedicineToday 2019; 20(10): 59-66

Dr Koirala is an Immunisation Fellow at the National Centre for Immunisation Research and Surveillance (NCIRS), Sydney; Paediatric Infectious Diseases Specialist at Nepean Hospital, Kingswood; and Clinical Associate Lecturer at The University of Sydney Children's Hospital Westmead Clinical School, Sydney. Dr Deng is a Staff Specialist at NCIRS, Sydney; Paediatrician at The Children's Hospital at Westmead, Sydney; and Clinical Associate Lecturer at The University of Sydney Children's Hospital Westmead Clinical School, Sydney. Dr Wood is a Senior Staff Specialist at NCIRS, Sydney; Paediatrician at The Children's Hospital at Westmead, Sydney; and Associate Professor at The University of Sydney Children's Hospital Westmead Clinical School, Sydney, NSW.

Immunisation in Australia started in 1804 with the first smallpox vaccine, culminating in the National Immunisation Program (NIP), which began in 1997. Since then the program has expanded to include new vaccines, altered schedules and novel monitoring tools as new technology and evidence have become available. Since early 2019, there have been a number of changes to immunisation recommendations and this article aims to inform GPs on what is new, who to ask for help and where to find further information. Some practice points on vaccination are summarised in Box 1.

Influenza

Influenza is a viral illness of the respiratory tract caused by influenza A and B viruses. These viruses cause major and minor epidemics of seasonal influenza in most years, usually during the winter months but can be present throughout the year (Figure 1), especially with increasing overseas travel.[1] Severe complications of influenza include pneumonia, myocarditis, bacterial coinfection, encephalitis and death. Children, older people, pregnant women, Aboriginal and Torres Strait Islander (Indigenous) people and people with comorbidities have a higher risk of complication from influenza compared with the general population.[2,3]

Influenza vaccination for people of Aboriginal or Torres Strait Islander background

Aboriginal and Torres Strait Islander people have a high burden of disease from influenza and influenza-related complications.[2,3] The risk of influenza-related hospitalisations between 2006 and 2010 was two to six times higher among people of Indigenous background compared with non-Indigenous people.[2] Until 2019, the seasonal influenza vaccine was nationally funded for Indigenous children aged 6 months to 5 years and Indigenous people aged 15 years and over. To close the gap, the seasonal influenza vaccine is now funded for all Aboriginal and Torres Strait Islander

1. PRACTICE POINTS ON VACCINATION

- The flu vaccine is free for all Indigenous people and will be funded for all children aged 6 months to 5 years from 2020
- The flu vaccine is safe for egg-allergic patients
- The MMR vaccine can be given to patients as young as 6 months of age for travel
- dTpa can be given as early as 20 weeks' gestation with every pregnancy
- Q fever vaccination is recommended for anyone working with animals
- Immunisation recommendations change – always refer to the updated online *Australian Immunisation Handbook*
- Immunisation specialists are available in every state for clinical assistance

people aged 6 months and over.[4] In July 2019, the Pharmaceutical Benefits Advisory Committee recommended listing of the quadrivalent influenza vaccine on the NIP for all children aged 6 months to 5 years from 2020.[5]

Influenza vaccination for older people

People aged 65 years and over have the highest influenza-related mortality and decreased effectiveness to standard trivalent influenza vaccine (TIV) compared with the younger population.[2,6] To improve the immune response to the influenza vaccine in this age group, 'enhanced' TIVs were developed. Two types of enhanced vaccine are available in Australia: a high-dose influenza vaccine that contains four times the haemagglutinin content of standard TIVs; and an adjuvanted influenza vaccine that contains adjuvant MF59 in addition to the standard haemagglutinin dose of each strain.[4,7] These vaccines increase protection compared with standard-dose TIVs, especially against influenza A (H3) strain, which causes a more common and severe disease in older people.[4,6,8-10] Clinical trials have shown reduced laboratory-confirmed influenza and influenza-related deaths in people aged 65 years and over who were vaccinated with enhanced TIVs compared with standard TIVs.[8-10] Moreover, the improved efficacy of enhanced TIVs against influenza A is likely to offset the loss of protection against the additional influenza B lineage found in the quadrivalent vaccine.[4]

In 2018, enhanced TIVs were recommended in preference to the quadrivalent influenza vaccines for people aged 65 years and over. Active surveillance of the safety of the 2019 influenza vaccine in people aged 65 years and over commenced on 1 April 2019, with data showing reported events following immunisation were consistent with expected outcomes: most people (94%) did not have any adverse reaction; of the 6% with reactions, the most common adverse effects were injection site reactions, fevers and rash; only 0.3% required medical attendance.[11,12] The adjuvanted TIV is funded through the NIP for people aged 65 years and over and the high-dose TIV is available privately.[4]

Influenza vaccination for people with egg allergy

Influenza vaccines in Australia are grown in embryonated chicken eggs and historically there have been concerns regarding the risk of anaphylaxis following influenza vaccination in people with egg allergy. However, manufacturing processes ensure that only a trace amount of ovalbumin remains within the vaccine formulation (usually less than 1 mcg of ovalbumin per dose), which is insufficient to cause anaphylaxis.[4]

In a 2014 review of 28 studies encompassing 4315 people with egg allergy (including 656 people with a history of anaphylaxis), no severe reactions were reported after influenza vaccination.[13] Vaccine allergy testing, split dosing or graded administration are no longer recommended when vaccinating people with egg allergy as they have shown no difference in the rate of adverse reactions.[14] People with egg allergy do not need to be referred to specialist hospital-based vaccination clinics for influenza vaccination; however, anyone administering a vaccine should have training and equipment for the rapid recognition and treatment of anaphylaxis.[4] The Australasian Society of Clinical Immunology and Allergy has developed guidelines on vaccinating egg-allergic people (www.allergy.org.au/hp/

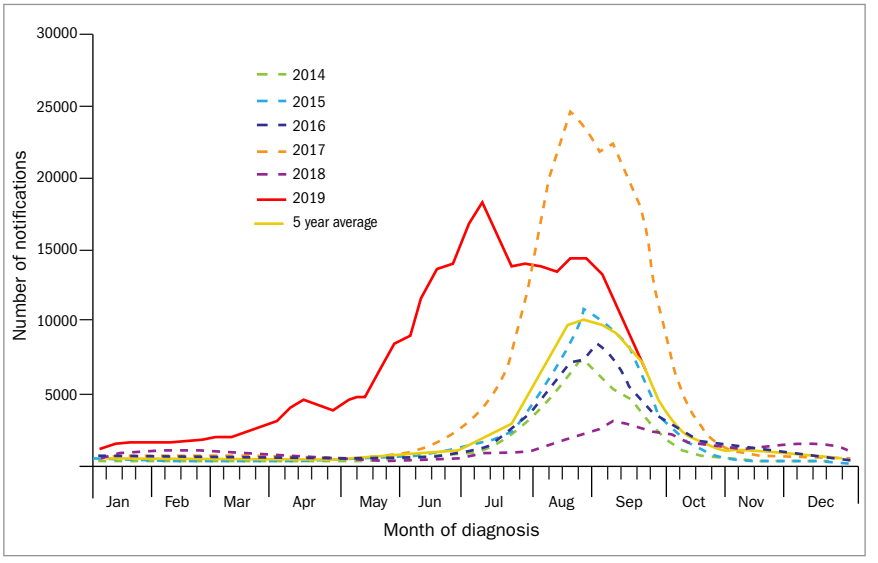


Figure 1. Notifications of laboratory confirmed influenza in Australia from 1 January 2013 to 22 September 2019, by month of diagnosis.

Reproduced with permission from the Australian Government Department of Health, 2019. Australian Influenza Surveillance Report 2019 No 11. Available online at: www1.health.gov.au/internet/main/publishing.nsf/Content/3CE94FB1E75C4A08CA2584820016014O/$File/flu-11-2019.pdf (accessed October 2019).

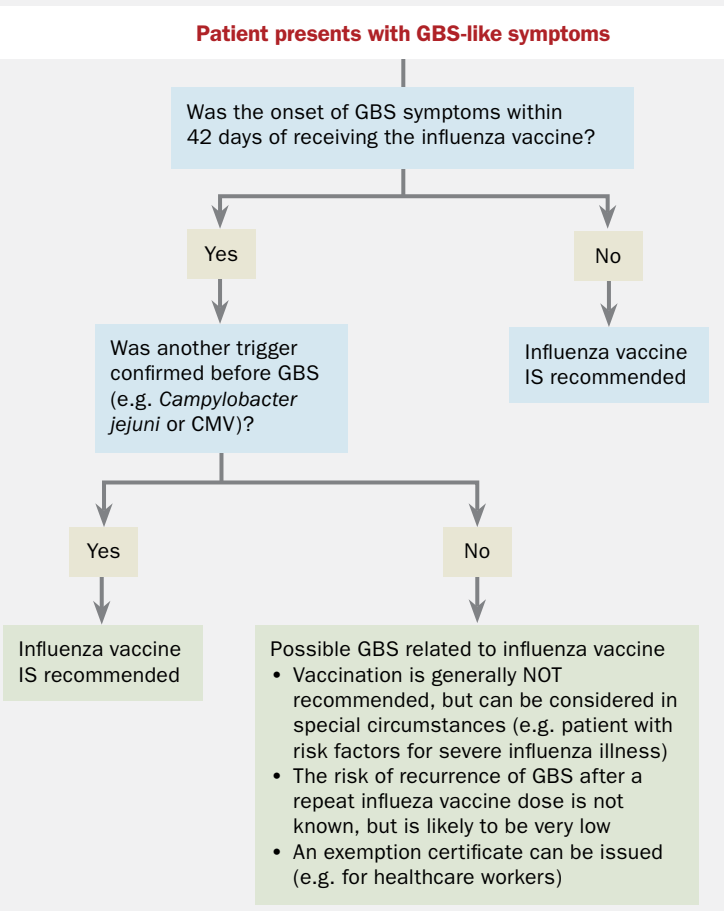
papersvaccination-of-the-egg-allergic-individual).[14]

Influenza and Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is a rare, acute immune-mediated polyneuropathy, commonly preceded and thought to be triggered by gastrointestinal or respiratory infections, including influenza. Concerns about the association between GBS and influenza vaccination arose after an increased number of cases of GBS were reported following swine flu vaccination in 1976.[15] Further studies have shown that GBS is rare after seasonal influenza vaccination, and at most may account for one additional case of GBS per million vaccine doses.[15-17]

The risk of developing GBS after influenza is 15 times higher than after influenza vaccination. Therefore, in patients with a history of GBS, the benefits of vaccination may outweigh the risk of recurrent GBS after vaccination.[18] Reassuringly, no recurrences of GBS were reported in 214 patients with a history of GBS, pooled from three studies, who received a total of 1195 doses of influenza vaccine after their GBS diagnosis.[19-21] Another study reported a recurrence of GBS-like symptoms following influenza vaccination in eight out of 211 patients with a history of GBS, but formal diagnosis of a relapse was not confirmed, most symptoms were mild and no patient required treatment or hospitalisation.[22] When considering vaccination of a patient with a past history of GBS, GPs should consider the patient's risk factors for severe influenza illness such as diabetes, any respiratory or cardiac condition, temporal association with the influenza vaccine and the possibility of a reasonable alternative trigger such as *Campylobacter* gastroenteritis. Vaccination is recommended unless the previous onset of GBS, without a potential alternative trigger, occurred within six weeks (42 days) of receiving the influenza vaccine (Flowchart).

APPROACH TO INFLUENZA VACCINATION IN PATIENTS WITH A HISTORY OF GUILLAIN–BARRÉ SYNDROME



Abbreviations: CMV = Cytomegalovirus; GBS = Guillain-Barré syndrome.
Reproduced with permission from the National Centre for Immunisation Research and Surveillance.

Measles

Measles is a highly infectious disease caused by a paramyxovirus and spread by aerosolised or droplet respiratory secretions. Complications of measles include otitis media, diarrhoea, pneumonia and encephalopathy, and measles remains one of the leading causes of death among young children.[23] Measles outbreaks have increased globally over the past few years, with the WHO estimating a 300% increase in reported cases in the first three months of 2019 resulting from gaps in vaccine coverage.[24]

In Australia, children are typically vaccinated against measles from 12 months of age, and therefore most measles cases are imported, occurring in unvaccinated or undervaccinated individuals infected while travelling to endemic or outbreak regions. Due to the constant importation of measles, there is a risk of spread to unvaccinated individuals, in particular children under the age of 1 year, in people who have not received two doses of measles-containing vaccine and immunocompromised individuals who cannot receive live vaccines.[25] As a consequence, to improve measles immunity in the community, the *Australian Immunisation Handbook* has updated its recommendations as follows:

- children as young as 6 months of age can receive the measles, mumps and rubella (MMR) vaccine
- all Australians should receive two doses of the MMR vaccine.

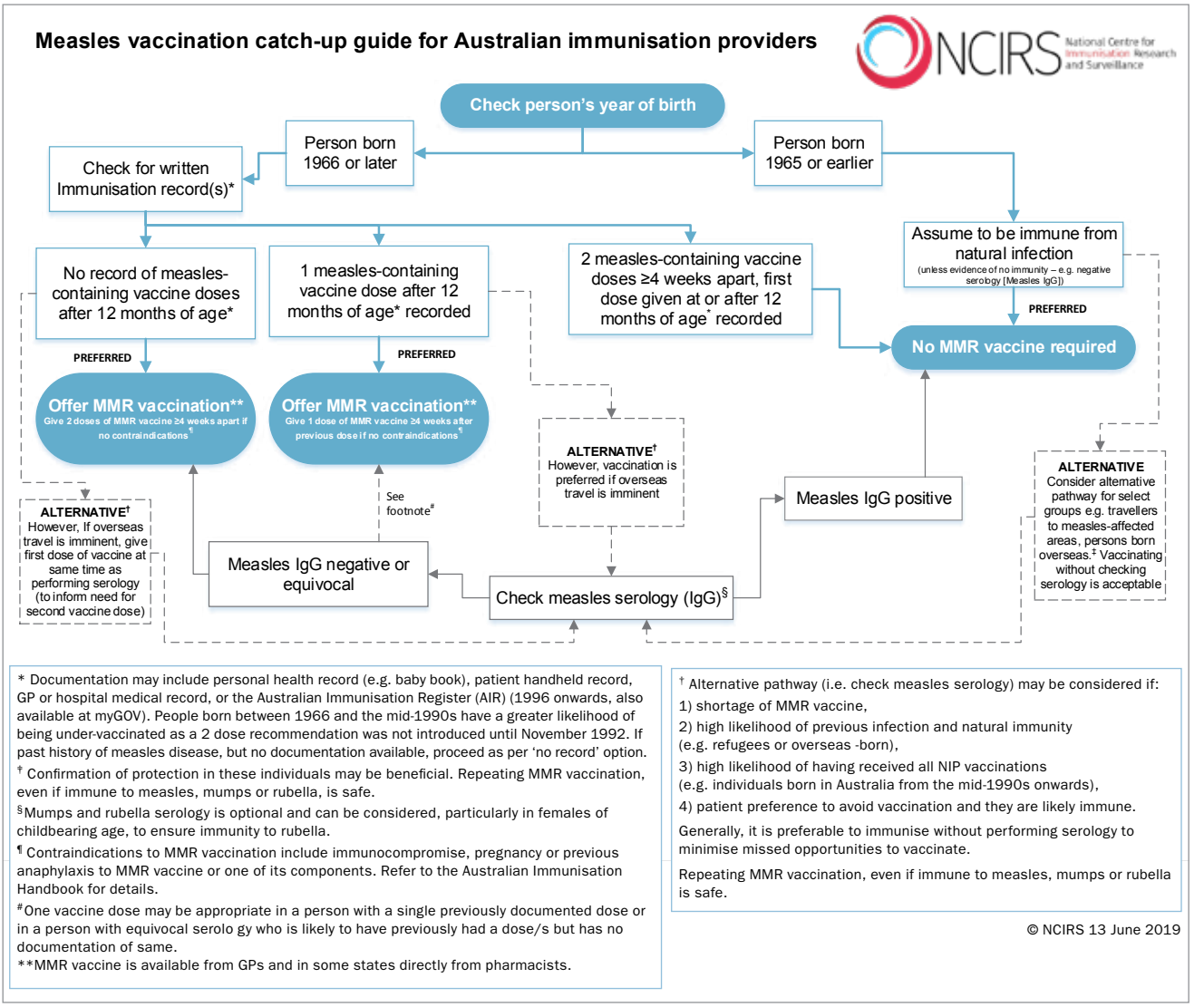


Figure 2. Measles vaccination catch up guide for Australian immunisation providers.[35] Reproduced with permission from the National Centre for Immunisation Research and Surveillance.

Measles vaccination from age 6 months

The *Australian Immunisation Handbook* has lowered the recommended age that children can receive the MMR vaccine from age 9 months to 6 months for children travelling to endemic areas, in outbreak situations and for postexposure prophylaxis in line with WHO and Centers for Disease Control and Prevention (CDC) recommendations.[4] The change in recommendation comes as a result of increasing evidence suggesting that vaccinated women have an earlier decline in circulating antibodies compared with women who have been infected with measles, resulting in lower titres of maternal antibodies being transferred to the fetus during pregnancy.[26-29] These lower titres result in a shorter period of protection in infants and a longer period of time that they are at risk of measles infection before their first dose of MMR vaccine. Countries that have lowered the recommended age of measles vaccination to as young as 6 months of age, including the US, Canada, UK and New Zealand, have reported no additional safety concerns.[30] Vaccinating infants between 6 and 11 months of age provides short-term protective antibody levels in a large proportion of infants and should be considered in addition to the routine two-dose schedule at 12 and 18 months to ensure long-term immunity.[24]

Two doses of the MMR vaccine for all

To prevent measles outbreaks, it is essential that all eligible individuals living in

Australia are immune to measles. Before 1966, the measles virus was circulating in the community and individuals born before that year are likely to have a natural immunity to measles.[31] People who were born between 1966 and 1994 may have received only a single dose of a measles-containing vaccine and, therefore, a proportion may not be immune to measles.[32]

One dose of measles-containing vaccine is 95 to 96% effective. Effectiveness increases to 99% after a second dose.[33,34] It is therefore recommended that all eligible individuals born after 1966 who are living in or visiting Australia receive two doses of a measles-containing vaccine. This requires that some patients receive catch-up vaccinations.[4] A flow chart (Figure 2) has been created by NCIRS to aid GPs in advising patients on catch-up vaccinations.[35] When it is uncertain whether a person has natural immunity or has received two doses of measles-containing vaccine, an additional MMR vaccine should be administered. There is no known increase in adverse events from vaccinating people with pre-existing immunity to measles.[4]

Routine serological testing for measles IgG to assess immunity from either natural infection or vaccination is not recommended in lieu of vaccination, but may be an alternative way to confirm measles immunity, particularly in populations where the MMR vaccine is contraindicated.[4,35] Sensitivity of the test varies by assay and time since vaccination.[36-38]

Pregnancy and vaccination

Vaccination needs should be assessed for women planning pregnancy and those who are pregnant. It is important that GPs discuss immunisation with women planning pregnancy and ensure that they are up-to-date on their immunisation schedules, particularly against rubella and chicken pox. These live vaccines can harm the fetus if contracted during pregnancy and should be given before pregnancy not during. Influenza and diphtheria-tetanus-acellular pertussis (dTpa) vaccines are recommended for pregnant women and are funded by the NIP.

Whooping cough vaccination in pregnancy

The pertussis vaccine (dTpa) is an inactivated vaccine provided free for pregnant women under the NIP, and recommended to be given in each pregnancy (even pregnancies that are closely spaced). Vaccination in pregnancy allows for maternal antibody production and in utero transfer to the fetus, protecting up to 90% of infants until the age of 3 months against hospitalisation from pertussis when the mother is vaccinated at least seven days before delivery.[39-41] The vaccine also protects pregnant women from contracting pertussis and reduces the likelihood of it spreading to other adults and their children. The recommended timing of the pertussis vaccination in pregnancy has expanded from between 28 and 32 weeks to between 20 and 32 weeks. This allows greater opportunities for health services to offer vaccination to pregnant women, to protect premature infants and to improve vaccine coverage.[4]

If the vaccine has not been given by 32 weeks of pregnancy it can still be given at any time during the third trimester. Additionally, if a pregnant woman receives the vaccine earlier than 20 weeks, she does not need a repeat dose during the same pregnancy. Evidence shows transfer of pertussis antibodies to the infant in women who received dTpa vaccine as early as 13 weeks' gestation.[42]

The vaccine is safe and well tolerated in pregnancy. Safety studies suggest that vaccination in the second and third trimester is not associated with clinically significant harm to the fetus or the mother.[42] Active surveillance of 5085 pregnant Australian women between 1 July 2018 and 30 June 2019 showed 94% had no adverse effects following dTpa vaccination. The most common adverse event was injection site pain (2.4%), followed by injection site swelling or erythema (1.7%). Fever occurred in 0.8% of women and only 0.5% of women required any medical attendance.[43] The only absolute contraindication to dTpa in pregnancy is a history of anaphylaxis to the vaccine.[4]

Influenza vaccination in pregnancy

Influenza in pregnant women and children less than 6 months of age is related to increased disease severity and risk of complications such as premature delivery and neonatal or perinatal death.[44-47] Vaccination during pregnancy ensures protection for both the mother and her infant up to 6 months of age, after which children are eligible to receive their own vaccine.[48-52] The seasonal influenza vaccine has been shown to decrease influenza cases in pregnant women by 50% and hospitalisation by 35 to 40%.[46,51,53,54] Infants less than 6 months of age were half as likely to develop influenza and 72% less likely to require hospitalisations when their mother received the influenza vaccine in pregnancy.[48] The seasonal influenza vaccine is safe throughout all trimesters of pregnancy and only one dose is recommended each season.[4,50,55] Pregnant women are advised to receive a second dose of the influenza vaccine if their first dose was the previous year's seasonal influenza vaccine.[12]

Despite the efficacy and safety data, influenza vaccine uptake is still not universal, and data from Australian states and territories estimate a minimum of 25%, and up to 60%, of pregnant women may not receive the vaccine.[56-58] GPs play a significant role in increasing vaccine uptake as women are more likely to receive the influenza vaccine if recommended by their healthcare provider.[59-61]

Pneumococcal disease

Pneumococcal disease is an infection caused by the Gram-positive encapsulated bacterium *Streptococcus pneumoniae*. Invasive pneumococcal disease (IPD) refers to severe infection usually causing sepsis, bacteraemic pneumonia or meningitis. Young children, older people, people of Aboriginal or Torres Strait Islander descent, patients who have or are at risk of cerebrospinal fluid leak or people who are immunocompromised have the highest increased risk of IPD.[62] Protection against pneumococcal disease is serotype specific. Two vaccines exist in Australia: a 13-valent

pneumococcal conjugate vaccine (13vPCV) and a 23-valent pneumococcal polysaccharide vaccine (23vPPV).[4,63] The 13vPCV is funded in the NIP infant vaccination schedule as it induces long-lasting immune responses, even in children under 2 years of age.[64] The 23vPPV offers protection, albeit shorter lasting, to more pneumococcal serotypes and is currently recommended for Indigenous people at 50 years of age and non-Indigenous people at 65 years of age.[62] This recommendation is likely to change in the next 12 months as the Pharmaceutical Benefits Advisory Committee has proposed, based on cost-effective analysis, that the 13vPCV replace the first dose of 23vPPV for Aboriginal and Torres Strait Islander adults at 50 years of age and for all other healthy adults at 70 years of age.[65]

Recommendations on the infant pneumococcal immunisation schedule were updated in July 2018. The current recommendation for children with no risk factors is to receive 13vPCV at age 2 months (or 6 weeks), 4 months and a booster at 12 months of age (2+1 schedule) to generate longer lasting immunity and improved herd immunity in children compared with the original 3+0 schedule (2, 4, 6 months of age).[4] Children of Indigenous background or with risk factors for IPD are funded through the NIP to receive four doses (3+1) of the 13vPCV at 2, 4, 6 and 12 months of age and 23vPPV at 5 years of age.[4] Additional pneumococcal vaccines, as detailed in the *Australian Immunisation Handbook*, continue to be recommended for adults and children aged 5 years and over, with risk factors for IPD, depending on the severity of risk and history of previous pneumococcal vaccination.[4,62]

The PneumoSmart vaccination tool

The PneumoSmart vaccination tool was developed by the Immunisation Coalition to help immunisation providers correctly provide pneumococcal vaccination for people aged 5 years or over, based on the recommendations from the *Australian Immunisation Handbook*. The algorithm incorporates a person's age, Indigenous status, comorbidities and previous pneumococcal vaccinations to develop a table recommending the type of vaccine, intervals between doses and whether the vaccine is funded through the NIP (https://immunisationcoalition.org.au/pvt).[66]

2. USEFUL RESOURCES FOR GPs ON VACCINATION

The following resources are useful for GPs to refer to when looking for information on immunisation.

The Australian Immunisation Handbook (https://immunisationhandbook.health.gov.au) is a free, up-to-date online reference that uses the best scientific evidence available to provide clinical guidelines for healthcare professionals.[4] The handbook provides information on vaccine preventable diseases, vaccines available in Australia, immunisation schedules and methods of administering vaccines safely and effectively. The online handbook is continually updated and supersedes the current 2014 print edition.

National Centre for Immunisation Research and Surveillance (NCIRS) (ncirs.org.au) offer numerous useful resources for GPs and the general public.

- Fact sheets on vaccine preventable diseases, vaccine safety and clinical resources have been developed principally for immunisation providers (http://ncirs.org.au/health-professionals/ncirs-fact-sheets-faqs).
- NCIRS also run a series of webinars on current topics around immunisation and vaccine preventable diseases about every six weeks (http://ncirs.org.au/NCIRSSeminars).
- Sharing knowledge about immunisation (SKAI) is a set of online vaccination communication support tools designed to assist patient-centred communication around immunisation (www.ncirs.org.au/our-work/sharing-knowledge-about-immunisation). The parent-focused website 'Talking about immunisation' contains information about common concerns around vaccination in both written and video format (www.talkingaboutimmunisation.org.au).

AusVaxSafety (www.ausvaxsafety.org.au) is an NCIRS-led collaboration established in 2014 to monitor adverse events in children following immunisation with influenza vaccines through responses solicited via automated SMS or email on a wide range of infant, pregnancy, adolescent and elderly vaccines.[11] Data on current event rates are reported via safety surveillance graphs and compared to expected rates according to existing data.

The **Immunisation Coalition** (www.immunisationcoalition.org.au) is an independent, not-for-profit organisation that works in close collaboration with consumer advocacy groups and professional and government bodies to provide current information on immunisation. The website provides the PneumoSmart calculator, fact sheets and webinars on vaccine-preventable diseases.

The Melbourne Vaccine Education Centre (MVEC) (https://mvec.mcri.edu.au) is based at the Murdoch Children's Research Institute and provides information on immunisation on a range of topics aimed at immunisation providers and members of the public including regularly updated fact sheets, links to the National Immunisation Schedule, information on how to plan catch-up immunisation schedules using the Australian Immunisation Register (AIR) and information on how to manage vaccination adverse events. The webpage also alerts clinicians to schedule updates, new guidelines and proposed changes to the childhood immunisation arrangements for family assistance payments.

The National Vaccine Storage Guidelines (Strive for 5) (www.health.gov.au/resources/publications/national-vaccine-storage-guidelines-strive-for-5) are updated national vaccine storage guidelines prompting all immunisation service providers, including GPs, to strive to keep vaccines stored at 5°C – the halfway point between the recommended temperature range of 2 to 8°C, with a permanent data logger in place to measure temperature at preset 5-minute intervals. Useful printable tools such as checklists and refrigerator temperature charts are included in the guideline.

Q fever

Q fever is a zoonotic disease caused by the intracellular bacterium *Coxiella burnetii*. Although the disease can be asymptomatic, it can often present with severe flu-like symptoms and be complicated by

pneumonia and hepatitis. Some people go on to develop chronic Q fever, which may manifest as endocarditis. Ruminants such as cattle, sheep and goats are the main reservoir for human infection but a wide variety of animals including birds, ticks and marsupials can be infected. The environmental form of *C. burnetii* is resistant to heat and desiccation. The bacteria can persist for long periods in the environment and be transported long distances by wind and dust. Humans are infected via direct contact with animals or inhalation of contaminated aerosols.[67,68]

Early diagnosis and vaccination

Q fever, despite being undernotified, remains a highly vaccine-preventable disease, especially for rural residents. A large serosurvey reported a seropositivity of 3.6% among blood donors in NSW and Queensland, with higher seroprevalence among those living in rural areas. However, 0.9% of urban dwellers with no risk factors also had evidence of exposure.[69]

People who are at high risk of contracting Q fever and for whom the vaccine is recommeded include those who work on farms, in veterinary practice or in abattoirs, manage or breed animals or handle veterinary specimens. The Q fever vaccine is licensed for use in people from 15 years of age but studies are underway to assess its safety and efficacy in children as young as 10 years of age.[70]

Candidates require prevaccination testing with serum antibody and skin testing to ensure there has been no past exposure to *C. burnetii* and to minimise adverse effects following vaccination.[4] Test results can be uploaded onto the Australian Q fever register (https://qfever.org/findvaccinator), and authorised users (usually meat processors and medical practitioners) are able to check a person's Q fever immune status.[71] The register also provides a list of medical practitioners who are experienced in testing and vaccinating against Q fever.

A study found that 40% of people for whom the vaccination is recommended were aware of the vaccine, and only 10% were vaccinated, with a perceived lack of risk being the main reported reason for not being vaccinated.[69] To increase awareness of Q fever and vaccination among GPs, a new Q fever educational resource has been developed by the Australian College of Rural and Remote Medicine (ACRRM).[72] This two-hour online course updates providers on Q fever diagnosis and vaccination and is available for free to all ACRRM members and subscribers. Nonmembers can also enrol for a fee. The module provides education about pathogenesis and the clinical presentation of Q fever, exposure risks in Australia, treatment, prevaccination testing and Q fever vaccination.[72]

Catch-up vaccinations

Free catch-up vaccinations are available for all people under 20 years of age and to all refugees and humanitarian entrants regardless of age.[4]

Immunisation calculator

A web-based immunisation calculator is available through South Australian Health to help clinicians draft a catch-up schedule for children under 10 years of age who have missed or received delayed vaccination (https://immunisationcalculator.sahealth.sa.gov.au/ImmuCalculator.aspx).[73] A similar calculator is being developed for the online *Australian Immunisation Handbook* and checking the catch-up resources on their website (https://immunisationhandbook.health.gov.au/catch-up-vaccination) on a regular basis is strongly recommended.

Adverse events following immunisation

Although vaccines are generally safe, occasionally a patient may experience a reaction following vaccination. Any negative reaction that follows immunisation is considered an adverse event following immunisation (AEFI). The adverse event does not need to be causal for it to be classified as an AEFI and may be any unfavourable or unintended sign or symptom, disease or abnormal laboratory finding. Up to 10% of people can experience a common AEFI such as an injection site reaction, pain or fever.[4,74]

AEFI reporting

In the event of a serious, uncommon or rare AEFI, the immunisation provider should seek advice from their local specialist immunisation clinic or contact their state or territory health authorities. This advice is important to determine the relationship of the adverse event to vaccination and the benefit and risks of further vaccination and to ensure the development of a plan for future vaccination. Methods of reporting vary between each state and territory. Information can be found on the NCIRS website (www.ncirs.org.au/health-professionals specialist-immunisation-services).[43]

All states and territories offer specialist clinic review for patients who have experienced AEFIs. Most clinics will see children, others will also review adults and some have teleconferencing abilities. Information can be found at www.ncirs.org.au/health-professionals specialist-immunisation-services.

Conclusion

There are some constants to immunisation such as a comprehensive and methodical immunisation schedule, and nationwide and global immunisation coverage to stop the spread of vaccine-preventable diseases. That said, with novel technology, research and surveillance methods, new vaccines are being developed and tested, and there is the ability for constant review of disease epidemiology, vaccine efficacy and adverse events. Immunisation programs are therefore constantly evolving. As such, we encourage GPs to stay updated and informed using key web resources and tools. Useful resources for GPs on vaccination are summarised in Box 2. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Keeping up with vaccinations

What's new, what's available and who to ask for help

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References

1. Paules C, Subbarao K. Influenza. Lancet 2017; 390: 697-708.
2. Li-Kim-Moy J, Yin JK, Patel C, et al. Australian vaccine preventable disease epidemiological review series: influenza. Commun Dis Intell 2016; 40: E482-E495.
3. Naidu L, Chiu C, Habig A, et al. Vaccine preventable diseases and vaccination coverage in Aboriginal and Torres Strait Islander people, Australia 2006-2010. Commun Dis Intell Q Rep 2013; 37 Suppl: S1-S95.
4. Australian Technical Advisory Group on Immunisation (ATAGI). Australian immunisation handbook. Canberra: Australian Government Department of Health; 2018. Available online at: https://immunisationhandbook.health.gov.au (accessed October 2019).
5. Pharmaceutical Benefits Advisory Committee. July 2019 PBAC meeting - positive recommendations. Canberra: Australian Government Department of Health; 2019. Available online at: www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2019-07/positive-recommendations-07-2019.pdf (accessed October 2019).
6. Cheng AC, Holmes M, Dwyer DE, et al. Influenza epidemiology in patients admitted to sentinel Australian hospitals in 2017: the Influenza Complications Alert Network (FluCAN). Commun Dis Intell (2018) 2019; 43. doi: 10.33321/cdi.2019.43.39.
7. O'Hagan D, Ott GS, De Gregorio E, Seubert A. The mechanism of action of MF59 - an innately attractive adjuvant formulation. Vaccine 2012; 30: 4341-4348.
8. Frey SE, Reyes MR, Reynales H, et al. Comparison of the safety and immunogenicity of an MF59®-adjuvanted with a non-adjuvanted seasonal influenza vaccine in elderly subjects. Vaccine 2014; 32: 5027-5034.
9. Mannino S, Villa M, Apolone G, et al. Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. Am J Epidemiol 2012; 176: 527-533.
10. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis 2009; 200: 172-180.
11. AusVaxSafety. Influenza vaccine safety data. AusVaxSafety 2019. Available online at: www.ausvaxsafety.org.au/safety-data/influenza-vaccine (accessed October 2019).
12. National Centre for Immunisation Research and Surveillance. National Centre for Immunisation Research and Surveillance. Sydney: NCIRS; 2019. Available online at: http://ncirs.org.au (accessed October 2019).
13. Kelso JM. Administering influenza vaccine to egg-allergic persons. Expert Rev Vaccines 2014; 13: 1049-1057.
14. Australasian Society of Clinical Immunology and Allergy. ASCIA Guidelines - Vaccination of the egg-allergic individual. Available online at: www.allergy.org.au/images/stories/pospapers/ASCIA_Guidelines_vaccination_egg_allergic_individual_2017.pdf (accessed October 2019).
15. Vellozzi C, Iqbal S, Broder K. Guillain-Barré syndrome, influenza, and influenza vaccination: the epidemiologic evidence. Clin Infect Dis 2014; 58: 1149-1155.
16. Tokars JI, Lewis P, DeStefano F, et al. The risk of Guillain–Barré syndrome associated with influenza A (H1N1) 2009 monovalent vaccine and 2009–2010 seasonal influenza vaccines: results from self-controlled analyses. Pharmacoepidemiol Drug Saf 2012; 21: 546-552.
17. Principi N, Esposito S. Vaccine-preventable diseases, vaccines and Guillain-Barré syndrome. Vaccine 2019; 37: 5544-5550.
18. Kwong JC, Vasa PP, Campitelli MA, et al. Risk of Guillain-Barré syndrome after seasonal influenza vaccination and influenza health-care encounters: a self-controlled study. Lancet Infect Dis 2013; 13: 769-776.
19. Baxter R, Lewis N, Bakshi N, Vellozzi C, Klein NP. Recurrent Guillain-Barre syndrome following vaccination. Clin Infect Dis 2012; 54: 800-804.
20. Kuitwaard K, van Koningsveld R, Ruts L, Jacobs BC, van Doorn PA. Recurrent Guillain–Barré syndrome. J Neurol Neurosurg Psychiatry 2009; 80: 56-59.
21. Wijdicks EF, Fletcher DD, Lawn ND. Influenza vaccine and the risk of relapse of Guillain–Barre syndrome. Neurology 2000; 55: 452-453.
22. Pritchard J, Mukherjee R, Hughes R. Risk of relapse of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy following immunisation. J Neurol Neurosurg Psychiatry 2002; 73: 348-349.
23. Kimberlin DW, Brady MT, Jackson MA, Long SS. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca: American Academy of Paediatrics, 2019.
24. Gans HA, Arvin AM, Galinus J, Logan L, DeHovitz R, Maldonado Y. Deficiency of the humoral immune response to measles vaccine in infants immunized at age 6 months. JAMA 1998; 280: 527-532.
25. Measles Outbreaks 2019. Australian Government Department of Health. Available online at: www1.health.gov.au/internet/main/publishing.nsf/Content/ohp-measles-outbreaks-2019.htm (accessed October 2019).
26. Brugha R, Ramsay M, Forsey T, Brown D. A study of maternally derived measles antibody in infants born to naturally infected and vaccinated women. Epidemiol Infect 1996; 117: 519-524.
27. Guerra FM, Crowcroft NS, Friedman L, et al. Waning of measles maternal antibody in infants in measles elimination settings – a systematic literature review. Vaccine 2018; 36: 1248-1255.
28. Maldonado YA, Lawrence EC, DeHovitz R, Hartzell H, Albrecht P. Early loss of passive measles antibody in infants of mothers with vaccine-induced immunity. Paediatrics 1995; 96: 447-450.
29. Waaijenborg S, Hahné SJ, Mollema L, et al. Waning of maternal antibodies against measles, mumps, rubella, and varicella in communities with contrasting vaccination coverage. J Infect Dis 2013; 208: 10-16.
30. World Health Organization. New measles surveillance data for 2019. Geneva: WHO; 2019. Available online at: www.who.int/immunization/newsroom/measles-data-2019/en/ (accessed October 2019).
31. Chiu C, Dey A, Wang H, et al. Vaccine preventable diseases in Australia, 2005 to 2007. Commun Dis Intell Q Rep 2010; 34: S1. Available online at: www1.health.gov.au/internet/publications/publishing.nsf/Content/cda-cdi34suppl.htm/$FILE/cdi34suppl.pdf (accessed October 2019).
32. Significant events in measles, mumps and rubella vaccination practice in Australia. National Centre for immunisation research and surveillance, 2018. Available online at: http://ncirs.org.au/sites/default/files/2019-07/Measles-mumps-rubella-history-July%202019.pdf (accessed October 2019).
33. Pillsbury A, Quinn H. An assessment of measles vaccine effectiveness,

Australia, 2006-2012. Western Pac Surveill Response 2015; 6: 43-50.
34. Bianco E, Price D, Jefferson T, Demicheli V. Vaccines for measles mumps and rubella in children. Cochrane Database Syst Rev 2012; (2): CD004407. doi: 10.1002/14651858.CD004407.pub3.
35. National Centre for Immunisation Research and Surveillance. Measles vaccination catch-up guidelines for Australian immunisation providers. Sydney: NCIRS; 2019. Available online at: http://ncirs.org.au/sites/default/files/2019-06/NCIRS%20Measles%20vaccination%20catch-up%20guide%20for%20immunisation%20providers13062019.pdf (accessed October 2019).
36. Chen RT, Markowitz LE, Albrecht P, et al. Measles antibody: reevaluation of protective titers. J Infect Dis 1990; 162: 1036-1042.
37. Cohen B, Parry R, Doblas D, et al. Measles immunity testing: comparison of two measles IgG ELISAs with plaque reduction neutralisation assay. J Virol Methods 2006; 131: 209-212.
38. Manual for the laboratory diagnosis of measles and rubella virus infection. Geneva: World Health Organization; 2007. Available online at: www.who.int/ihr/elibrary/manual_diagn_lab_mea_rub_en.pdf (accessed October 2019).
39. Skoff TH, Blain AE, Watt J, et al. Impact of the US maternal tetanus, diphtheria, and acellular pertussis vaccination program on preventing pertussis in infants < 2 months of age: a case-control evaluation. Clin Infect Dis 2017; 65: 1977-1983.
40. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014; 384: 1521-1528.
41. Saul N, Wang K, Bag S, et al. Effectiveness of maternal pertussis vaccination in preventing infection and disease in infants: the NSW Public Health Network case-control study. Vaccine 2018; 36: 1887-1892.
42. Eberhardt CS, Blanchard-Rohner G, Lemaître B, et al. Maternal immunization earlier in pregnancy maximizes antibody transfer and expected infant seropositivity against pertussis. Clin Infect Dis 2016; 62: 829-836.
43. National Centre for Immunisation Research and Surveillance. Specialist Immunisation Clinic. 2019. Available online at: www.ncirs.org.au/nswiss (accessed October 2019).
44. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. AJOG 2012; 207 Suppl: S3-S8.
45. Mertz D, Geraci J, Winkup J, Gessner BD, Ortiz JR, Loeb M. Pregnancy as a risk factor for severe outcomes from influenza virus infection: a systematic review and meta-analysis of observational studies. Vaccine 2017; 35: 521-528.
46. Thompson MG, Kwong JC, Regan AK, et al. Influenza vaccine effectiveness in preventing influenza-associated hospitalizations during pregnancy: a multi-country retrospective test negative design study, 2010–2016. Clin Infect Dis 2018; 68: 1444-1453.
47. Blyth CC, Macartney KK, McRae J, et al. Influenza epidemiology, vaccine coverage and vaccine effectiveness in children admitted to sentinel Australian hospitals in 2017: results from the PAEDS-FluCAN collaboration. Clin Infect Dis 2018; 68: 940-948.
48. Nunes MC, Madhi SA. Influenza vaccination during pregnancy for prevention of influenza confirmed illness in the infants: a systematic review and meta-analysis. Hum Vaccin Immunother 2018; 14: 758-766.
49. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. NEJM 2008; 359: 1555-1564.
50. Giles ML, Krishnaswamy S, Macartney K, Cheng A. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. Hum Vaccin Immunother 2019; 15: 687-699.
51. Tapia MD, Sow SO, Tamboura B, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. Lancet Infect Dis 2016; 16: 1026-1035.
52. Steinhoff MC, Katz J, Englund JA, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. Lancet Infect Dis 2017; 17: 981-989.
53. Madhi SA, Cutland CL, Kuwanda L, et al. Influenza vaccination of pregnant women and protection of their infants. NEJM 2014; 371: 918-931.
54. Regan AK, Klerk Nd, Moore HC, Omer SB, Shellam G, Effler PV. Effectiveness of seasonal trivalent influenza vaccination against hospital-attended acute respiratory infections in pregnant women: a retrospective cohort study. Vaccine 2016; 34: 3649-3656.
55. Fell DB, Azziz-Baumgartner E, Baker MG, et al. Influenza epidemiology and immunization during pregnancy: Final report of a World Health Organization working group. Vaccine 2017; 35: 5738-5750.
56. Mak DB, Regan AK, Vo DT, Effler PV. Antenatal influenza and pertussis vaccination in Western Australia: a cross-sectional survey of vaccine uptake and influencing factors. BMC Pregnancy Childbirth 2018; 18: 416.
57. Carlsona S, Deya A, Bearda F. An evaluation of the 2016 influenza vaccination in pregnancy campaign in NSW, Australia. Public Health Res Pract 2019. Epub ahead of print. doi: 10.17061/phrp29121908.
58. Overton K, Webby R, Markey P, Krause V. Influenza and pertussis vaccination coverage in pregnant women in the Northern Territory in 2015 - new recommendations to be assessed. NT Dis Control Bull 2016; 23: 1-8.
59. Danchin MH, Costa-Pinto J, Attwell K, et al. Vaccine decision-making begins in pregnancy: correlation between vaccine concerns, intentions and maternal vaccination with subsequent childhood vaccine uptake. Vaccine 2018; 36: 6473-6479.
60. Mohammed H, Clarke M, Koehler A, Watson M, Marshall H. Factors associated with uptake of influenza and pertussis vaccines among pregnant women in South Australia. PloS One 2018; 13: e0197867.
61. Krishnaswamy S, Cheng AC, Wallace EM, Buttery J, Giles ML. Understanding the barriers to uptake of antenatal vaccination by women from culturally and linguistically diverse backgrounds: a cross-sectional study. Hum Vaccin Immunother 2018; 14: 1591-1598.
62. Jayasinghe S. Pneumococcal disease and vaccination recommendations: the state of play. RMT 2019; 4(2): 16-22.
63. Geno KA, Gilbert GL, Song JY, et al. Pneumococcal capsules and their types: past, present, and future. Clin Microbiol Rev 2015; 28: 871-899.
64. Klein DL. Pneumococcal conjugate vaccines: review and update. Microb Drug Resist 1995; 1: 49-58.
65. Pharmaceutical Benefits Advisory Committee. July 2019 PBAC outcomes - other matters. Canberra: Australian Government Department of Health; 2019. Available online at: www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2019-07/other-matters-07-2019.pdf (accessed October 2019).
66. Immunisation coalition. The PneumoSmart Vaccination Tool. Melbourne 2016. Available online at: https://immunisationcoalition.org.au/pvt/ (accessed October 2019).
67. Eastwood K, Graves SR, Massey PD, Bosward K, Hutchinson P. Q fever: a rural disease with potential urban consequences. Aust J Gen Pract 2018; 47: 112-116.
68. Eldin C, Mélenotte C, Mediannikov O, et al. From Q fever to Coxiella burnetii infection: a paradigm change. Clin Microbiol Rev 2017; 30: 115-190.
69. Gidding HF, Faddy HM, Durrheim DN, et al. Seroprevalence of Q fever among metropolitan and non-metropolitan blood donors in New South Wales and Queensland, 2014–2015. Med J Aust 2019; 210: 309-315.
70. National Centre for Immunisation Research and Surveillance. Clinical research. Sydney: NCIRS; 2019. Available online at: www.ncirs.org.au/our-work/clinical-research (accessed October 2019).
71. Australian Meat Processor Corporation. Australian Q fever Register. Sydeny: AMPC; 2019. Available online at: www.qfever.org (accessed October 2019).
72. Q-fever - early diagnosis and vaccination. Brisbane; 2018. Australian college of rural and remote medicine. Available online at: www.acrrm.org.au/search/find-online-learning/details?id=11347 (accessed October 2019).
73. SA Health. Immunisation Calculator. SA Health, 2019. Available online at: https://immunisationcalculator.sahealth.sa.gov.au/ImmuCalculator.aspx (accessed September 2019).
74. National Centre for Immunisation Research and Surveillance. Injection site reactions. Sydney: NCIRS; 2019. Available online at: www.ncirs.org.au/new-resource-injection-site-reactions-information-sheet (accessed October 2019).

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Brief report

A high proportion of interseasonal childhood influenza cases in 2019 were travel related

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Background

Influenza is considered a seasonal disease in temperate regions, with annual epidemics between May and October in the Southern Hemisphere and the reverse in the Northern Hemisphere. In tropical regions, influenza can circulate year round.[1]

In 2019, Australia experienced a higher than usual number of laboratory-confirmed influenza cases in the months preceding the typical influenza season.[2] International travellers are at risk of acquiring influenza infection when travelling to regions where the virus is circulating and importing the virus into their home country on return. These cases can function as sentinels for sustained transmission.[3] Preliminary data from a case–control study found that travellers played a role in introducing influenza infection into New South Wales (NSW) in the 2018–2019 summer period.[4] We aimed to describe travel-related influenza cases presenting to a single tertiary paediatric hospital in NSW in 2019.

Methods

The Children's Hospital at Westmead in Sydney, NSW, is a GeoSentinel surveillance network associate site that systemically collects clinical information about ill returning travellers who are identified in the emergency department using a standardised case report form, as described elsewhere.[5] Through this network, we identified influenza cases from returning travellers who attended the hospital between January and October 2019. An influenza case was defined as an individual with influenza infection confirmed on a respiratory sample by a polymerase chain reaction (PCR) test at the hospital. A travel-related case was defined as a case with symptom onset during international travel or within 4 days following return. Cases were excluded if testing was performed more than 48 hours following hospital admission,

to exclude hospital acquisition, or if the patient had re-presented with a repeat positive test within 14 days of previous testing. Travel-related cases were compared with cases with no history of travel that presented to hospital over the same period. Month of travel and demographic details were compared between groups. Destination and reason for travel were described for travel-related cases.

Results

There were 879 laboratory-confirmed influenza presentations to The Children's Hospital at Westmead from January to October 2019, of which 25 (2.8%) were travel related (see Supplementary Figure 1, available from: doi.org/10.6084/m9.figshare.12331403). One probable travel-related case, where family members were influenza A positive but the patient was not tested, was excluded.

Almost three-quarters of travel-related cases (17/25) occurred in the interseasonal period between January and April. In this period, 12.3% (17/138) of all influenza cases were travel related, compared with 1.1% (8/741) between May and October. This difference in proportion was statistically significant (X^2 53.18; df 1; N = 879; $p < 0.001$). Influenza A accounted for a significantly greater proportion of travel-related cases (80%) compared with nontravel-related cases (60%) (Table 1). The most frequent destinations for travel were India (n = 8), Pakistan (n = 3) and the Philippines (n = 3). The most common reason for travel was visiting friends and relatives (n = 10), accounting for 67% (10/15) of travel-related cases where reason for travel was known. None of the cases were known to be vaccinated for influenza before travel.

Table 1. Demographic and clinical details of influenza cases at The Children's Hospital at Westmead, January–October 2019

Demographic	Clinical details	All cases	Travel related	Nontravel related
N		879	25	854
Sex	Male, *n* (%)	492 (56.0)	15 (60.0)	477 (55.9)
	Female, *n* (%)	387 (44.0)	10 (40.0)	377 (44.1)
Age	Median years (interquartile range)	4.4 (1.7–7.6)	2.7 (1.6–5.3)	4.5 (1.7–7.6)
Influenza strain	A (total), *n* (%)	531 (60.4)	20 (80.0)	511 (59.8)
	A subytpe H1N1, *n* (%)	100 (11.4)	12 (48.0)	88 (10.3)
	A subtype H3N2, *n* (%)	112 (12.7)	3 (12.0)	109 (12.8)
	A not typed, *n* (%)	319 (36.3)	5 (20.0)	314 (36.8)
	B, *n* (%)	346 (39.4)	5 (20.0)	341 (39.9)
	Both A and B, *n* (%)	2 (0.2)	0 (0.0)	2 (0.2)
Timing of travel	January–April, *n* (%)	138 (15.8)	17 (68.0)	121 (14.2)
	May–October, *n* (%)	741 (84.3)	8 (32.0)	733 (85.8)
Travel destination[a]	India, *n* (%)		8 (32.0)	
	Pakistan, *n* (%)		3 (12.0)	
	Philippines, *n* (%)		3 (12.0)	
	China, *n* (%)		2 (8.0)	
	Singapore, *n* (%)		2 (8.0)	
	Sri Lanka, *n* (%)		2 (8.0)	
Travel reason	Tourism, *n* (%)		3 (12.0)	
	Visiting friends and relatives, *n* (%)		10 (40.0)	
	Visiting Australia[b], *n* (%)		2 (8.0)	
	Unknown, *n* (%)		10 (40.0)	

[a] Destinations with single case: Fiji, Jordan, New Zealand, UK, US
[b] From Sweden

Discussion

Despite small numbers, our study found that travel-related influenza in children occurred predominantly in the interseasonal period and contributed to a significantly higher proportion of cases in this period than in the usual influenza season. A large proportion of travel related to visiting friends and relatives in neighbouring Asian countries, in tropical regions where influenza can circulate year round. Because of the small number of cases and the absence of subtyping in a significant proportion of cases, we were unable to make comparisons with contemporaneously circulating subtypes worldwide. However, consistent with a larger statewide study[4], our study suggests that importation of influenza by travellers may have contributed to the early spread and surge of influenza cases in NSW in 2019.

Although vaccination is the best way to protect against influenza infection, none of our travel-related cases had a documented influenza vaccination before travel. Our study suggests that influenza vaccine needs greater consideration and promotion as a travel vaccine. Travellers should receive influenza vaccine when travelling to regions where influenza is circulating or in settings with an increased risk of transmission, including large tourist groups, cruises and mass gatherings. For those who have received a current Southern Hemisphere influenza vaccine and are travelling to the Northern Hemisphere during its influenza season, a second dose of vaccine in the same year should be considered, as per updated recommendations in the *Australian Immunisation Handbook*.[6]

Conclusion

A relatively high proportion of interseasonal influenza cases in children are travel related. Influenza vaccination for travellers should be promoted to reduce the importation and spread of influenza virus in the community.

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Peer review and provenance

Externally peer reviewed, not commissioned.

Competing interests

None declared.

Author contributions

LD performed the analysis and drafted the manuscript. PM undertook the GeoSentinel surveillance and reviewed and revised the manuscript. GS sourced data, and reviewed and revised the manuscript. KL reviewed and revised the manuscript. PB devised the study, designed the analysis, and reviewed and revised the manuscript.

References

1 Monto AS. Epidemiology of influenza. Vaccine. 2008;26 Suppl 4:D45–8.

2. Department of Health. Australian influenza surveillance report. No 12, 23 September to 6 October 2019. Canberra: Australian Government Department of Health; 2019 [cited 2019 Nov 26]. Available from: www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/$File/flu-12-2019.pdf

3. Davis XM, Hay KA, Plier DA, Chaves SS, Lim PL, Caumes E, et al. International travelers as sentinels for sustained influenza transmission during the 2009 influenza A(H1N1)pdm09 pandemic. J Travel Med. 2013;20(3):177–84.

4. Marsh C, Andrews RM, Sheppeard V, Gilmour R, Tobin S. Drivers of a summer influenza epidemic – New South Wales, Australia, 2018–2019. Canberra: Public Health Association of Australia Communicable Disease Conference; 2019 [cited 2020 Jun 8]. p. 13. Available from: 03294849-f971-41a4-9848-27a9ba197989.filesusr.com/ugd/a52314_e5df56502c8d414eb22b1f0ae37c4d36.pdf

5. Freedman DO, Kozarsky PE, Weld LH, Cetron MS. GeoSentinel: the global emerging infections sentinel network of the International Society of Travel Medicine. J Travel Med. 1999;6(2):94–8.

6. Australian Technical Advisory Group on Immunisation (ATAGI). People who are traveling during the influenza season are strongly recommended to receive influenza vaccine. Australian Immunisation Handbook. Canberra: Australian Government Department of Health; 2018 [cited 2019 Nov 26]. Available from: immunisationhandbook.health.gov.au/recommendations/people-who-are-travelling-during-the-influenza-season-are-strongly-recommended-to

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ORIGINAL ARTICLE

Longer term outcomes following serogroup B invasive meningococcal disease

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Aim: To characterise the physical, psychological, and quality of life burden associated with serogroup B invasive meningococcal disease (IMD) in children.

Methods: Children aged up to 14 years at the time of serogroup B IMD, who were admitted to intensive care units of two tertiary paediatric hospitals in New South Wales, Australia between January 2009 and December 2013 were recruited. Children underwent clinical and neuropsychological assessments up to 6 years post-disease.

Results: Eleven children were assessed, with a median age of 16 months (range 4–46 months) at time of disease. The median follow-up time was 50 months (range 10–67 months). Seven (63.6%) cases had one or more long-term sequelae involving permanent and evolving physical disability. Three cases had ongoing medical conditions including two with seizures and one with ataxia and hypermetropia. Five required ongoing medical and allied health care. Other complications identified included anxiety, speech delay, low average full-scale IQ score (median 85, interquartile range 89–103) and borderline memory impairment.

Conclusions: Serogroup B IMD is associated with significant long-term morbidity and burden on the child and family with substantial economic implications. The impact of this on the total cost of IMD needs to be further quantified, and better considered in vaccine cost-effectiveness analyses.

Key words: developmental; general paediatrics; immunisation; infectious disease.

What is already known on this topic

1 Serogroup B meningococcal disease (MenB) is the most common cause of invasive meningococcal disease in Australia.
2 MenB can cause major sequelae including cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment or hydrocephalus.

What this paper adds

1 Delayed MenB sequelae can be identified in studies with longer follow-up periods, including skin graft necrosis, osseous damage and speech delay up to 5 years following infection.
2 Some survivors of MenB disease continue to require ongoing medical and allied health assistance, as frequently as weekly following initial disease.
3 These contribute to the economic health burden that exists up to 5 years following infection and therefore need to be considered when assessing the burden of disease including cost-effectiveness evaluation of vaccination.

Invasive meningococcal disease (IMD) is a rare but serious condition with significant morbidity and mortality.[1] Serogroup B meningococcal (MenB) disease has been the most common cause of IMD in Australia for decades, accounting for 63–88% of annual notified cases where a serogroup was identified.[2,3] While the incidence of invasive MenB disease declined from 1.5 per 100 000 in 2002 to 0.4 per 100 000 in 2013,[3] it has increased since to 0.6 per 100 000 in 2017[4] and remains the major cause of IMD in children aged 2 years or younger, and young people aged 15–24 years old.

Sequelae following serogroup B IMD can be long-lasting, complex and significant. A systematic review of over 26 follow-up studies of IMD reported a median risk of 7.2% for a major sequela following meningococcal meningitis, defined as cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment or hydrocephalus.[5] A similar risk was reported in a cohort of 105 child survivors in Western Australia where 8.6% had long term morbidity following IMD of any serogroup including hearing loss, limb amputation and permanent skin defects.[6] A retrospective study of South Australian children found that the

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Conflict of interest: None declare.

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Table 1 Neuropsychological testing

Domain	Test	Sub-domains	Age range	Clinical impairment range
Assessor administered				
General intelligence†	WPPSI-IV	Verbal comprehension Visual spatial Fluid reasoning Working memory Processing speed	2 years 6 months to 7 years 7 months	≤70
	WISC-IV	Verbal comprehension Perceptual reasoning Working memory Processing speed	6 years to 16 years 11 months	≤70
	Bayley-III	Cognitive	All ages	≤69
Academic achievement†	WIAT-II	Word reading Numerical operations Spelling Reading comprehension	4 years to 16 years 11 months	≤70
Verbal memory‡	CVLT-C	Short and long delay recall	5 years to 16 years 11 months	-2SD
Parent questionnaires				
Executive function‡	BRIEF-P	Inhibitory self-control Flexibility Emergent metacognition Global executive composite	2 years to 5 years 11 months	≥65
	BRIEF	Behaviour regulation Metacognition Global executive composite	5–18 years	≥65
Behaviour‡	BASC-2	Internalising problems Externalising problems Behavioural symptoms Adaptive skills	≥2 years	≥70 and ≤30 for adaptive skills
	SDQ	Emotional symptoms Conduct problems Hyperactivity/Inattention Peer relationship problems Prosocial behaviour	4–17 years	≥20
Visual motor‡	VMI-V	Visual-motor abilities	≥2 years	≤70

†Standard scores M (SD) = 100 (15).

‡Tscores M (SD) = 50 (10).

BASC-2, Behaviour Assessment System for Children, Second Edition[10]; Bayley-III, Bayley Scales for Infant and Toddler Development, Third Edition; Beery VMI-V, Beery-Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition[11]; BRIEF, Behaviour Rating Inventory of Executive Function[12]; BRIEF-P, Behaviour Rating Inventory of Executive Function, Preschool Version[13]; CVLT-C, California Verbal Learning Test - Children's Version[14]; SDQ, Strengths and Difficulties Questionnaire; WIAT-II, Wechsler Individual Achievement Test – Second Edition[15]; WISC-IV, Wechsler Intelligence Scale for Children – Fourth Edition[16]; WPPSI-IV, Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition.[17]

rate of sequelae following serogroup B IMD (41.3%, 31/75) was higher than non-B IMD cases (29.4%, 10/34), with the most common sequelae of Men B being skin necrosis, scarring, neurological problems and bone/joint damage.[7] In addition, serogroup B IMD was associated with significantly higher inpatient costs and longer length of hospitalisation, after adjusting for covariates including age, gender and past medical conditions when compared to non-B IMD cases.[7] A large UK study of children with serogroup B IMD (median age 1.65 years at the time of disease) showed that at around 4 years post disease they were more likely to have lower full-scale IQ, poorer executive function and/or impaired memory compared to healthy controls.[8] In addition, 26% (61/235) of children with serogroup B IMD had a psychological disorder, most commonly anxiety, behavioural disorders and Attention Deficit Hyperactivity Disorder (ADHD).

In Australia, there has been multi-level government response to the rising serogroup W and Y incidence.[9] In 2016, states and territories funded the quadrivalent meningococcal conjugate vaccine (MenACWY) in adolescents and in 2019, this became federally supported replacing the meningococcal C vaccination in 12-month-olds in the National Immunisation Program. However, MenB vaccination remained not considered by Pharmaceutical Benefits Advisory Committee to be cost effective for all children and infants. In 2020, MenB vaccine has been funded for

Table 2 Case details and physical outcomes

	Cases, *n* (%)
n	11
Sex (male)	6 (54.5)
Remote/Regional area	3 (27.3)
Age at disease, months, median (range)	16 (7–29)
Age at assessment, months, median (range)	70 (56–82)
Time to follow up, months	49 (39–61)
LOS, days, median (range)	18 (8–68)
ICU LOS, days, median (range)	2 (1–8)
Acute complications	
Hypotension	5 (45.5)
Coagulopathy	5 (45.5)
Acute renal failure	2 (18.2)
Seizures	2 (18.2)
Long term sequelae	
Amputation	3 (27.3)
Skin necrosis	3 (27.3)
Epilepsy	2 (18.2)
Speech impairment	1 (9.1)
Visual impairment	1 (9.1)
Hearing loss (>20 dB)	0 (0.0)
Ongoing specialist involvement	
Paediatrician	4 (36.4)
Orthopaedic surgeons	3 (27.3)
Rehabilitation	2 (18.2)
Neurology	1 (9.1)
Plastics/Burns	2 (18.2)
Pain management	1 (9.1)
Other (renal)	1 (9.1)
Ongoing allied health involvement	
Orthotics	2 (18.2)
Physiotherapy	2 (18.2)
Occupational therapy	1 (9.1)
Psychologist	1 (9.1)
Pharmacy	1 (9.1)
Dentist	1 (9.1)
Speech	1 (9.1)

ICU, intensive care unit; LOS, length of stay.

Aboriginal and Torres Strait Islander children and people with at-risk medical conditions only. Better understanding of ongoing morbidity and burden of disease beyond the acute hospitalisation for children and families following serogroup B IMD in the Australian context is required for improved cost-effectiveness evaluation of MenB vaccination programmes.

We therefore aimed to describe the long-term sequelae of meningococcal disease in a resource-rich country; to gauge the physical, psychological and potential economic cost of meningococcal disease that may assist in the cost–benefit assessment of a public health intervention such as the introduction of new vaccines to prevent this serogroup B IMD. Herein, we present a case series of 11 children who were admitted to an intensive care unit (ICU) of a paediatric hospital with serogroup B IMD to characterise the physical, psychological, and quality of life burden associated with severe meningococcal disease.

Methods

Children aged up to 14 years old who were admitted to either Sydney Children's Hospitals Randwick or The Children's Hospital at Westmead ICUs between January 2009 and December 2013 with laboratory-confirmed serogroup B IMD were retrospectively recruited in 2014. Cases were identified through hospital admissions coded with International Classification of Diseases, Ninth Revision and Tenth Revision (ICD-9, ICD-10) diagnosis code for meningococcal meningitis (ICD-9 code 036.0 or ICD-10 code A39.0 to A39.9). Each case was cross-checked with laboratory records of *Neisseria meningitidis*, serotype B, by culture or PCR. Caregivers of cases were contacted by telephone to obtain consent for the study.

Recruited children presented to The Children's Hospital at Westmead between 1 July 2014 and 30 November 2014 for assessment with their caregivers. The assessment included clinical examination by a paediatric medical officer, visual field and acuity test by orthoptist, hearing test by audiologist, and age-appropriate psychological tests administered by a psychologist. Children and care givers also completed questionnaires as part of the neuropsychological assessment. Table 1 outlines the psychological tests and questionnaires used for each domain and age group and test defined cut-off scores for clinical impairment[10–17] Details on socio-demographics, long-term sequelae, readmissions to hospital related to IMD and type and frequency of any ongoing engagement with health services were collected *via* caregiver interviews using a standardised proforma. Long term sequelae were defined as any complication related to IMD that was not resolved at hospital discharge or that was discovered after discharge and was likely to have been caused by IMD.

Highest level of maternal education was collected as a contributing factor to cognitive function. Caregivers were also given a parent-report questionnaire, Health Utility Index (HUI-3) to complete at home. HUI-3 is a health-related quality of life assessment tool that assesses functional capacity rather than performance to define the extent to which deficits in health status inhibit normal function across eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. A calculated utility score is rated from 0 (deceased) to 1.0 (perfectly healthy). Parents were requested to return the questionnaire by pre-paid post and given reminders weekly for 4 weeks.

This study was approved by Sydney Children's Hospital Network Human Research Ethics Committee (HREC/13/SCHN/403).

Results

We identified 24 consecutive children with confirmed serogroup B IMD between 2009 and 2013 who were admitted to ICU, of which 11 (45.8%) were recruited, 12 were unable to be contacted and 1 declined participation. The median age at initial presentation of IMD was 16 months (range 4–46 months) with similar sex distribution (54.5% male). Their median age at the time of assessment was 5 years and 10 months (range 1 year 8 months to 8 years 7 months) with the median time from presentation to assessment being 49 months (range 10–67 months). Three cases were from remote or regional areas. Of the 10 families that provided maternal education information, three mothers

Table 3 Complications and ongoing health-care requirements for each case

Case	Sex	Age at time of IMD, months	LOS total, days	LOS ICU, days	Inpatient complications	Time to follow up, months	Age at follow up, years/ months	Long-term sequelae	Ongoing health-care involvement	Outpatient per year	Admissions	Regular medications	HUI
1	M	6	25	9	Coagulopathy Hypotension Pleural effusion Increased intracranial pressure	67	6 years 2 months	Leg length discrepancy from tibial growth plate damage Finger amputations (3 digits) with necrotic lesions skin grafts for ankle	General practice, monthly Orthopaedics, 6 monthly Orthotics, 6 monthly Physiotherapy, 2 monthly Pain, yearly Burns, yearly General paediatrics, 6 monthly	26	8	Yes	0.43
2	F	6	18	7	Hypotension	62	5 years 9 months	Ataxia Hypermetropia	NR	0	0	No	0.68
3	F	6	11	3	Anaemia Respiratory distress Seizures	31	3 years 1 month	Epilepsy	General practice, 2 monthly General paediatrics, yearly	7	0	Yes	1.00
4	M	8	57	45	Coagulopathy Hypotension Renal failure	10	1 year 8 months	Finger and toe amputations (7 digits) with necrotic lesions Skin grafts for knee and wrist Hypoxic ischemic encephalopathy Epilepsy	General practice, 2 monthly Orthopaedics, 6 monthly Rehabilitation, 6 monthly Neurology, 6 monthly Orthotics, 3 monthly General paediatrics, 6 monthly	18	1	Yes	0.75
5	M	12	7	1	Coagulopathy Left foot ulceration	50	5 years 2 months	NR	NR	0	0	No	NC
6	F	15	9	2	NR	49	5 years 5 months	NR	NR	0	0	No	NC

(*Continues*)

Table 3 (Continued)

Case	Sex	Age at time of IMD, months	LOS total, days	LOS ICU, days	Inpatient complications	Time to follow up, months	Age at follow up, years/ months	Long-term sequelae	Ongoing health-care involvement	Outpatient per year	Admissions	Regular medications	HUI
7	F	17	153	2	Seizures	48	5 years 10 months	NR	NR	0	0	No	1.00
8	F	34	78	33	Coagulopathy Hypotension Renal failure	52	7 years 5 months	Leg amputations (bilateral below knee) Fingers amputations (6 digits) with necrotic lesions Skin graft for chest and face	General practice, 2 monthly Rehabilitation/ Brain injury clinic, 6 monthly Nephrology, 6 monthly Dentist, 6 monthly Orthopaedics, 6 monthly Occupational therapy, 3 monthly Orthotics, 6 monthly Physiotherapy, 3 monthly General paediatrics, 6 monthly	26	1	Yes	0.48
9	M	36	7	1	NR	22	4 years 10 months	NR	NR	0	0	No	1.00
10	M	32	6	1	NR	61	6 years 2 months	Anxiety	Psychologist, 3 monthly General paediatrics, 6 monthly	6	0	No	0.77
11	M	46	141	1	Coagulopathy Hypotension	62	5 years 9 months	Periostitis right distal tibia Speech delay	Speech therapy, weekly General paediatrics, 6 monthly	54	0	No	0.96

ICU, intensive care unit, LOS, length of stay; NC, not completed; NR, none reported.

Table 4 Developmental assessment scores for each case and proportion with clinically significant impairment

Test†	Cases											SD −1 to −2, *n* (%)	Clinical impairment, *n* (%)
	1	2	3	4	5	6	7	8	9	10	11		
Age at assessment, months	74	69	37	20	62	65	70	89	49	94	103		
IQ (centile)	90 (25)	106 (66)	96 (39)	100 (50)	84 (14)	84 (14)	80 (9)	86 (18)	119 (90)	105 (61)	87 (19)	3/10 (30)	0/11 (0)
Academic achievement													
Word reading	88	102	NA	NA	80	71	NC	93	110	92	84	3/8 (37)	0/8 (0)
Numerical operations	92	101	NA	NA	NC	NC	NC	82	119	101	79	2/8 (25)	0/6 (0)
Spelling	71	109	NA	NA	NC	80	NC	86	107	89	89	1/7 (14)	0/7 (0)
Reading comprehension	NC	NC	NA	NA	NC	NC	NC	86	NC	89	40	1/3 (33)	1/3 (33)
Memory, CVLT-C													
Short delay *Z*-score	−0.5	1.5	NA	NA	−1.5	−0.5	−0.5	0.0	NA	−1.0	−1.0	3/8 (37)	0/8 (0)
Long delay Z-score	−1.5	1.5	NA	NA	−2.5	−1.0	−1.5	1.0	NA	−2.0	0.5	4/8 (50)	2/8 (25)
Executive function, BRIEF(-P)													
Global executive composite	61	62	45	NA	44	44	56	54	64	53	65	4/10 (40)	1/10 (10)
Behaviour, BASC-2													
Externalising	64	45	45	NA	42	44	46	36	57	43	69	2/10 (20)	0/10 (0)
Internalising	55	74	57	NA	43	51	50	47	75	47	71	3/10 (30)	3/10 (30)
Behaviour	64	54	48	NA	38	46	44	44	58	47	75	2/10 (20)	1/10 (10)
Adaptive skills	32	67	50	NA	54	59	53	53	41	55	37	1/10 (10)	0/10 (0)
Behaviour, SDQ	NC	19	13	NA	6	3	5	6	10	4	17	2/9 (22)	0/9 (0)
Visual motor, Beery VMI	96	114	108	NA	91	102	96	93	106	109	109	0/10 (0)	0/10 (0)

†Unless specified, all scores reported are standard scores.

BASC-2, Behaviour Assessment System for Children, Second Edition; Beery VMI, Beery-Buktenica Developmental Test of Visual-Motor Integration; BRIEF-P, Behaviour Rating Inventory of Executive Function; CVLT-C, California Verbal Learning Test - Children's Version; IQ, intelligence quotient; NA, not applicable; NC, not completed; Preschool Version; SDQ, Strengths and Difficulties Questionnaire.

completed year 10, four completed year 12 and three completed vocational training. There were no university graduates.

Hospitalisation duration ranged from 6 to 153 days (median 18, interquartile range (IQR) 8–68) and ICU admission duration ranged from 1 to 45 days (median 2, IQR 1–8). Three cases were transferred to paediatric ICU from a regional NSW hospital. Clinical details and outcomes are summarised in Table 2. Five cases had hypotension or shock, five had coagulopathy, two had acute renal failure and two had seizures. Three cases had amputations, with other complications reported included pleural effusions, respiratory distress and limb ulceration.

Seven (63.6%) cases had one or more long-term sequelae. Table 2 summarises the case details and physical outcomes and Table 3 details the complications and ongoing health care requirements for each case by age at presentation. Case 1 developed leg length discrepancy and bony overgrowth over his knees secondary to tibial growth plate damage diagnosed 3 years after the initial IMD, requiring eight readmissions for repeat osteostomies, tibial and femoral plate insertions and revisions. He also required repeat skin graft revisions secondary to the bony protrusions over his knees. At follow up, 5.5 years following his initial IMD, he was accessing health care every 2 weeks for follow up. Case 2 was identified to have ataxia at 18 months old that is ongoing and was found to have hypermetropia on vision testing that was not previously identified. Case 3 developed epilepsy that has been well-controlled and co-managed by the general practitioner and paediatrician. Case 4 developed multiple necrotic lesions over his amputated digits with bony protrusions in his foot which required surgical repair 6 months following the initial admission. While he only required one readmission, he required outpatient reviews on a fortnightly to monthly basis at 10 months post-IMD, with ongoing long-term follow-up planned. Case 8 sustained multiple long-term sequelae following her IMD which was complicated by multi-organ failure. She developed hypoxic brain injury with specific difficulties with working memory, reduced working speed, difficulties with organisation and performance of complex tasks. Her lower limb amputations and finger amputations have resulted in many functional impairments. She requires bilateral prostheses for walking, as well as a wheelchair to reduce fatigue. Her protheses require regular replacement with growth. Her finger amputations have impacted on her ability to perform fine motor activities, requiring regular occupational therapy input in assistive technology, home and personal item modifications for independent function. Despite these, she is dependent in most activities of daily living. While she has only had one readmission for skin graft revision, she accesses some form of health care every fortnight. Case 10 was diagnosed anxiety at age 5, two and half years following IMD, requiring regular psychologist support, though it is unclear if the anxiety is directly related to the case's IMD. Case 11 developed speech delay at 6 years, nearly 2 years following IMD, requiring ongoing weekly speech therapy. He also had periostitis of his right tibia 1 year following IMD which lasted for 10 months, although its aetiology is unclear.

Cases with physical disability reported a more impaired (lower) HUI score compared to other cases. Of the nine cases that completed the HUI questionnaire, scores tended to be poorer for those with more long-term sequelae reported. HUI scores ranged from 0.43 to 0.75 for those with physical complications requiring readmissions and frequent outpatient visits (Table 3). Two families did not return their HUI questionnaires. All patients had normal hearing on audiology assessment and case 2 had hypermetropia on vision testing.

The median standardised full-scale IQ score was 90 (IQR 84–105), with 5 out of 11 in the low average range (IQ score 80–89). Four children had borderline recall memory on CVLT-C testing (Table 4). Four children had clinically significant behavioural concerns on parent-reported BASC-2, with internalising problems, such as depression and anxiety, being most significant. By contrast, all children had average or high average visual motor skills on Beery VMI-V.

Discussion

We present a case series examining the immediate and longer-term outcomes of children following severe serogroup B IMD requiring ICU admission. Nearly half of the cases presented with immediate complications including shock, coagulopathy, acute renal failure and seizures. While the majority of the long-term sequelae seen were similar to previously reported,[5–7,18] we identified that some sequelae can occur many years following the initial event. These included physical, such as leg length discrepancy requiring repeated surgery, and potential neurodevelopmental complications such as speech delay and anxiety. These late onset complications would have been under ascertained in previous studies with shorter follow-up duration.

Children with physical complications in our cohort required ongoing care from multiple health-care providers. Previous studies have focused on inpatient cost and follow-up care up to 1 year only when considering the economic burden of IMD.[7,19,20] Our study suggests that there are ongoing and new medical costs for children with serogroup B IMD, including readmissions for surgery and ongoing regular medical and allied health visits, that may not have previously been considered when assessing the economic burden of IMD. When these were considered along with a substantial quality of life adjustment factor by UK's Joint Committee on Vaccination and Immunisation, their revised cost-effectiveness analysis led to the introduction of a MenB vaccine in their infant immunisation programme.[21] A small proportion of our cohort had low average IQ scores on follow up, with working memory being the most common difficulty. Specific memory testing found more than half had borderline short and long-term memory. These findings may be accounted for by a lower maternal level of education in our cohort as maternal education is the strongest socio-economic predictor of infant development.[22,23] However, our findings are also consistent with a large prospective case–control study which reported that children with MenB IMD had poorer IQ, executive function, planning and reduced memory compared to controls.[8] Long-term impairments in social and practical reasoning, attention and executive functioning were also identified by Vermunt *et al.*[24] in survivors of meningococcal septic shock. In contrast to our study, however, they found cognitive function to be comparable to the general population overall. Working memory is a known predictor of academic achievement, independent of intelligence.[25,26] Alloway *et al.*[25] found children's working memory at 5 years was the best predictor of literacy and numeracy outcomes 6 years later. Children with serogroup

B IMD may therefore be at risk poor school performance with the potential to longer term impact on their future.

We found that nearly half of the parents reported behavioural concerns, with anxiety being the most common. This is consistent with other studies on psychological outcomes following meningococcal disease overall[27,28] and in MenB disease specifically.[8] We identified a larger percentage of reported behavioural concerns compared to Vermunt *et al*.[29] that identified 5–20% of meningococcal septic shock survivors reporting ongoing problems including behavioural and emotional concerns, likely as a result of our small sample size. Vermunt *et al*. found that a younger age at time of illness was associated with higher scores of externalising and rule-breaking behaviour while our study reported internalising problems being the most common suggesting that MenB disease can affect individuals differently.

Finally, parent ratings indicated children with serogroup B IMD have poorer HUI scores overall compared to the population mean.[30] The HUI score was generally lower for those with more severe physical complications requiring readmissions and frequent outpatient visits, reflecting their poorer quality of life. This contrasts Buysse *et al*.'s[31] study which found health-related quality of life of survivors of meningococcal septic shock was predicted by behavioural problems more than major physical sequelae. The impact of serogroup IMD on the quality of life of children can be significant and requires further longitudinal examination.

The strengths of this study include the follow-up duration of some of these cases and the ability to detail ongoing complications and health-care requirements through medical record review and parent interviews. Each case also had a comprehensive neurodevelopmental assessment examining all domains that has previously been identified as at risk of impairment following IMD. We were able to quantify the quality of life in these children using a well-recognised standardised index (HUI-3). Our study was limited by the small sample size and absence of controls as comparators and absence of cost analysis. However, by reviewing ICU cases, we have better elucidated and highlighted ongoing sequelae of severe cases which can contribute disproportionately to cost-effectiveness analyses. Finally, the duration of follow up in each case varied widely as a result of the retrospective recruitment of cases. However, we tried to limit recall bias by thorough review of medical records for follow-up reviews and appointments for all cases.

Conclusions

In conclusion, our case series showed that serogroup B IMD is associated with significant short and long-term morbidity. Serogroup B IMD poses an ongoing burden on the child, family, medical resources and therefore the economy. This long-term burden needs to be further quantified and better considered in future vaccine cost-effectiveness analyses.

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References

1 Hart CA, Thomson APJ. Meningococcal disease and its management in children. *BMJ* 2006; **333**: 685–90.
2 Lahra MM, Enriquez RP. Australian Meningococcal Surveillance Programme annual report, 2015. *Commun. Dis. Intell. Q. Rep.* 2016; **40**: E503–11.
3 Archer BN, Chiu CK, Jayasinghe SH *et al*. Epidemiology of invasive meningococcal B disease in Australia, 1999–2015: Priority populations for vaccination. *Med. J. Aust.* 2017; **207**: 382–7.
4 National Notifiable Diseases Surveillance System (NDSS), Department of Health. Invasive Meningococcal Disease National Surveillance Report, Quarter 4, 2017. In: Protection Office of Health Protection, ed. Department of Health; 2018; 1–6.
5 Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: A systematic review and meta-analysis. *Lancet Infect. Dis.* 2010; **10**: 317–28.
6 Olesch CA, Knight GJ. Invasive meningococcal infection in Western Australia. *J. Paediatr. Child Health* 1999; **35**: 42–8.
7 Wang B, Haji Ali Afzali H, Marshall H. The inpatient costs and hospital service use associated with invasive meningococcal disease in South Australian children. *Vaccine* 2014; **32**: 4791–8.
8 Viner RM, Booy R, Johnson H *et al*. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): A case-control study. *Lancet Neurol.* 2012; **11**: 774–83.
9 Martin NV, Ong KS, Howden BP *et al*. Rise in invasive serogroup W meningococcal disease in Australia 2013–2015. *Commun. Dis. Intell. Q. Rep.* 2016; **40**: E454–e9.
10 Reynolds CR, Kamphaus RW. *Behavior Assessment System for Children, Second Edition: Manual*. Circle Pines, MN: American Guidance Service Publishing; 2004.
11 Beery KE, Beery NA. *Beery-Buktenica Developmental Test of Visual-Motor Integration: Administration, Scoring and Teaching Manual*, 5th edn. Minneapolis, MN: MN Pearson Inc.; 2004.
12 Gioia GA, Isquith PK, Guy SC, Kenworthy L. *Behavior Rating Inventory of Executive Function: Professional Manual*. Psychological Assessment Resources Inc: Lutz, FL; 2000.
13 Gioia GA, Espy KA, Isquith PK. *Behavior Rating Inventory of Executive Function – Preschool Version: Professional Manual*. Psychological Assessment Resources Inc: Lutz, FL; 2003.
14 Delis D, Kramer J, Kaplan E, Ober B. *California Verbal Learning Test – Children's Version*. San Antonio, TX: The Psychological Corporation; 1994.
15 Wechsler D. *Wechsler Individual Achievement Test: Manual*, 2nd edn. New York, NY: The Psychological Corporation; 2005.
16 Wechsler D. *Wechsler Intelligence Scale for Children: Manual*, 4th edn. New York, NY: The Psychological Corporation; 2003.
17 Wechsler D. *Wechsler Preschool & Primary Scale of Intelligence: Manual*, 4th edn. New York, NY: The Psychological Corporation; 2014.
18 Harrison LH, Pass MA, Mendelsohn AB *et al*. Invasive meningococcal disease in adolescents and young adults. *JAMA* 2001; **286**: 694–9.
19 Davis KL, Misurski D, Miller JM, Bell TJ, Bapat B. Cost of acute hospitalization and post-discharge follow-up care for meningococcal disease in the US. *Hum. Vaccin.* 2011; **7**: 96–101.
20 O'Brien JA, Caro JJ, Getsios D. Managing meningococcal disease in the United States: Hospital case characteristics and costs by age. *Value Health* 2006; **9**: 236–43.
21 Joint Committee on Vaccination and Immunisation. JCVI Position Statement on Use of Bexsero® Meningococcal B Vaccine in the UK. In: England Public Health, ed. The Joint Committee on Vaccination and Immunisation; 2014.
22 Bradley RH, Corwyn RF. Socioeconomic status and child development. *Annu. Rev. Psychol.* 2002; **53**: 371–99.

23 Richels CG, Johnson KN, Walden TA, Conture EG. The relation of socioeconomic status and parent education on the vocabulary and language skills of children who do and do not stutter. *J. Commun. Disord.* 2013; **46**: 361–74.
24 Vermunt LC, Buysse CM, Aarsen FK *et al*. Long-term cognitive functioning in children and adolescents who survived septic shock caused by Neisseria meningitidis. *Br. J. Clin. Psychol.* 2009; **48** (Pt 2): 195–208.
25 Alloway TP, Alloway RG. Investigating the predictive roles of working memory and IQ in academic attainment. *J. Exp. Child Psychol.* 2010; **106**: 20–9.
26 Maehler C, Schuchardt K. The importance of working memory for school achievement in primary school children with intellectual or learning disabilities. *Res. Dev. Disabil.* 2016; **58**: 1–8.
27 Fellick JM, Sills JA, Marzouk O, Hart CA, Cooke RW, Thomson AP. Neurodevelopmental outcome in meningococcal disease: a case-control study. *Arch. Dis. Child.* 2001; **85**: 6–11.
28 Garralda ME, Gledhill J, Nadel S, Neasham D, O'Connor M, Shears D. Longer-term psychiatric adjustment of children and parents after meningococcal disease. *Pediatr. Crit. Care Med.* 2009; **10**: 675–80.
29 Vermunt LC, Buysse CM, Joosten KF *et al*. Survivors of septic shock caused by *Neisseria meningitidis* in childhood: Psychosocial outcomes in young adulthood. *Pediatr. Crit. Care Med.* 2011; **12**: e302–9.
30 Pogany L, Barr RD, Shaw A, Speechley KN, Barrera M, Maunsell E. Health status in survivors of cancer in childhood and adolescence. *Qual. Life Res.* 2006; **15**: 143–57.
31 Buysse CM, Vermunt LC, Raat H *et al*. Surviving meningococcal septic shock in childhood: Long-term overall outcome and the effect on health-related quality of life. *Crit. Care* 2010; **14**: R124.

Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study

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Summary

Background School closures have occurred globally during the COVID-19 pandemic. However, empiric data on transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among children and in educational settings are scarce. In Australia, most schools have remained open during the first epidemic wave, albeit with reduced student physical attendance at the epidemic peak. We examined SARS-CoV-2 transmission among children and staff in schools and early childhood education and care (ECEC) settings in the Australian state of New South Wales (NSW).

Methods Laboratory-confirmed paediatric (aged ≤18 years) and adult COVID-19 cases who attended a school or ECEC setting while considered infectious (defined as 24 h before symptom onset based on national guidelines during the study period) in NSW from Jan 25 to April 10, 2020, were investigated for onward transmission. All identified school and ECEC settings close contacts were required to home quarantine for 14 days, and were monitored and offered SARS-CoV-2 nucleic acid testing if symptomatic. Enhanced investigations in selected educational settings included nucleic acid testing and SARS-CoV-2 antibody testing in symptomatic and asymptomatic contacts. Secondary attack rates were calculated and compared with state-wide COVID-19 rates.

Findings 15 schools and ten ECEC settings had children (n=12) or adults (n=15) attend while infectious, with 1448 contacts monitored. Of these, 633 (43·7%) of 1448 had nucleic acid testing, or antibody testing, or both, with 18 secondary cases identified (attack rate 1·2%). Five secondary cases (three children; two adults) were identified (attack rate 0·5%; 5/914) in three schools. No secondary transmission occurred in nine of ten ECEC settings among 497 contacts. However, one outbreak in an ECEC setting involved transmission to six adults and seven children (attack rate 35·1%; 13/37). Across all settings, five (28·0%) of 18 secondary infections were asymptomatic (three infants [all aged 1 year], one adolescent [age 15 years], and one adult).

Interpretation SARS-CoV-2 transmission rates were low in NSW educational settings during the first COVID-19 epidemic wave, consistent with mild infrequent disease in the 1·8 million child population. With effective case-contact testing and epidemic management strategies and associated small numbers of attendances while infected, children and teachers did not contribute significantly to COVID-19 transmission via attendance in educational settings. These findings could be used to inform modelling and public health policy regarding school closures during the COVID-19 pandemic.

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Introduction

The global COVID-19 pandemic has been addressed through implementation of aggressive public health measures focused on restricting mobility and ensuring physical distancing. Most countries have enforced school closures to mitigate transmission.[1] However, evidence suggests that COVID-19 is less prevalent in children and generally causes milder illness, when compared with adults.[2–6] The extent to which children are asymptomatically infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and what role they have in virus transmission, particularly in schools, remains unclear. It appears children are less likely to be the primary infection source in household clusters, compared with adults.[7,8]

School closures might be effective in controlling pandemic influenza because children are important in transmission, and have high hospitalisation rates and severe outcomes from influenza.[9,10] However, school closures have significant social and economic impacts on children and families, with widespread implications for national and global economies.[11] Although past experiences of school closures might inform expectations of social and economic impacts, modelled effects of school closures have varied depending on the assumptions regarding children's role in SARS-CoV-2 transmission.[12] In China, schools were already closed for school holidays and remained so for a number of months,[13] and, to date, data on COVID-19 from school or childcare settings are scarce.[14–16]

Australian strategies to delay and reduce the impact of COVID-19 following the first case in a traveller from Wuhan, China, on Jan 25, 2020, included thorough incoming traveller and community surveillance, high

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Research in context

Evidence before this study

Data on COVID-19 in schools are scarce, particularly given many schools have been closed in response to the pandemic. We searched PubMed and medRxiv on June 5, 2020, for studies published from Jan 1, 2020, reporting transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in educational settings since the start of the outbreak in China, using the search terms COVID-19, SARS-CoV-2, transmission, schools, and children, as well as manually searching the references used in other relevant papers. Terms were searched individually and in combination as necessary, and no language restrictions were used. We identified some studies that included mention of student cases as part of a larger outbreak. We identified one article that detailed transmission in a school setting in Ireland in children aged 10 years and older; however, this study had few participants, a short study period (10 days), no data on testing rates, or serological testing in follow-up.

Added value of this study

We examined SARS-CoV-2 transmission among children and adults in 25 educational settings (primary and secondary schools, and early childhood education and care settings) together with the rate and characteristics of all paediatric COVID-19 cases in the Australian state of New South Wales over a 3-month period. We found a low incidence of attendance of children and staff members with COVID-19 at educational facilities, and low rates of SARS-CoV-2 transmission in the 15 schools and childcare settings where a case occurred. The exception was an outbreak in a childcare centre. The use of enhanced surveillance and serological testing of close contacts within the educational setting enabled detection of a small number of asymptomatic SARS-CoV-2 secondary infections in schools and the childcare setting.

Implications of all the available evidence

This is the first comprehensive population-based assessment of SARS-CoV-2 transmission among children and adults in educational facilities. Our results show that where effective case-contact testing and epidemic control strategies exist for the population, children and teachers did not contribute significantly to COVID-19 transmission via attendance in educational settings. This study will assist modellers, policy makers, health-care providers, and the public to understand the risk of COVID-19 occurring in educational facilities and help in decision making around school closures and reopenings. Our data also provide insights that can assist in comparing the economic and community costs of school closures against the potential benefits of reduced virus transmission.

testing rates, rapid case isolation and contact tracing, and border closures and quarantine.[17] Major changes in population behaviour and a low infection rate have ensued.[17] Consistent with national policy, most of Australia's eight states and territories, including the most populous state New South Wales (NSW), kept schools open during the pandemic.[18] In NSW, guidance for physical distancing, hygiene measures, and educational facility cleaning was issued. At the epidemic peak on March 23, 2020, distance (online) learning was implemented, and physical attendance recommended to be limited to children who needed to attend in person (eg, children of health-care workers or those without other care options).[18] Early childhood education and care (ECEC) settings for children aged 6 weeks to 5 years remained open.

This study aimed to prospectively examine SARS-CoV-2 transmission among children and adults in educational settings and to provide real-time evidence for decision making on school-based policies related to COVID-19. We secondarily aimed to examine the rate and characteristics of NSW paediatric COVID-19 cases in both educational settings and the wider population.

Methods

Study setting

This study was done in NSW, Australia, population 8·1 million, of which 1·8 million residents (23·0%) are aged 18 years or younger.[19] Among laboratory-confirmed COVID-19 cases in NSW, we identified all children (aged ≤18 years) and staff who attended school or ECEC settings while considered infectious (defined as 24 h before symptom onset based on national guidelines during the study period[20]). All NSW schools (n=3103; public, independent, and Catholic) providing either primary (ages approximately 5–12 years), or secondary school education (ages approximately 13–18 years), or both, and any ECEC setting (approximately n=4600; ages approximately 6 weeks to 5 years) were eligible for inclusion. The estimated numbers of school staff and enrolled students state wide for 2020 were 143 084 and 1 232 367, respectively. Estimates of numbers of ECEC setting staffing and enrolment were not available.

The study period for index case identification was from Jan 25 (first NSW COVID-19 case notification) to April 9, 2020 (when the 10-week school term 1 ended and scheduled holidays commenced). From March 22, 2020, children were encouraged to stay home for distance learning until term 1 end; however, schools remained open if home schooling was not an option. The follow-up period for close contacts of COVID-19 cases extended to May 1, 2020.

The study was commissioned by the NSW Department of Health under the Public Health Act 2010 (NSW) and

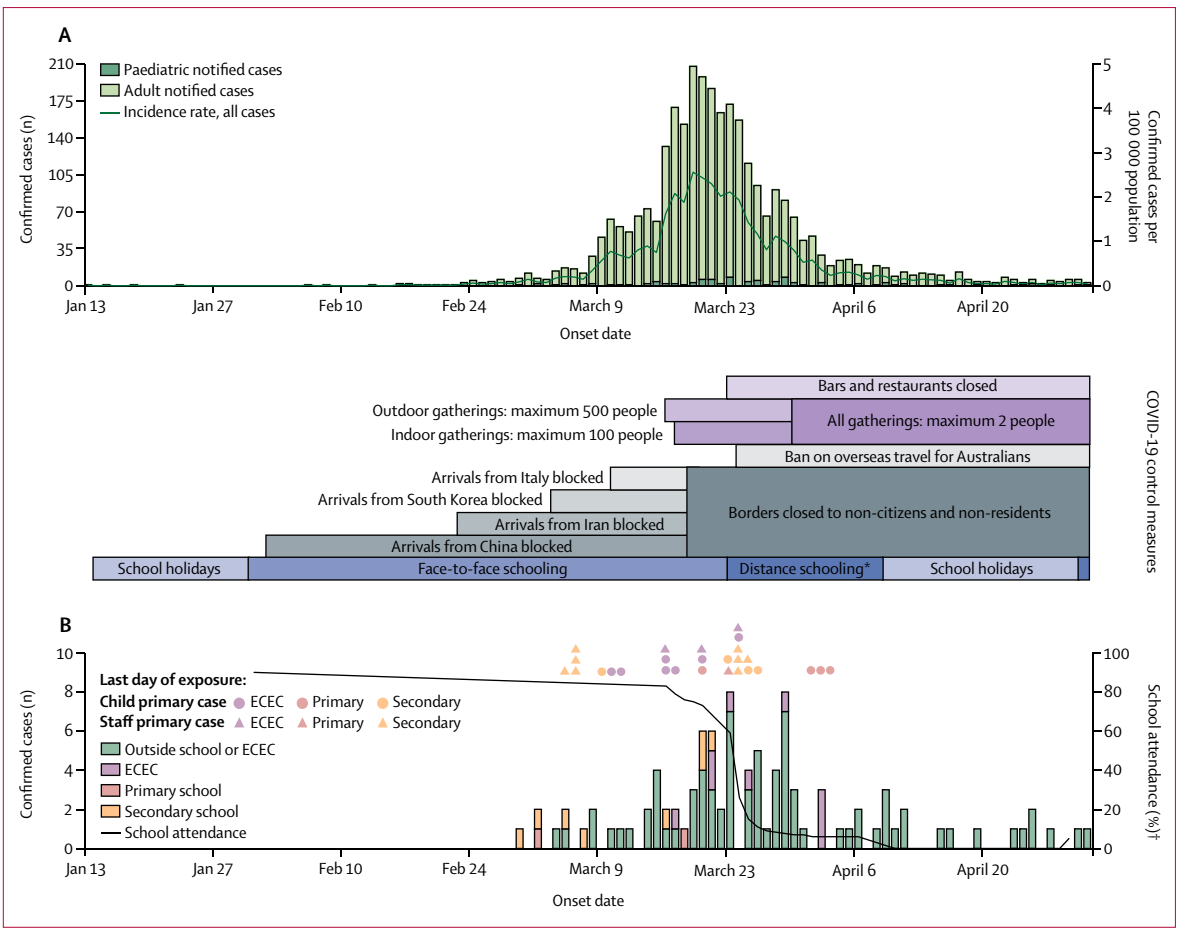

***Figure*: Onset date of total (A) and paediatric (B) confirmed COVID-19 cases in NSW, Jan 13–May 1, 2020, relative to control measures and school attendance**
Nucleic acid testing used for confirmation of severe acute respiratory syndrome coronavirus 2 infection, and definition of COVID-19 case. If people were asymptomatic, specimen positive date was used. ECEC=early childhood education and care settings. NSW=New South Wales. *Distance (remote) learning recommended, but schools also remained open for face-to-face attendance as required. After school holidays, preference for distance learning continued for 2 weeks before resumption of full face-to-face learning. †Excluding ECEC.

implemented in conjunction with approval and support from the NSW Department of Education.

Population-level data

All laboratory-confirmed COVID-19 cases in NSW, using SARS-CoV-2 nucleic acid testing,[20] were recorded and monitored daily using the NSW Notifiable Conditions Information Management System. All cases (or their parent or carers) were interviewed at diagnosis to determine links to known COVID-19 cases, ascertain movements, and identify close contacts while infectious, including at educational facilities. Descriptive data for all laboratory-confirmed cases with onset from Jan 13 to May 1, 2020, were analysed.

School and ECEC setting case and close contact definitions and management

A COVID-19 school or ECECs index case was defined as the first identified laboratory-confirmed case who attended the facility while infectious. A school or ECEC setting primary case was defined as the initial infectious case or cases in that setting, and might or might not have been the index case. A secondary case was defined as a close contact with SARS-CoV-2 infection (detected through nucleic acid testing or serological testing, or both), which was considered likely to have occurred via transmission in that educational setting (based on no other epidemiological link or risk factor). Data on all cases' potential sources of infection and close contacts were obtained from interviews with cases, families, and school officials, and review of school timetables. Close contacts were defined as children or staff with face-to-face contact for at least 15 min, or who shared a closed indoor space for at least 40 min (generally the same class or lesson, typically consisting of 20–30 students) with a case during their infectious period. All close contacts quarantined at home for 14 days, had regular text message or telephone call contact to enquire about symptoms, and were instructed to be tested if they developed COVID-19-related symptoms at designated

	Sex		Age group						Existing medical condition	Hospitalisation	ICU admission	Total (rate per 100 000 population)
	Male	Female	0 to <5 years	5 to <13 years	13 to ≤18 years	19 to ≤39 years	40 to ≤59 years	≥60 years				
Paediatric cases												
Within school or ECEC	13 (68%)	6 (32%)	9 (47%)	3 (16%)	7 (37%)	..	..	..	5 (26%)	3 (16%)	0	19
Primary case	6 (50%)	6 (50%)	3 (25%)	2 (17%)	7 (58%)	..	..	..	4 (33%)	3 (25%)	0	12
Secondary case	7 (100%)	0	6 (86%)	1 (14%)	0	..	..	..	1 (14%)	0	0	7
Outside school or ECEC	35 (44%)	43 (55%)	11 (14%)	27 (34%)	40 (51%)	..	..	..	9 (12%)	6 (8%)	1 (1%)	78
All	48 (49%)	49 (51%)	21 (21%)	30 (31%)	47 (48%)	..	..	..	14 (14%)	9* (9%)	1 (1%)	97 (5)
Adult cases												
Within school or ECEC	1 (5%)	21 (95%)	..	..	..	12 (55%)	9 (41%)	1 (5%)	4 (18%)	4 (18%)	2 (9%)	22
Primary case	1 (7%)	14 (93%)	..	..	..	8 (53%)	6 (40%)	1 (7%)	3 (20%)	2 (13%)	0	15
Secondary case	0	7 (100%)	..	..	..	4 (57%)	3 (43%)	0	1 (14%)	2 (29%)	2 (29%)	7
Outside school or ECEC	1450 (50%)	1463 (50%)	..	..	..	1156 (40%)	821 (28%)	937 (32%)	849 (29%)	296 (10%)	75 (3%)	2914
All	1451 (49%)	1484 (51%)	..	..	..	1168 (40%)	830 (28%)	938 (32%)	853 (29%)	300 (10%)	77 (3%)	2936 (47)

Data are n (%), unless otherwise stated. ECEC=early childhood education and care setting. ICU=intensive care unit. NSW=New South Wales. *Most were hospitalised early in the epidemic response for isolation purposes only and had mild symptoms.

Table 1: **Demographic and clinical data on all paediatric and adult COVID-19 cases in NSW, Australia, from Jan 13 to May 1, 2020, including links to an educational setting as either a primary or secondary case**

COVID-19 testing facilities. Schools and ECEC settings closed temporarily on case notification and generally reopened within 24–48 h after environmental cleaning and public health measures were instituted. We reviewed data for all close contacts for a minimum of 30 days from last exposure to the primary case, to ensure that any potential new cases were identified and investigated.

Targeted enhanced school and ECEC setting-based investigations

Selected educational settings were offered participation in enhanced investigations, in addition to routine public health management if logistically feasible and authorisation was provided by local public health and education authorities. Close contacts or their parents or carers were provided with information on enhanced investigations and informed consent was obtained (appendix). Participants could opt out at any time.

See Online for appendix

Enhanced investigations of close contacts included a survey requesting more details on extent of contact with the case, and symptoms before and during quarantine; upper respiratory tract (nasopharyngeal) swab for nucleic acid testing 5–10 days after last case contact if not previously collected and irrespective of symptoms; and serological testing after day 21 following last case contact. Swabs were collected at home either by visiting healthcare workers, or by the case or parent or carer using written and video instructions. Blood was collected at home visits, dedicated school-based collection days, or pathology collection centres.

Laboratory testing

Ten public and three private NSW laboratories were validated and did SARS-CoV-2 nucleic acid testing during the study period. Blood and nasopharyngeal specimens for enhanced surveillance were tested by the NSW Pathology reference laboratory, the Institute for Clinical Pathology and Medical Research. Nucleic acid testing was done using an in-house real-time PCR as previously described.[21] SARS-CoV-2-specific IgG, IgA, and IgM detection was done using an indirect immunofluorescence assay (IFA) that has a sensitivity compared with nucleic acid testing of detecting any of SARS-CoV-2-specific IgG, IgA, or IgM when samples were collected at least 14 days after illness onset of 91·3% (95% CI 84·9–95·6) and specificity of 98·9% (95% CI 98·4–99·3%; MVNO, personal communication).

Data analyses

Percentages were calculated to describe demographic, laboratory, and epidemiological characteristics of all NSW cases, school or ECEC setting cases, and close contacts. Attack rates were calculated for different transmission scenarios and with denominators including all close contacts or only close contacts who were tested for SARS-CoV-2. School attendance data were obtained from the NSW Department of Education. Population

	Primary cases			Days when contacts' NAT done post last exposure*	Child close contacts				Staff close contact			
	Age (years), sex (M or F)	Source of infection (all acquired locally)	Days infectious at school*		Age (years)	n	Contacts' NAT done†	NAT positive of contacts tested†	Age (years)	n	Contacts' NAT done†	NAT positive of contacts tested†
SS												
SS 1	16, M	Household	4	3 (2–5)	16 (16–16)	58	19 (33%)	0	51 (48–53)	11	2 (18%)	0
SS 2‡	14, M; 15, F	Household	Unknown§; 5	5 (3–8)	15 (15–15)	193	117 (61%)	0	41 (27–49)	18	12 (67%)	0
SS 3	12, F	Household	4	4 (4–5)	12 (12–12)	66	20 (30%)	0	38 (34–39)	11	5 (46%)	0
SS 4	48, F	Source unknown	1	6 (5–7)	15 (13–15)	46	15 (33%)	0	47 (42–53)	11	6 (54%)	0
SS 5	53, F	Source unknown	1	4 (4–4)	14 (13–15)	4	1 (25%)	0	38 (36–46)	6	5 (83%)	0
SS 6‡	13, F; 15, M	Household	5; 2	10 (8–13)	15 (13–15)	65	13 (20%)	0	41 (30–45)	9	2 (22%)	0
SS 7	16, M	Household	3	11 (11–12)	16 (16–16)	131	9 (7%)	0	55 (48–64)	8	1 (13%)	0
SS 8	18, M	Household	2	14 (11–14)	17 (16–17)	8	1 (13%)	0	44 (31–56)	7	3 (43%)	0
SS 9	34, F	Source unknown	1	NA	16 (16–16)	10	0	0	NA	0	0	0
SS 10	65, F	Source unknown	4	12 (10–15)	13 (13–15)	19	1 (5%)	0	50 (44–53)	15	3 (20%)	0
All SSs	8, 4¶	NA	3 (2–4)‖	5 (4–8)	15 (14–16)	600	196 (33%)	0	44 (34–53)	96	39 (41%)	0
PS												
PS 1‡**	46, F	Non-household contact	1	6 (6–7)	7 (6–10)	66	28 (42%)	1 (4%)	45 (37–52)	15	8 (53%)	1 (13%)¶
PS 2†	10, F	Source unknown	10	12 (11–12)	10 (10–10)	43	6 (14%)	0	60 (60–61)	2	1 (50%)	0
PS 3	31, F	Household	3	7 (7–8)	10 (10–11)	15	1 (7%)	0	32 (31–47)	7	5 (71%)	0
PS 4	21 ,M	Non-household contact	4	7 (5–8)	7 (5–9)	27	4 (15%)	0	24 (23–24)	2	2 (100%)	0
PS 5	19, F	Non-household contact	5	7 (6–10)	7 (6–8)	28	3 (11%)	0	25 (20–29)	13	4 (31%)	0
All PSs	1, 4¶	NA	4 (3–5)‖	6 (6–11)	9 (7–10)	179	42 (23%)	1 (2%)	36 (26–52)	39	20 (51%)	1 (5%)
ECEC												
ECEC 1‡	36, F	Non-household contact	1	10 (8–13)	4 (4–4)	16	16 (100%)	0	NA	0	0	0
ECEC 2	50, F	Non-household contact	2	5 (3–6)	4 (3–4)	43	18 (42%)	0	47 (42–50)	6	2 (33%)	0
ECEC 3‡	56, F	Acquired locally, source unknown	9	7 (7–9)	2 (1–3)	151	79 (52%)	0	30 (26–36)	25	19 (76%)	0
ECEC 4	30, F	Source unknown	1	8 (7–8)	2 (1–3)	31	13 (42%9)	0	32 (26–39)	9	2 (22%)	0
ECEC 5	3, F	Source unknown	1	18 (15–19)	3 (3–4)	34	1 (3%)	0	26 (22–32)	18	3 (17%)	0
ECEC 6‡	49, F	Source unknown	1	16 (14–17)	1 (2–3)	25	23 (92%)	6 (26%)	38 (31–43)	12	11 (92%)	6 (55%)
ECEC 7	2, M	Source unknown	1	17 (15–17)	3 (2–4)	43	11 (26%)	0	40 (38–50)	14	5 (36%)	0
ECEC 8	21, F	Non-household contact	2	4 (4–4)	N/A	0	0	0	31 (25–36)	15	9 (60%)	0
ECEC 9	1, F	Source unknown	1	3 (3–3)	1 (1–1)	8	5 (63%)	0	23 (20–31)	5	3 (60%)	0
ECEC 10	38, F	Source unknown	2	5 (5–7)	3 (2–3)	55	16 (29%)	0	29 (27–36)	24	9 (38%)	0
All ECEC	3, 7¶	NA	1 (1–2)‖	8 (6–12)	3 (2–4)	406	182 (45%)	6 (3%)	34 (26–41)	128	63 (49%)	6 (10%)
All settings	12 (14), 15 (38)††	9 household; 6 non-household contact; 12 source unknown	2 (1–4)‖	7 (5–10)	10 (3–15)	1185	420 (35%)	7 (2%)	37 (27–48)	263	122 (46%)	7 (6%)

Data are n; median (IQR); or n (%), unless otherwise stated. M=male. F=female. NAT=nucleic acid test. SS=secondary school. PS=primary school. NA=Not applicable. ECEC=early childhood education and care setting. NSW=New South Wales. *Day test done post last day of exposure (D0) to the infectious cases. †Close contacts were managed in home quarantine and instructed to be tested if symptoms developed; also includes some asymptomatic cases (see table 3). ‡Settings where enhanced surveillance was done (see table 3). §Unknown exposure duration as asymptomatic case. ¶Data are number of children, number of staff. ‖Data are median (IQR). **The primary case notification was late after exposure and symptom onset and occurred shortly before notification of the secondary staff case. Close contact follow-up for the primary case was incomplete and probably reduced the total number of primary case contacts having an NAT test. Close contacts of the secondary case included the child who was a tertiary case in this setting (see table 3). ††Data are number of children (median), number of staff (median).

Table 2: **Primary COVID-19 cases and close contacts who attended 25 educational settings from March 5 to April 9, 2020, in NSW, Australia**

	Symptomatic (n=65)				Asymptomatic (n=223)				Symptoms unknown (n=352)*				Total secondary cases	Percentage of contacts tested
	n	NAT	Serology	Any test	n	NAT	Serology	Any test	n	NAT*	Serology	Any test		
Child contacts														
SS 2	20	0/19	1/16 (6%)	1/20 (5%)	90	0/51	0/52	0/74	83	0/47	0/3	0/47	1	73%
SS 6	4	0/4	0/3	0/4	43	0/5	1/36 (3%)	1/36 (3%)†	18	0/4	0/4	0/6	1	70%
PS 1	2	1/2 (50%)	1/2 (50%)	1/2 (50%)	18	0/18	0/13	0/18	46	0/8	0/1	0/8	1	42%
PS 2	1	0/1	0/1	0/1	8	0/1	0/6	0/6	34	0/4	0/8	0/12	0	44%
ECEC 1	0	0/0	0/0	0/0	0	0/0	0/0	0/0	16	0/16	0/5	0/16	0	100%
ECEC 3	21	0/18	0/4	0/20	22	0/6	0/7	0/11	108	0/55	0/4	0/59	0	60%
ECEC 6	7	3/6 (50%)	3/6 (50%)	4/7 (57%)	13	3/13 (23%)	2/8 (25%)	3/13 (23%)	5	0/4	0/2	0/4	7	96%
All	55	4/50 (8%)	5/32 (16%)	6/54 (11·%)	194	3/94 (3%)	3/122 (3%)	4/158 (3%)	310	0/138	0/27	0/152	10	65%
Adult contacts														
SS 2	1	0/1	0/0	0/1	8	0/4	0/3	0/5	9	0/7	0/2	0/7	0	72%
SS 6	0	0/0	0/0	0/0	7	0/1	1/5 (20%)	1/5 (20%)	2	0/1	0/1	0/1	1	67%
PS 1	1	1/1 (100%)	0/0	1/1 (100%)	5	0/3	0/4	0/5	9	0/4	0/1	0/4	1	67%
PS 2	0	0/0	0/0	0/0	0	0/0	0/0	0/0	2	0/1	0/2	0/2	0	100%
ECEC 1	0	0/0	0/0	0/0	0	0/0	0/0	0/0	0	0/0	0/0	0/0	0	100%
ECEC 3	2	0/2	0/1	0/2	4	0/1	0/1	0/1	19	0/16	0/2	0/17	0	80%
ECEC 6	6	6/6 (100%)	2/2 (100%)	6/6 (100%)	5	0/4	0/2	0/4	1	0/1	0/1	0/1	6	92%
All	10	7/10 (70%)	2/3 (67%)	7/10 (70%)	29	0/13	1/15 (7%)	1/20 (5%)	42	0/30	0/9	0/32	8	77%
Total	65	11/60 (18%)	7/35 (20%)	13/64 (20%)	223	3/107 (3%)	4/137 (3%)	5/178 (3%)	352	0/168	0/36	0/184	18	67%

Data are n/N (% positive of those contacts tested), unless otherwise stated. NAT=nucleic acid test. SS=secondary school. PS=primary school. ECEC=early childhood education and care setting. NSW=New South Wales. *55% of all contacts did not complete a detailed symptom questionnaire and other data on symptoms at time of testing could not be obtained. †Asymptomatic in post-exposure period but reported influenza-like illness in period before primary case onset.

***Table 3*: Details of secondary cases resulting from COVID-19 transmission in seven NSW educational settings where enhanced surveillance of symptomatic and asymptomatic close contacts was done**

data were obtained from the Australian Bureau of Statistics. Data cleaning and analysis were done using Stata, version 14.2.

Role of the funding source

The funder of the study had no role in study design, data analysis, data interpretation, or writing of the report. The funder contributed to collection of data. KM, HEQ, AJP, AK, LD, NWi, ALK, MVNO, CD, and NWo had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

As of May 1, 2020, NSW had 3033 confirmed COVID-19 cases, representing 37·5 cases per 100 000 population and 44·8% of 6777 cases nationally (figure). In NSW, 1760 (58·0%) of 3033 cases were acquired overseas and 54 (1·8%) of 3033 cases were acquired interstate. Of 1220 locally acquired cases, 416 (34·1%) had an unknown source or were under investigation. Children aged 18 years or younger accounted for 97 (3·2%) of 3033 cases in NSW. 9% (n=9) of children with COVID-19 were admitted to hospital (most for isolation purposes only), with one child, aged 18 years, admitted to intensive care (table 1).

Notification of the first COVID-19 case in an educational setting was on March 5, 2020 (figure). Among 97 nucleic acid testing-confirmed cases in children to April 9, 2020, 19 (19·6%) attended an educational setting while infectious and were included in the study (table 1; figure). Of the other 78 paediatric cases, 44 (56·4%) were locally acquired from contact with a confirmed case, mostly from their household (70·5%; table 1).

The timing of measures implemented to ensure physical distancing and decrease population movement and school attendance rates are shown in the figure. Rates declined from approximately 90·0% to 5·0% after recommendations for distance learning were made on March 23, 2020, and immediately before school holidays commenced on April 10, 2020. Cases peaked in late March, with primary cases in schools occurring earlier in the outbreak and primary cases in ECEC settings occurring later in the outbreak (figure).

There were 27 primary cases identified in 25 schools (n=15) and ECEC settings (n=10); of 27 cases, 15 (55·6%) were staff and 12 (44·4%) were children (tables 1, 2). Of the child cases, eight (median age 15 years; range 14–16) were in secondary schools, with one (age 10 years) in primary school. Three ECEC setting primary cases were children (median age 2 years; range 2–3). Staff (median age 38 years; range 31–50) were the primary cases in four (40·0%) of

ten secondary schools, four (80·0%) of five primary schools, and seven (70·0%) of ten ECEC settings. The median time that primary cases attended the setting while infectious was 2 days (range 1–10). Infection was locally acquired for all primary cases, but the source was unknown for many (12 [44·4%] of 27). Where known, a household member was usually the source, especially for children (table 2).

Secondary transmission occurred in four of 25 settings: three schools (five cases), and one ECEC setting that had an outbreak (table 2). In total, 663 (43·7%) of 1448 close contacts were tested by nucleic acid testing or serology, or both; 18 secondary cases were identified among the total 1448 close contacts (attack rate 1·2%). Among close child and staff contacts who had laboratory testing done, the attack rate was 2·8% (tables 3, 4).

Seven of the 25 educational settings (four schools; three ECEC settings) participated in enhanced investigations (table 3). Among contacts who completed symptom questionnaires (44·9%), 65 (22·6%) of 288 developed symptoms consistent with COVID-19 during the 14-day quarantine, such as fever, sore throat, cough, or rhinorrhea. In these seven settings, 426 (66·6%) of 640 close contacts had nucleic acid testing or serological testing, or both. Secondary attack rates among symptomatic and asymptomatic contacts are shown in table 3.

Five secondary cases occurred in schools: one child in one secondary school; one child and one staff member in another secondary school; and one staff member, followed by one child in one primary school (table 3). This primary school was the only school to have a second-generation infection. Overall, two children were symptomatic and had nucleic acid testing (one positive on day 6 and the other negative on day 4 after last exposure), whereas one child and one staff member were asymptomatic and did not have nucleic acid testing. One symptomatic staff member had nucleic acid testing only (table 3). The attack rate in the tested population in schools was five (1·3%) of 375.

No SARS-CoV-2 transmission occurred in two of the three ECEC settings that participated in enhanced surveillance (25 staff and 167 child contacts). The third ECEC setting had a large outbreak first recognised via an index case in a child aged 2 years, but subsequently found related to a primary case in one staff member (infection source unknown; tables 2 and 3). Overall, six other staff and seven children were infected (attack rate 35·1%). Among the infected close contacts, three of 13 were infants (age 1 year) who remained asymptomatic.

The overall child to child transmission rate was 0·3%, and the attack rate for child to staff member was 1·0% (table 4). The rate of staff member to child transmission was lower (1·5%) than staff to staff transmission (4·4%). Excluding the single ECEC setting with the large outbreak, staff member to child (0·2%) and staff member to staff member (0·7%) transmission rates were lower compared with all settings.

	Secondary attack
All settings, all contacts, including single ECEC outbreak	1·2% (18/1448)
All settings, all contacts, excluding single ECEC outbreak*	0·4% (5/1411)
All settings, all child case to child contacts	0·3% (2/649)
All settings, all child case to staff member contacts	1·0% (1/103)
All settings, all staff member case to child contacts	1·5% (8/536)
All settings, all staff member case to staff member contacts	4·4% (7/160)
All settings, all staff member case to child contact, excluding single ECEC outbreak*	0·2% (1/511)
All settings, all staff member case to staff member contacts, excluding single ECEC outbreak*	0·7% (1/148)
All settings, tested population	2·8% (18/633)
All settings, tested population, excluding single ECEC outbreak	0·8% (5/598)
All schools, all contacts	0·5% (5/914)
All schools, tested population	1·3% (5/375)
Single ECEC outbreak,* all contacts	35·1% (13/37)
Child close contacts	28·0% (7/25)
Staff close contacts	50·0% (6/12)

Data are rate % (n/N). SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ECEC=early childhood education and care. *This outbreak resulted in at least four generations of infection and there was no evidence of child to child or child to staff transmission (unpublished).

Table 4: **Secondary attack rates of SARS-CoV-2 infection by educational setting and testing approach**

Discussion

This study of SARS-CoV-2 transmission in schools and early childcare settings in a defined population of 8·1 million Australians shows low case rates and secondary infections among children and staff attending educational facilities throughout the first epidemic wave of the COVID-19 pandemic. School closures during the COVID-19 pandemic have affected more than 90% of the world's student population,[1] and contributed to reducing overall population mobility, including via reduced parent and carer workforce participation. However, the insufficiency of data on age-specific and setting-specific susceptibility and transmissibility of SARS-CoV-2 has limited our understanding of what school closure, or reopening, might contribute to COVID-19 control.[9,12] Our data provide multiple insights that need to be viewed in the context of our setting. First, and related to overall epidemic activity in NSW, the reported incidence of an infectious child or staff member attending an educational facility was low, occurring in only 25 of 7700 NSW facilities. Second, despite only 10·0% of school attendees being staff during the first part of the epidemic, when student attendance was high, overall, primary COVID-19 cases were staff members in 56·0% of educational settings; this is consistent with higher population-based rates of COVID-19 in adults than children. Third, secondary transmission of SARS-CoV-2 only occurred in three of 15 schools and one of ten ECEC settings. Only one setting,

an ECEC setting, had a sustained outbreak of COVID-19 following infection in a staff member, which was not apparent until investigation of a child index case. Excluding this single ECEC setting outbreak, the overall attack rate was five (0·4%) in 1411, or one in every 282 contacts. Continued operation of schools throughout the moderate first epidemic wave in NSW, albeit with reduced face-to-face attendance in line with public health guidance, did not appear to contribute significantly to SARS-CoV-2 transmission (attack rate 0·5%). Attendance rates were still high during the period when transmission, in the two secondary and one primary schools, occurred. This finding was in contrast to other settings in NSW, where multiple outbreaks were contemporaneously identified, including aged-care facilities and mass gatherings, such as weddings and religious services.[22]

An important component of our study was enhanced follow-up in a subset of educational settings, including in both asymptomatic and symptomatic adult and child contacts. This resulted in laboratory testing in two-thirds of close contacts. The use of serology facilitated identification of four additional secondary cases, including an asymptomatic student and staff member, who were not detected using routinely deployed nucleic acid testing and increased secondary case numbers from that in our preliminary report[23] to the NSW and Australian Government (n=2). By comparison, a small study[16] from Ireland of six COVID-19 cases in three schools, over less than 2 weeks, suggested no transmission to 1115 close contacts. However, children aged younger than 10 years and data on testing rates were not included. In our study, the attack rate among the tested population across all schools was low (1·3%) and was zero in nine of the ten ECEC settings. The single ECEC setting outbreak was complex and occurred early on in the epidemic in NSW. 13 (35·1%) of 37 contacts in this small centre were infected; three of the seven infected children (all aged <3 years) remained asymptomatic and the others had mild disease. Transmission chains between staff and from staff to children were apparent. Child to child or child to staff transmission appeared unlikely to have occurred but could not be excluded. In addition, delayed primary case diagnosis, due to adherence to narrow nucleic acid testing criteria recommended at the time, close mixing of staff and children and shared physical amenities, probably contributed to the several generations of transmission (data not shown; unpublished). In summary, our findings add to emerging data[7,9] on the direction of transmission from household and similar settings, such as ECEC settings, that suggest children are unlikely to initiate, or propagate, outbreaks.

We report a correspondingly low rate of paediatric disease (97 cases among 1·8 million aged 18 years or younger; 5·2 per 100 000; 3·2% of total) across NSW, providing additional evidence of reduced transmission resulting in clinical disease to and between children. Studies from multiple countries have consistently shown lower rates of COVID-19 and mild disease in children compared with adults, even in settings with much higher population-based disease rates than Australia.[2–5,24] Multiple hypotheses are being explored to explain the decreased susceptibility of children to SARS-CoV-2, including differences in immune responses[25] and age-dependent expression of the angiotensin converting enzyme 2 (ACE2) virus receptor;[26] however, the mechanisms responsible for this phenomenon remain unclear.

The low case and transmission rates in NSW schools and childcare settings reported here were underpinned by rapid and effective state and national public health, and community, responses.[17] Although community-based transmission occurred in some areas, particularly in Sydney (based on the proportion of cases [34·2%] with a local or unknown source of infection despite intensive contact tracing, and an effective reproductive number above 1 until mid-March, 2020), the NSW epidemic was smaller and of shorter duration compared with that seen in many other countries.[17,27] Tracking SARS-CoV-2 transmission was possible in this epidemic context because frequent simultaneous case introductions to schools and ECEC settings were not occurring, and enabled by continued operation of educational facilities throughout the epidemic period, albeit with reduced face-to-face attendance in the weeks before school holidays. Higher SARS-CoV-2 primary case and transmission rates might have occurred in schools and ECEC settings if the epidemic had escalated or if extensive testing, tracing, quarantine of exposed close contacts, and other public health mitigation measures were not simultaneously and effectively implemented. Although there are no specific data on adherence to these measures by the public in NSW, several strategies were in place to support a high compliance rate, including for quarantine of close contacts identified in this study. These strategies included regular wellbeing calls by public health staff to facilitate access to essential goods without breaching isolation, and issuing of fines to people found in breach of isolation requirements during random house calls by NSW police. Interpretation of our findings needs to be made in the context of the epidemic characteristics and COVID-19 response in NSW.

Our study is also limited by several factors. First, the majority of close contacts were tested after developing symptoms, so infected contacts with no or mild symptoms might have been missed. Symptom data were also incomplete and might have been affected by participant recall bias. Additional enhanced surveillance was limited by geographical location and school or ECEC settings' willingness to participate during a challenging time. Second, transmission rates reported might have been affected by the sensitivity and specificity of assays (nucleic acid testing and the IFA for virus-specific antibody) used for the detection of SARS-CoV-2 infection. When compared with nucleic acid testing for the diagnosis of SARS-CoV-2 infection, the IFA is reported to have high sensitivity and specificity in a mixed patient population

(asymptomatic individuals to patients requiring intensive care unit admission). We did not attempt transmission rates to adjust for test performance characteristics, given the non-uniform application of diagnostic testing methods in this study. Third, variation in close contact definitions used across settings, declining school attendance rates in the 2 weeks before school holidays, and differing types of contact could not be controlled for and might have influenced attack rates. However, although face-to-face attendance declined rapidly later in the study period in response to public health advice, the number of close contacts monitored (1411; 1185 children and 263 adults) was still substantial. The national public health definition of the infectious period for cases was extended from 24 h to 48 h before symptom onset after our study period based on the latest evidence. It is probable that additional close contacts would have been identified in our study had the 48-h presymptomatic contact definition been operational before the commencement of our study. Future studies in school settings in Australia or other countries using this criteria for the potential infectious period will build on our findings. Finally, we were unable to assess adherence to or the effect on transmission of recommendations regarding hygiene or physical distancing in educational settings, and these progressively increased in magnitude over the study period.

The possible benefits of school closures on SARS-CoV-2 transmission reduction must be considered against the adverse effects on child wellbeing, including the potential to exacerbate inequality.[28] Although this study did not aim to assess the impact of school operation on the NSW epidemic, and it is unlikely that the effect of school closure alone can be disentangled from other broader pandemic control measures,[29] our findings provide evidence that SARS-CoV-2 transmission in educational settings can be kept low and manageable in the context of an effective epidemic response. These data should inform modelling and decision making regarding planned return of children and teachers to classrooms as pandemic control evolves. Where pandemic mitigation measures result in strong disease control, we anticipate that schools can be open in a safe way, for the educational, social, and economic good of the community as we adapt to living with COVID-19.

Contributors

KM, HEQ, AK, LD, NWi, ALK, CD, and NWo contributed to the study design. KM, HEQ, AJP, AK, LD, NWi, ALK, and NWo contributed to the literature review. KM, HEQ, AJP, AK, LD, NWi, MVNO, and NWo analysed the data. KM, HEQ, AJP, AK, LD, NWi, and NWo contributed to writing of the Article. KM, HEQ, AJP, AK, LD, NWi, ALK, and NWo contributed to the preparation of the Article. ALK contributed to data collection and MVNO contributed to laboratory testing. All authors contributed to data interpretation and Article review. The NSW COVID-19 Schools Study Team contributed to the study design, study recruitment, specimen collection, and participant interviews and follow-up.

NSW COVID-19 Schools Study Team

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Declaration of interests

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References

1 UNESCO. COVID-19 educational disruption and response. Paris: UNESCO, 2020. https://en.unesco.org/covid19/educationresponse (accessed April 9, 2020).
2 Bialek S, Gierke R, Hughes M, McNamara LA, Pilishvili T, Skoff T. Coronavirus disease 2019 in children - United States, February 12–April 2, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69:** 422–26.
3 Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics* 2020; **145:** e20200702.
4 Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic population. *N Engl J Med* 2020; **382:** 2302–15.
5 Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. *N Engl J Med* 2020; **382:** 1663–65.
6 Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis* 2020; **20:** 689–96.
7 Zhu Y, Bloxham CJ, Hulme KD, et al. Children are unlikely to have been the primary source of household SARS-CoV-2 infections. *medRxiv* 2020; published online March 30. https://doi.org/10.1101/2020.03.26.20044826 (preprint).
8 Viner RM, Mytton OT, Bonell C, et al. Susceptibility to and transmission of COVID-19 amongst children and adolescents compared with adults: a systematic review and meta-analysis. *medRxiv* 2020; published online May 24. https://doi.org/10.1101/2020.05.20.20108126 (preprint).
9 Viner RM, Russell SJ, Croker H, et al. School closure and management practices during coronavirus outbreaks including COVID-19: a rapid systematic review. *Lancet Child Adolesc Health* 2020; **4:** 397–404.
10 Jackson C, Vynnycky E, Hawker J, Olowokure B, Mangtani P. School closures and influenza: systematic review of epidemiological studies. *BMJ Open* 2013; **3:** e002149.
11 Chen WC, Huang AS, Chuang JH, Chiu CC, Kuo HS. Social and economic impact of school closure resulting from pandemic influenza A/H1N1. *J Infect* 2011; **62:** 200–03.
12 Prem K, Liu Y, Russell TW, et al. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. *Lancet Public Health* 2020; **5:** e261–70.

13 Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet* 2020; **395:** 470–73.

14 Fontanet A, Tondeur L, Madec Y, et al. Cluster of COVID-19 in northern France: a retrospective closed cohort study. *medRxiv* 2020; published online April 23. https://doi.org/10.1101/2020.04.18.20071134 (preprint).

15 Danis K, Epaulard O, Bénet T, et al. Cluster of coronavirus disease 2019 (COVID-19) in the French Alps, 2020. *Clin Infect Dis* 2020; published online April 11. https://doi.org/10.1093/cid/ciaa424 (preprint).

16 Heavey L, Casey G, Kelly C, Kelly D, McDarby G. No evidence of secondary transmission of COVID-19 from children attending school in Ireland, 2020. *Euro Surveill* 2020; **25:** 2000903.

17 McAnulty JM, Ward K. Suppressing the epidemic in New South Wales. *N Engl J Med* 2020; **382:** e74.

18 Australian Government Department of Health. Australian Health Protection Principal Committee (AHPPC) coronavirus (COVID-19) statement on 17 March 2020. 2020. https://www.health.gov.au/news/australian-health-protection-principal-committee-ahppc-coronavirus-covid-19-statement-on-17-march-2020-0 (accessed June 6, 2020).

19 Australian Bureau of Statistics. Australian demographic statistics, December 2019. Estimated resident population by single year of age, New South Wales. 2020. https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Dec%202019?OpenDocument (accessed July 22, 2020).

20 Australian Government Department of Health. Coronavirus disease 2019 (COVID-19) Communicable Diseases Network Australia (CDNA) national guidelines for public health units—COVID-19. 2020. https://www1.health.gov.au/internet/main/publishing.nsf/Content/cdna-song-novel-coronavirus.htm (accessed April 25, 2020).

21 Rahman H, Carter I, Basile K, et al. Interpret with caution: an evaluation of the commercial AusDiagnostics versus in-house developed assays for the detection of SARS-CoV-2 virus. *J Clin Virol* 2020; **127:** 104374.

22 New South Wales Government Department of Health. 2020 media releases from NSW Health. 2020. https://www.health.nsw.gov.au/news/Pages/2020-nsw-health.aspx (accessed June 30, 2020).

23 New South Wales Government Department of Health. COVID-19 schools transmission investigation project team. COVID-19 in schools—the experience in NSW. 2020. http://ncirs.org.au/sites/default/files/2020-04/NCIRS%20NSW%20Schools%20COVID_Summary_FINAL%20public_26%20April%202020.pdf (accessed May 26, 2020).

24 Lavezzo E, Franchin E, Ciavarella C, et al. Suppression of COVID-19 outbreak in the municipality of Vo, Italy. *medRxiv* 2020; published online April 18. https://doi.org/10.1101/2020.04.17.20053157 (preprint).

25 Carsetti R, Quintarelli C, Quinti I, et al. The immune system of children: the key to understanding SARS-CoV-2 susceptibility? *Lancet Child Adolesc Health* 2020; **4:** 414–16.

26 Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. *JAMA* 2020; **323:** 2427–29.

27 Price DJ, Shearer FM, Meehan MT, et al. Early analysis of the Australian COVID-19 epidemic. *medRxiv* 2020; published online April 30. https://doi.org/10.1101/2020.04.25.20080127 (preprint).

28 Armitage R, Nellums LB. Considering inequalities in the school closure response to COVID-19. *Lancet Glob Health* 2020; **8:** e644.

29 Cowling BJ, Ali ST, Ng TWY, et al. Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in Hong Kong: an observational study. *Lancet Public Health* 2020; **5:** e279–88.