



**Australian Government**  
**Department of Health and Ageing**  
**Therapeutic Goods Administration**

**INVESTIGATION INTO FEBRILE REACTIONS IN YOUNG CHILDREN FOLLOWING  
2010 SEASONAL TRIVALENT INFLUENZA VACCINATION**

**Status Report as at 2 July 2010**  
**Updated 24 September 2010**

## **Background**

Since 2008 Western Australia (WA) has funded a seasonal influenza vaccination program for all WA children aged 6 months to < 5 years. WA Health suspended this year's program on 22 April 2010 following reports of an apparent increase in febrile reactions following vaccination during March-April over the number that would be expected from records for 2008 and 2009, despite a similar uptake of seasonal vaccine in 2009 and 2010.

At the time the WA program was suspended the Therapeutic Goods Administration (TGA) had received 25 spontaneous reports of febrile convulsions following vaccination in children under 10 years across Australia, with 16 of these reported from WA, 14 of which were notified to the TGA on 20 April 2010. In comparison, in the first 6 months of 2008 the TGA received a total of 5 reports of convulsions in association with administration of seasonal influenza vaccine in children aged 0 to 10 years (none from WA) and in the first 6 months of 2009 only 1 report was received.

To explore this apparent safety signal, the TGA has undertaken an extensive range of investigations, to address the following key questions:

1. *Is there a real excess of fever/febrile convulsions attributable to 2010 Southern Hemisphere trivalent influenza vaccine (TIV)?*
2. *Is the apparent signal in WA also apparent in other states? If not, are there factors specific to the conduct of the immunization program in WA that would account for different rates of Adverse Events Following Immunization (AEFIs) in WA than in other states?*
3. *Is the situation in 2010 different to previous years?*
4. *If there is an excess of fever/febrile convulsions, is it attributable to a specific vaccine brand? If so, can any definitive conclusions be drawn about the relative safety of the other TIVs?*
5. *Are there any clinical or other contributing factors that could contribute to an apparent excess of fever/febrile convulsions?*
6. *Are there any vaccine quality or compositional issues that could account for the observed pattern of febrile reactions?*

In order to do this the TGA has

- **worked closely with Australian Technical Advisory Group on Immunisation (ATAGI) and the National Centre for Immunisation Research & Surveillance (NCIRS)** in undertaking and analysing epidemiological investigations. TGA has also been assisted by an expert pharmacoepidemiology panel established in 2009 to advise on the monitoring of the monovalent H1N1 vaccine (Panvax).

- **undertaken a detailed case review** of each reported case of febrile convulsion, using de-identified clinical data provided by states and territories;
- **reviewed paediatric clinical trial data for the monovalent pandemic H1N1 (PANVAX) vaccine** and undertook additional analyses;
- **reviewed and analysed distribution data, clinical trial data, manufacturing process information and information about the experience of other countries** using the various brands of the southern hemisphere 2010 TIV.
- **inspected and audited vaccine manufacturing facilities;** and
- **undertaken extensive laboratory analyses**, guided by a special expert panel chaired by Professor Peter Doherty, to assist in the interpretation of the results and to advise on methods for further testing.

### Adverse Events Following Immunization (AEFIs) reported to TGA

There are currently four 2010 trivalent seasonal influenza vaccines approved for use in Australia, three of which have paediatric indications. They are FLUVAX/FLUVAX JR (sponsor CSL), INFLUVAC (Solvay/Abbott) and VAXIGRIP (Sanofi-Pasteur). [A fourth brand, INTANZA (Sanofi-Pasteur), is only approved for use in adults and is not included in the National Immunisation Program (NIP).

As at 4 June 2010 the TGA had received a total of 1,729 AEFI reports concerning 2010 TIV. The summary data are presented in Table 1, listed by vaccine type.

It is important to note that these data reflect all cases reported to the TGA as *suspected reactions* to influenza vaccination, prior to detailed case review. It is therefore likely that these numbers include errors and duplicates and may change as further information is received by the TGA.

**Table 1: Summary of AEFI reports initially received by TGA to 04/06/2010**

Vaccine Type	Total	0-5 age group	Fever	Convulsion
Influenza vaccine not specified	257	194	182	26
FLUVAX/FLUVAX JR	1379	1023	948	96
VAXIGRIP	16	5	4	0
INFLUVAC	67	22	18	1
<b>TOTAL</b>	<b>1729</b>	<b>1244</b>	<b>1152</b>	<b>123</b>

Table 2 presents the regional distribution of those AEFIs reported in relation to FLUVAX or FLUVAX JR, or where the vaccine type was not specified.

**Table 2: Breakdown of AEFIs reported post FLUVAX/FLUVAX JR, or vaccine not specified**

Origin	Total	0-5 yr	Fever	Convulsion
ACT	48	30	27	2
NSW	138	77	73	7
NT	10	8	8	0
QLD	273	201	190	13
SA	272	164	156	4
TAS	52	33	30	1
VIC	197	152	135	16
WA	601	517	482	72
S/T not known	48	35	29	7
<b>TOTAL</b>	<b>1636</b>	<b>1217</b>	<b>1130</b>	<b>122</b>

Each of the febrile convulsion case reports has since undergone careful review and case ascertainment within the TGA, using de-identified clinical data provided by states and territories.

On the basis of this detailed review, the TGA has concluded that there have been **100 confirmed cases of febrile convulsions** in children under the age of 5 years across Australia, 58 of which were reported from WA. Of the 100 cases, 99 are considered causally related to vaccination with seasonal influenza vaccine and 1 case is considered unrelated because of the lack of a temporal association with vaccine administration.

Of the 99 cases considered causally related, 74 are considered very likely to be related to influenza vaccination because no other potential causative factors have been identified. The remaining 25 cases are only possibly causally related to the vaccine because they could also be explained by the concomitant administration of one or more other vaccines and/or a concurrent infection.

FLUVAX or FLUVAX JUNIOR was used in all 66 cases where the brand of the seasonal influenza vaccine was reported.

Of the 100 cases of febrile convulsion, 25 were directly observed by a medical or allied health practitioner. Of these 25 cases, 17 are considered very likely to be causally related to vaccination with the seasonal influenza vaccine and 8 are only possibly causally related to the vaccine because they can also be explained by the concomitant administration of other vaccines and/or concurrent infection.

In the remaining 75 cases the diagnosis of febrile convulsion was made by a health care professional on the basis of a history obtained after the event. Of these, 57 are considered very likely to be causally related to vaccination with the seasonal influenza vaccine, a further 17 are considered possibly causally related to the vaccine because they can also be explained by the use of concomitant vaccines and/or concurrent infection, and 1 was considered causally unrelated.

## **Epidemiological Analyses**

A number of epidemiological analyses have been undertaken by ATAGI in conjunction with NCIRS and also by individual jurisdictions. A summary of those analyses is presented here.

The data collated to date suggest that CSL's 2010 trivalent influenza vaccine (TIV) products FLUVAX and FLUVAX JUNIOR are associated with febrile reactions in the 4 - 24 hours following vaccine administration at higher rates than documented following seasonal TIV administration in previous years in Australia.

- This higher frequency of early fever responses is associated with substantially higher rates of TIV-associated febrile convulsions in children 6 months to less than 5 years of age, particularly in WA, where the highest numbers of children in this age group have been vaccinated in 2010, but also in other states.
- While there is no clear literature-based estimate for expected rates of influenza vaccine-attributable febrile convulsions, rates of febrile seizures in children 6 months to 3 years, identified by the US CDC Vaccine Safety Datalink (VSD) project over the period 2005-06 to 2009-10 were 0.16/1,000 in the 7 day period post TIV administration and 0.03/1,000 for day 0 (day of administration of vaccine).
- While caution must be used in the interpretation of AEFI data in a stimulated reporting environment there is an apparent rate of febrile convulsions following TIV of approximately 9 per 1,000 doses in WA and approximately 5 per 1,000 doses in other jurisdictions, compared with 0.06 per 1,000 doses for PANVAX at the time of suspension of the program.<sup>1</sup> Subsequent analysis of adverse events associated with PANVAX has shown the rate of

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<sup>1</sup> Previously the rate of febrile convulsions associated with Panvax was specified incorrectly as 0.6/1000 doses. At the time of preparation of this report the correct figure was in fact 0.06/1000, as shown above.

febrile convulsions associated with this vaccine in Australia at between 0.08/1000 and 0.17/1000.

- The clinical pattern of vaccine-associated and non vaccine-associated febrile convulsions is similar, and in keeping with historical experience of febrile convulsions.
- The available data suggest that rates of febrile convulsions following CSL's monovalent pandemic H1N1 vaccine (PANVAX) and INFLUVAC are similar, and similar to the low rates of reported febrile convulsions from all TIV vaccines in previous years. However, the available data for INFLUVAC are limited and to date there has been only very limited use of VAXIGRIP in Australia.
- There are no apparent clinical or epidemiologic factors that would point to a plausible explanation for the observed rates of fever and febrile convulsion.

These conclusions have been drawn from the following epidemiological analyses summarised here:

- 1) A vaccine-specific, uncontrolled cohort study from WA using denominator data directly obtained by surveying vaccinating GPs showed that in 2010:
  - a. For children aged less than 3 years, the rate of febrile convulsions per 1,000 doses administered were approximately 7/1,000 for FLUVAX (adult) vaccine; 10/1,000 for FLUVAX JUNIOR; and 0 for INFLUVAC from 1,450 doses administered. Only 48 doses of VAXIGRIP were administered, with no febrile convulsions.
  - b. For children aged 3-4 years, the rates of febrile convulsions were substantially lower at 1.5 (95% Confidence Interval 0.6 to 3.5) for FLUVAX adult, slightly higher at 14.0 (95%CI 5.5 to 35.5) on a smaller denominator for FLUVAX JUNIOR, while the rate was again zero (95%CI 0 to 2.1) for INFLUVAC in 1,800 doses given,
  - c. Rates of febrile reactions in children under 3 years of age were approximately 50/1,000 for FLUVAX, 40/1,000 for FLUVAX JUNIOR, and 5 for INFLUVAC. Rates were substantially lower in 3 and 4 year olds, but still 10 to 20-fold higher for FLUVAX or FLUVAX JUNIOR than for INFLUVAC.
- 2) A controlled cohort study using denominator data inferred from 2009 Australian Childhood Immunisation Register (ACIR) records showed risk ratios for febrile convulsions in vaccinees vs non-vaccinees of approximately 5, both in children 6 months to < 3 years, and in those aged 3-4 years. By contrast, the estimated rates for 2009 were 0.3/1,000 and zero for vaccinees, and 0.6 and 0.1 for non-vaccinees, in those aged 6 months to < 3 years and 3-4 years, respectively.
- 3) Rates of febrile convulsions in PANVAX and FLUVAX recipients in 2010 in Queensland children aged less than 5 years showed a risk ratio of approximately 7 for FLUVAX (based on approximately 80,000 doses of PANVAX and 18,000 doses of FLUVAX administered).
- 4) Time series data from WA show a marked increase in febrile convulsion presentations to ED immediately following TIV vaccination commencement on 8 March 2010, no presentations on Sundays and over the Easter holiday period (when it would be expected that minimal vaccination would be undertaken) and a prompt return to pre-vaccination period levels following cessation of the WA vaccination program on 22 April 2010. Data for the same period in 2008 and 2009 do not show similar phenomena.
- 5) A cohort study from three NSW hospitals using retrospective data obtained via parental report on children aged under 5 years who received FLUVAX, PANVAX or INFLUVAC found that fever was reported in 46% of children who received FLUVAX, 16% following PANVAX,<sup>2</sup> and 7% following INFLUVAC. Parents were unaware of the brand of TIV that had been administered to their child. The risk ratios for fever following FLUVAX vs PANVAX and FLUVAX vs INFLUVAC were approximately 3 (CI 1.8 to 4.3) and 6.5 (CI 3.1 to 13.9) respectively.

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<sup>2</sup> This was previously reported as 10%; however updated data have shown a rate of 16%.

- 6) No available clinical or epidemiologic factors offer a plausible explanation of observed fever or febrile convulsion rates. WA data show that the presence of associated respiratory symptoms was less common ( $p < 0.001$ ) in post-vaccination febrile convulsion patients than in other febrile seizure patients. Viral studies were not undertaken in most of the febrile convulsion cases, and this together with the short time to onset of symptoms following vaccination (mean 7.2 hours; range 5.9 to 8.4 hours) suggests that concomitant infection is not a likely explanation for the majority of vaccine-associated febrile events. Approximately one in four vaccinees with a febrile convulsion had an underlying medical condition. The mean age of post-vaccination febrile seizure patients was the same as that in febrile seizure patients who had not been vaccinated (2 years). About 30% of post-vaccination febrile convulsion patients had received a TIV in the previous year.
- 7) An analysis of primary care presentations showed significant increases (rate ratios of 1.5-1.9) in numbers of visits day 1 post receipt of FLUVAX in 2010 compared with rates in 2008 or 2009 in both WA and other jurisdictions, with similar denominators in 2009 and 2010. Similar increases were not seen for PANVAX.

It is important to note that the numbers of febrile reactions and febrile convulsions used in these analyses to calculate risk ratios are based on numbers of suspected cases reported by states and territories prior to the TGA's review of individual cases. Following detailed adjudication of individual case reports the number of confirmed cases is lower than the number of cases originally reported, and while this has led to lower risk ratios this does not alter the overall conclusion of a confirmed safety signal.

#### **Additional Analyses of Paediatric Clinical Trial Data**

To explore whether the observed increase in reactogenicity was the result of the inclusion of a novel strain of H1N1 in the 2010 seasonal TIV, TGA reviewed data from CSL's two clinical studies of trivalent seasonal influenza vaccines and two clinical studies of monovalent pH1N1 (2009) vaccine.

Additional analyses of the data from the trials were undertaken to determine the relationship, if any, between baseline serological status and febrile reactions, and between prior exposure to TIV and the occurrence of fever. In both Study 060 (Australia) and Study 062 (USA) there were numbers of subjects showing H1N1 seropositivity at baseline. In Study 060, 18% of subjects in Cohort A (6 - 35 months) had titres  $> 1:10$  at baseline and 6.7% had titres  $> 1:40$  at baseline and in Cohort B (3 - 9 years) 45% had titres  $> 1:10$  at baseline and 30% had titres  $> 1:40$  at baseline. In Study 062 the proportions with baseline seropositivity were lower but still around 11% for titre  $> 1:10$  in the younger age cohort and 18% for titre  $> 1:10$  in the older age cohort.

These analyses showed that baseline seropositivity to H1N1 was associated with significantly lower likelihood of a febrile response to vaccination. Logistic regressions of the occurrence of fever following Dose 1 and following Dose 2 versus age group, dosage, and baseline seropositivity to pH1N1 found that baseline seropositivity was associated with a significantly reduced odds ratio of fever following Dose 1, (OR 0.24; CI 0.14 to 0.40), but not following Dose 2 (OR 0.89; CI 0.48 to 1.57). Frequency and intensity of fever also tended to be lower among those who had had previous influenza vaccination (OR 0.64; CI 0.52 to 0.79).

This suggests that rather than a "priming effect" arising through prior exposure to H1N1 (and/or prior TIV), children previously unexposed to TIV antigens or H1N1 (either wild virus or via vaccination) are at greater risk of a febrile response to TIV. This is consistent with the finding that only 30% of the cases of febrile convulsions reported in association with 2010 TIV had received a prior seasonal influenza vaccination.

#### **Inspection of Manufacturing Facilities**

As part of the investigation into the occurrence of febrile reactions following administration of 2010 seasonal TIV an onsite audit of the CSL vaccine manufacturing facility at Parkville was conducted by TGA inspectors on 12-13 May 2010.

Initial discussions with the manufacturer identified that CSL had made three changes to its manufacturing process since the 2009 seasonal influenza campaign intended to increase the

virus yield undertaken to maximise production of the 2009 pandemic H1N1 vaccine. The onsite audit was undertaken to assess these changes and the overall effectiveness of the quality system to manage non-conforming product, process deviations and change control. Review of the validation data demonstrated that the changes appeared to have had no impact on the quality of the vaccines produced.

At the time of the TGA audit, the TGA was aware that the US FDA's Centre for Biologics Evaluation and Research had concerns regarding the facility's manufacture of multi-dose influenza vaccine vials supplied to the US. The TGA had contacted the US FDA regarding its inspection findings as soon as it became aware of the fact that an FDA audit team had visited the CSL facility to seek information that may have informed the investigation of adverse events in Australia. The TGA and the FDA were able to jointly establish that the matters raised in the FDA audit that occurred between the 18<sup>th</sup> and 28<sup>th</sup> of April 2010 did not relate to the single dose influenza vaccine associated with febrile convulsions in Australia, and that they were not directly relevant to the investigation of the cause of adverse reactions in Australia as the US audit findings related only to multidose vaccine vials supplied in the United States.

The FDA audit found no evidence that the drugs manufactured at the Parkville site failed to meet their quality specifications and have not identified any health risks associated with products currently available. The FDA has subsequently written to CSL regarding the identified manufacturing deficiencies relating to the US supplied products.

The TGA conducted a second audit of the Parkville facility in June with further detailed inspections covering the full manufacture of influenza vaccines from seed lot to filling of vials and syringes. The TGA auditors also reviewed CSL's investigations and corrective actions arising from the US FDA inspection.

At this stage, based on findings from the two TGA audits and information from the US FDA audit, it has not been possible to identify a manufacturing deficiency that is causally linked to the occurrence of a higher than expected rate of febrile convulsions.

### **TGA Laboratory testing**

The TGA has undertaken an extensive range of testing of both retention and field samples of vaccine and this is continuing. To date no abnormalities in pharmacopoeial parameters (endotoxin and potency) have been identified in either retention or field samples. Additional testing has not shown any significant presence of whole virus particles, viable virus (cell culture) or contamination in the finished product.

Protein characterisation using size exclusion HPLC has shown different characteristic profiles for the different vaccines, which is expected given differences in manufacturing of each product, however no unexpected peaks were observed.

Initial tests have also not detected the presence of RNA in FLUVAX however additional, more sensitive tests are on-going. Preliminary results of testing of in-vitro cytokine stimulation of peripheral monocytes suggest that FLUVAX may elicit greater TNF alpha expression than PANVAX and other TIVs, however no differences have been observed in the extent of expression of interferon alpha, and no differences were seen in the expression of either cytokine between 2009 and 2010 samples of each vaccine. These studies are ongoing and further analyses are required before definitive conclusions may be drawn. The UK National Institute for Biological Standards and Control (NIBSC) is assisting with monocyte activation tests.

Additional pyrogenicity testing is currently being undertaken by the US Centers for Disease Control and Prevention (CDC), together with mass spectrophotometry and related assays to further investigate differential protein profiles and provide relative measurements of the major proteins.

### **TGA Assessment**

With respect to FLUVAX Vaccine 2010 (AUST R 91583) and FLUVAX JUNIOR Vaccine 2010 (AUST R 14917) the TGA has concluded that, while epidemiological analyses to date

demonstrate an excess of fever and febrile convulsions in children 6 months to 5 years, the overall risk benefit balance of both products remains positive.

Nevertheless in view of the signal reflected in these epidemiological analyses, amendments to the Product Information documents for both products have been made:

- under Precautions, notification of an increase in reports of fever and febrile convulsions in young children during the 2010 Southern Hemisphere influenza season, and that the individual risk benefit balance for the use of FLUVAX in children aged less than 5 years should be carefully considered.
- under Post Marketing Adverse Events, references to rates of fever and febrile convulsions reported in 2010.

In addition, in light of the current suspension of seasonal influenza vaccination programs in children under 5, CSL has withdrawn remaining stocks of FLUVAX JUNIOR to provide further samples for ongoing testing. FLUVAX will remain available for use in young children should individual circumstances warrant.

While the pattern of AEFIs most clearly points to an increased risk with FLUVAX, there is currently no evidence of a similar safety signal from the other seasonal influenza vaccines INFLUVAC and VAXIGRIP, although numbers of administered doses of these vaccines at this time are too small to be certain that the matter is confined to the FLUVAX vaccine.

To date, despite extensive analyses the biological basis for the excess cases of fever and febrile convulsions remains unclear. For this reason, at the present time it is considered appropriate to reserve the use of TIV to those children under 5 in whom the risks of a possible febrile reaction or other AEFI are considered to be outweighed by the benefits of vaccination.