Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine

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ABSTRACT
Background: The 2010 influenza vaccination program for children aged 6 months to 4 years in Western Australia (WA) was suspended following reports of severe febrile reactions, including febrile convulsions, following vaccination with trivalent inactivated influenza vaccine (TIV).
Methods: To investigate the association between severe febrile reactions and TIV, three studies were conducted: (i) rates of febrile convulsions within 72 h of receiving TIV in 2010 were estimated by vaccine formulation and batch; (ii) numbers of children presenting to hospital emergency departments with febrile convulsions from 2008 to 2010 were compared; and (iii) a retrospective cohort study of 360 children was conducted to compare the reactogenicity of available TIV formulations.
Findings: In 2010, an estimated maximum of 18 816 doses of TIV were administered and 63 febrile convulsions were recorded, giving an estimated rate of 3.3 (95% CI 2.6 to 4.2) per 1000 doses of TIV administered. The odds of a TIV-associated febrile convulsion was highly elevated in 2010 (p<0.001) and was associated with the vaccine formulations of one manufacturer—Fluvax and Fluvax Junior (CSL Biotherapies). The risk of both febrile convulsions (p<0.0001) and other febrile reactions (p<0.001) was significantly greater for Fluvax formulations compared to the major alternate brand. The risk of febrile events was not associated with prior receipt of TIV or monovalent 2009 H1N1 pandemic vaccine. The biological cause of the febrile reactions is currently unknown.
Interpretation: One brand of influenza vaccine was responsible for the increase in febrile reactions, including febrile convulsions. Until the biological reason for this is determined and remediation undertaken, childhood influenza vaccination programs should not include Fluvax-type formulations and enhanced surveillance for febrile reactions in children receiving TIV should be undertaken.

INTRODUCTION
Infants and young children are known to have an increased risk of severe disease from influenza A virus infection.1 2 Influenza-related hospitalisation rates for children less than 2 years of age are considerably higher than for older children and are comparable to rates in other groups considered to be at higher risk for complications from influenza, including the elderly.3 Some countries recommend universal annual vaccination for infants and
children, including the USA, where vaccination is recommended for children aged 6 months and above.3 The Department of Health in the state of Western Australia (WA) has been offering trivalent inactivated influenza vaccine (TIV) to children aged 6 months to 4 years since 2008, following the deaths of three preschool-aged children from influenza the previous year. Additionally, a new program providing TIV to children with underlying medical conditions was implemented throughout Australia in 2010.4

The medical literature supports the safety of TIV in young children.5–8 Fever has been found to be a relatively common adverse event in the few prospective clinical trials that aim to determine the safety of TIV in children, with rates ranging from 10% to 40%.9–11 Few studies large enough to accurately quantify the rate of uncommon potential adverse events, including febrile convulsions, following TIV administration have been published. A recent analysis from the US Vaccine Adverse Event Reporting System, which relies on passive reports, found that in children less than 2 years of age, seizures of any type, although rare, were the most commonly reported serious adverse events.6 A large population-based study from the US Vaccine Safety Datalink program found only one documented febrile convolution (which occurred on day 3) in the 3 days following administration of 69,359 doses of TIV to children under 2 years of age (1.4 per 100,000).8

In 2010, distribution of TIV to immunisation providers in WA (general medical practitioners and government health services) began on 8 March and the childhood influenza vaccination program was publicly launched on 19 March. During the week beginning 12 April 2010, emergency department (ED) clinicians at a specialist paediatric referral hospital noted an apparent increase in children presenting with fever, vomiting and occasionally febrile convulsions, usually within 12 h of vaccination with TIV. Further reports led to a temporary suspension of the WA program for children under 5 years of age on 22 April 2010 to allow time to investigate whether this signal represented a true increase in adverse events, and whether any increase was common to all TIV formulations or specific to a particular formulation or batch(es). The following day, the federal government suspended the use of 2010 seasonal influenza vaccine for all children aged 5 years and under across Australia.

In Australia, there is a dual system for reporting adverse events following immunisation (AEFI). In seven of eight Australian states and territories, AEFI are notified conditions, meaning there is a legal requirement to report them to state/territory health authorities.12 Vaccination providers and members of the public can also report AEFI directly to an established national drug adverse event reporting system.13 Reports received by either route are shared between national and state bodies. Because data from such passive surveillance systems for adverse events are limited due to lack of a denominator, under-reporting and biased reporting, we undertook a number of analytical studies to determine the association between severe febrile adverse events and administration of the 2010 TIV to children aged 6 months through 4 years in WA.

METHODS
Setting
WA has a total population of 2.3 million people, with 78% residing in the capital, Perth. An estimated 134,000 children aged 6 months through 4 years were eligible for free TIV in 2010.

Vaccines from three manufacturers were used in the paediatric influenza vaccination program in 2010: CSL Biotherapies (Parkville, Australia) supplied Fluvax (0.5 ml) and the identically formulated Fluvax Junior (0.25 ml), Solvay Pharmaceuticals (Pymble, Australia) supplied Influvac, and Sanofi Pasteur (Lyon, France) supplied Vaxigrip. Fluvax Junior was indicated for use in children aged 6 months to 3 years and the other formulations for use in those aged 6 months and over.

All contained the three influenza haemagglutinin antigens recommended by the WHO for the 2010 Southern hemisphere influenza season (A/California/7/2009 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus and B/Brisbane/60/2008-like virus).14 The recommended doses were 7.5 μg of each antigen for those aged 6–36 months (0.25 ml vaccine) and 15 μg of each antigen for 4-year-olds (0.5 ml vaccine). It is recommended that children aged less than 10 years receive two doses at least 1 month apart in the first year of vaccination, and one dose in subsequent years. As fewer than 100 doses of Vaxigrip were given to children prior to cessation of the program, this formulation was excluded from assessment.

Ethics approval was not required for this study as the data were gathered as part of a public health investigation.

Febrile convulsions following 2010 TIV vaccination
The period between the time TIV was made available to providers in 2010 and the suspension of the program was 46 days. We defined the investigation period as 49 days (the 46-day period of the TIV program plus 3 days to capture febrile convulsions occurring after the last TIV vaccination). Febrile convulsions occurring outside the
investigation period were assumed to be unrelated to 2010 TIV.

Febrile convulsion cases during the investigation period were identified through passive notifications to the national AEFI reporting system and from ED diagnostic codes using the WA Emergency Department Information System (EDIS). EDIS collects discharge diagnosis data in near real-time from EDs at nine Perth hospitals that have a combined catchment of approximately 1.76 million people (77% of the total population of WA). Children aged 6 months through 4 years who presented to an EDIS-enrolled hospital during the investigation period and were assigned an ICD-10 code of R56.0 (febrile convulsion)13 were investigated.

To identify a possible temporal relationship between EDIS-reported febrile convulsions and prior receipt of TIV, we cross-checked the reported febrile convulsion episodes with vaccination data recorded with the Australian Childhood Immunisation Register (ACIR). Verification was also sought from the child’s primary care givers and/or the child’s vaccine provider to determine if the child had received TIV in the 72 h prior to the febrile convulsion. The influenza vaccination histories of cases were obtained from ACIR and the child’s primary care giver or vaccine provider. The case details for all 2010 R56.0-coded febrile convulsions were identified through review of the case records and details for any additional febrile convulsion cases identified through passive reporting were collected from interviews with the primary care giver or vaccination provider using a standardised survey instrument. All records were reviewed by one author (CB) to ensure diagnostic accuracy. A febrile convulsion was defined as any generalised convulsive seizure (level 1, 2 or 3 according to the Brighton Collaboration case definitions16) that occurred in a febrile child (temperature on presentation to a health practitioner >37.5°C). A vaccine associated febrile convulsion was defined as any febrile convulsion that occurred within 72 h of either the first or subsequent dose of TIV for which an alternative cause of fever could not be identified either clinically or microbiologically.

A number of data sources were analysed to ascertain the contribution of childhood infective causes to the febrile convulsion cases over this time period: results of microbiological work-up of the febrile convulsion cases, presentations of gastroenteritis or influenza-like illness to participants in the WA General Practice Sentinel Surveillance Network and to EDIS-enrolled hospitals, and review of microbiological results from the only metropolitan paediatric hospital laboratory in Perth.

Rates of TIV-associated febrile adverse events in 2010

We obtained denominator data by surveying WA vaccine providers following the suspension of the program using a standardised form that requested information on numbers of children vaccinated by age group (6–24 months, 3–4 years) and vaccine brand/formulation and batch number. To account for possible under-ascertainment of the number of vaccine doses administered due to non-response by vaccine providers, the final totals were adjusted upwards by a factor of 1.4. This figure was determined to provide the upper limit of the number of doses that might really have been given. To estimate rates of both convulsive and ‘other’ (non-convulsive) febrile reactions per 1000 TIV vaccinations, cases of febrile convulsions were determined from passive reports and R56.0-coded presentations to EDIS-enrolled hospitals (as described above), and cases of ‘other’ febrile reactions were derived from passive reports by doctors, other immunisation providers and parents to the AEFI reporting system.

Comparing TIV-associated febrile convulsions in 2008–2010

To examine whether the number of febrile convulsions in children aged 6 months through 4 years had increased in 2010, we compared the R56.0-coded visits to the nine EDIS-enrolled hospitals for 2010 to those identified using the same data extraction process for corresponding 49-day periods following commencement of the paediatric TIV program in both 2008 (from 31 March) and 2009 (from 17 February). As for febrile convulsions reported in 2010, we cross-checked records of children with febrile convulsions identified in 2008 and 2009 with the ACIR and sought verification from the child’s primary care givers and/or the child’s vaccination provider.

Retrospective cohort study of paediatric TIV recipients

To assess the comparative reactogenicity of the three main TIV formulations, we conducted a retrospective cohort study to quantify the proportion of children experiencing a range of post-TIV vaccination symptoms. All children less than 5 years of age who had received the 2010 TIV at a large Perth public immunisation clinic were stratified by age and brand of vaccine administered. We then randomly selected 120 children from each of the three vaccine groups: Fluvax, Fluvax Junior and Influvac. The Fluvax and Influvac groups were stratified by age, with 60 children aged ≤2 years and 60 aged 3–4 years selected from each group. All children in the Fluvax Junior group were aged ≤2 years.

Primary care givers were interviewed by telephone using a standardised questionnaire, which sought information about symptoms in the 72 h following the 2010 TIV vaccination, body temperature measurement or self-reported fever, healthcare attendance, and prior history of vaccination with seasonal TIV or monovalent pandemic influenza vaccine. If the child received two doses of TIV, information was recorded about the first vaccination experience. Interviewers were blinded to the brand/formulation of vaccine the child had received.

Statistical analysis

Simple descriptive statistics were generated using Microsoft Excel or EpiInfo v 3.5.1 (CDC, Atlanta, Georgia, USA). For comparisons of adverse events by vaccine formulations, rates per 1000 vaccine doses and 95% CIs were determined. Relative risks (adjusted for
age for the under-5 year category) and Mantel–Haenszel $\chi^2$ statistics were calculated for the combined Fluvax vaccines compared to Influvac. Fisher’s exact test was used if expected cell frequencies were $<5$.

For analyses of adverse event data from the retrospective cohort study of TIV recipients from a large immunisation clinic, we computed odds ratios comparing events associated with combined Fluvax vaccines to Influvac, and controlled for age (continuous) using unconditional logistic regression. A multivariate logistic regression model was also computed to determine if vaccine brand was still associated with ‘fever’ or a ‘significant febrile adverse event’ (defined as fever $\geq 39^\circ C$ recorded at home or during healthcare attendance and/or rigors and/or a febrile convulsion) while simultaneously controlling for three potential a priori confounders: age, prior vaccination with monovalent pandemic vaccine and prior vaccination with TIV, as dichotomous variables.

**RESULTS**

**Characteristics of febrile convulsion cases occurring in 2010**

Based upon the uptake of influenza vaccine by children in 2008 and 2009, it is estimated that 85% of children vaccinated with the 2010 TIV resided in the catchment area of the EDIS-enrolled hospitals. During the investigation period, a total of 99 children aged 6 months–4 years presented to Perth EDIS-enrolled hospitals and were coded as R56.0 febrile convulsions. Of these, 38 (37.4%) occurred within 72 h of receipt of TIV. An additional 25 TIV-associated febrile convulsion cases that met diagnostic criteria were reported by ED clinicians, primary care givers or vaccine providers to the national AEFI reporting system, bringing the total number of TIV-associated febrile convulsions in 2010 to 63. The TIV brand/formulation could be determined for 62 of these 63 cases.

Of the 63 cases of febrile convulsions found to be associated with TIV, vaccination data for 41 (65%) were determined from cross-checking ACIR records (with corroborations by their primary care giver and/or immunisation provider), and the remaining 22 cases (35%) had their influenza vaccination status ascertained through interviews with their primary care giver and/or immunisation provider alone. The number of doses of vaccine cases had received in 2010 (either one or two) were known for 57 of 63 (90%), and all of these experienced their febrile convulsion after their first dose.

The demographic and clinical features of the 2010 cases derived from case record review and/or interviews with their primary care givers or vaccine providers are shown in table 1. The median time from receipt of TIV to onset of symptoms in the febrile convulsion cases was

<table>
<thead>
<tr>
<th>Febrile convulsion presentations (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and past history</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Median age (years)</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>History of febrile convulsions</td>
</tr>
<tr>
<td>History of seizures (other than febrile convulsions)</td>
</tr>
<tr>
<td>History of AEFI</td>
</tr>
<tr>
<td>Chronic medical condition*</td>
</tr>
<tr>
<td>Symptoms on presentation</td>
</tr>
<tr>
<td>Fever (self-report)</td>
</tr>
<tr>
<td>Recorded temperature $\geq 38^\circ C$</td>
</tr>
<tr>
<td>Rigors</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Local swelling</td>
</tr>
<tr>
<td>Admitted to hospital</td>
</tr>
<tr>
<td>Admitted to intensive care unit</td>
</tr>
<tr>
<td>Sequelae</td>
</tr>
<tr>
<td>Time from vaccination to symptom onset</td>
</tr>
<tr>
<td>Median time (h)</td>
</tr>
<tr>
<td>Mean time (h)</td>
</tr>
<tr>
<td>Onset within 12 h</td>
</tr>
</tbody>
</table>

*Chronic medical conditions included diabetes, chronic heart, respiratory, renal, neurological and blood disease, metabolic disease and impaired immunity.
†Mean length of stay 3 days; range 1–50 days.
‡Hypoxic ischaemic encephalopathy.
§Data available for 57 cases.
AEFI, adverse event following immunisation.
7 h, with 93% having onset within 12 h. Vomiting was a conspicuous symptom, reported by 57.1% of cases, but local reactions were infrequent, with only 4.8% of cases reporting swelling at the injection site.

Figure 1 shows the temporal distribution of febrile convulsions from 1 January to 2 May 2010, and the timing of the vaccination program. Presentations of febrile convulsions increased following introduction of the TIV program and decreased to baseline soon after its suspension.

Presentations of gastroenteritis or influenza-like illness to participants in the WA General Practice Sentinel Surveillance Network and to EDIS-enrolled hospitals over the study period indicated low rates of gastrointestinal and respiratory viral illness in the community. Paediatric hospital laboratory data did not show an appreciable increase in childhood respiratory and gastrointestinal pathogens. Only a minority of children presenting to EDs with febrile convulsions in 2010 had a microbiological investigation conducted, as an infective cause of the fever was not often suspected. Of those who did have specimens taken, no pathogens were detected that could explain their illness.

Rates of adverse events by vaccine
From the vaccine provider survey, it was estimated that up to 18,816 TIV vaccinations had occurred in children aged 6 months–4 years in WA prior to the program’s suspension, giving a conservatively estimated rate of 3.3 (95% CI 2.6 to 4.2) febrile convulsions per 1000 doses.

The rate of febrile convulsions and other febrile reactions, by vaccine brand and formulation, is shown in table 2. There was a significantly increased risk of both febrile convulsions and ‘other’ febrile reactions associated with Fluvax, Fluvax Junior or both Fluvax preparations combined, compared to Influvac. Adjusted for age, children receiving a Fluvax formulation were 14.8 times (95% CI 8.3 to 26.7) more likely to have a reported other febrile reaction than children receiving Influvac (p<0.0001). Relative risk could not be calculated for febrile convulsions, as no such events were reported for the estimated 4720 doses of Influvac given in children under 5 years of age, compared to an estimated rate of 4.4 per 1000 doses (95% CI 3.4 to 5.6) of Fluvax products (p<0.0001 for age adjusted comparison).

The risk of other febrile reactions appeared to be consistent across batches of the adult Fluvax and Fluvax Junior products (data not shown). However, there was a significantly increased rate of febrile convulsions associated with Fluvax Junior (8.1 per 1000 doses (95% CI 5.6 to 11.8)) versus Fluvax (3.3 per 1000 doses (95% CI 2.4 to 4.6)): this was only partly explained by the fact that Fluvax Junior was used more frequently in children under 3 years of age, as the rate in children aged 3–4 years was also significantly elevated when compared to Fluvax. Although there was some variability in the risk of febrile convulsions across batches of Fluvax (but not for Fluvax Junior, as one batch dominated usage), this did not reach statistical significance (data not shown).
Febrile reactions to TIV in WA children

<table>
<thead>
<tr>
<th>Fluvar</th>
<th>Rate/1000 TIV doses (95% CI)</th>
<th>n/N</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvax</td>
<td>29/5754 49.0 (43.7 to 54.9)</td>
<td>138/2915 47.3 (40.2 to 55.5)</td>
<td>0/2124 0 (0 to 1.8)</td>
</tr>
<tr>
<td>Fluvax Junior</td>
<td>127/5015 25.3 (21.3 to 30.0)</td>
<td>11/413 26.6 (14.9 to 47.0)</td>
<td>2/2596 0.8 (0.2 to 2.9)</td>
</tr>
<tr>
<td>Combined Fluvax and Fluvax Junior</td>
<td>420/8669 48.4 (44.1 to 52.7)</td>
<td>138/5428 25.4 (21.3 to 30.0)</td>
<td>3/2596 0 (0 to 1.8)</td>
</tr>
<tr>
<td>All</td>
<td>558/14096 39.6 (36.5 to 42.9)</td>
<td>555/14096 39.6 (36.5 to 42.9)</td>
<td>11/4720 2.3 (1.3 to 4.1)</td>
</tr>
</tbody>
</table>
approximately 500 per 100 000 doses for children from other Australian states.17

Second, there was a marked increase in the number of TIV-attributable febrile convulsions reported from Perth metropolitan EDs in 2010 compared to similar periods in both 2008 and 2009, years for which the available data indicate 32% and 34% of the 6-month through 4-year-old cohort in the metropolitan area received at least one dose of TIV, respectively.18

Third, of the three brands of TIV used in the program, the elevated risk of febrile convulsions and other febrile reactions was found to be clearly associated with the Fluvax and Fluvax Junior formulations, but not with Influvac, for which no febrile convulsions were identified in WA against an estimate of over 4000 doses given. The excess of febrile reactions was not due to a particular batch of the Fluvax product, as several batches were implicated. The reason for the higher rate of febrile convulsions associated with Fluvax Junior compared to Fluvax is unclear, but it did not appear to be explained by the younger age of Fluvax Junior recipients. As the rates of non-convulsive febrile reactions were almost identical for the two Fluvax formulations, it seems unlikely that the apparent difference in the rate of febrile convulsions represents a real difference between the formulations related to some variation in concentration of whatever factor is responsible for the excess in serious adverse events. However, this possibility cannot be discounted.

Fourth, the febrile convulsions resulting from vaccination with the Fluvax vaccines are unlikely to represent a new, distinct clinical syndrome associated with the vaccine. Rather, the data indicate that the febrile convulsions were occurring against a background of increased rates of febrile reactions following vaccination. This conclusion is supported by the results of the vaccine provider survey and the retrospective cohort study, which both showed a clearly higher rate of febrile reactions in recipients of Fluvax and Fluvax Junior compared to those receiving Influvac. There was no evidence that the elevated rate of febrile convulsions in 2010 resulted from an increased incidence of childhood infections.

The major limitation of this study results from the absence of reliable prospective data from an established, timely surveillance system designed to monitor adverse events resulting from vaccination. Accordingly, several data sources were used to gather numerator and denominator data, some already established and some created ad hoc and requiring retrospective data collection. However, the strength of the statistical associations found, together with the consistency of findings using different data sources and the tight temporal association of the febrile convulsions with TIV (95% of cases having symptom onset within 12 h of vaccination), suggest the conclusions are robust. Reporting bias relating to the number of febrile convulsion cases being reported in 2010, or to Fluvax-related events in particular, cannot explain this finding as there was no communication to the public or the clinicians prior to the recognition of the association and the program’s cessation.

This is the first report of an elevated rate of severe febrile reactions to TIV in children, and the biological mechanism has, to date, not been definitively identified despite an extensive laboratory investigation of Fluvax and Fluvax Junior undertaken by the Therapeutic Goods Administration, the Australian regulator of prescription medicines including vaccines. These studies are ongoing, but endotoxins or abnormal levels of whole virus particles have not been identified. Pyrogenicity studies in different animal models have shown conflicting results. The Therapeutic Goods Administration has hypothesised that high content and enzyme activity of neuraminidase in the H1N1 component of the 2010 TIV compared to previous years may be responsible for different cytokine responses and the increased pyrogenicity of the CSL vaccine.17 In the meantime, the Australian government recommended use of vaccines other than the CSL products in children under 5 years of age for the remainder of 201019 and in 201120, and the

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Not temporally related§ to TIV</th>
<th>Temporally related§ to TIV</th>
<th>Unknown¶</th>
<th>OR of temporally related§ febrile convulsions</th>
<th>p Value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>74</td>
<td>70</td>
<td>1</td>
<td>3</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>2009</td>
<td>68</td>
<td>65</td>
<td>0</td>
<td>3</td>
<td>0 (0–19)</td>
<td>0.34</td>
</tr>
<tr>
<td>2010</td>
<td>99</td>
<td>60</td>
<td>38</td>
<td>1</td>
<td>44 (6–894)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Unadjusted estimates of number of TIV doses given were 26 037 in 2008, 11 909 in 2009 (both derived from program data) and 11 243 in 2010 (derived from vaccine provider survey).

†ICD-10 code R56.0 ‘febrile convulsion’. No febrile convulsions were recorded for children who had received monovalent H1N1 pandemic influenza vaccine.

‡The 49-day period allows for febrile convulsion to develop 72 h after vaccination up to day 46.

§A temporal relationship is defined as febrile convulsion occurring within 72 h of receiving TIV.

¶‘Unknown’ if either not listed on the Australian Childhood Immunisation Register or uncontactable by telephone after four attempts, and immunisation provider not known. ‘Unknowns’ were excluded from statistical analysis.

TIV, trivalent inactivated influenza vaccine.
### Table 4

Number of children enrolled in the retrospective cohort study who were reported by primary care givers as having symptoms, or prior vaccination, and receiving trivalent inactivated influenza vaccine (TIV) in 2010, by brand and formulation.

<table>
<thead>
<tr>
<th>Percentage of children with symptom</th>
<th>CF versus Influvac</th>
<th>CF versus Influvac (controlling for age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate $\chi^2$</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Reported symptom</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever*</td>
<td>0.0001</td>
<td>5.1 (2.9 to 9.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.0001</td>
<td>3.5 (1.8 to 7.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.0001</td>
<td>6.0 (1.8 to 20.3)</td>
</tr>
<tr>
<td>Rigours</td>
<td>0.0006</td>
<td>16.0 (2.1 to 119.5)</td>
</tr>
<tr>
<td>Swelling</td>
<td>0.06</td>
<td>1.1 (0.5 to 2.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.052</td>
<td>5.3 (0.7 to 43.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>0.14</td>
<td>3.8 (0.5 to 31.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>0.18</td>
<td>4.3 (0.5 to 37.5)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Significant SFAE</td>
<td>0.0001</td>
<td>7.0 (2.7 to 18.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentage of children answering ‘Yes’ (n)</th>
<th>CF versus Influvac</th>
<th>CF versus Influvac (controlling for age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate $\chi^2$</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Prior influenza vaccination history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had monovalent 2009 H1N1 pandemic influenza vaccine? (n=104)</td>
<td>0.37</td>
<td>0.9 (0.4 to 1.6)</td>
</tr>
<tr>
<td>Had seasonal influenza vaccine before 2010? (n=107)</td>
<td>0.19</td>
<td>1.5 (0.9 to 2.6)</td>
</tr>
</tbody>
</table>

SFAE, significant febrile adverse event (defined as fever $\geq 39\,^\circ C$ and/or rigours and/or a febrile convulsion).

*Self-reported fever, whether measured or not.
US Advisory Committee on Immunization Practices has recommended that the CSL Biotherapies TIV marketed in the USA (Afluria) not be used in children aged from 6 months to 8 years.21

The data from WA indicate that the elevated risk of febrile adverse events was associated with TIV from a single manufacturer. Experience in New Zealand, the only other Southern hemisphere country to use Fluvarix and Fluvarix Junior and vaccine from another manufacturer in 2010, corroborates this finding.19 Furthermore, and reassuringly, the low rate of febrile adverse events and symptoms associated with Influvac in our studies, and Vaxigrip in New Zealand,19 indicates that TIV containing pandemic (H1N1) 2009 antigen are not inherently highly pyrogenic. Therefore, it seems reasonable that countries implement paediatric vaccination programs as usual using vaccine brands other than those of CSL Biotherapies. However, until a cause can be determined for the Australian findings, and further national and international data are available, it is recommended that enhanced surveillance be undertaken for febrile reactions and other adverse events in all children under 5 years of age receiving TIV.

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Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine

P K Armstrong, G K Dowse, P V Effler, D Carcione, C C Blyth, P C Richmond, G C Geelhoed, F Mascaro, M Scully and T S Weeramanthri

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