

# Review of adverse events after influenza vaccination in children

Influenza Specialist Group  
Annual General Meeting  
31 Jan – 1 Feb 2016

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## My little girl nearly died from the flu: Jab recommended for kids



Four-year-old Rosie Baxter nearly died after contracting the flu *Source: Supplied*

# Addressing burden: Vaccination is key

- Australian flu vaccination rates in children very low
  - 1.0-1.6% of all 6m-<7y per year (2010-2014)<sup>1</sup>
  - 5-8% in WA free program (for 6m - <5 years)<sup>1</sup>
- Universal paediatric vaccination ?on the horizon
  - US/Canada: all healthy children >6 months
  - UK: staged introduction of LAIV from 2013-2014 season
  - Likely herd immunity effects<sup>2</sup> (UK LAIV evidence)

1. ACIR data. Personal communication. Brynley Hull

2. Pebody et al. *Eurosurveillance*. 2015;20:pii=30029

# 2010: Unexpected Febrile Seizures in Children aged <5 years

- Temporary **national suspension** of flu vaccination
- 5-7 febrile seizures per 1000 vaccinated children<sup>1,2</sup>
- only with **bioCSL** Fluvax<sup>®</sup> and Fluvax Junior<sup>®</sup>
- Dramatic effects on **parental confidence** in flu vaccine and **flu vaccine uptake**<sup>3</sup>

1. TGA Report: <https://www.tga.gov.au/file/555/download>

2. Armstrong et al: *BMJ open*. 2011;1:e000016

3. Blyth et al: *Vaccine*. 2014;32:4075-4081.



DAILY NEWS 4 October 2010

## Australia blames a flu vaccine for child convulsions

Flu shots with side-effects on offer again

NATASHA BITA, CONSUMER EDITOR The Australian February 16, 2012 12:00AM 7 comments

Kirsten Button with her baby S...

Banned vaccine to be used agai...



Perth mother Kirsten Button with her toddler Saba, who suffered brain damage after a Fluvax shot in 2010. Picture: Colin Murty  
Source: The Australian

**A FLU vaccine banned for children and found to trigger the most side-effects in adults has again been selected for the nation's flu immunisation program, on the grounds an Australian-made product would guarantee supply.**

NEWS



## Parents recount flu jab nightmare

## Toddler who was given an adult flu shot is left severely brain damaged and unable to walk or talk

JANE HANSEN THE SUNDAY TELEGRAPH NOVEMBER 09, 2013 10:00PM



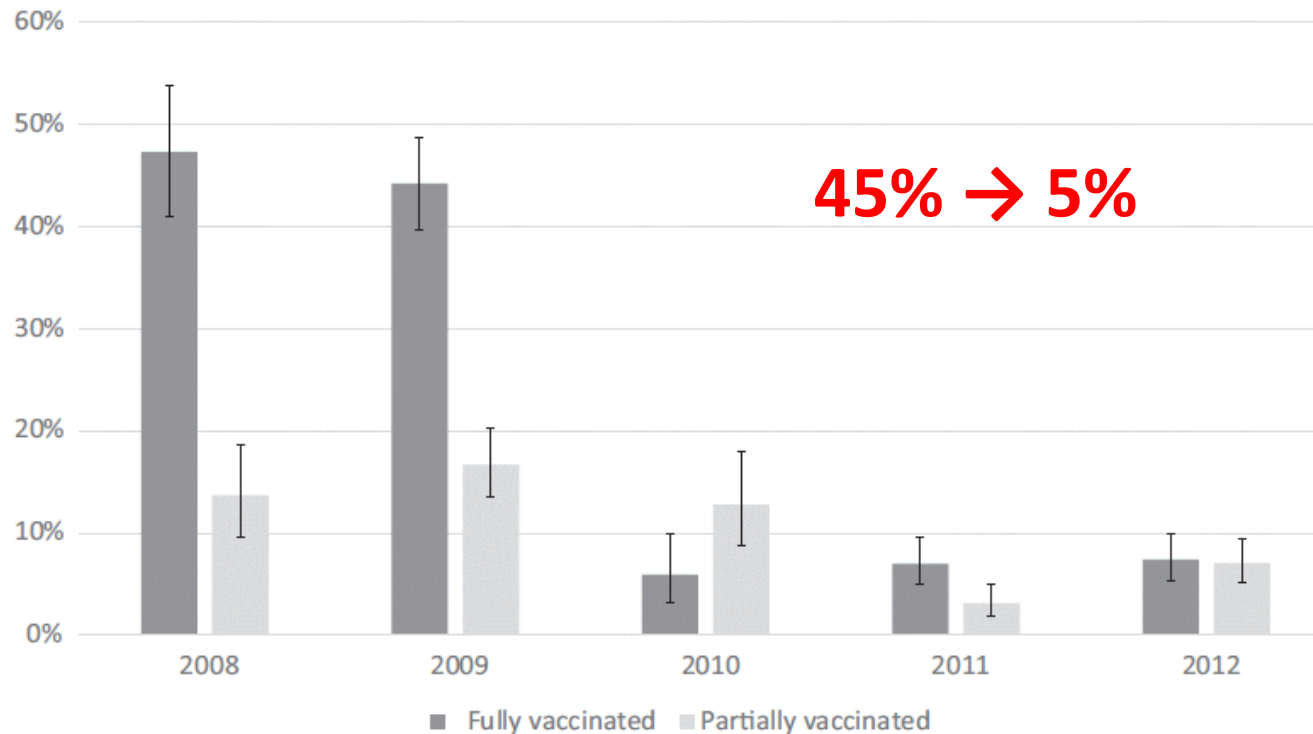
HOME » NEWS » HEALTH » HEALTH NEWS

## Swine flu vaccine safety probed over link to rare sleep disorder

The safety of a swine flu vaccine is to be investigated by European drugs regulators after it was linked to a rare condition that causes people to fall asleep suddenly.

# Influenza vaccine coverage in WA

*C.C. Blyth et al. / Vaccine 32 (2014) 4075–4081*



- Parents concerned re side effects:  
**39.2%** (2008-2009) → **67.7%** (2010-2012)

# Outline

- WHAT do we know about safety of influenza vaccines in children
  - Systematic review of fever after TIV
  - Brief review of lessons from bioCSL
  - Safety surveillance in the post-bioCSL era
  - New vaccines: QIV



# Large body of evidence suggests TIV is safe in children

- US Post-marketing surveillance (PMS) studies
- Goodman et al (2006) Pediatrics. 2006;117(5):e821-6.
  - 13,383 children aged 6-23m.
  - **No elevated hazard ratios** after dose 1 TIV incl seizure
- Hambidge et al (2006) JAMA. 2006;296(16):1990-7.
  - 45,356 children aged 6-23 months. **No serious MAEs associated** incl febrile seizures
- Glanz et al (2011) Arch Pediatr Adolesc Med. 2011;165:749-755
  - 66,283 children aged 24-59m
  - **No serious MAEs** associated with TIV



# What is the expected rate of fever after TIV in children?

The screenshot shows the Eurosurveillance website interface. At the top, the Eurosurveillance logo is displayed with the text 'Impact factor 5.7'. Below the logo is a navigation bar with links: HOME, ARCHIVES, ABOUT US, EDITORIAL POLICY, FOR AUTHORS, FOR REVIEWERS, LINKS, and 15-YEAR. On the left side, there is a search bar and a sidebar with links: Submit article, RSS Feed, Follow us on Twitter, Subscribe, Unsubscribe, Contact, and Sitemap. The main content area shows the article title 'SYSTEMATIC REVIEW OF FEVER, FEBRILE CONVULSIONS AND SERIOUS ADVERSE EVENTS FOLLOWING ADMINISTRATION OF INACTIVATED TRIVALENT INFLUENZA VACCINES IN CHILDREN' by J Li-Kim-Moy et al. The authors' names and affiliations are listed below the title. The article is dated 18 June 2015.

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**Eurosurveillance, Volume 20, Issue 24, 18 June 2015**

**Review articles**

**SYSTEMATIC REVIEW OF FEVER, FEBRILE CONVULSIONS AND SERIOUS ADVERSE EVENTS FOLLOWING ADMINISTRATION OF INACTIVATED TRIVALENT INFLUENZA VACCINES IN CHILDREN**

J Li-Kim-Moy ([jean.likimmoy@health.nsw.gov.au](mailto:jean.likimmoy@health.nsw.gov.au))<sup>1,2</sup>, J K Yin<sup>1,2</sup>, H Rashid<sup>1</sup>, G Khandaker<sup>1,2,3</sup>, C King<sup>1,2</sup>, N Wood<sup>1,2</sup>, K K Macartney<sup>1,2,4</sup>, C Jones<sup>2,3,4,5</sup>, R Booy<sup>1,2,4,5</sup>

Li-Kim-Moy et al. *Eurosurveillance*. 2015;20:pii=21159.

# Systematic Review of Fever after TIV in children

- Published and unpublished trial data of TIV in children 2005-2012
- Proportion meta-analysis of fever rates
- 6-35 months and 3-17 years.
- $\geq 38^{\circ}\text{C}$  definition
- Vaccine dose number, vaccine type and vaccine manufacturer

# Pooled estimates of fever post TIV

Fever in RCTs of TIV	Age	Dose	Number of children	Overall fever estimate <sup>a</sup> (%)	95% CI	I <sup>2</sup>
Non-adjuvanted vaccines	6–35m	Dose 1	1,543	6.7	3.0–11.8	87.7
		Dose 2	1,501	7.6	3.5–13.0	87.6
	3–17y	Dose 1	795	6.9	5.2–8.7	NA <sup>b</sup>
		Dose 2	775	5.4	1.2–12.1	NA <sup>b</sup>

Excludes bioCSL vaccines. No RCTs available at the time

# Wood et al 2014

Med J Aust. 2014;201:596-600.

- Active surveillance study
- 2013 season
- 981 children
- AE within 72 hours post inactivated TIV

Outcome	Total
<b>Systemic reaction of any severity</b>	
Fever	47 (5.5%) [4.1%–7.3%]
Headache	26 (3.1%) [2.0%–4.4%]
Nausea, vomiting or abdominal pain	39 (4.6%) [3.3%–6.2%]
Convulsion	1 (0.1%) [0.01%–0.7%]
Rash	15 (1.8%) [1.0%–2.9%]
Rigors	6 (0.7%) [0.3%–1.5%]
Fatigue	73 (8.6%) [6.8%–10.7%]
Any systemic reaction†	157 (18.4%) [15.9%–21.2%]
<b>Injection site reaction of any severity</b>	
Swelling or lump	49 (5.8%) [4.3%–7.5%]
Pain or tenderness	158 (18.5%) [16.0%–21.3%]
Any injection site reaction†	181 (21.2%) [18.5%–24.1%]

# bioCSL flu vaccine studies

- 2 uncontrolled clinical trials. Age cohorts
- Nolan et al. (2009) Influenza Other Respi Viruses. 2009;3(6):315-25.

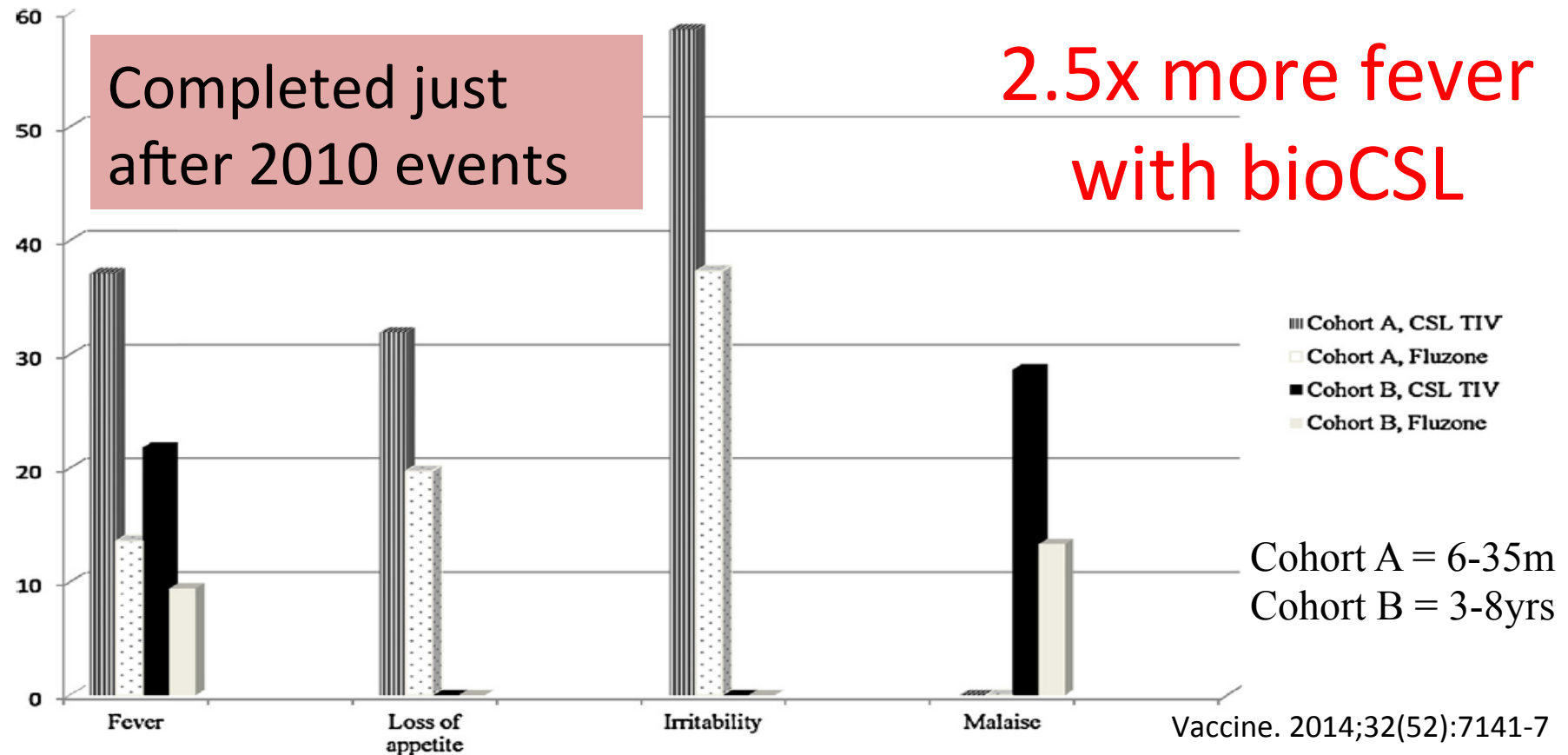
Fever rate	Dose 1	Dose 2	2 <sup>nd</sup> year booster
6-35 months	22.5%	22.5%	39.5%
≥3 - <9 years	15.6%	8.2%	27.0%

- Lambert et al. (2013) Influenza Other Respir Viruses. 2013;7(5):676-85.

Fever rate	Dose 1	Dose 2
6-35 months	28.6%	17.9%
≥3 - <9 years	19.5%	9.9%


Li-Kim-Moy et al. *Eurosurveillance*. 2015;20:pii=21159.

# bioCSL RCT in children: Brady 2014



	Age	Afluria - BioCSL	Fluzone - Sanofi	p value
<b>Fever rate</b>	6-35m	37.1 % (229)	13.6% (228)	p<0.001
	3-8y	21.8% (252)	9.4% (255)	p<0.001
	9-17y	6.3% (254)	4.0% (250)	

# BioCSL's root cause analysis



Contents lists available at [ScienceDirect](#)


## Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)

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### 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

Steve Rockman<sup>a</sup>, Allison Dyson<sup>b,1</sup>, Sandra Koernig<sup>b,1</sup>, Dorit Becher<sup>b</sup>, Milica Ng<sup>b</sup>, Adriana Baz Morelli<sup>b</sup>, Megan Barnden<sup>b</sup>, Mimi L.K. Tang<sup>c,d,e</sup>, Martin Pearce<sup>b</sup>, Eugene Maraskovsky<sup>b,\*</sup>



Contents lists available at [ScienceDirect](#)

## Vaccine

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### Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine

Steve Rockman<sup>a</sup>, Dorit Becher<sup>b</sup>, Allison Dyson<sup>b,1</sup>, Sandra Koernig<sup>b,1</sup>, Adriana Baz Morelli<sup>b</sup>, Megan Barnden<sup>b</sup>, Sarina Camuglia<sup>a</sup>, Peter Soupourmas<sup>b</sup>, Martin Pearce<sup>b</sup>, Eugene Maraskovsky<sup>b,\*</sup>

<sup>a</sup> bioCSL, Parkville 3052, Victoria, Australia  
<sup>b</sup> CSL Limited, Parkville 3052, Victoria, Australia

Vaccine. 2014;32(30):3861-8.

Vaccine. 2014;32(30):3869-76.



# bioCSL root cause analysis

- **Reactogenic strains.** A/H1N1pdm09, B Brisbane
- **Poor splitting** (Sodium taurodeoxycholate used by bioCSL only)
- **Viral RNA fragments retained**
- **Excessive cytokine response**
- **Trials underway of reformulated CSL Flu vaccine** with increased TDOC for B strains

# REVIEW OF THE MANAGEMENT OF ADVERSE EVENTS ASSOCIATED WITH PANVAX AND FLUVAX (HORVATH REVIEW)

## OUTCOMES OF RECOMMENDATIONS

### INTRODUCTION

- Horvath review: 25 May 2011
  - Improved data collection on vaccine usage and vaccine safety
  - Systems for timely reporting of AEFI

[http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/clinical-updates-and-news/\\$File/Horvath-review-outcomes.pdf](http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/clinical-updates-and-news/$File/Horvath-review-outcomes.pdf)

## RAPID COMMUNICATIONS

# Real-time safety surveillance of seasonal influenza vaccines in children, Australia, 2015

A Pillsbury<sup>1</sup>, P Cashman<sup>2,3</sup>, A Leeb<sup>4</sup>, A Regan<sup>5,6</sup>, D Westphal<sup>5,7,8</sup>, T Snelling<sup>7,9</sup>, C Blyth<sup>7,9,10</sup>, N Crawford<sup>11,12,13</sup>, N Wood<sup>11,14</sup>, K Macartney<sup>12,15</sup>, on behalf of the AusVaxSafety, surveillance team<sup>16</sup>

1. National Centre for Immunisation Research and Surveillance, The Children's Hospital at Westmead, NSW, Australia
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3. The University of Newcastle, NSW, Australia
4. Illawarra Medical Centre, WA, Australia
5. Communicable Disease Control Directorate, Western Australia Department of Health, WA, Australia
6. School of Pathology and Laboratory Medicine, University of Western Australia, WA, Australia
7. Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, University of Western Australia, WA, Australia
8. National Centre for Epidemiology and Population Health, Research School of Population Health, The Australian National University, ACT, Australia
9. Princess Margaret Hospital, WA, Australia
10. University of Western Australia School of Paediatrics and Child Health, Princess Margaret Hospital, WA, Australia
11. Department of General Medicine, Royal Children's Hospital, Victoria, Australia
12. SAEFVIC, Murdoch Childrens Research Institute, Victoria, Australia
13. Department of Paediatrics, The University of Melbourne, Victoria, Australia
14. Discipline of Paediatrics and Child Health, University of Sydney, NSW, Australia
15. Department of Microbiology and Infectious Diseases, The Children's Hospital at Westmead, NSW, Australia
16. The members of the group are listed at the end of the article.

**Correspondence:** Alexis Pillsbury (alexis.pillsbury@health.nsw.gov.au)

**Citation style for this article:**

Pillsbury A, Cashman P, Leeb A, Regan A, Westphal D, Snelling T, Blyth C, Crawford N, Wood N, Macartney K. Real-time safety surveillance of seasonal influenza vaccines in children, Australia, 2015. Euro Surveill. 2015;20(43):pii=30050. DOI: <http://dx.doi.org/10.2807/1560-7917.ES.2015.20.43.30050>

2015;20(34):pii=30002. DOI: <http://dx.doi.org/10.2807/1560-7917.ES.2015.20.34.30002>

Article submitted on 14 October 2015 / accepted on 29 October 2015 / published on 29 October 2015

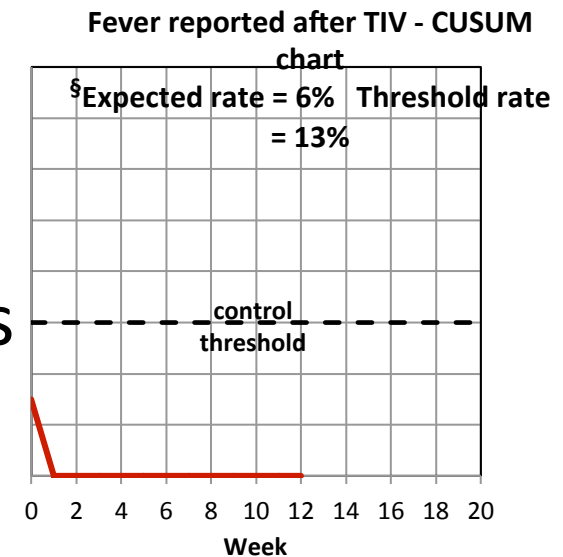
# AusVaxSafety

- Active surveillance of adverse events after flu vaccination in children
- Utilises the Vaxtracker and SmartVax reporting tools
- Now 5 states
- Automated SMS/email to parents
- AEs during 72 hours
- Reply by smartphone/web survey

Surveillance mechanism	Jurisdiction (n=4)	Participating sentinel surveillance sites (n=69)			
		AMS	GP	Hospital clinic	Community clinic
Vaxtracker	NSW	7	32	2	1
	SA			1	
Vaxtracker/ SmartVax*	Vic		1	2	
SmartVax	WA		21	1	1
Both	All	7	54	6	2

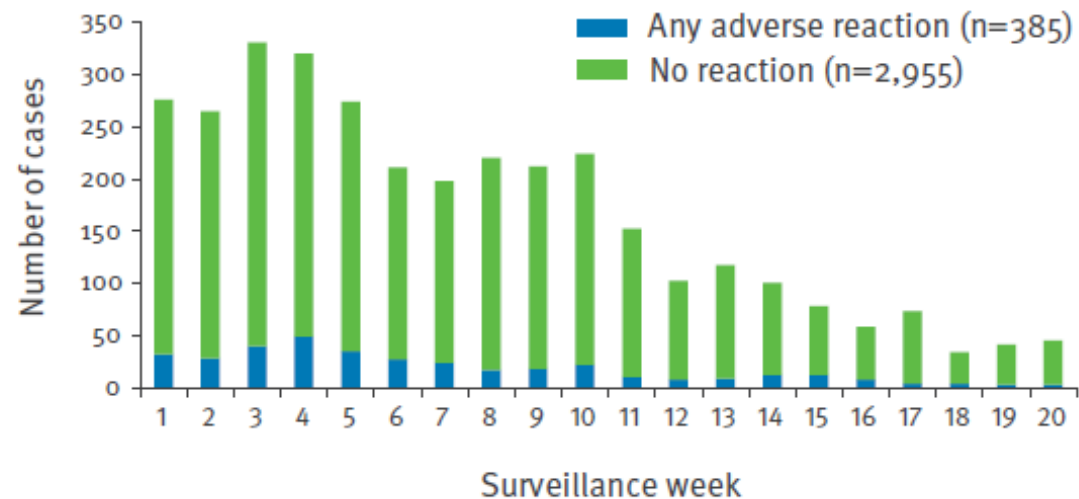
# AusVaxSafety

- Fever meta-analysis + Wood study + 2014 results guided thresholds
  - Expected fever rate 6%
  - Threshold fever rate for signal 13%
- fast initial response cumulative summation and Bayesian methods allowed **rapid signal detection**.
- **Weekly report** to DoH and TGA
- Safety established within 3 weeks



## FIGURE

*AusVaxSafety* participants with and without post-vaccine reaction, by week of vaccination, and cumulative percentage of participants, Australia, 1 April–31 August 2015 (n = 3,340)



- 4.4% Fever overall
- 8.7% fever (concomitant vaccines) vs 3.3% flu vacc only ( $p < 0.001$ )
- 1.1% medical attendance
- 0.2% (5/3340) febrile seizures. 4 had prev sz

# Changes overseas

- European Medicines Agency
  - CHMP: Committee for Medicinal products for human use
  - Licensing requirements of influenza vaccines changing
  - Vaccine manufacturers **must conduct annual enhanced safety surveillance** capable of rapidly detecting new safety signals

1. Wijnans L. Influenza and other respiratory viruses. 2016. 10(1), 2–8.
2. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2014/04/WC500165492.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/04/WC500165492.pdf)



# What's around the corner

- **Quadrivalent influenza vaccines (QIV)**
  - 4 strains. Higher antigen dose
- 2016: first year of funded QIV under NIP.
  - No TIV on NIP, but will be available in private market
- Clinical trials suggest similar safety profile to TIV

RCTs	Age	Manufacturer	QIV (n)	Safety Conclusions
Domachowske (2013)	6m-17y	GSK	915	AE similar to TIV
Rodriguez Weber (2014)	18-47m	GSK	298	AE similar to TIV
Langley (2013)	6m-17y	GSK	1233	More local pain with QIV
Langley (2015)	6-35m	GSK	299	AE similar to TIV
Cadorna-Carlos (2015)	9-17y	Sanofi	329	AE similar to TIV
Greenberg (2014)	6m-8y	Sanofi	2893	AE similar to TIV
Wang (2015)	6-35m	Sanofi	158	AE similar to TIV

# QIVs on NIP

Brand	Manufacturer	Dose	Registered for
FluQuadri Junior®	Sanofi	0.25mL	6m to <3 years
Fluarix Tetra®	GSK	0.5mL	≥3 years

- NIP vaccines only for **at-risk** and **indigenous children**
- **Multiple brands** TIV/QIV on private market for **healthy**
- Risk of inadvertent use GSK product in <3y.o.
- No evidence of harm. RCTs used 0.5mL (Aust adult dose).

**ATAGI Clinical Advice has information on  
available brands for various age groups**

## NEWS



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The Daily Telegraph 

# Adult flu shot CSL Fluvax has been given to 43 underage kids despite ban

JANE HANSEN THE DAILY TELEGRAPH NOVEMBER 23, 2013 10:00PM

# Summary

- Large body of evidence shows flu vaccines currently registered for use in children to be safe
- Close monitoring needed for new vaccines including strain changes, QIV, & bioCSL vac
- Real time surveillance at the beginning of each flu season documenting AEs in place
- GP/Public awareness of safety monitoring and results will aid public confidence & vac uptake

# Acknowledgements

- A/Prof Kristine Macartney
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- Dr Clayton Chiu
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