

Adverse Events Following Immunisation



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October 2010

www.ncirs.usyd.edu.au

Outline

- Definition
- Classification
- Expected vs Unexpected Reactions
- AEFI Myths
- Reporting AEFI
- AEFI Clinics

What is an AEFI?

“An adverse event following immunisation (AEFI) is an unwanted or unexpected event occurring after the administration of vaccine(s). Such an event may be caused by the vaccine(s) or may occur by chance after the vaccination (i.e. it would have occurred regardless of vaccination).”

(AIH, 9th ed, p58)

AEFI Classification

1. Programme-related
2. Vaccine-induced
3. Coincidental
4. Unknown

1. Programme-related

- Mostly the result of inappropriate practice:
 - inappropriate route or site
 - vaccine prepared incorrectly
 - contraindications ignored or not sought
 - inappropriate intervals in between doses
 - inappropriate equipment i.e wrong size needle

Inappropriate site??



1. Programme-related

- Sometimes it's about the process
- e.g fainting during mass vaccination campaigns



CDC Image Library, 2010

Herald Sun
Australia's biggest-selling daily newspaper

Vaccine is safe, says creator

Reko Rennie
May 22, 2007

Immunologist and Gardasil creator Ian Frazer says a cervical cancer vaccine is safe, despite five Victorian schoolgirls falling ill after they were immunised.

Oz School Girls Hospitalized After HPV Vaccine

By Danialle Cronin
5-24-7

Six Canberra schoolgirls were taken to hospital after they suffered a bad reaction to a vaccine to protect them against cervical cancer, health officials said yesterday. Girls in Sydney and Melbourne had also complained about side-effects including dizziness, fainting



2. Vaccine-induced

- Specifically caused by the vaccine or vaccine component
- Direct effects of vaccine
 - Local reactions, fever, rash
- Unknown underlying medical condition
 - e.g. vaccine associated disease → unknown immune deficiency
- Idiosyncratic response
 - Anaphylaxis immediately post vaccination

3. Coincidental

- Not true adverse reactions
- Linked because of timing
 - Gastro following HPV vaccination
 - Cold with coryzal symptoms following flu vaccination



Case Study

- 6 month old female from Coonamble
- Experienced a pale/floppy episode + rash around mouth ~ 9 hours post 4 month vaccination
- Transferred to hospital by ambulance
- Otherwise well
- Mother just commenced S-26 to compliment breast feeds
- Referred to Allergy Clinic & AEFI Clinic for review

Management

- Skin prick testing confirmed allergy to cow's milk
- Given Infanrix-hexa & Prevenar and closely observed within clinic
- Was not admitted
- No recurrence of symptoms post vaccination
- Saw dietician on same day of AEFI clinic visit
- Parents happy to have an answer for symptoms



Expected vs Unexpected AEFI



Expected (Common AEFI)

- All drugs have side effects
- Occur commonly
- Local reactions:
 - Pain, redness, swelling at injection site
 - ↑ incidence after booster doses of DTPa containing vaccines
- Systemic reactions:
 - Fever, malaise, myalgia, irritability, headache, loss of appetite
- Unless significant do not need to be reported

Local reaction



- 5th dose DTPa
- Sometimes includes lymph node involvement
- 24 - 48 hrs post vaccination, last ~ 4 - 5 days
- Common after dose 2 23vPPV
- Doesn't usually require A/B treatment unless infected (i.e. fever & pain)

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Local reaction



- Incorrect site - child >12 months

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Expected (Common AEFI)

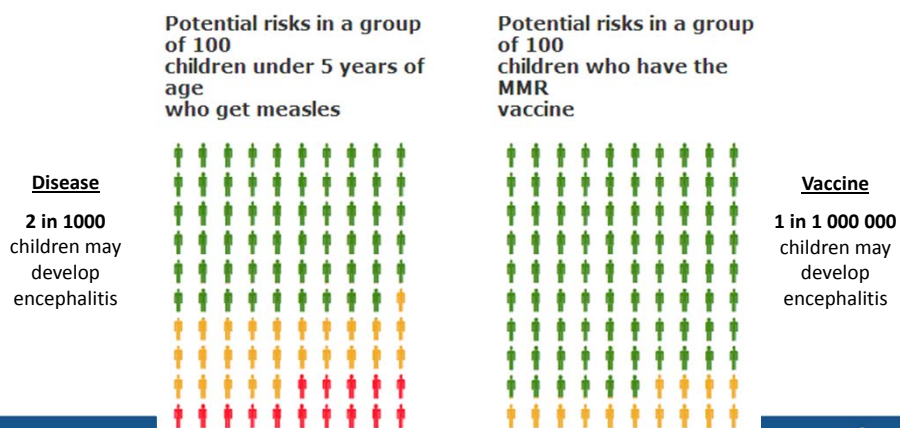
- Vaccine specific
 - MMR - high fever and rash 5 - 12 days post vaccination
 - HPV - headache, nausea
 - VZV - maculopapular or papulovesicular rash
 - Rotavirus - diarrhoea
- Use supportive treatment for symptoms



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Unexpected (Rare AEFI)

- Rate is hundreds/thousands times less frequent than complications from disease



NCIRS MMR Decision Aid, 2010

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Unexpected (Rare AEFI)

- Abscess
- HHE
- Seizures
- Intussusception
- Idiopathic Thrombocytopaenic Purpura (ITP)
- GBS
- Anaphylaxis
- 9th ed. Handbook pp 360 - 363 full list
- Plus **ANY** unusual event that doesn't fit list but is of medical or epidemiological interest

HHE

- HHE = Hypotonic Hyporesponsive Episode
- Sudden onset reduced muscle tone
- Hyporesponsiveness
- Pallor or cyanosis
- Median onset = 3-4 hours after vaccination
 - can occur up to 48hrs post
- Median duration = 6-30 minutes
 - some parents report time to full recovery = 10 days

HHE

- Pathogenesis
 - not known
 - ? glucose, ? pain response
 - ? infant syncope
- No long term sequelae
- Management
 - not generally contraindication for subsequent doses
 - AEFI clinic
 - low recurrence risk

Case Study

- 8 month old male
- Multiple food allergies
- Ex prem - central sleep apnoea
- Birth & 2 month old immunisations - uneventful
- At 4 months within minutes of Hexa, Prevenar, Rota
 - Pale, hyporesponsive followed by;
 - Raised red fine rash on face then chest
 - Nil respiratory component
 - Nil adrenaline
 - Emergency department

Management

- 6 month schedule NOW due
- DDX - HHE with rash OR anaphylaxis
- Parental & GP anxiety - future vaccines ?
- Admit and immunology review
 - Intradermal testing with vaccines - negative
- Vaccinated in hospital - nil recurrence

GBS

- GBS = (Guillain-Barré Syndrome)
- Acute onset of muscle weakness +/- paralysis
- More common in older adults
- Most people recover
 - Some have permanent nerve damage
 - 5% - 6% die
- Cause remains unclear - *Campylobacter jejuni* infection linked

GBS

- 1976 swine flu vaccine linked to slight ↑ in incidence of GBS
 - 1 extra case per 100 000 people
- 1 study found an association of an ↑ of 1 case per 1 million people vaccinated with seasonal flu (2010 WHO active global surveillance)
- Chance of getting flu much higher than getting GBS post vaccination
- Can reactivate
 - Flu vaccine contraindicated in patients who've had previous episode

GBS and H1N1 vaccine - CDC study

TABLE 2. Preliminary incidence rates* and rate ratios for persons with confirmed or probable Guillain-Barré syndrome, by 2009 H1N1 vaccination status and age group — Emerging Infections Program, United States, October 1, 2009–March 31, 2010†

Age group (yrs)	Vaccination coverage [‡]	Documented receipt of monovalent 2009 H1N1 vaccine in the 42 days preceding illness onset						Rate ratio (95% CI) [¶]
		Yes			No			
		No.	Person-years	Rate	No.	Person-years	Rate	
≤24	32.5%	6	643,310	0.93	37	6,801,172	0.54	1.71 (0.40–3.61)
≥25	23.0%	21	763,496	2.75	216	14,024,546	1.54	1.79 (1.08–2.68)
Total	26.1%	27	1,406,806	1.92	253	20,825,718	1.21	1.77 (1.12–2.56)**

* Per 100,000 person-years.

† Hospitalization as of March 31, 2010, reported as of May 10, 2010.

‡ Vaccination coverage for persons with reported vaccination during October 2009–March 2010 who were interviewed during November 2009–April 24, 2010 (National 2009 H1N1 Flu Survey [NHFS]) or November 2009–April 25, 2010 (Behavioral Risk Factor Surveillance System [BRFSS]), using combined estimates from BRFSS and NHFS with Kaplan-Meier survival analysis procedure. Included in person-year estimates were second doses (22.9%, 95% CI = 18.7–27.1) for children aged 6 months–9 years.

¶ Confidence interval.

** Age adjusted total rate ratio and 95% CI.

H1N1 = 0.8 excess cases per 1 million vaccinated

Anaphylaxis

- Rare BUT can be fatal!!
- Need to be able to distinguish between anaphylaxis, convulsions & fainting

		Vasovagal	Anaphylaxis
Onset		Immediate, usually within minutes of or during vaccine administration.	Usually within 15 minutes, but can occur within hours, of vaccine administration.
Signs/ Symptoms	Skin	Generalised pallor, cool, clammy skin.	Skin itchiness, generalised skin erythema (redness), urticaria (wheals) or angioedema (localised oedema of the deeper layers of the skin or subcutaneous tissues).
	Resp	Normal respiration; may be shallow, but not laboured.	Cough, wheeze, stridor, or signs of respiratory distress (tachypnoea, cyanosis, rib recession).
	Cardio vascular	Bradycardia, weak/absent peripheral pulse, strong carotid pulse. Hypotension – usually transient and corrects in supine position.	Tachycardia, weak/absent peripheral and carotid pulse. Hypotension – sustained and no improvement without specific treatment.
	Neuro	Feels faint, light-headed. Loss of consciousness – improves once supine or head down position.	Sense of severe anxiety and distress. Loss of consciousness – no improvement once supine or head down position.

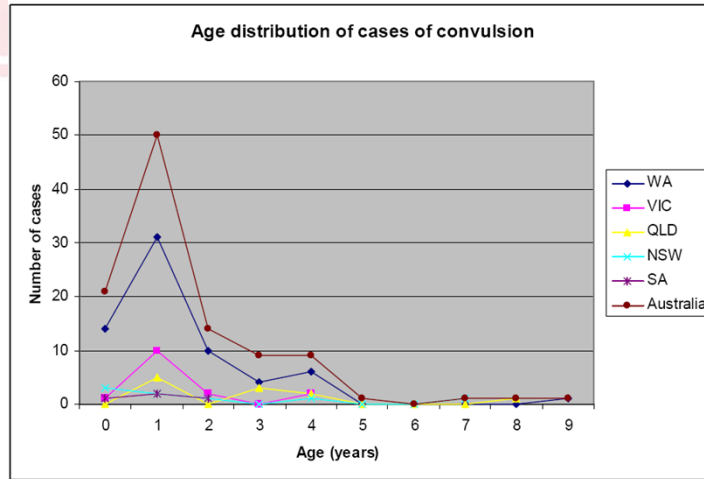
Anaphylaxis management

- Adrenaline
 - 1:1000, 0.01mL/kg up to max 0.5mL, deep IM injection
- Be prepared to repeat every 5 minutes until patient improves or trained help arrives
- Give oxygen if available
- Commence basic life support i.e. CPR if required
- Always admit to hospital if adrenaline administered

Seasonal Influenza Vaccine 2010

- WA commences 2010 seasonal influenza vaccination on 19 March
 - Funded for all children 6 months to 5 years
- WA suspends childhood program 4 weeks later due to increased reports of febrile convulsions post flu vaccination
- Prompts CMO to suspend vaccination of children \leq 5yrs nationally - 23 April
- National investigation commences
 - General Public & Immunisation Providers encouraged to report high fevers &/or febrile convulsions post flu vaccination

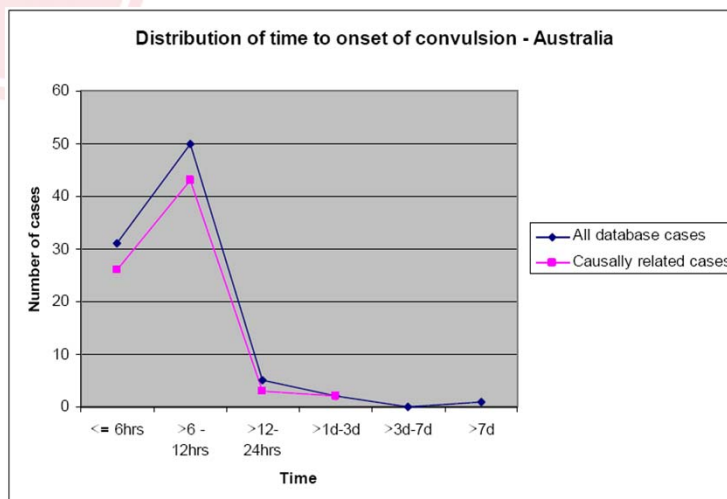
TGA Epidemiological Analyses



DoHA - TGA "Overview of Vaccine Regulation and Safety Monitoring and Investigation into Adverse Events Following 2010 Seasonal Influenza Vaccination in Young Children." 8th October 2010 <http://www.tga.gov.au/alerts/medicines/vaccine-overview.htm>

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Febrile convulsion following seasonal flu vaccine 2010

- Fluvax® or Fluvax® Junior (CSL)
 - up to 9 per 1,000 doses
- Panvax® (monovalent H1N1 vaccine)
 - between 0.08/1000 & 0.17/1000 doses
- Seasonal flu vaccine
 - 0.16/1000 doses
 - US CDC Vaccine Safety Datalink project from 2005-06 to 2009-10

Why FLUVAX?

- TGA conducted a detailed inspection of CSL vaccine manufacturing facility
 - No increased risk associated with quality, safety or efficacy of CSL's vaccine products
- Working hypothesis linked to content level of neuraminidase
 - H1N1 neuraminidase level in this year's seasonal flu vaccine is higher than previous seasons
 - Excess neuraminidase enzyme activity may be pyrogenic
 - Further investigations continuing

Current situation

- 27 July CMO advises that vaccination of children with seasonal influenza vaccine may resume using Inluvac and Vaxigrip
- Studies continuing to inform 2011 seasonal influenza vaccination composition and program

Fit-inducing vaccine to be pulled

Natasha Bita, Consumer editor | The Australian | November 01, 2010 12:00AM

 Recommend  20 people recommend this.

A FLU vaccine that sent children into fits is likely to be withdrawn for under-fives next year, the Health Department has revealed.

Chief Medical Officer Jim Bishop said Australian drug giant CSL had "indicated" it would not seek approval from the Therapeutic Goods Administration to use its Fluvax vaccine in young children next year.

"They've given us an indication they won't be applying for it to be used in children under five, so that's out of the picture," Professor Bishop told The Australian yesterday. "The manufacturing (processes) for seasonal flu vaccines are all slightly different, and it's only the CSL product that's produced the problem."

Non febrile seizures in infants and vaccination



De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study

Samuel F Berkovic, Louise Harkin, Jacinta M McMahon, James T Pelekanos, Sameer M Zuberi, Elaine C Wirdl, Deepak S Gill, Xenia Iona, John C Mulley, Ingrid E Scheffer

Summary

Lancet Neurol 2006; 5: 488-92
Published Online
April 20, 2006
DOI:10.1016/S1473-4422(06)70446-X

Background Vaccination, particularly for pertussis, has been implicated as a direct cause of an encephalopathy with refractory seizures and intellectual impairment. We postulated that cases of so-called vaccine encephalopathy could have mutations in the neuronal sodium channel $\alpha 1$ subunit gene (SCN1A) because of a clinical resemblance to severe myoclonic epilepsy of infancy (SMEI) for which such mutations have been identified.

- 12 / 14 "vaccine encephalopathy" had previously unrecognised Dravet syndrome
 - 11 / 12 had SCN1A mutation
- Did vaccination trigger the onset of Dravet syndrome?
- Did vaccination result in worse neurological outcomes?

Rotavirus & Intussusception

- 23 September 2010 - FDA adds information to Warnings/Precautions section of Rotarix
- Interim results of postmarketing study in Mexico suggests increased risk of IS in the 31 day period after dose 1 of Rotarix
- USA - increased risk translates to potentially 0-4 additional cases of IS hospitalisations per 100 000 infants in USA (mostly within 7 days of dose 1)
- No changes to Indications or Contraindications for Rotarix use
- Studies currently underway in Australia

SHORT REPORT

Multiple Sclerosis 2009; 15: 116–119

CNS demyelination and quadrivalent HPV vaccination

I Sutton^{1,2}, R Lahoria³, IL Tan¹, P Clouston⁴ and MH Bamett^{2,3}

Vaccination is generally considered safe in patients with multiple sclerosis (MS). We report five patients who presented with multifocal or atypical demyelinating syndromes within 21 days of immunization with the quadrivalent human papilloma virus (HPV) vaccine, Gardasil[®]. Although the target population for vaccination, young females, has an inherently high risk for MS, the temporal association with demyelinating events in these cases may be explained by the potent immuno-stimulatory properties of HPV virus-like particles which comprise the vaccine. A prospective case-control study of patients with MS or clinically isolated demyelinating syndromes receiving the Gardasil[®] vaccine may provide relevant safety data in this population. *Multiple Sclerosis* 2009; 15: 116–119. <http://msj.sagepub.com>

5 cases, aged 16-26 yrs

Onset 1-21 days post HPV vaccine

Clinically isolated syndrome (2 cases) and Clinically definite MS (3 cases)

HPV VLPs – TNF alpha , IL-6, IL-12 stimulated

Authors caution – using HPV vaccine in MS patients

LETTER TO THE EDITOR

Post-H1N1 Narcolepsy-Cataplexy

Yves Dauvilliers, MD, PhD¹; Jacques Montplaisir, MD, PhD^{2,3}; Valérie Cochen, MD, PhD¹; Alex Desautels, MD^{2,4}; Mali Einen, BA⁵; Ling Lin, MD, PhD⁵; Minae Kawashima, PhD⁵; Sophie Bayard, PhD¹; Christelle Monaca, MD, PhD⁵; Michel Tiberge, MD⁷; Daniel Filipini, MD²; Asit Tripathy, MD⁸; Bich Hong Nguyen, MD^{1,9}; Suresh Kotagal, MD¹⁰; Emmanuel Mignot, MD, PhD⁵

¹National Reference Network for Orphan Diseases (Narcolepsy and Idiopathic Hypersomnia), Department of Neurology, Gui-de-Chauliac Hosp INSERM U888 Montpellier, France; ²Sleep Disorder Center, Sacré-Coeur Hospital, Montréal, Canada; ³Department of Psychiatry, University of Montréal, Montréal, Canada; ⁴Department of Neurology, University of Montréal, Montréal, Canada; ⁵Center for Sleep Sciences and Medicine, Stanford University, Stanford, CA; ⁶Department of Clinical Neurophysiology, Roger-Salengro Hospital, Lille, France; ⁷Department of Neurology, Rangue Hospital, Toulouse, France; ⁸Blank Children's Hospital, Des Moines, IA; ⁹Department of Pediatrics, Université de Montréal, Montréal, Canada; ¹⁰Department of Neurology, Mayo Clinic, Rochester, MN

- Probable autoimmune condition – with environmental trigger
 - influenza
- 14 cases of narcolepsy after H1N1 – (Pandemrix)
 - mean onset 7 weeks post vax (range 2 days -20 wks)
 - All HLA DQB1* 0602 positive
 - 11 cases has AISO3 adjuvant

Sleep 2010; 33 Vol11

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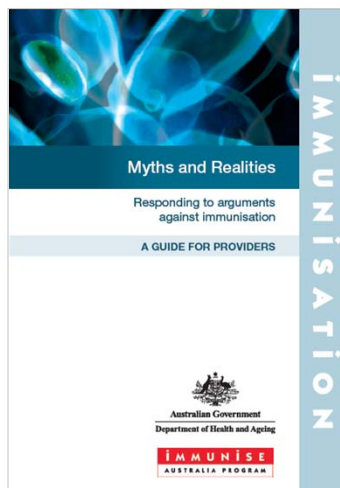
AEFI Myths



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Reported events - no causal evidence

- SIDS
- Autism and MMR vaccine
- Inflammatory bowel disease and MMR vaccine
- MS and Hep B vaccine
- Diabetes and HIB vaccine
- Asthma
- MMR vaccine and egg allergy
- ? influenza vaccine and egg allergy



- Narrated slide set available at:
<http://ncirs.edu.au/immunisation/education/tools/index.php>



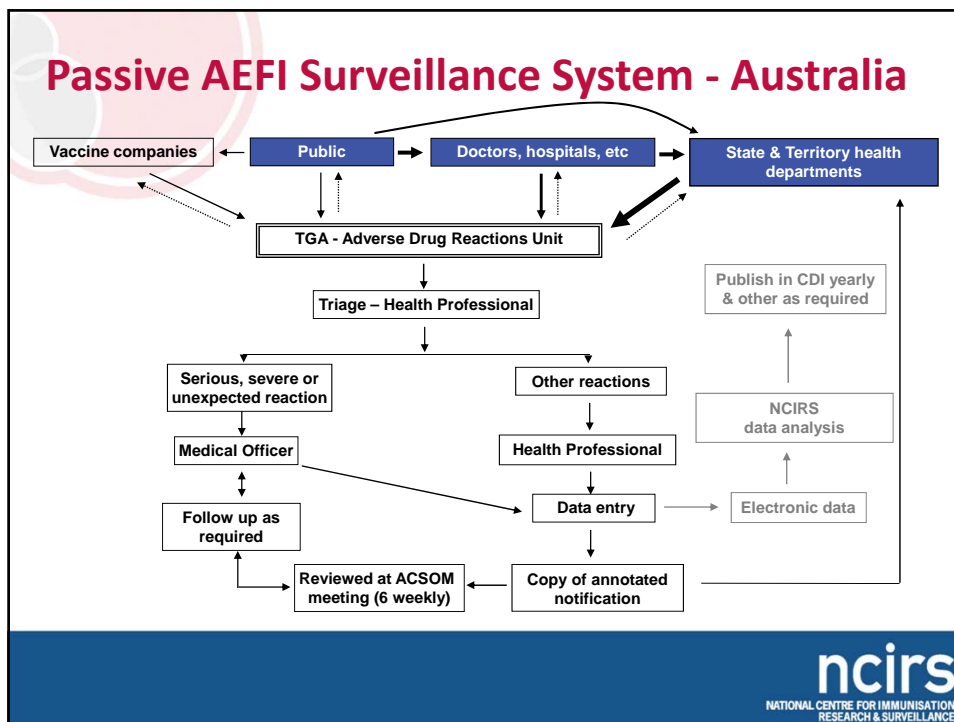
Reporting AEFIs



ACSOM

- Advisory Committee on the Safety Of Medicines
- Advises and makes recommendations to the TGA
- Committee made up of independent experts
- Reports are assessed by a health professional and entered into the Adverse Drug Reactions System
- Examples of actions that TGA can take:
 - Publicize reaction details in CDI or TGA website
 - Amend medicine's product information
 - Restrict availability of the medicine

Passive AEFI Surveillance System - Australia

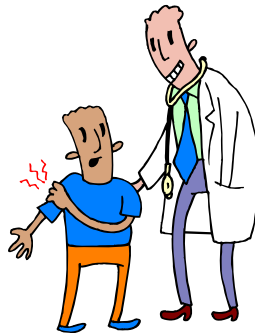


How to report

- AEFI are considered Notifiable Conditions under the NSW Public Health Act in NSW
- Contact local Public Health Unit by phone
- Anyone can report a reaction to a vaccine i.e. clinical or non-clinical personnel
- No time limit on reporting
- Report anything that is serious, unexpected or unusual
 - Remember list in Handbook 9th ed. pp 360-363



AEFI Clinics...



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Children's Hospital at Westmead

Specialist clinic

- Assess & manage children and adolescents who have:
 - experienced an AEFI
 - have a medical risk factor
 - have multiple allergies
- Subsequent doses given under close supervision or admission if indicated
- Detailed discussion with parents with questions
- Provide advice & feedback to Immunisation Providers



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What to refer:

- HHE
- Seizures
- Rash + urticaria within 48 hours of vaccination
- Neurological symptoms
- Intussusception
- Premature babies with history of apnoeic episodes
- Anaphylaxis
- Anything else you're concerned about



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Children's Hospital at Westmead

Contact details

- Kath Cannings - Immunisation Adverse Events CNC
- Ph: 9845 1414
- Email: kathryc1@chw.edu.au
- Fax: 9845 1418
- Dr Nicholas Wood - Staff Specialist Paediatrician
- Clinics held every Friday morning



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What about adults?

- Currently setting up service
- Refer as per children/adolescents
- Network of specialists for review



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