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

Introduction

Since Edward Jenner's creation of the world's first vaccine against smallpox more than 200 years ago, human beings have been benefiting from vaccination. Infectious diseases such as polio, rubella, measles, diphtheria, smallpox and pertussis, leading causes of childhood mortality at the turn of the 20th century, have been contained through the development and widespread administration of vaccines.

Beyond childhood vaccinations, the development of vaccines against communicable diseases such as hepatitis A and B, meningococcal, human papillomavirus and influenza has resulted in improvements in quality of life and longevity to greater numbers in the community. The benefits of disease containment reach beyond the individual to the community through the reduction of the spread of disease, with ensuing economic and social benefits.

Yet despite advances in vaccines and immunisation, seasonal influenza remains a considerable burden, both clinically and economically, through ill health and premature death. It has been estimated that influenza epidemic kills up to 500,000 people worldwide each year. In 2009 the total number of laboratory confirmed influenza cases in Australia was 44,221.[1] Between 1997 and 2005 the average number of deaths in children aged 0-4 years due to influenza and pneumonia was 41. For all age groups, the average annual number of deaths due to influenza and pneumonia during this period was 2686.[2] In addition, in the first quarter of 2010 the Australian Sentinel Practice Research Network reported an average of 89 influenza-like-illness notifications per week, or 1–9 cases per 1000 consultations a week for influenza-like-illness.[3] In a recent Australian study of children hospitalised with influenza, more than 12% developed pneumonia, and over 7% required admission to intensive care. In Australian children aged less than five years, deaths from influenza have been reported at a rate of 0.2 per 100,000 children.[4]

1 Department of Health and Ageing. Communicable Diseases Intelligence Quarterly Report. December 2009, Vol 33 Number 4

2 Australian Institute of Health and Welfare (AIHW) 2007. GRIM (General Record of Incidence of Mortality) Books. AIHW: Canberra.

3 Department of Health and Ageing. Communicable Diseases Intelligence Quarterly Report. June 2010, Vol 34 Number 2.

4 Brotherton J, Wang H, Schaffer A, Quinn H, Menzies R, Hull B, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2003 to 2005. Commun Dis Intell 2007; 31:Suppl–152.

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National Immunisation Program

The **National Immunisation Program** (NIP) is a collaborative program between the Australian, and State and Territory governments to increase national immunisation rates. The program funds free vaccination for eligible Australians against vaccine-preventable diseases, administers the Australian Childhood Immunisation Register (ACIR), and communicates information to the general public and health professionals. The **Office of Health Protection** (OHP) within the Department of Health and Ageing (DoHA) is responsible for the development, implementation and evaluation of national immunisation policies and programs including Commonwealth funding of vaccines. The role of the Australian Government is to provide national leadership on the development and implementation of immunisation policy, fund the NIP vaccines, direct and support research into vaccine-preventable diseases and to make resources available for best practice in immunisation. Under the National Healthcare Agreement, the States and Territories are to maintain immunisation rates for vaccines in the national schedule. States and territories are responsible for managing the distribution of vaccines to public and private immunisation providers. States and territories also fund local education and communication activities, run immunisation programs through schools, and contribute to notification payments paid to providers for submitting data to the ACIR. The Australian Government provides funding for Medicare Australia for the ACIR and the General Practice Immunisation Incentives Scheme (GPII) and subsidises individual consultations which involve immunisation through the Medicare Benefits Schedule. The Victorian Cytology Service is also funded by the Australian Government for the administration of the National HPV Vaccination Program Register.

The **National Immunisation Committee** (NIC) is the peak group responsible for overseeing the development, implementation and delivery of the Immunise Australia Program. The NIC reports to the Australian Health Protection Committee through the Communicable Diseases Network Australia (CDNA).

The **Australian Technical Advisory Group on Immunisation** (ATAGI) provides advice to the Minister for Health and Ageing on the Immunise Australia Program, the medical administration of vaccines available in Australia, including those on the NIP, and other related issues.

The **National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases** (NCIRS) was established by the Commonwealth Department of Health in August 1997. NCIRS has partnerships with DoHA, the NSW Department of Health, and the Children's Hospital at Westmead. The Centre's primary function is to perform research aimed at reducing the incidence of vaccine preventable diseases and improving vaccine uptake in children and adults. NCIRS provides independent expert advice on all aspects of vaccine-preventable diseases as well as social and other issues related to immunisation.

The **Immunise Australia Program** implements the National Immunisation Program Schedule which currently includes vaccines against 16 diseases. The National Immunisation Program (NIP) has significantly reduced the incidence of Vaccine-Preventable Diseases (VPD) in Australia. VPDs prevented by vaccines in the NIP are notifiable through the National Notifiable Diseases Surveillance System (NNDSS).

VPDs will always remain a threat in Australia as natural disease cycles can result in regular resurgences, such as the recent pertussis outbreak; disease importations have the potential to start outbreaks in Australia, exemplified by the recent measles outbreaks; and many VPDs can cause a range of disease severity amongst the population, mild in most but severe in some, such as influenza. High vaccination coverage rates contribute to herd immunity – suppressing circulation of VPDs and protecting those at risk in our population, including those too young to be vaccinated.

Seasonal influenza vaccines are available through the NIP, to people who meet eligibility criteria, and the private market. Eligibility for free seasonal influenza vaccine is based on a person's health status, not their income / concessional status. During the 2010 influenza season, the following groups of high risk individuals are eligible to receive the free seasonal influenza vaccine:

- individuals 65 years of age and older;
- all Aboriginal and Torres Strait Islander people aged 15 years and older;
- individuals aged 6 months and older with conditions predisposing to severe influenza; and
- pregnant women.

The impact of an influenza season and its severity are difficult to measure due to the nature of the illness, and comparisons between seasons need to be interpreted with caution due to changes in testing practices and surveillance measures. Notifications since 2007 have been affected by heightened media attention due to several paediatric deaths in that year and differing diagnostic testing patterns compared to previous years. Notifications from 2008 and 2010 have been at similar levels to 2007, and substantially lower than during the pandemic season in 2009.

Regulation of Vaccines

In Australia, vaccines and other prescription medicines are regulated by the Therapeutic Goods Administration (TGA) in accordance with the provisions of the *Therapeutic Goods Act 1989* (the Act). It is a requirement of the Act that therapeutic products imported into, supplied in, or exported from Australia be included in the Australian Register of Therapeutic Goods (ARTG).

In order for a vaccine to be included in the ARTG, a sponsoring company is required to make an application which consists of data to support the quality, safety and efficacy of the product for its intended use, and which is then subject to rigorous evaluation by the TGA. TGA's data requirements are largely based on those applying in the European Union, supplemented by Australia-specific requirements where necessary. Extensive guidance is available to assist with the interpretation of the requirements, including documents relating specifically to the registration of vaccines.

The quality control aspects of an application cover the batch production processes to ensure that the medicine is produced to a consistent standard as defined by the product specification. This quality specification places controls on the purity and potency of the medicine as well as on other aspects necessary to ensure the efficacy of the product.

Recognising the important role of vaccines for public health, the pre-market quality review of vaccine submissions is supplemented by a batch release program operated by TGA in accordance with recommendations of the World Health Organization. Through this program, production and quality control data for each batch of a vaccine are assessed prior to it being supplied in Australia. The TGA also operates a batch testing program for the most widely used vaccines, including influenza vaccines, in which aspects such as the potency and sterility of the vaccine are checked.

The pre-clinical data supplied to TGA for assessment include studies designed to assess the toxicological profile of the medicine. These studies commonly include data on the safety of the product when tested in animals.

The third component of an application to include a vaccine, or other prescription medicine, in the ARTG is the submission of clinical data. This part of a submission consists of clinical trial data in humans. These data are used to support both the safety and efficacy of the product for the indications proposed by the product sponsor. The clinical data requirements vary with different products and different types of submission. In general, well-designed trials conducted in a sufficient number of subjects representing the target population and of a sufficient duration are

usually required in order to demonstrate the efficacy and safety of the product for the proposed indication. The clinical evaluators assess the balance of benefits and risks based on the submitted clinical trial data and then recommend approval or rejection of the application based on that overall assessment. Each medicine and vaccine carries the risk of adverse effects in some people; the key issue in the regulatory decision is to determine that the overall balance of risks and benefits is positive in the population in whom the product is intended to be used.

As part of the evaluation process, the TGA delegate will refer an application or a new chemical entity (NCE) or major extension of indication to the Advisory Committee on Prescription Medicines (ACPM). The ACPM is a statutory committee whose members are appointed by the Minister. The Committee meets every two months and considers applications referred to it by TGA delegates, providing advice on a range of issues, but with particular emphasis on NCEs and extension of indications for already marketed prescription products.

Since April 2009, the TGA has required sponsors to submit a formal risk management plan (RMP) with each application for registration or extension of indication of a new medicine or vaccine. RMPs are intended to set out those activities and interventions that will be undertaken to identify, characterise and mitigate known or anticipated risks relating to a new medicine or vaccine, recognising that premarketing trials cannot prospectively identify all safety issues.

The decision-maker with respect to an application for marketing approval is a delegate of the Secretary of the Department of Health and Ageing, within the TGA. The delegate takes into account (but is not bound by) the views of the ACPM before making a decision to approve or reject a product. Approvals may be subject to conditions such as restrictions on the use of a product to certain patient groups, or compliance with an agreed RMP. The Product Information and the Consumer Medicines Information are made available on the TGA website to assist health professionals and consumers to better understand the benefits and risks of medicines.

Premarket assessment and authorisation of seasonal influenza vaccine

Seasonal influenza vaccines present particular challenges for registration processes because of the short time between the selection of the seasonal influenza virus strains and the beginning of the next influenza season. Australia proceeds with its annual influenza vaccination program without requiring a clinical trial of the vaccine to ensure timely vaccine availability and based on many years of safe effective use of the seasonal vaccine in several million people. Where there are no changes to the manufacturing process other than the virus strain, the application can be processed as a strain change rather than as an application for new product approval. This pragmatic approach is taken because the manufacturing process for the vaccine varies little from year to year, and there is lengthy experience with influenza vaccination.

In Europe, very small scale studies are conducted with the seasonal trivalent influenza vaccine to confirm immunogenicity (that the vaccine produces an immune response) and gross safety in 50 patients aged between 18 and 60 years, and 50 patients aged 60 years and over. While the results of these studies are available to the TGA, the small number of patients involved means they cannot identify common or rare adverse effects such as the febrile convulsions in young children seen in 2010. Post-market safety monitoring is therefore particularly important for identifying new signals for seasonal vaccines.

TGA's post-market monitoring of vaccines

As noted above, all medicines and vaccines confer a risk of adverse effects in some people. It is therefore extremely important to monitor the safety of vaccines in use in the community. The TGA is responsible for administering the post-market vaccine safety surveillance system as part of its overall function of monitoring the safety of medicines in Australia. Effective systems for the identification, reporting, and evaluation of adverse events following immunisation (AEFIs) are

essential to ensuring public confidence in major vaccination programs. National monitoring of the safety of vaccines by the TGA is undertaken in accordance with protocols that include arrangements for the prompt and regular sharing of information between the TGA and state and territory health authorities. Effective monitoring is thus reliant on the cooperation of the states and territories.

The current mechanisms for reporting adverse events following immunisation have been endorsed on several occasions by states and territories, both within the National Immunisation Committee and through the Australian Technical Advisory Group on Immunisation (ATAGI), as recently as 2007. Not only is the TGA best placed to manage the national reporting of AEFIs, the TGA can meet its legislated responsibilities for ensuring the quality, safety and efficacy of vaccines it has registered only if it has confidence in coordinated and cooperative national monitoring and reporting.

The primary function of the AEFI monitoring system is to detect early warning signals and generate hypotheses about possible new vaccine adverse events or changes in frequency of known ones.

Voluntary reporting of AEFIs

The core of the post-market monitoring system is a surveillance framework that relies in large part on voluntarily reporting of AEFIs by immunisation providers and consumers, with mandatory reporting by sponsors of all adverse events of which they become aware.

AEFI reports received from sponsors, vaccination providers and consumers received by the TGA will not necessarily be complete. The reports are promptly triaged as serious or non-serious based on internationally-accepted criteria, and then coded using standard terminology in accordance with the Medical Dictionary for Regulatory Activities (MedDRA), a document endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Reports received by the TGA are entered into the database within 48 hours of receipt - in most cases within 24 hours. Individual reports of serious AEFIs are reviewed by a medical officer, and medical officers at the TGA also undertake a weekly review of adverse event reports related to vaccines to assist in identifying clusters of reports or unusual reports.

TGA staff may request advice about AEFIs from the TGA's Advisory Committee on the Safety of Medicines (ACSOM), and as potential safety signals are identified, the TGA may also convene an ad-hoc expert advisory committee to augment its in-house and statutory committee expertise. This is an effective way of rapidly undertaking focused assessment of emerging safety signals.

Communication with states and territories

Although the TGA is responsible for administering the national vaccine safety monitoring system, the system involves a coordinated approach from the TGA and the states and territories. AEFIs are notifiable conditions in the ACT, NSW, NT, QLD, SA, VIC and WA and must therefore be reported directly to the relevant health authority. These state and territory health authorities then forward AEFI notifications to the TGA. In Tasmania, immunisation providers report directly to the TGA. The TGA triages and codes reports from state and territory health authorities in the same way as reports received from sponsors, healthcare providers and consumers.

All AEFI reports received by the TGA are forwarded to the relevant health department on a monthly basis. This arrangement ensures that each health department has access to all reports of AEFIs occurring in that jurisdiction irrespective of whether they were reported via the health department or directly to the TGA. In this way, each jurisdiction is at liberty to carry out any

analysis it requires for its own purposes using the same dataset that is available to the TGA for that jurisdiction.

Several states in Australia have relatively recently implemented changes to their passive surveillance systems in order to capture a larger proportion of AEFIs, and respond more robustly to AEFI reports within their state. For example, the Victorian system SAEFVIC actively encourages parental reporting and provides flexible and multiple modality reporting. Since 1997, the South Australian government has also implemented an enhanced vaccine surveillance system and a strategy to actively promote and encourage AEFI notification to immunisation providers and members of the public. The National Immunisation Committee members have highlighted that measures such as better access to information for healthcare providers and the public about vaccine safety data and better risk/benefit communication strategies have led to improved satisfaction and improved reporting rates in their states.

AEFI reports received by the TGA are routinely passed in de-identified form to the National Centre for Immunisation Research & Surveillance (NCIRS) for various analyses, including the preparation of regular national AEFI surveillance reports, national immunisation program evaluations, reports to ATAGI, and ad-hoc analyses. Annual surveillance reports have been prepared by NCIRS in collaboration with the TGA and published in *Communicable Diseases Intelligence* since 2003.

Adverse events following 2010 seasonal influenza vaccination in young children

The investigation of a series of adverse events associated with the use of the 2010 seasonal influenza vaccine provides an example of the way in which the Australian vaccine program and its attendant monitoring framework operate effectively to respond to emerging safety issues, even when a vaccine is being utilised outside the nationally recommended guidelines.

Since 2008, Western Australia (WA) has funded a seasonal influenza vaccination program for all WA children aged 6 months to less than 5 years. WA Health suspended the 2010 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.

On 23 April the Chief Medical Officer, Professor Bishop, suspended the use of seasonal influenza vaccine in children 5 years and under pending an investigation of the safety signal. At that time a joint working party of ATAGI and the TGA was established to consider the reports of febrile convulsion in children and to provide advice around the possible resumption of the program. The working party returned its findings in July 2010, with the result that the Chief Medical Officer recommended Fluvax Junior not be used in children under five years of age, and that the other seasonal influenza vaccines available in Australia (Vaxigrip and Influvac) be used instead.

TGA Investigation

To investigate the cause of this safety signal, the TGA has undertaken an extensive investigation including:

- working closely with ATAGI and NCIRS in undertaking epidemiological investigations;
- conducting a detailed case review of each report of febrile convulsion;
- reviewing paediatric clinical trial data for the monovalent pandemic H1N1 (PANVAX) vaccine;
- reviewing and analysing 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 trivalent influenza vaccine (TIV);
- auditing vaccine manufacturing facilities;

- undertaking 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.

A timeline of the investigation is at **Attachment A**. An interim report of this investigation was published on the TGA website on 2 July 2010 <http://www.tga.gov.au/alerts/medicines/fluvaccine-report100702.htm>. Public advisories issued by the TGA and the Department of Health and Ageing are listed at **Attachment B**.

The investigation focused on addressing the following key questions:

- Is there a real excess of fever/febrile convulsions attributable to 2010 Southern Hemisphere TIV?
- Is the apparent signal in WA also apparent in other states? If not, are there factors specific to the conduct of the immunisation program in WA that would account for different rates of Adverse Events Following Immunisation (AEFIs) in WA than in other states?
- Is the situation in 2010 different to previous years?
- 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?
- Are there any clinical or other contributing factors that could contribute to an apparent excess of fever/febrile convulsions?
- Are there any vaccine quality or compositional issues that could account for the observed pattern of febrile reactions?

Summary of Adverse Events Following Immunisation (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 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.

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
TOTAL	1729	1244	1152	123

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
TOTAL	1636	1217	1130	122

Each of the febrile convulsion case reports underwent 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 concluded that there were 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 one 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 one was considered causally unrelated.

Detailed accounts of the process and outcomes of the case ascertainment and review undertaken by the TGA are at **Attachments C and D.**

Epidemiological Analyses

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

The data indicate that CSL's 2010 trivalent influenza vaccine (TIV) products FLUVAX and FLUVAX JUNIOR were 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 was 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 were 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 7 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. Subsequent analysis of adverse events associated with PANVAX has shown the rate of febrile convulsions associated with this vaccine in Australia at between 0.08/1,000 and 0.17/1,000.

The clinical pattern of vaccine-associated and non-vaccine-associated febrile convulsions is similar, and in keeping with historical experience of febrile convulsions.

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:

- A vaccine-specific, uncontrolled cohort study from WA using denominator data directly obtained by surveying vaccinating GPs showed that in 2010:
    - 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.
    - 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,
    - 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.
- 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.
- 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).
- 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.

- 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, 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.

No available clinical or epidemiologic factors offer a plausible explanation for the 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.

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.

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, the 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.

TGA Inspection of CSL Manufacturing Facilities

All manufacturing facilities of therapeutic goods are assessed for compliance with international standards of Good Manufacturing Practice (GMP). GMP audits are undertaken to ensure manufacturers have suitable facilities and equipment, quality systems and procedures, and trained personnel to consistently manufacture therapeutic goods to approved specifications of quality, safety and efficacy. The TGA audits CSL's vaccine manufacturing facilities annually.

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 identified that CSL had made three changes to its manufacturing process since the 2009 seasonal influenza campaign to increase the virus yield in order 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 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 (CBER) 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.

As the US audit findings related only to multidose vaccine vials supplied in the United States, the TGA and FDA were able to jointly establish that the matters raised in the April 2010 FDA audit did not relate to the single dose influenza vaccine associated with febrile reactions in Australia, and thus were not directly relevant to the investigation of the cause of adverse reactions in Australia. The FDA audit found no evidence that the drugs manufactured at the Parkville site failed to meet their quality specifications and did not identify any safety issues associated with products currently available. The FDA has subsequently accepted CSL 's response in addressing the identified manufacturing deficiencies relating to the US supplied products.

The TGA undertook a further, more detailed annual audit of CSL's facilities on 18 and 21–23 June 2010. The audit team included microbiologists, chemists, biotechnology and vaccine specialists and a laboratory specialist involved in the TGA's vaccine testing program. The audit covered the full manufacture of influenza vaccines from seed lot to filling of vials and syringes and reviewed CSL's investigations and corrective actions arising from the US FDA inspection. The audit included detailed visual inspection, examination of batch records, review of manufacturing procedures, and a thorough inspection of test records. Equipment qualification, calibration and facility maintenance was reviewed, and process validations and other scientific studies were examined. The TGA conducted a detailed review of CSL's investigations into deviations, out-of-specification products and customer complaints, including its investigation of discolouration reported in multi-dose vaccine vials.

A number of inconsistencies with Good Manufacturing Practices were observed at the CSL audits. This is not uncommon during larger, longer and more complex inspections. The observations largely related to inadequate investigations and the physical inspection process for filled syringes and vials. The TGA completed a risk assessment at the conclusion of its most recent audit and was satisfied that the observations did not present an increased risk to the quality, safety or efficacy of CSL's vaccine products. CSL has provided the TGA with details of its corrective actions and the TGA is monitoring these actions, with an on-site follow-up audit planned for November 2010.

Based on findings from the two TGA audits and information from the US FDA audit, no manufacturing deficiency has been identified that is causally linked to the occurrence of a higher than expected rate of febrile reactions to influenza vaccination.

TGA Laboratory Testing of 2010 Seasonal TIV

The TGA has undertaken extensive testing of both retention and field samples of influenza vaccines and this has been informed and guided by a special panel of experts chaired by Nobel laureate Professor Peter Doherty. The TGA is also working collaboratively with other regulatory agencies and laboratories in Australia and around the world, including Melbourne University and Monash Institute of Medical Research in Australia, the US Centers for Disease Control and Prevention (CDC) and the UK National Institute for Biological Standards and Control (NIBSC).

Overview

Generally, the virus in influenza vaccines marketed in Australia is inactivated, broken up and filtered so that the vaccine contains non-viable components of the virus and is predominantly 'split' i.e. without any significant numbers of whole virus particles. Pharmacopoeial monographs document the specifications and requirements the vaccine must meet in order to be considered safe, effective and of suitable quality.

Testing by the TGA found no abnormalities in pharmacopoeial parameters, such as the presence of endotoxins (bacterial chemicals that can cause fever) and potency in either retention or field samples, and additional testing has not shown any significant presence of whole virus particles, viable virus or contamination in the finished product.

The capacity of the vaccines to be pyrogenic (produce fever) is being extensively investigated. Preliminary analyses of results from pyrogenicity studies in ferrets suggest that there may be significant differences in changes to body temperature following inoculation with different vaccines. These studies are being conducted by the US CDC and are ongoing.

Cytokines are chemicals in the body that are signalling molecules used for communication between cells. Stimulation of the release of certain cytokines is associated with pyrogenicity; as a result the capacity of the different vaccines to induce particular cytokine responses is also being investigated. Results from studies at the laboratory bench suggest that there may be differences in the production of some cytokines between the different influenza vaccines. Further studies are now being conducted in animal models to try to characterise the nature and degree of cytokine responses to different influenza vaccines.

Viral proteins such as haemagglutinin and neuraminidase play a major role in the immunogenicity and possibly the pyrogenicity of the influenza vaccines. These proteins are found at varying levels in vaccine preparations. A vaccine manufactured by the same method by the same manufacturer will have a particular chromatographic protein profile that can be used as a signature for that particular vaccine product.

Protein analysis, using size exclusion HPLC techniques, has shown anticipated differences in characteristic protein profiles for the different vaccines. However, the profiles suggest that the content of one of the proteins in the 2010 seasonal influenza vaccine may be higher than in previous years.

Further studies, using mass spectrometry techniques, suggest that the neuraminidase content of the H1N1 component of this year's seasonal influenza vaccine is higher than in previous seasonal influenza vaccines. Reports from manufacturers also indicate that the enzyme activity of neuraminidase is higher in this year's vaccine compared to previous years. Studies into the content and activity of neuraminidase and its contributory role as a pyrogen are ongoing.

Current working hypothesis

The content of neuraminidase appears to be higher in the H1N1 strain used in the 2010 seasonal vaccine. Excess neuraminidase enzyme activity may be pyrogenic and may thus be contributing to the increase in febrile reactions in young children receiving the vaccine for the first time. While the different brands of seasonal influenza vaccines are utilising the same strains of virus, there are differences in manufacturing processes that may result in different levels of activity of the neuraminidase enzyme, which in turn may result in different cytokine responses and degrees of pyrogenicity.

Although the extensive analyses undertaken to date have generated this working hypothesis, further investigation is required to confirm that this is in fact the biological basis for the excess cases of fever and febrile convulsions seen during the 2010 influenza season.

A detailed report of the TGA's laboratory investigation is at **Attachment E.**

TGA regulatory actions to date

From its investigations to date the TGA has concluded that although there was an excess of fever and febrile convulsions in children 6 months to 5 years following vaccination with FLUVAX or FLUVAX Junior, the overall risk benefit balance of both products remains positive for most people for whom influenza vaccine is indicated, and both remain on the Australian Register of Therapeutic Goods.

However, despite extensive analyses the biological basis for the excess cases of fever and febrile convulsions remains unclear, and it is therefore important to effectively mitigate the risks by limiting exposure to those at greatest risk.

The TGA therefore considers it appropriate that the use of TIV be limited 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.

TGA's proposed actions regarding 2011 seasonal trivalent influenza vaccine

Consistent with the NIP recommendations, in 2011 the TGA will limit the approved use of FLUVAX in children under the age of 5 to those considered at high risk of complications of influenza, in whom the benefits of influenza vaccination are considered to outweigh the risks of an adverse reaction. In addition, the FLUVAX product will carry a boxed warning advising immunisation providers of the risks of febrile reactions in young children. The TGA is also currently in discussion with influenza vaccine providers regarding the development of an active surveillance program for influenza vaccination in children 9 and under.

The TGA will be working with consumers, healthcare providers and state and territory health authorities to raise the level of awareness of the existing mechanisms of reporting adverse events to the TGA.

Conclusion

It is an unfortunate fact that all medicines have the potential to cause side effects. In the case of the 2010 seasonal influenza vaccine an increase in the expected rate of febrile convulsions led to Commonwealth and State authorities launching a rapid and far reaching investigation that prevented further harm once the problem had been identified.

There are important lessons for vaccine programs arising from this investigation:

- There is a need to ensure prompt reporting of adverse events to the TGA to allow an effective and timely national response.

- There is a need for state authorities to have well-considered and specific monitoring programs in place well before embarking on any large scale trial vaccine programs.
- There is a need to ensure the public are provided with accurate, factual information to allow them to make informed decisions about the use of vaccines.
- There needs to be greater public awareness of the mechanisms to report adverse events, and of the effective mechanisms in place in Australia to respond rapidly to emerging safety signals with any medicine.

The investigation of the febrile convulsions associated with the use of the 2010 seasonal vaccine in children provides support for the effective vaccine monitoring framework that has been established by the Commonwealth in partnership with States and Territories. The TGA will be working with consumers, healthcare professionals and relevant government health authorities to ensure that the lessons learned from this event are utilised to prevent similar events in future.

Attachment A

Timeline of the Investigation into Febrile Reactions in Young Children Following 2010 Seasonal Trivalent Influenza Vaccination

Date	Who/what	Action
19 March 2010	WA Health	Seasonal influenza vaccination commences in Western Australia (WA).
31 March 2010	CDCD WA Health	First cluster of reports of febrile convulsions received by WA Health but are not passed on to the TGA
13 April 2010	CDCD WA Health	Advises the TGA it has reports of febrile convulsions in children. TGA requests documentation be provided.
20 April 2010	CDCD WA Health	Sends first tranche of AEFI reports to the TGA. No clinical case records provided at that time.
22 April 2010	WA Health	WA announces suspension of its childhood vaccine program.
23 April 2010	CMO	CMO announces temporary suspension of seasonal influenza vaccine to children 5 years of age and under.
23 April 2010	TGA	The TGA convenes expert scientific advisory panel to review available information
24, 25 April 2010	ATAGI	ATAGI - TGA working group develop data collection templates for epidemiological investigation
26 April 2010	AHPC / CDNA	Data collection templates circulated to state and territory members.
27 April 2010	TGA	Review of batch release data commences.
27 April 2010	ATAGI	ATAGI Chair and TGA National Manager meet with WA Health to request provision of data from WA to the TGA to allow investigation.
29 April 2010	TGA	Laboratory analysis of field and retention samples begins
30 April to early May 2010	Department	ATAGI Working Party and NCIRS continue to collate and analyse the data being provided by jurisdictions.
4 May 2010	TGA	Meets with NCIRS to review epidemiological analyses.
4 May 2010	TGA	TGA expert panel on vaccine testing convened, chaired by Prof Peter Doherty
10 May 2010	TGA	TGA reviews distribution and ADR data with vaccine sponsors
11 May 2010	TGA	TGA pharmacoepidemiology expert panel reconvened by teleconference to review planned and completed epidemiological analyses; endorses planned analyses
13 May 2010	Department	ATAGI-TGA Working Party, NCIRS, and Department meet to review the evidence being provided by jurisdictions.
13,14 May 2010	TGA	TGA GMP audit of CSL manufacturing facilities
14 May 2010	TGA	TGA expert panel on vaccine testing meets
20 May 2010	ATAGI	ATAGI-TGA working party interim report to the CMO recommends continued suspension of vaccination in children < 5 years while laboratory testing, manufacturing inspections and epidemiological analyses continue.
1 June 2010	TGA	Samples sent to NIBSC for further in vitro analyses.
2 June 2010	TGA	TGA's Advisory Committee on the Safety of Medicines (ACSOM) meets to review issues with 2010 seasonal TIV.
7 June 2010	TGA	Samples sent to CDC in vitro and in vivo analyses.
10 June 2010	Department	ATAGI meets.
18,21-23 June 2010	TGA	TGA inspection of CSL manufacturing facilities.
2 July 2010	TGA	TGA issues interim report on the investigations to date.
27 July 2010	CMO	Advises resumption of vaccination, using Influvac and Vaxigrip.
24 September	TGA	TGA updates interim report of investigation.

Attachment B

TGA and DoHA public advisory statements about adverse events associated with 2010 seasonal trivalent influenza vaccine

23 April 2010
TGA: Western Australian reports of adverse reactions to 2010 seasonal flu vaccine in children
http://www.tga.gov.au/alerts/medicines/fluvaccine.htm

23 April 2010
DOHA: Seasonal Flu Vaccine and young children
http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-yr10-dept-dept230410.htm

30 April 2010
DOHA: Health authorities continue to put seasonal flu vaccine on hold for young children
http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-yr10-dept-dept300410.htm

1 June 2010
DOHA: Seasonal Flu Vaccine Remains Suspended for young children without risk factors - Advice from the Chief Medical Officer
http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-yr10-dept-dept010610.htm

2 July 2010
TGA: Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination — Status report as at 2 July 2010
http://www.tga.gov.au/alerts/medicines/fluvaccine-report100702.htm

30 July 2010
DOHA: Seasonal flu vaccination for young children can be resumed - Updated advice from the Chief Medical Officer
http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-yr10-dept-dept300710.htm

24 September 2010
TGA: Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination — Updated 24 September 2010
http://www.tga.gov.au/alerts/medicines/fluvaccine-report100702.htm

Attachment C

Analysis of reports from Western Australia of convulsion following administration of seasonal trivalent influenza vaccine 2010

1. Purpose of this report

This document provides a quantification of all Western Australian reports of convulsion/febrile convulsion following seasonal influenza vaccination in 2010 known to the TGA as at close of business 7 May 2010, with an analysis of clinical presentation and causal relationship with the vaccine.

This particular analysis was undertaken because a potential safety signal was first identified in WA and that State has been the largest source of reports of convulsion as a suspected adverse event following immunisation (AEFI) with seasonal influenza vaccine. In addition, WA health authorities have submitted medical records for many of their reports, providing much more comprehensive clinical information than is available from across the other jurisdictions.

In addition, an analysis of reports Australia-wide is also being undertaken. The findings from that analysis will be provided in a second report. It should be noted that the extent of clinical information for cases from jurisdictions other than WA is somewhat less comprehensive than that made available for reports from WA.

2. Introduction

WA has historically provided a state-funded childhood seasonal influenza vaccine program for all WA children aged 6 months to < 5 years. WA Health suspended this year's program on 22 April 2010 with the reason that more than 40 children had experienced febrile convulsions following vaccination for seasonal influenza in March and April this year. It had been determined by WA Health that the number of presentations to emergency departments for febrile illnesses and, in particular, febrile convulsion in WA over March-April was higher than would be expected from historical records for 2008 and 2009, despite similar uptake of vaccine in 2009 and 2010.

At the time the WA program was suspended, the TGA had received 25 spontaneous reports (including 2 duplicate reports) of convulsion in children under the age of 10 yrs Australia-wide. Of these, 16 reports (including 2 duplicate reports) had been submitted from WA – 14 had been received by the TGA as recently as 20 April 2010. In comparison, in the first 6 months of 2008 the TGA had received a total of 5 reports of convulsion in association with administration of seasonal influenza vaccines in children aged 0 to 10yrs (none from WA) and in the first 6 months of 2009 only 1 report (none from WA) was received for the same cohort.

The seasonal influenza vaccine used for WA's 2010 program was a trivalent formulation comprising the H1N1 2009 strain (A/California/7/2009), the H3N2 strain (A/Perth/16/2009) and a B strain (B/Brisbane/60/2008). Such vaccine is available via 3 vaccine manufacturers – CSL (Fluvax® and Fluvax Junior®), Sanofi Pasteur (Vaxigrip®, Vaxigrip Junior®), and Solvay (Influvac®).

These same vaccine types have also been supplied under the National Immunisation Program (NIP) for all children and adults aged 6 months to 64 years who have underlying medical conditions that put them at increased risk of complications from influenza. It became apparent, subsequently via email exchanges and at a National Immunisation Committee (NIC) meeting held on 22 April 2010, that health authorities in several other jurisdictions (South Australia and Victoria) had been observing higher than expected rates of reporting of AEFIs in children under the age of 5yrs, particularly cases of fever and vomiting.

Subsequently, on 23 April 2010 the Commonwealth's Chief Medical Officer suspended the use of seasonal influenza vaccine under the NIP for children 5 years and under. It was agreed by the Australian Health Protection Committee (AHPC) that DoHA's Office of Health Protection (OHP) and the TGA would work collaboratively with States and Territories to collect information as follows:

- each jurisdiction was to complete a standardised template to provide data on:
  - seasonal influenza vaccine distribution;
  - AEFIs reported in children from 6 months to 10 years of age since 1 March 2010; and
  - presentations at emergency departments of large metropolitan paediatric centres by children aged 6 months to 10 years with fever and/or febrile convulsions for the period 1 March to 30 April in the three years 2008, 2009, and 2010.

  Completed templates were to be submitted to the OHP by close of business 28 April 2010. These spreadsheets were made available to the TGA; and
- each reporter of an AEFI case of seizure/convulsion was asked to obtain follow-up clinical information in a standardised format (similar to that used for surveillance during the 2009 Panvax rollout) for submission to the TGA.

In addition, on 29 April 2010 the TGA requested that WA send photocopies of the medical case notes of children with febrile convulsions to the TGA for analysis.

For this review the TGA ADRS database was searched using the 'Reporter' software to identify all reports of convulsion occurring in children aged 10 years or less for 2010. The search captured all reaction terms that mapped to 'convulsion' plus 'status epilepticus'. This broad approach was used to capture reports of febrile convulsion that may have been miscoded or misreported as other types of convulsion. A cut-off date of COB 7 May 2010 was chosen to allow sufficient time for the assessment and investigation of the individual reports by the TGA, which included collation, reconciliation and review of clinical information submitted to the TGA.

The TGA's ADRS cases were then reconciled with:

- the 2010 cases identified in the spreadsheets submitted by each State and Territory;
- information contained within the follow-up clinical information documents sent in by each AEFI reporter (where available); and
- in the case of reports from WA, clinical case/medical records (where submitted).

3. Reports from WA on TGA ADRS database

As at COB 7 May 2010 there were 73 reports of convulsion in children aged 10 years or younger associated with seasonal influenza vaccination on the TGA's ADRS database. These reports have been received and assessed by the TGA and included on the ADRS database as cases of convulsion based on the TGA's assessment of the information provided.

The vast majority of reports were generated through the public health system, with contributions from the Infection Control Unit at the Princess Margaret Hospital (PMH) (28 reports), with a further report from a specialist at PMH; WA Health (27 reports); and Fremantle, St John of God and Mt Tom Price Hospitals (1 report each). The remaining reports were from GPs or medical centres (10 reports); the AME Line (2 reports – both parental); and directly from parents (2 reports).

One of the reports (ADRS No. 264165) had already been identified as a duplicate and denoted as such in the database. A further 6 reports (ADRS Nos 265168, 265516, 265744, 265762, 265835,

265859) were found to be duplicates during the course of this investigation. When the duplicates are accounted for, there are 66 unique cases of convulsion. These cases are discussed in detail in section 5.

In comparison, at the same date there were 116 reports Australia-wide on the TGA ADRS database. Of these 7 were the duplicate reports from WA and there were a further 2 duplicates reports – one from Victoria (ADRS No. 265272) and one from SA (ADRS No. 265284), giving 107 unique reports distributed across the jurisdictions as follows:

WA	66	VIC	15	QLD	11
NSW	8	SA	4	ACT	2
TAS	1	NT	0		

Figure 1 shows the cumulative number of reports of convulsion over time for both WA and Australia. It includes the duplicates, to give a sense of how many reports the TGA had received and when. It shows a relatively low reporting rate up to 20 April 2010, when WA submitted a batch of 14 reports, and then a further marked increase from 27 April through 30 April (once again largely due to reporting activity in WA). Thereafter, the reports from WA plateau whereas reporting continued from other states and territories as cases were identified by them.

Medical records/case notes have been made available for 38/66 (57.6%) of the unique cases[1] and clinical follow-up information for an additional 18/66 (27.2%) cases. Only 10/66 (15.2%) cases had no follow-up information available for review – 7 of these were from GPs or medical centres (ADRS Nos 264879, 265750, 265757, 266136, 266140, 266196 and 266575); 2 were from parents (ADRS Nos 265921 – via AME Line – and 266318); and 1 was reported by WA Health (ADRS No. 265337). ADRS No. 265337 was lodged via the web and contained scant information and did not identify the source of the case. Interestingly, this case does not appear on any of the spreadsheets submitted subsequently by WA Health, even though the lodgement date preceded the compilation of the spreadsheet.

Of the 66 unique cases in WA, 42 (64%) occurred in males, 23 (35%) in females and gender was unknown in 1 (1%). This is in keeping with the known predominance of febrile convulsions in males. Age ranged from 6 months to 9 years, with a median age of 1 year. The age distribution (Figure 2) shows that more than 80% of cases were aged 2 years or younger and 90% of cases were aged 3 years or younger. Note this was a fairly crude analysis using ages in years as calculated by the TGA ADRS database. Time constraints precluded the calculation of ages in months, calculation of average age and presentation of data by 6-month age intervals.

Time to onset of event ranged from 3 to 72hrs (mean 9hr; median 7hr) and more than 80% of cases had onset of the seizure event in ≤12hrs of vaccination. It is known that fever typically occurs within 6 to 12 hours in a significant proportion of children under the age of 3 years following their first influenza vaccination. However, in this particular series of cases (where more than 90% of children were aged 3 or less), 20/66 (30.3%) actually had onset within ≤ 6 hours of vaccination. In addition, 32/66 (48.5%) had onset in >6–12 hours; and 5/66 (7.6%) >12 hours after vaccination. Time to onset was unknown in 9/66 (13.6%) cases.

The brand of the vaccine used was known in 60/66 cases and all of these received Fluvax® or Fluvax Junior®. Batch numbers were available for 51 cases. A total of 23 different batches were implicated, but two batches – 27102 and 27801 – accounted for more than half of those cases (38 in total). A more complete summary of the brand and batch data can be found in Tables 1–3 where Australia-wide data are also documented.

[1] All but 2 of these cases (266319 and 266325) also had clinical information follow-up forms completed.

Previous seasonal influenza vaccination history was unknown in 18/66 (27.2%) cases, 34/66 (51.5%) cases had no previous vaccination with seasonal influenza vaccine and only 14/66 (21.2%) cases had received a previous vaccination.

4. Additional cases identified during the review

During the reconciliation process it became apparent that WA Health had identified 18 more cases of convulsion than appeared on printouts from the TGA's ADRS database. Of these 18 cases, 11 were listed in the spreadsheet with data lock date of 28 April 2010 submitted by WA Health (5 of these also had case notes submitted to the TGA by WA Health); 6 were only identified amongst case notes submitted to the TGA by WA Health and the remaining case was identified on the PMH's detailed spreadsheet.

Key points to note in the 18 additional cases are:

- a report had been received and coded by the TGA for 8 of the 18 cases but there had been no mention of convulsion in the initial report. Consequently these cases did not appear in printouts of database reports of convulsion.

  Four of these 8 cases were reported by the Infection Control Unit at PMH, of which 3 (ADRS Nos 265104, 265109, 265114) did not have any additional information. Of note, none of these cases appeared on the PMH spreadsheet and, in the absence of any other corroborating information, it would appear they had been misidentified in the original spreadsheet sent by WA Health. The fourth report from PMH (ADRS No. 265120) also had no mention of convulsion but this case appeared in the PMH spreadsheet. Furthermore, a clinical follow-up document and emergency department (ED) notes were available to the TGA for review. Of interest, the clinical follow-up document noted the parents had stated there was shaking with tonic-clonic activity. However the ED Dr's notes state "developed fever and shaking....°LOC/ tonic-clonic activity" and the diagnosis by the doctor was "high fevers" with no mention of febrile convulsion. This reviewer has interpreted the ED Dr's annotation as meaning there was no loss of consciousness and no tonic-clonic activity. It is not clear whether the information contained within the clinical follow-up document was obtained from a separate 'look-back' interview of the parents or was based on a transcription of the ED medical notes, in which case there has probably been a misinterpretation of the ED Dr's notes. Thus, this case cannot, based on the currently available information, be considered to have been medically corroborated and the diagnosis of febrile convulsion is quite insecure.

  A fifth case (ADRS No. 265934) appeared on the WA Health spreadsheet as a case of febrile convulsion. However, the clinical follow-up documentation received made no mention of convulsion and corroborated the original report of fever and vomiting. WA Health subsequently advised by email on 8 May 2010 that the final diagnosis for this case was rigors and not febrile convulsion.

  Two of the 8 cases (ADRS Nos 266443 and 266461) had presented to St John of God Hospital. They did not appear on the spreadsheet sent initially by WA Health but case notes were sent to the TGA. Neither of the original reports mentioned convulsion and the description from the case notes clearly indicates that no convulsion had occurred. WA Health subsequently advised via email on 19 May 2010 that paediatricians had reviewed these cases and concluded they were not cases of febrile convulsion.

  The final case (ADRS No. 265269) was originally reported by a medical practice as a case of fever, lethargy and anorexia. However, the clinical follow-up information document referred to a convulsion as well. Whilst the patient identifier and geographical location were able to be reconciled with the original report, the dates of vaccination and the event stated in the follow-up document were different from those in the original report, suggesting a transcription error

had occurred at some point (either in the original report or in the follow-up document). This reviewer decided to err on the side of being conservative and include this as having been a case of convulsion, albeit of low diagnostic security.

- suspected AEFI reports for 4 of the 18 cases had been received and coded by the TGA but the neurological features described in those reports were not considered by the coder to represent a convulsion.

  ED medical records were available for all 4 cases. In one case (ADRS No. 265373) the child, who had a history of chronic lung disease, presented to the ED because of high fever and respiratory distress and was observed to have a seizure whilst in the ED. Thus a diagnosis of febrile convulsion can be considered to be diagnostically secure in this case and the TGA's ADRS database will be amended accordingly. A further two cases (ADRS Nos 265118 and 265134) were discharged from the ED with a diagnosis of febrile convulsion, based on the ED Dr's interpretation of events related to them by a parent. Interestingly, in ADRS No. 265134 it was noted that, although the main symptom was "shaking legs", it was acknowledged within the history taken by the Dr that the child was in a sleeping bag and it was difficult to see what was actually happening, suggesting there could be some doubt about the diagnosis in that case. In the final case (ADRS No. 265152), both the original report and ED case notes point to localised myoclonic jerks and, therefore, this is not considered to be a case of convulsion, despite it appearing on the WA Health spreadsheet. Also, the child was aged 10 yrs and therefore outside of the typical age range for a diagnosis of febrile convulsion.

- 6 of the 18 cases (Joondalup Health Campus (JHC) cases 1, 2, 3 and 4; pt NW and pt HA) had not been reported to the TGA at all.

  Case notes were submitted for each of the JHC cases. Three of these, JHC cases 1, 2 and 4, all had a discharge diagnosis of febrile convulsion based on the history obtained by the ED registrar from a parent. However, for JHC case 2 there was no temporal relationship to the seasonal influenza vaccine, with the vaccination having occurred some 2 weeks earlier and the child had developed an URTI in the intervening period anyway. WA Health subsequently advised via email on 19 May 2010 that paediatricians had reviewed this case and concluded it was not a case of febrile convulsion. Also, for JHC case 3 the diagnosis was less secure, with the registrar recording a diagnosis of "?fever related to flu vac, ?seizure". This reviewer has accepted it may be a case of convulsion, as it would be reasonable to expect that the paediatricians reviewing JHC case 2 would have also reviewed the other cases from JHC and, in the absence of advice to the contrary, confirmed them as cases of febrile convulsion.

  Of the 2 remaining cases, one (pt NW) had been identified on the WA Health spreadsheet of 28 April 2010. A clinical information follow-up document had also been submitted and indicated the child had been reviewed at an ED. However the clinical information follow-up document contained minimal information, did not document the child's temperature or who had actually observed the seizure and did not document what the ED discharge diagnosis had been. Thus the diagnosis of febrile convulsion is less secure in this case. The final case (pt HA) was identified from the PMH spreadsheet. No other information is available for assessment and therefore the diagnosis of febrile convulsion is also considered to be less secure in this case. However, it must be acknowledged that cases on the PMH spreadsheet were or will be reviewed by staff specialist paediatricians at PMH. In the absence of advice to the contrary from WA Health, this case has been counted as a case of febrile convulsion at this point in time.

Based on the assessment above, this reviewer considers there were an additional 10 cases (ADRS Nos 265118, 265120, 265134, 265269 and 265373; JHC cases 1, 3 and 4; and pts HA and NW) that can be considered to represent reports of convulsion of varying degrees of diagnostic

certainty that should be assessed from a causality view point. The remaining 8 (ADRS Nos 265104, 265109, 265114, 265152, 265934, 266443, 266461 and JHC case 2) can be considered not to be cases of febrile convulsion.

5. Review of all WA cases of suspected febrile convulsion

This section presents a reconciliation of all 84 suspected cases of convulsion in children under the age of 10 that are known to the TGA by virtue of either having been coded as such on the TGA ADRS database (66 cases) or having been drawn to the attention of the TGA during the analysis of WA spreadsheets and case notes (18 cases). The following summary should be read in conjunction with Figure 3.

Figure 3 depicts these cases from the viewpoint of both the security of the diagnosis of febrile convulsion and causal relationship to the seasonal influenza vaccine. The information within the figure is located within two parts separated by a broken horizontal line. Cases appearing in boxes above the broken line have been assessed as either definitely not a febrile convulsion or not having been medically corroborated (little diagnostic security). These cases have not been subject to a causality assessment.

The cases below the broken line are arranged from right to left in order of decreasing diagnostic security: those where the seizure was witnessed by a medical or allied health professional represent the highest diagnostic security; those where the child was reviewed and a diagnosis of febrile convulsion made in an ED department are the next most secure; and those where a GP or medical centre has simply reported that a febrile convulsion has occurred having lower diagnostic security (for reasons outlined in further discussion below).

Within the groupings of diagnostic security, cases have been sub-grouped according to presence or otherwise of other factors, such as intercurrent infection, concomitant administration of other vaccines or an underlying seizure disorder, to which the event could also reasonably be attributed. Where such other factors were present, the causal relationship between the seasonal influenza vaccine and febrile convulsion would be possible[1]. These cases appear in unshaded boxes. Where no other factors are present and the seasonal influenza vaccine is therefore the sole suspected agent, the cases would be assigned a causality rating of very likely. These cases appear in the shaded boxes at the bottom of the figure. The shading of boxes is graduated to give a sense of the level of diagnostic security, with the darkest shading being the more secure.

Two of the 84 reports are in children aged more than 5 years and in both cases there were other factors present that would also preclude a diagnosis of febrile convulsion. In one case occurring in a child of 9 years of age (ADRS 265168), the child in question has suffered from a known seizure disorder (with abnormal EEG) since an episode of viral encephalitis in 2006. The seizure

[1] The WHO categories for causality of AFEIs apply, of which the most relevant are:
Very likely – a clinical event with a plausible time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals;
Probable – a clinical event with a reasonable time relationship to vaccine administration; is unlikely to be attributed to concurrent disease or other drugs or chemicals;
Possible – a clinical event with a reasonable time relationship to vaccine administration, but which could also be explained by concurrent disease or other drugs or chemicals;
Unlikely – a clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals.
The rating 'certain' is not applicable given the circumstances of this particular investigation. 'Certain' is used in rare instances where there is a demonstration of relationship, e.g. such as mumps vaccine-related aseptic meningitis with isolation of the vaccine strain. The rating 'unrelated' applies to events where there is an incompatible time relationship. This would have been appropriate for JHC case 2, had it not been disqualified on diagnostic grounds (see section 4)

activity had been poorly controlled in the last 6 months and, as recently as February this year, the parents had resisted increasing the child's dose of antiepileptic medication. In the second case (265152) the child was aged 10yrs and had presented with myoclonic jerks in his right arm (see also section 4).

There were 82 cases in children aged 5 years or younger, 19 of which have been assessed as not having experienced a febrile convulsion. Of these exclusions, 11 were notified to the TGA by WA Health – 6 on 8 May 2010 (ADRS Nos 265862, 265868, 265900, 265903, 265934 and 265984) and 5 on 19 May 2010 (ADRS Nos. 265977, 266325, 266443, 266461 and JHC case 2). In addition, this reviewer considers a further 8 cases should be excluded. Three of these (ADRS Nos 265104, 265109 and 265114) were discussed as cases where convulsion was not mentioned in the original AEFI report to the TGA and having probably been erroneously included in the WA spreadsheet of 28 April 2010. Of the other 5 cases, the clinical follow-up document for ADRS No. 265368 indicated that, after discussion with a parent who reported the convulsion, the paediatrician at PMH had concluded that seizure occurrence was unlikely (Note: this case did not appear on the PMH spreadsheet). In the second of these 5 cases, duplicate reports were received via the AME Line (parental report – ADRS No. 265744) and WA Health (PMH) (ADRS No. 265865). In this case the child had presented with a suspected febrile convulsion 3 weeks earlier and on that occasion been diagnosed with viral infection. On the day of the seasonal influenza vaccination the parents reported that they had later found the child to be "burning up", limp, unresponsive and cyanosed. No seizure was actually observed and they merely suspected that another convulsion had occurred. A plausible alternative diagnosis in this situation would be hypotonic-hyporesponsive episode. The medical records for this case have not been made available for review at this point in time.

In the third of the 5 cases (ADRS No. 265883), which was a report from a parent that was submitted via an immunisation clinic, the convulsion was described as spasm and flicking of the left arm (opposite side of vaccination), followed by a period of flaccidity. There was no mention of loss or alteration of consciousness and, indeed, the child was noted to be screaming/crying. There was no presentation to hospital and consequently no medical corroboration either. In the fourth of the 5 cases (ADRS No. 266318) a parent reported fever, convulsions, vomiting, rash and listlessness in her child who was admitted to PMH the same day as vaccination with the seasonal influenza vaccine. This case does not appear on the either WA Health spreadsheet or PMH spreadsheet, from which this reviewer has concluded that the diagnosis on admission/discharge from PMH was not a convulsion. Not surprisingly, no follow-up clinical information or case notes have been received for this report. In the last of the 5 cases (ADRS No. 265372) there was conflicting information as to whether the seizure was witnessed or not. The initial report stated that the child had a seizure at home witnessed by the mother. However, the ED case notes state that the presenting history was that child had fevers, was grunting and lethargic and that the mother was worried as the child may have had a seizure as he was prone to febrile convulsions. The ED Dr's provisional diagnosis was post Fluvax fever, query febrile convulsion. The discharge summary stated "child found drowsy and confused and mother concerned child was post ictal (although no seizure actually seen)". In this reviewer's opinion the documented symptoms were very non specific and could well have been a manifestation of high temperature alone and, in the absence of a witnessed seizure, a diagnosis of febrile convulsion is not supported.

Of the remaining 63 cases:

- 16 had a seizure that was actually witnessed by a medical or allied health professional (e.g. ED nurse or ambulance officer). These cases can be considered to have a secure diagnosis of convulsion. Medical records were received by the TGA for all but 2 of these cases (ADRS Nos 264879 and 265947).

- 31 cases had a seizure that was witnessed by a parent and in 16 cases the seizure witness was not identified. Combined, these 47 cases can be considered somewhat less secure diagnostically than those where the seizure was observed by health professionals. However, it must be recognised that the vast majority of febrile convulsion are only ever observed by parents and a final diagnosis is made by medical professionals on the basis of a history obtained from the parent(s) some time after the event. In this regard it has to be noted that 38 of the 47 cases presented to an ED for review and 7 of the 47 were the subject of a report from a GP/medical practice, where presumably the practitioner or a nurse had taken a history from a parent some time after the event and reached a diagnosis of febrile convulsion. Medical records were submitted for analysis for 28 of the 38 cases that presented to ED. However, no clinical information other than a clinical follow-up document for ADRS No. 265269 has been received for any of the cases that were reported by GPs or private medical practices. This is of significance because as a group the GP reports were of low quality, often merely stating that a "febrile convulsion" had occurred without providing any description of the event (in terms of level of consciousness, motor manifestations, recorded temperature etc) to allow an independent assessment of the diagnosis. Another two cases (ADRS Nos. 265120 and 265892) presented to ED but in the mind of this reviewer must be considered not to have been medically corroborated and thus appear within the box for that category in Figure 3, leaving 36 cases discussed under subsection (b), below. ADRS 265120 is discussed in section 4. For the case described in ADRS No. 265892, the follow-up clinical information document describes a child waking from sleep disorientated, shivering, with a temperature to 40.0°C. A convulsion was stated to have occurred half an hour later, following which he was taken to the ED. A second convulsion was said to have occurred in the ED but was again witnessed only by the parents. The ED triage notes refer only to "vomiting and rigoring" and the ED doctor's notes referred to shivering and shaking uncontrollably and a degree of uncertainty was expressed as to whether a convulsion had occurred - "?seizure/ ?rigor". There was no record of any seizure having occurred in the ED. The recorded diagnosis was "Post immunisation fever/?feb convulsion".
- 2 cases (ADRS Nos 265337 and 265921) did not present for medical review and have not been medically corroborated.

a. Cases of convulsion observed by a medical or allied health professional

A total of 16 cases have been reported where the seizure was observed by a medical or allied health professional. Of these, 14 occurred either in the ED or whilst the child was admitted to hospital, one (ADRS No. 265149) was observed by the child's parents who are both doctors, and one (ADRS No. 264879) was observed whilst the child was at a nursing clinic.

Two of the 16 cases were afebrile in the sense that the highest temperature recorded was well below 38.0°C, which is the threshold used in the standard definition of febrile convulsion[1]. In one of these (ADRS No. 264879), a 6 minute seizure was witnessed by staff at a nursing clinic who administered midazolam and oxygen. Later the child was evacuated to Derby Hospital where the final diagnosis was that of a non-febrile convulsion (temperature had been recorded as 37.5°C) and URTI. In the second of such cases (ADRS No. 265607), the highest temperature recorded was 37.2°C. This child was reported to have experienced 5 seizures, several of which were

[1] See the following 2 Brighton Collaboration definition documents:
- Bonhoffer J, Menkes J, Gold M et al. Generalised convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis and presentation. The Brighton Collaboration Fever Working Group. *Vaccine* 2004; 22: 557–562.
- Marcy S, Kohl K, Dagan R et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. The Brighton Collaboration Fever Working Group. *Vaccine* 2004; 22: 551–556.

witnessed while the child was in hospital. Temperatures recorded at the time of two of the seizures were 36.0 and 37.2°C, respectively. Of note, this patient had a known history of absence epilepsy for which he was receiving Tripletil. He had been admitted to hospital in March 2010 for management of seizures following multiple presentations to ED with up to 7 seizures per episode. An MRI had shown anterior band heterotopia which can be associated with epilepsy. Importantly, the seizures observed in hospital were confirmed by parents as being of the same character as the child's usual absence seizures, which would suggest a more likely causality related to the underlying seizure disorder.

In the remaining 14 of 16 cases, all were found to have temperatures in excess of 38.0°C:

- 1 of these cases (ADRS No. 265113) was also vaccinated with Varilix® at the time he received Fluvax® and, thus, the causal association of the febrile convulsion with Fluvax® is, at best, possible.
- 5 of the remaining 14 cases had intercurrent infection, which offer a plausible alternative causal explanation for the febrile convulsion. The causality for these cases is, therefore, only possible:
    - in ADRS No. 265160 the child had symptoms of a URTI at the time of vaccination and on review in ED was found to have inflamed tympanic membranes and throat, a crusted nose and cervical lympadenopathy;
    - in ADRS No.265338 the child had been found febrile and lethargic by her parents and was observed to have a prolonged seizure in ED where treatment with midazolam and phenytoin was required. The child experienced ongoing metabolic acidosis and hypoglycaemia and was subsequently found to have extensive brain ischaemia on MRI scanning. The child had previously had a 4 week history of cough and 1 week history of rhinorrhoea. She later tested positive for rhinovirus and RSV whilst undergoing treatment in hospital;
    - in ADRS No. 265379 a child with a known seizure disorder following an episode of encephalitis in 2007 presented to ED following a generalised tonic-clonic seizure of 1.5min duration and was observed to have a second seizure whilst in the ED. These seizures were quite different from those normally experienced by her, suggesting that this was not a presentation of the underlying seizure disorder. However, it is of note that the child had been unwell for a week with an URTI, which could have contributed to the fever of 39.1;
    - in ADRS No. 265840 a child presented to ED 3 days post vaccination because of ongoing abdominal pain, fever and rigors which predated the vaccination and was observed to have a seizure whilst in the ED (at which time her temperature was 38.1°C). She was subsequently found to have an *E coli* urinary tract infection on MSU culture; and
    - in the final case (ADRS No. 265870), the child had a seizure witnessed in ED where he had presented because of fever and malaise for several days with what was diagnosed as a viral URTI. Examination in the ED revealed the child had inflamed tonsils, pharynx and tympanic membranes as well as cervical lymphadenopathy.
- 8 of the remaining 14 febrile cases (ADRS Nos. 265110, 265149, 265373, 265596, 265741, 265946, 265947 and 266382) had no evidence of concurrent disease or exposure to other vaccines, medicines of chemicals that would offer an alternative causal explanation for the febrile convulsion. Medical records were available for 7 of these 8 cases (the exception being ADRS No.265947[1]) and provide robust evidence of both the diagnosis of febrile convulsion

[1] A clinical information follow-up form was submitted but merely restated the information in the original report.

and the absence of other likely causative agents. Thus, in these cases a causal relationship to the seasonal influenza vaccination is highly likely. With regard to ADRS No. 265947, a seizure was said to have been witnessed in the ED of PMH, with a temperature of 38.0°C. This patient is known to be immuno-compromised as a consequence of treatment with anti-rejection medication following a liver transplant for a metabolic disorder in 2008. The metabolic disorder had presumably been corrected as a result of the liver transplant, so the only alternative cause would be infection secondary to immunosuppression. However, there was no indication of this in the information received to date and the vaccination remains the sole suspected agent. Of note, however, this case does not appear on the PMH spreadsheet (although it did appear on the WA Health spreadsheet), so it is possible that on receipt of further information this case would be reclassified to one of only a possible causal relationship with the influenza vaccine.

b. Cases of convulsions observed by parent or other and presenting to ED department

There were 38 cases where a parent(s) was the only witness of the seizure, following which they presented to an ED, two of which were considered not to have been medically corroborated (ADRS Nos 265120 and 265892).

Of the remaining 36 cases, in one case (ADRS No. 265994) a 1-year-old child with a previous history of febrile convulsions presented to ED following a convulsion that was witnessed by the mother 12 hours after vaccination. No temperature recordings were available from either the initial report or the clinical follow-up information document. Ordinarily, one would expect that a parent might not have access to a thermometer, or think to take the child's temperature at the time of witnessing a febrile seizure but in most cases would relate the fact that the child was hot or "burning up". However, in this particular case, the mother had specifically stated the child did not have a temperature and was not hot to touch, suggesting that this was an afebrile seizure. Of note, there was a family history of convulsions. No medical records were available to allow further assessment of the case.

28 of the 36 cases presenting to ED had a temperature in excess of 38.0°C. Of these:

- 6 cases (ADRS Nos. 265107, 265134, 265162, 265664, 265974 and 266380) received vaccination with concomitant vaccines at the time they received Fluvax® and, thus, the causal association of the febrile convulsion with Fluvax® is, at best, possible. Two cases received more than one concomitant vaccine – ADRS No. 266380 received Hib/MMR/Men C and ADRS No. 265162 received Infanrix® and Prevanar® as well. The most common concomitant vaccines were Infanrix-Hexa® and Varilix® (2 cases each), with hepatitis B vaccine, Prevanar®, and Hib/MMR/Men C with once case each.
- 4 cases had intercurrent infection, which offers a plausible alternative causal explanation for the febrile convulsion. The causality for these cases is, therefore, only possible:
    - in ADRS No. 265141 the mother reported the child had a runny nose, cough and puffy eyes and the child was found to have throat inflammation on examination, suggestive of a viral URTI;
    - in ADRS No. 265611 the child had recently been receiving antibiotics for the treatment of pneumonia[1];
    - in ADRS No. 265879 a child receiving high dose steroids for chronic lung disease presented to ED at PMH with fever, shortness of breath, difficulty breathing and convulsions. Two days later RSV infection was diagnosed. Of note, this case does not appear on the PMH spreadsheet; and

[1] There was conflicting information from different sources as to the underlying infection. The report from PMH referred to URTI, whereas the clinical follow-up information document referred to pneumonia.

- in JHC case 4, the child was noted to have rhinorrhoea and the paediatric registrar at JHC made a diagnosis of "febrile convulsion with viral infection ?post immunisation".

- 18 cases (ADRS Nos 265112, 265116, 265118, 265138, 265339, 265364, 265586, 265592, 265849, 265895, 265942, 265948, 265987, 265991, 266319, 266381, JHC case 3 and pt HA) had no evidence of concurrent disease or exposure to other vaccines, medicines or chemicals that would offer an alternative causal explanation for the febrile convulsion, under which circumstances a causality rating of 'very likely' would apply. Medical records were made available for 16 of these cases (the exceptions being 265991 and pt HA) and provided varying degrees of detail in that some provided quite detailed descriptions of the characteristics of the motor manifestations and level of consciousness and investigation undertaken to exclude other causes, whereas in others simply stated "had febrile convulsion". In the case of the latter, it has to be accepted that the diagnosis of febrile convulsion based on the history obtained from the parents by medical professionals experienced in the assessment of such cases. However, some cases require further comment:
  - in ADRS No. 265116 it was difficult to reconcile the initial report from the PMH infection Control Unit, which stated a second seizure occurred in ED, with the ED notes that made no reference to a seizure in the ED;
  - in ADRS No. 265849 there was no record of an MSU having been collected in the child who had a history of vesico-ureteric reflux and recurrent urinary infections;
  - in ADRS No.265942 the mother of the child reported that the child had been pulling at his ears for several days prior to vaccination but had no fever until after the vaccination. The right ear drum was found to be red on examination in ED but it was not bulging and antibiotics were not prescribed and there was no mention of URTI in the discharge diagnosis; and
  - one further case (ADRS No. 265364) had an underlying absence seizure disorder as well as a very complex medical history that included a pineal cyst, growth hormone deficiency and Arnold Chiari malformation with gastrostomy and jejunostomy. As recently as 3 days prior to vaccination she had experienced an absence seizure. However, the seizure described on the day of influenza vaccination was generalised and tonic clonic in character, which is quite different to the underlying seizure disorder and, according to the mother, of the same character as during a recent hospital admission (discharge 10 days prior to the vaccination) for febrile convulsion secondary to sepsis of unknown origin. The underlying seizure disorder appears not to be a contributory factor in this case and the possibility of an infective cause also appears to have been ruled out by the presence of a normal blood count and no growth on blood cultures.

Of the remaining 7 cases in this group of 36, 5 cases (ADRS Nos. 265106, 265856, 265880, 265898 and pt NW) did not have a temperature recorded but in all cases were reported by the parent to have a fever or be hot to touch. In the other 2 cases (ADRS No. 265108 and JHC case 1) the recorded temperature at presentation to ED was above 37.5°C. Two of the 7 cases (ADRS Nos 265856 and 265880) received concomitant Varilix®at the time they received Fluvax® and, thus, the causal association of the febrile convulsion with Fluvax® is, at best, possible. ADRS Nos 265106, 265108, 265898, JHC case 1 and pt NW had no evidence of concurrent disease or exposure to other vaccines, medicines of chemicals that would offer an alternative causal explanation for the febrile convulsion, under which circumstances a causality rating of very likely would apply.

c. Cases reported by a GP or medical practice

All 7 reports where information has been obtained solely from GPs (ADRS Nos 265269, 2265750, 265757, 266136, 266140, 266196 and 266575) offered scant information and in the case of ADRS No. 265269 there was conflicting information in that the original report made no mention of a convulsion (see earlier discussion under section 4). None of the reports had any other apparent contributory factors such as intercurrent illness or other vaccines/medicines. Only 3 of the cases (ADRS Nos 265750, 265757 and 265269) included a recorded/ documented fever of $\geq 38.0^{\circ}C$.

d. Cases not medically corroborated

Four cases were not medically corroborated. ADRS Nos. 265120 and 265892 have been discussed previously. Of the other reports in this classification, one (ADRS No. 265337) was reported by WA Health via the web and contained scant information and did not identify the source of the case. Interestingly, this case does not appear on any of the spreadsheets submitted subsequently by WA Health, even though the lodgement date preceded the compilation of the spreadsheet. In the second case (ADRS No. 265921), a parental report via the AME Line, the child was stated to have had a "convulsion" while "blisteringly hot" in which the shoulders were contracted and the knees drawn every 15 to 30 secs. This does not appear to have the frequency of repetitive movement one would associate with a convulsion and there was no apparent loss of consciousness. In the absence of medical corroboration and/or additional information in either of these cases, the diagnosis of febrile convulsion is somewhat doubtful and no assessment of causality has been made.

6. Summary of cases from WA

On the basis of a review of all information available, there were 57 cases of febrile convulsion in children under the age of 5yrs reported to the TGA as at close of business on 7 May 2010, 38 of which are very likely to be causally related to vaccination with the seasonal influenza vaccine. A further 19 cases are only possibly causally related to the vaccine because they can also be explained by the use of concomitant vaccines and/or concurrent infection. Fluvax® or Fluvax Junior® was used in all 54 cases where the brand of the seasonal influenza vaccine was known.

Of the 57 cases of febrile convulsion, 15 can be considered to have the highest diagnostic security on the basis that they were observed by a medical or allied health practitioner. Of these 15 cases, 8 are very likely to be causally related to vaccination with the seasonal influenza vaccine and 7 are only possibly causally related to the vaccine because they can also be explained by the use of concomitant vaccines and/or concurrent infection. In the remaining 42 cases the seizures were observed by parents and the diagnosis of febrile convulsion was made by a medical professional on the basis of a history obtained from the parent(s) after the event – 35 presented to an ED and 7 to a GP/medical centre. Of these 42 cases, 30 are highly likely to be causally related to vaccination with the seasonal influenza vaccine and a further 12 are possibly causally related to the vaccine because they can also be explained by the use of concomitant vaccines and/or concurrent infection.

These WA data confirm the presence of a safety signal of febrile convulsion for Fluvax® or Fluvax Junior®, demonstrating the need for risk quantification through epidemiological methods.

7. Post script

A cut-off date of 7 May 2010 was chosen for this review to allow sufficient time for the assessment and investigation of reports by the TGA which included consideration of the large amount of information submitted by WA Health to assist in the review of cases. Only 2 reports of convulsion from WA have been submitted to the TGA since the 7 May:

- ADRS No. 266788 was a 4-year-old male child with a previous history of seasonal influenza vaccination who had a febrile convulsion following immunisation with his first dose of Fluvax® (Batch number 26902). The seizure was witnessed by his mother and he was treated in hospital. Time to onset was 7 hours. The child's temperature was not reported. Fluvax® was the sole suspected causative agent.
- ADRS No. 267314 was a 3 year old male who was found fitting by his mother 5.5 hours after vaccination with Fluvax® (Batch number 27002). No follow-up information has been received from the reporter in response to a request from the TGA. Within the original AEFI report there was no information about the child's medical history or previous seasonal influenza vaccination history – although the reporter stated this was the "4th dose", which may reflect immunisations in previous years. It was stated that a doctor friend staying at the house gave paracetamol and tepid sponging, which is suggestive of the child having a fever although a temperature recording was not given. It is not explicitly stated that the doctor friend observed the seizure which would have increased the security of the diagnosis. On the basis of the information provided so far, Fluvax® appears to be the sole suspected causative agent.

Neither report is a duplicate of any case received to date.

Also, on 21 May 2010 WA Health advised by email (TRIM R10/104697) that a further 2 PMH cases had been re-classified as <u>not</u> being febrile convulsions following review by paediatricians at PMH – ADRS Nos 265104 and 265879:

- ADRS No. 265104 had been already excluded by this reviewer on the basis that the initial AEFI report did not mention a convulsion and the case did not appear on the PMH spreadsheet; and
- ADRS 265879 was considered by this reviewer to be only possibly causally related to seasonal influenza vaccine because the child had developed RSV infection shortly after the presentation to ED. No case notes were submitted for this case by the 19 May 2010 cut-off for this review and so the assessment was based on an original AEFI report and a completed clinical follow-up information document submitted by WA Health.

This gives a total of 58 cases of febrile convulsion in WA.

Figure 1 Cumulative reports of convulsion to 7 May 2010

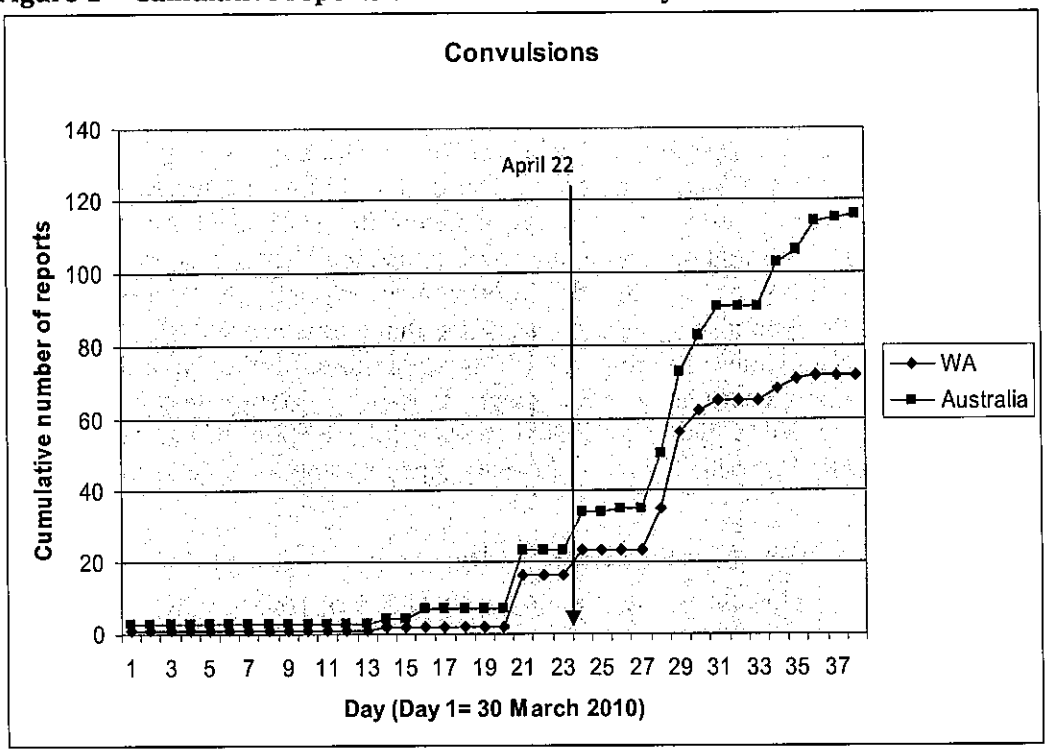


Figure 2 Age distribution for reports of convulsion on database at 7 May 2010

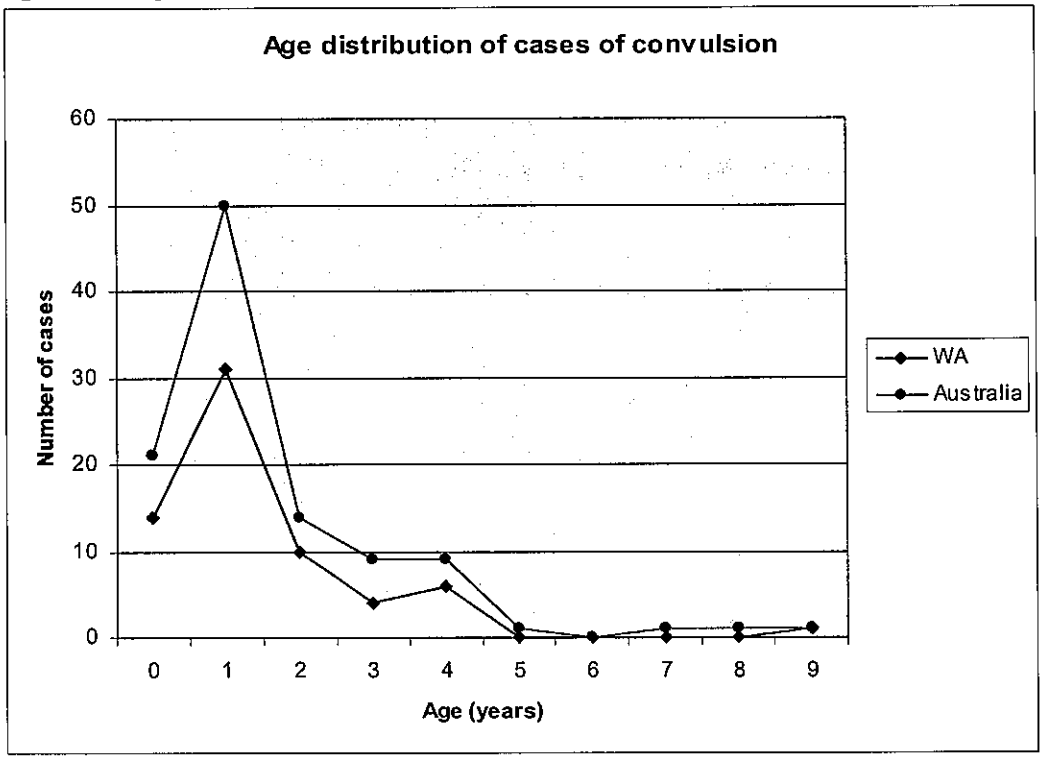


Table 1 Time to onset of convulsion – TGA ADRS data

	WA database	AUST database
Range	3hr – 72hr	5min – 2 weeks
Mean	8.9hr	12.7hr (minus outlier 9.0)
Median	7hr	7.5 (minus outlier 7.25)
≤ 6hr	20 (30.3%)	30 (28.0%)
>6-12hr	32 (48.5%)	50(46.7%)
>12-24hr	4 (6.1%)	5 (4.7%)
>1d-3d	1 (1.5%)	2 (1.9%)
>3d-7d		
>7d		1 (0.9%)
NR	9 (13.6%)	19 (17.8%)
	66	107

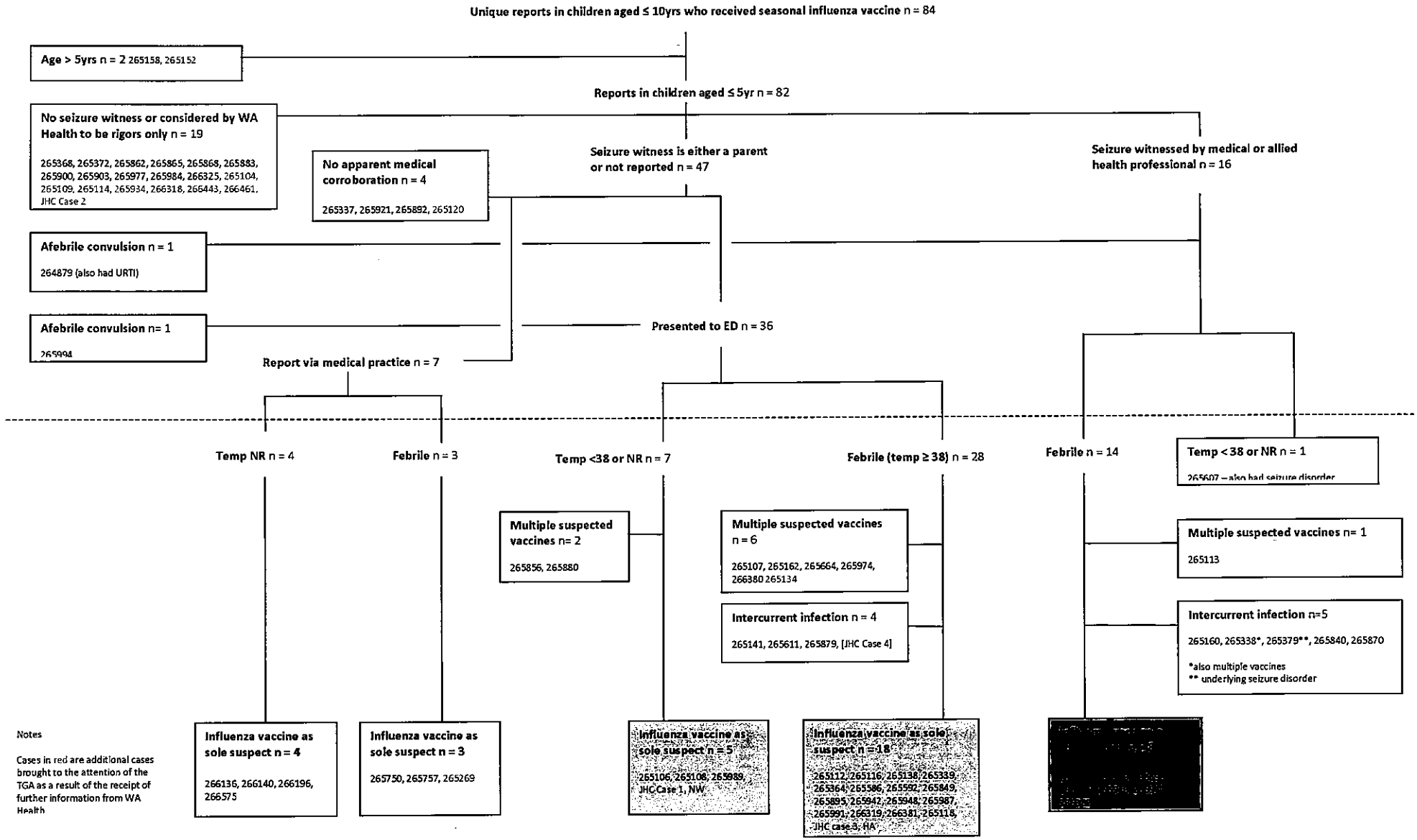
Table 2 Brand of seasonal influenza vaccine associated with TGA ADRS reports

	WA	VIC	QLD	NSW	SA	ACT	TAS	
FLUVAX	60	10	10	7	4	2	1	94
Batch no	51	5	7	6	4	1	-	74 (68% reports)
INFLUVAC		1	1		1			2
Batch no		1	1		1			2 (100%)
VAXIGRIP								
UNK	6	4		1				11
	66	15	11	8	4	2	1	107

Table 3 Fluvax/Fluvax Jr batches associated with suspected cases of febrile convulsion – Australia-wide

Batch	AUST	WA	VIC	QLD	NSW	SA	ACT	TAS
20801	1	1						
22702	1	1						
26102	1		1					
26103	1	1						
26201	1				1			
26202	1	1						
26301	1	1						
26302	1	1						
26403	1			1				
26802	2	1			1			
26901	4	3		1				
26902	2	2						
27001	1					1		
27002	2	1					1	
27101	3			3				
27102	12	12						
27401	2		2					
27402	1		1					
27501	1					1		
27702	3				2	1		
27801	29	26	1	1	1			
27802	1				1			
28001	2			1		1		
Total	74	51	5	7	6	4	1	

Figure 3 All reports of convulsion from WA – database plus additional cases submitted by WA Health



Analysis of Australia-wide reports of convulsion following administration of seasonal trivalent influenza vaccine 2010

1. Purpose of this report

This is the second of two reports about convulsion as an adverse event following immunisation (AEFI) with seasonal trivalent influenza vaccine in children under the age of 10 years. It provides a quantification of all reports known to the TGA as at close of business (COB) 7 May 2010, with an analysis of clinical presentation and causal relationship with the vaccine. The analysis is based on all information available to the TGA as at COB 19 May 2010.

An earlier report on cases from WA ("the Report from WA" or RWA) provided a detailed analysis of cases from that State, undertaken because a potential safety signal was first identified in WA and that State had been the largest source of AEFI reports for the trivalent seasonal influenza vaccine. In addition, WA health authorities had submitted medical records for many of their reports, providing much more comprehensive clinical information than is available from across the other jurisdictions.

This second report has been structured in a manner similar to the RWA and should be read in conjunction with the RWA, which contains the relevant background information, including the methodology employed for identification and causality assessment of cases.

2. Reports on the TGA ADRS database

As at COB 7 May 2010 there were 116 AEFI reports of convulsion in children under the age of 10 years Australia-wide on the TGA ADRS database. The WA reports are summarised in the RWA. Reports from other States and Territories are presented in this report.

Two of the reports (ADRS Nos 264165 and 265824) had already been identified as duplicates and denoted as such in the database. There were an additional 7 reports (ADRS Nos 265168, 265516, 265744, 265762, 265835, 265859 and 266295) identified as duplicates during the course of the investigation, giving a total of 9 duplicates – 7 from WA and 1 each from Victoria and SA. When the duplicates were accounted for, there were 107 unique cases distributed across the jurisdictions as follows:

WA	66	VIC	15	QLD	11
NSW	8	SA	4	ACT	2
TAS	1	NT	0		

Key summary demographic characteristics of the cases in each jurisdiction and Australia as a whole are shown in Table 1. The individual cases are reviewed in section 4.

Of the 107 unique cases Australia-wide, 63 (59%) occurred in males, 43 (40%) in females and gender was unknown in 1 (1%). This is in keeping with the known predominance of febrile convulsions in males. Age ranged from 6 months to 9 years, with a median age of 1 year. The age distributions across the States and Territories and for Australia as a whole are shown in (Figure 1). Results for the ACT, Tasmania and the NT are not shown as they had only 2, 1 and 0 cases, respectively. The distributions for WA, Victoria and Qld are similar to that for Australia, which is not surprising given that these 3 States were the major contributors of cases. The numbers of cases in the remaining States were too low to provide any meaningful trends. Overall, 85/107 (79.4%) cases were aged 2 years or younger and 94/107 (88%) cases were aged 3 years or younger. Note this was a fairly crude analysis using ages in years as calculated by the TGA

ADRS database. Time constraints precluded the calculation of ages in months, calculation of average age and presentation of data by 6-month age intervals.

Times to onset of event across the States and Territories and for Australia as a whole are shown in (Figure 2). Once again, the results for the ACT, Tasmania and the NT are not shown. The distributions for WA, Victoria and Qld are again similar to that for Australia and the numbers of cases in the remaining States were too low to provide any meaningful trends.

Across the jurisdictions the time to onset ranged from 5-10 minutes to 2 weeks. There were 3 cases that have been considered as 'outliers' by this reviewer – 2 from Victoria (ADRS Nos 266280 and 266283) and 1 from Qld (ADRS No. 266569). Two of these outliers (ADRS Nos 266283 and 266569) had onset of symptoms within 10 minutes of vaccination. In the first case (ADRS No. 266283) the child was reported to have started shaking, become stiff and pale 5 to 10 minutes post vaccine. The child was reported to be awake but non responsive and to have a fever although the actual temperature was not reported. The "episode" lasted 10 minutes and the child presented to an emergency department (ED) within 20 minutes, by which time the episode (i.e. all symptoms and signs) had resolved without any treatment. The time course for this case – for a fever to develop to such a magnitude as to cause a convulsion and then spontaneously resolve – is quite unusual and therefore questionable. No clinical follow-up form or ED case notes have been received for this case. In the second report (ADRS No. 266569), a parent reported that he saw his daughter faint and hit her head 10 minutes post vaccination and then she had a convulsion. Apparently a nurse told the father the convulsion was caused by the head injury. However, in the opinion of this reviewer, this is more likely to be a case of syncopal convulsion. The third outlier case (ADRS No. 266280) was that of a 1-year-old child who developed an URTI complicated by severe asthma 2 days post vaccination and then had a febrile convulsion (with temperature at that time of 39.9°C) some 2 weeks post vaccination. This reviewer considers there is no temporal relationship between the vaccination and the febrile convulsion and there is also a confounding factor of the infection that occurred in the intervening period, so that the febrile convulsion is unrelated to the seasonal influenza vaccine.

When the outliers are excluded, the mean and median time to onset for Australia-wide cases was 9hr and 7.25hr, respectively, noting that almost 18% cases did not have a time to onset recorded (see Table 1). Very similar mean and median results were seen for the 3 largest contributing states of WA, Vic and Qld. Also, despite low numbers of cases in SA and the ACT, the mean and median times were also similar. The results for NSW were somewhat higher, largely due to the fact that 2 of the 6 cases with a reported time to onset had times to onset of 20.5hr and 48hr, respectively. It is known that fever typically occurs within 6 to 12 hours in a significant proportion of children under the age of 3 years following their first influenza vaccination. However, in this particular series of cases (where approximately 90% children were aged 3 or less), 31/107 (28.0%) actually had onset within $\leq$ 6 hours of vaccination. In addition, 50/107 (46.7%) had onset in >6 – 12 hours; and 5/107 (4.7%) > 12 hours after vaccination. Time to onset was unknown in 18/107 (17.8%) cases.

The brand of the vaccine used was known in 96 cases, 94 of which received Fluvax® or Fluvax Junior® and 2 of which received Influvac®. Batch numbers were available for 74 cases. A total of 23 different batches were implicated, but two batches – 27102 and 27801 – accounted for more than half of those cases (41 in total).

Previous seasonal influenza vaccination history was unknown in 49/107 (45.8%) cases, 41/107 (38.3%) cases had no previous vaccination with seasonal influenza vaccine and only 17/107 (15.9%) cases had received a previous seasonal influenza vaccination.

3. Additional cases identified during the review

In the aftermath of the suspension of the use of seasonal influenza vaccine under the National Immunisation Program (NIP) for children less than 5 years of age, to assist the TGA in its investigation each jurisdiction was asked and agreed to complete a standardised template to provide data on:

- seasonal influenza vaccine distribution;
- AEFIs reported in children from 6 months to 10 years of age since 1 March 2010; and
- presentations at emergency departments of large metropolitan paediatric centres by children aged 6months to 10 years with fever and/or febrile convulsions for the period 1 March to 30 April in the three years 2008, 2009, and 2010.

Each reporter of an AEFI case of seizure/convulsion was also asked to obtain follow-up clinical information in a standardised format (similar to that used for surveillance during the 2009 Panvax rollout) for submission to the TGA.

As a result of the abovementioned processes, 31 additional cases were identified across the jurisdictions as follows:

WA	18	VIC	4	QLD	0
NSW	3	SA	4	ACT	1
TAS	1	NT	0		

The 18 additional cases for WA were summarised in the RWA, with the conclusion that there were 10 additional cases that could be considered to represent reports of convulsion of varying degrees of diagnostic certainty that required assessment from a causality view point.

Key points of note in the 13 additional cases from other jurisdictions in this report are:

- Two cases (ADRS Nos 265453 and 265498), both from SA, had been reported by the Immunisation Section of the Communicable Diseases Branch of SA Health via the web without any mention of convulsion in the initial report. There was no indication of any motor manifestations or loss or alteration of consciousness that would indicate some sort of seizure activity. However, the spreadsheet submitted by SA Health had indicated that both patients had experienced febrile convulsions. In the absence of any follow-up information to the contrary, these reports are considered by this reviewer to be reports of febrile reactions and the spreadsheet entries to be erroneous.
- None of the remaining 11 additional cases had been reported to the TGA. These have been identified by the State or Territory in which they occurred and by a case number.

  One case (SA case 1) was witnessed by an ambulance officer and required treatment with i.m. midazolam. The temperature was recorded at 39.5°C. This case can be considered diagnostically secure.

  Another case (NSW case 2) was witnessed by nursing staff. However, although the child received midazolam for a presumed seizure whilst being an inpatient for a febrile reaction post vaccination, when the case was reviewed clinically it was concluded that a convulsion was unlikely to have occurred. Therefore, this reviewer considers this case was not medically corroborated.

  Two remaining cases from NSW (NSW cases 1 and 3) both had ED discharge diagnoses of febrile convulsion, with recorded temperatures in excess of 39°C. The seizure witnesses were not reported for either case and have been presumed by this reviewer to be parents rather than medical or allied health professionals.

Four cases were from Victoria – 2 of these cases (Vic Cases 1 and 2) appeared in the consolidated spreadsheet titled 'Dept of Health Fluvax Report VIC 28 Apr 2010.xls'. In Vic case 1, the child was found "rigoring" and crying in her sleep by her mother and when roused the child complained of being cold. This description does not fit with that of a convulsion in that there does not appear to have been any tonic-clonic motor manifestations and no loss of consciousness. Indeed the child was able to converse with her mother to indicate she felt cold. The child was not reviewed at an ED. In Vic case 2, the child presented to an ED with a temperature of 42.0°C after an episode of "body shaking", with leaning to one side and staring gaze. The seizure witness in this case was not reported but it does not appear to have been witnessed by a medical or allied professional. Furthermore, the description of the motor manifestations is not entirely clear and the alteration of consciousness may be more in keeping with an absence type atypical febrile seizure. This reviewer decided to err on the side of being conservative and include this as having been a case of convulsion, albeit of lesser diagnostic security. The 2 remaining Victorian cases, Vic cases 3 and 4, were listed on a spreadsheet for Monash Medical Centre but did not appear on the Victorian Health Department's main spreadsheet, which casts some doubt as to whether these were truly considered to be cases of febrile convulsion. In Vic case 3, the child was aged 6 years and highest temperature recorded was 37.1°C, which would preclude a diagnosis of febrile convulsion. This child was also noted to have nasal congestion and ear pain, suggestive of an underlying URTI. Vic case 4 had no clinical information beyond a simple description of "vomiting, fever, rigors and convulsion" with a temperature of 38.5°C and no apparent underlying contributory factors. The seizure does not appear to have been witnessed by a medical or allied professional and is, therefore, diagnostically less secure.

Of the remaining 3 cases, one (SA case 2) had reasonably well described tonic-clonic motor manifestations and disturbance of consciousness, associated with a temperature of 40.2°C. The events were witnessed by a parent rather than medical professional. Another case from Tasmania (Tas case 1) was merely documented as a case of febrile convulsion with temperature of 38.3°C with no information about who witnessed the seizure. In the final case (ACT case 1) it is not clear that a seizure even occurred. It was merely recorded that the mother heard strange noises from the child, with the comment "?seizure ?post ictal". This case is not considered by this reviewer to have been medically corroborated.

Based on the assessment above, this reviewer considers there were an additional 7 cases (SA case 1, SA case 2, NSW case 1, NSW case 3, Vic case 2, Vic case 4 and Tas case 1) that can be considered to represent reports of convulsion. Four of the remaining 6 cases (ADRS Nos 265453 and 265498, Vic case 1 and Vic case 3) can be considered not to be cases of febrile convulsion and 2 (NSW case 2 and ACT case 1) have not been medically corroborated.

Australia-wide, there were 17 additional confirmed cases of febrile convulsion (WA 10; SA 2; NSW 2; Vic 2 and Tas 1).

For States and Territories other than WA, the additional cases were identified from the spreadsheets provided from the sentinel paediatric centres. In WA, whilst the additional cases were identified mostly from the spreadsheets, cases were also identified through completed clinical follow-up forms and medical records provided to the TGA[1]. These activities were coordinated by WA Health, which not only gave a high completion rate for the follow-up clinical information forms, but also higher case ascertainment.

[1] As noted in the RWA, on 29 April 2010 the TGA requested that photocopies of the medical case notes of children with febrile convulsions be sent to the TGA for analysis. Some of the case notes, as well as clinical follow-up forms received from WA Health were for cases that did not appear in the TGA's ADRS database.

4. Review of all cases of suspected febrile convulsions

Overall, there were 138 suspected cases of convulsion in children under the age of 10 Australia-wide that were known to the TGA by virtue of either having been coded as such on the TGA ADRS database (107 cases) or having been drawn to the attention of the TGA during the analysis of spreadsheets submitted from sentinel paediatric hospitals and/or case notes (31 cases). The cases were distributed by jurisdiction as follows:

WA	84	VIC	19	QLD	11
NSW	11	SA	8	ACT	3
TAS	2	NT	0		

The following summary of the cases should be read in conjunction with Figure 3 which is an adaptation from Figure 3 of the RWA. Note the disposition of the 84 cases from WA will not be re-discussed here. The WA cases in Figure 3 of this current report appear in red font.

As explained in the RWA, Figure 3 depicts the cases from the viewpoint of both the security of the diagnosis of febrile convulsion and causal relationship to the seasonal influenza vaccine. The information within the figure is located within two parts separated by a broken horizontal line. Cases appearing in boxes above the broken line have been assessed as either definitely not a febrile convulsion or not having been medically corroborated (little diagnostic security). These cases have not been subject to a causality assessment. The cases below the broken line are arranged from right to left in order of decreasing diagnostic security: those where the seizure was witnessed by a medical or allied health professional represent the highest diagnostic security; those where the child was reviewed and a diagnosis of febrile convulsion made in an ED department are the next most secure.

Within the groupings of diagnostic security cases have been sub-grouped according to presence or otherwise of other factors, such as intercurrent infection, concomitant administration of other vaccines or an underlying seizure disorder, to which the event could also reasonably be attributed. Where such other factors were present, the causal relationship between the seasonal influenza vaccine and febrile convulsion would be possible[1]. These cases appear in unshaded boxes. Where no other factors are present and the seasonal influenza vaccine is therefore the sole suspected agent, the cases would be assigned a causality rating of very likely. These cases appear in the shaded boxes at the bottom of the figure. The shading of boxes is graduated to give a sense of the level of diagnostic security, with the darkest shading being the more secure.

Six of the 138 reports were in children aged more than 5 years. In addition to being older than 5 years, five of these cases had other factors that would also preclude a diagnosis of febrile convulsion. Two of these cases (ADRS Nos 265152 and 265168) were from WA and discussed in the RWA. The third case (ADRS No. 266156) was identified in a report from a public health unit

[1] The WHO categories for causality of AFEIs apply, of which the most relevant are:
Very likely – a clinical event with a plausible time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals;
Probable – a clinical event with a reasonable time relationship to vaccine administration; is unlikely to be attributed to concurrent disease or other drugs or chemicals;
Possible – a clinical event with a reasonable time relationship to vaccine administration, but which could also be explained by concurrent disease or other drugs or chemicals;
Unlikely – a clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals.
The rating 'certain' is not applicable given the circumstances of this particular investigation. 'Certain' is used in rare instances where there is a demonstration of relationship, e.g. such as mumps vaccine-related aseptic meningitis with isolation of the vaccine strain. The rating 'unrelated' applies to events where there is an incompatible time relationship.

in NSW that described a 30 second episode of shaking, eyes rolling and crying in a 5 ½ year old boy. The event was referred to as a "slight seizure". Importantly, there was no loss or alteration of consciousness as the child was said to be crying and the eye rolling and shaking were the only apparent motor manifestations. Without a clearer description of tonic-clonic activity, it is possible this was merely a case of rigors. In the fourth case (ADRS No. 264956), also from NSW, an 8-year-old girl was reported to have developed a fever of 38.4°C and some 20 hours after vaccination experienced multiple seizures, two of which were witnessed by ambulance officers and one in the ED. This case was reported via the AME Line and contained quite detailed descriptions of the event and background medical and immunisation history of the child. No other possible causative agents were identified for this particular case. Neither of the remaining 2 cases from other jurisdictions had evidence of a fever. One of these cases (ADRS No. 266569) was a consumer report in which a parent reported his daughter fainted, hit her head and then convulsed approximately 10 minutes post vaccination, with no suggestion that a fever was present. The features of this case are more consistent with syncopal convulsion. In the other case, Vic case 3, the child was aged 6 years and the highest temperature recorded was only 37.1°C. This child was also noted to have nasal congestion and ear pain, suggestive of an underlying URTI.

There were 132 cases in children aged 5 years or younger, 22 of which have been assessed as not having experienced a febrile convulsion. Of these exclusions, 19 were from WA and these have been discussed at length in the RWA. The 3 remaining excluded cases ADRS Nos 265453 and 265498 and Vic case 1 were so called 'additional' cases identified from spreadsheets submitted to the TGA and have been discussed in section 3 of this report.

Of the remaining 110 cases:

- 27 had a seizure that was actually witnessed by a medical practitioner or allied health professional (e.g. ED nurse or ambulance officer). 16 such reports came from WA and all but two of these had medical records available for review – these have been assessed in detail in the RWA. Ordinarily such reports would be considered to have the highest diagnostic security. However, one case, NSW case 2, was witnessed by nursing staff and, although the child received midazolam for a presumed seizure whilst being an inpatient for a febrile reaction post vaccination, when the case was reviewed clinically it was concluded that a convulsion was unlikely to have occurred. Therefore, this reviewer considers this case was not medically corroborated.
- 52 cases had a seizure that was witnessed by a parent and in 31 cases the seizure witness was not identified. Combined, these 83 cases can be considered somewhat less secure diagnostically than those where the seizure was observed by health professionals. However, it must be recognised that the vast majority of febrile convulsions are only ever observed by parents and a final diagnosis is made by medical professionals on the basis of a history obtained from the parent(s) some time after the event. In this regard it has to be noted that 70 of the 83 cases presented to an ED for review and 8 of the 83 were the subject of a report from a GP/medical practice[1].
- Only 5 cases (ADRS Nos 265337, 265344, 265921, 266578 and 266579) were not medically corroborated because they did not present for medical review at either an ED or a GP/medical

[1] There were 8 reports from GPs/medical centres in WA, 1 of which (ADRS No. 266325) had information from both a GP, who was the initial reporter, and medical notes from JHC. The medical notes were far more comprehensive than the GP report and so, for the purposes of the WA analysis, this case has been included among those that presented to ED and so in effect there were 7 "GP reports" from WA. In comparison, in the other jurisdictions combined, there were a total of 7 reports from GPs/medical centres. However, 6 of these appeared on spreadsheets from sentinel paediatric hospitals indicating they had received some sort of review in an ED. They are therefore considered among the 64 cases that presented to an ED. The remaining case (ADRS No. 266123) has been added to the 7 "GP reports" from WA.

centre. These appear in the box with the heading "No apparent medical corroboration" on the far left hand side and above the broken line of Figure 3. It should be noted that there were two additional cases that appeared in the corresponding box in Figure 3 of the RWA – ADRS Nos 265120 and 265892. In the RWA report it was acknowledged that these cases had presented to an ED but the occurrence of a convulsion had not been medically corroborated and thus they appeared along-side cases for which no medical review had been sought. For the purposes of this second report, largely because there are a number more cases in a similar vein (viz ADRS Nos 266023, 266025, 266283 and ACT case1), it was considered more appropriate by this reviewer to include them in the analysis of cases that presented to an ED. In other words they have moved boxes but remain above the broken line as non cases of febrile convulsion.

a. Cases of convulsion observed by a medical or allied health professional

A total of 27 cases have been reported where the seizure was observed by a medical or allied health professional. Of these, two cases are not considered to have been febrile convulsions. ADRS No, 264879 was a case from WA and is discussed in the RWA. The second case (NSW Case 2) had a so called seizure observed by nursing staff whilst the child was febrile (with temperature of 40.0°C) but, on medical review, was considered unlikely to have been a convulsion – suggesting that it may have been rigors that were in fact observed.

A third case (ADRS No. 265607), from WA (discussed in the RWA) was thought more likely to be due to an underlying seizure disorder. Interestingly the highest recorded temperature for this child was well below 38.0°C. Two further cases (ADRS Nos 264975 and 266033) did not have any temperature recorded in the reports received by the TGA. ADRS No. 264975 was a scant GP report of a child who was admitted to hospital with severe febrile convulsions. It is apparent that the child must have experienced repeated or ongoing seizures as he was eventually admitted to ICU. In ADRS No. 266033 a 14-month-old boy had sudden onset of febrile convulsions that required treatment with PR diazepam, indicating that the seizures were observed by medically trained staff. There was no suggestion of any other causative agent in either of these cases and, thus, the causal role of seasonal influenza vaccine is considered to be very likely.

There were 22 cases were a temperature in excess of 38.0°C was documented in association with a convulsion:

- 2 of these cases (ADRS Nos. 265113 and 265272) were also vaccinated with Varilrix® at the time they received Fluvax® and, thus, the causal association of the febrile convulsion with Fluvax® is, at best, possible.
- 5 of the cases (ADRS Nos 265160, 265338, 265379, 265840 and 265870) had intercurrent infection, which offer a plausible alternative causal explanation for the febrile convulsion. The causality for these cases is, therefore, only possible. All these cases came from WA and were discussed in the RWA.
- 15 cases had no evidence of concurrent disease or exposure to other vaccines, medicines or chemicals that would offer an alternative causal explanation for the febrile convulsion. Thus, in these cases a causal relationship to the seasonal influenza vaccination is highly likely. More than half of these reports came from WA (ADRS Nos. 265110, 265149, 265373, 265596, 265741, 265946, 265947 and 266382). Medical records were available for 7 of these 8 cases and were considered to provide robust evidence of both the diagnosis of febrile convulsion and the absence of other likely causative agents (see RWA for more detailed discussion). The remaining reports (ADRS Nos 265324, 265381, 266110, 266288, 266560, 266731 and SA case 1) were reasonably well documented, although only 1 case (ADRS No. 265324) had detailed follow-up information in the form of hospital case notes and 1 case

(ADRS Nos 266560) had a completed clinical follow-up document which provided an actual description of the seizure observed in the ED.

b. Cases of convulsions observed by parent or other and presenting to ED department

There were 70 cases where a parent(s) was the only witness of the seizure, following which they presented with the child to an ED.

In one case (ADRS No. 265994), from WA, a 1 year old child with a previous history of febrile convulsions presented to ED following a convulsion that was witnessed by the mother 12 hours after vaccination. No temperature recordings were available from either the initial report or the clinical follow-up information document. Ordinarily, one would expect that a parent might not have access to a thermometer, or think to take the child's temperature at the time of witnessing a febrile seizure but in most cases would relate the fact that the child was hot or "burning up". However, in this particular case, the mother had specifically stated the child did not have a temperature and was not hot to touch, suggesting that this was an afebrile seizure. Of note, there was a family history of convulsions. No medical records were available to allow further assessment of the case.

A further 6 cases can be considered not to have been medically corroborated as being a febrile convulsion even though the child presented to an ED. Two of these (ADRS Nos 265120 and 265892) were discussed in the RWA. Of the remaining 4 cases in this subgroup, ACT case 1 was discussed on page 4 of this report. In another case from the ACT (ADRS No. 266025), a medical centre reported a 2-year-old child had experienced a high fever and "?seizure". Importantly, there was no loss of consciousness and it was stated the child was distressed and pulling at his ears at the time whilst he was kicking his legs out and stiffening his body – which would not be consistent with a true convulsion. Furthermore, this case did not appear on the ACT spreadsheet despite the child having presented to the sentinel hospital. In ADRS No. 266032 a child presented to ED after one of her parents had observed what was reported to have been 3 convulsions in her sleep. However, the comments from NSW Health contained within the supporting documents for this case on the TGA's ADRS database stated this was considered unlikely to be a true convulsion. The last case (ADRS No. 266283) was an outlier for time to onset of the event –with the fever and convulsion reported to have occurred within 5 to 10 minutes of vaccination, all of which had resolved by the time the child presented to ED at RCH. Of note, this case does not appear on the spreadsheets submitted by the Victorian Department of Health, which included all cases with final diagnosis of febrile convulsion at RCH.

51 of the 70 cases presenting to ED had a temperature in excess of 38.0°C. Of these:

- 9 cases received vaccination with concomitant vaccines at the time they received Fluvax® and, thus, the causal association of the febrile convulsion with Fluvax® is, at best, possible. Six of these were from WA (ADRS Nos. 265107, 265134, 265162, 265664, 265974 and 266380) and have been discussed in the RWA. Of the 3 cases from other jurisdictions, 2 received more than one concomitant vaccine – ADRS No. 264495 also received Hib/MMR/Men C and ADRS No. 265490 also received the standard immunisations for a 1-year-old. The remaining case (ADRS No. 266284) also received Varilrix®.
- 4 cases had intercurrent infection, which offers a plausible alternative causal explanation for the febrile convulsion and the causality for these cases is, therefore, only possible. All 4 cases (ADRS Nos 265141, 265611, 265879 and JHC case 4) were from WA and have been discussed in the RWA[1].

[1] Note ADRS No. 265879 was also discussed in the *Post Script* section of the RWA in relation to additional information received after the cut-off of 19 May 2010. See also *Post Script* section of this report.

- 1 case (ADRS No. 266280) had no temporal relationship with the seasonal influenza vaccine, occurring some 2 weeks after vaccination, during which time the child also experienced a viral URTI. This case is therefore considered to have a causality rating as being unrelated.
- ADRS No. 266296 was a report of a febrile convulsion lasting 20 minutes with onset 10hrs post vaccination, at which time the child's temperature was 40.8°C. There was no evidence of the child having any intercurrent infection or having received concomitant vaccines. However, it was noted by this reviewer that the treatment rendered included "midazolam....by mother as per usual regime", suggesting an underlying seizure disorder. A request for additional information, in particular the child's current medical conditions and past medical history, was sent to the reporter but no further information has been received to date. In the absence of this important additional information, a role of the underlying seizure disorder has not been excluded and, therefore, the causality for this case is only possible.
- 36 cases had no evidence of concurrent disease or exposure to other vaccines, medicines or chemicals that would offer an alternative causal explanation for the febrile convulsion, under which circumstances a causality rating of 'very likely' would apply. Half of the cases (ADRS Nos 265112, 265116, 265118, 265138, 265339, 265364, 265586, 265592, 265849, 265895, 265942, 265948, 265987, 265991, 266319, 266381, JHC case 3 and pt HA) came from WA. Comment on these cases appears in the RWA. Of the 18 cases from jurisdictions other than WA:
    - 6 were identified as additional cases from the spreadsheets submitted by jurisdictional health authorities – NSW case 1, NSW case 3, Vic case 2, Vic case 4, SA case 2, Tas case 1. Generally the spreadsheets contained minimal descriptive information;
    - 6 (ADRS Nos 264965, 265127, 265526, 265976, 266337 and 266564) had completed clinical follow-up documents which confirmed the occurrence of a seizure, however no medical records or discharge summaries were available for these cases; and
    - 6 cases (ADRS Nos 265716, 265958, 266151, 266267, 266287 and 266563) had no information available other than the original database report but the event was corroborated by a spreadsheet from the corresponding jurisdictional health authority for all cases except ADRS No. 266151.

12 cases presenting to an ED either did not have a temperature recorded or the temperature was below 38.0°C. 10 cases had no temperature reading recorded and, of these, 5 were from WA (ADRS Nos. 265106, 265856, 265880, 265898 and pt NW) and were reported by the parent to have a fever or be hot to touch. The 5 cases from other jurisdictions (ADRS Nos 264505, 265563, 266128, 266565 and 266594) also had minimal information but again there was usually a comment that a fever had been present. Only two cases, both from WA (ADRS Nos 265108 and JHC case 1) had temperatures recorded and in both cases the recorded temperature at presentation to ED was above 37.5°C. Three of the 12 cases (ADRS Nos 264505, 265856 and 265880) received concomitant Varilix® at the time they received Fluvax® and, thus, the causal association of the febrile convulsion with Fluvax® is, at best, possible. A fourth case (ADRS No. 266594) also received concomitant Infanrix and Pneumococcal vaccine. This child also had a history of cerebral palsy secondary to hypoxia with an underlying seizure disorder requiring treatment with phenobarbitone. ADRS Nos 265106, 265108, 265563, 265898, 266128, 266565, JHC case 1 and pt NW had no evidence of concurrent disease or exposure to other vaccines, medicines or chemicals that would offer an alternative causal explanation for the febrile convulsion, under which circumstances a causality rating of very likely would apply.

c. Cases reported by a GP or medical practice

There were 8 reports where information has been obtained solely from GPs (ADRS Nos 265269, 2265750, 265757, 266123, 266136, 266140, 266196 and 266575). All of these, except ADRS No. 266123, were from WA and have been discussed in the RWA. ADRS No. 266123 was a somewhat scant report of a seizure/febrile convulsion in association with a temperature of 38.5°C and increased respiratory rate in an 8-month-old child. There was no mention of any other potential causative agents.

d. Cases not medically corroborated

A total of 5 cases were not medically corroborated because they did not present for medical review at either an ED or a GP/medical centre. ADRS Nos 265337 and 265921 were from WA and have been discussed in the RWA. ADRS Nos 265344, 266578 and 266579 were parental reports direct to the TGA that merely stated the child had "convulsed"[1].

5. Summary of cases Australia-wide

On the basis of a review of all information available, there were 96 confirmed cases of febrile convulsion in children under the age of 5 years reported to the TGA as at close of business on 7 May 2010, 57 of which were from WA. Of the 96 cases, 95 were causally related to vaccination with the seasonal influenza and 1 case was considered unrelated by this reviewer because of the absence of a temporal relationship between the convulsion and vaccination. Of the 95 causally related cases, 69 have a causality rating of 'very likely' because no other potential causative factors have been identified. The remaining 26 cases are only possibly causally related to the vaccine because they can also be explained by the use of concomitant vaccines and/or concurrent infection. Fluvax® or Fluvax Junior® was used in all 62 cases where the brand of the seasonal influenza vaccine was known. Twenty one different batches were implicated, with two batches accounting for more than half of the cases – 27801 (22 cases) and 27102 (12 cases).

Of the 96 cases of febrile convulsion, 25 can be considered to have the highest diagnostic security on the basis that they were observed by a medical or allied health practitioner. Of these 25 cases, 17 are 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 use of concomitant vaccines and/or concurrent infection. In the remaining 71 cases the seizures were observed by parents and the diagnosis of febrile convulsion was made by a medical professional on the basis of a history obtained from the parent(s) after the event – 63 presented to an ED and 8 to a GP/medical centre. Of these 71 cases, 52 are highly likely to be causally related to vaccination with the seasonal influenza vaccine, a further 18 are 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 causally unrelated.

The distributions of patient age and time to onset of convulsion in the 95 confirmed cases that were causally related to the vaccination are shown in figures 4 and 5, respectively. These figures display two sets of results – those for 'All database cases', which are reproduced from the TGA ADRS data analysed in section 2 of this report (see also figures 1 and 2) and those for 'Causally related cases', which represents the 95 causally related, confirmed cases identified by the analysis in section 4. It can be appreciated that the distributions are very similar. Also, of the 95 causally related cases, 54 (57%) were male and 41 (43%) were female) which is, again, very similar to the analysis presented in section 2.

[1] ADRS Nos 266578 and 266579 were from the same parent for different children.

6. Postscript

A cut-off date of 7 May 2010 was chosen for this review to allow sufficient time for the assessment and investigation of reports by the TGA, which included consideration of the large amount of information submitted by the various jurisdictions.

At the time of finalising this report a further 19 reports had been lodged on the TGA's ADRS database:

- 7 were from WA. ADRS Nos 266788 and 267314 had been covered in the post script of the RWA and are new cases. The remaining 5 cases had in fact been identified in the WA spreadsheets and therefore considered as part of the RWA and counted amongst the 138 cases considered in section 5 above:

  ADRS No. 268285

  ADRS No. 268286

  ADRS No. 268290

  ADRS No. 268296

  ADRS No. 268294

- 6 were reports from CSL – ADRS Nos. 266733, 266739, 266741, 266744, 266826 and 266828. 4 of the 6 reports (ADRS Nos 266739, 266741, 266744 and 266826) were based solely on media reports of reactions to the influenza vaccine and, collectively, contained insufficient information to permit verification of the diagnosis or assessment and classification of the cause. As a case in point, the information contained with ADRS 265744 referred to a doctor being quoted in the media that a patient with initials BK had been taken to John Hunter Hospital with a fever of 44 degrees and a heart rate of 220bpm. There was, apparently, no mention of a seizure by the doctor. However, the report then also stated that another media report had said the patient suffered from fever and convulsion. Clearly such hearsay is not able to be evaluated further.

  In another report (ADRS No. 266828), a pharmacist reported to CSL that a 19-month-old boy had a febrile convulsion and turned purple 5 hours after vaccination with Fluvax® and went to hospital. No patient details (i.e. initials, DOB or MRN) or no medical history were provided to allow further assessment of this case. In the remaining case (ADRS 266733), a consumer report to CSL, a 1-year-old child (MV) developed a fever in excess of 40°C approximately 6.5hrs after vaccination with Fluvax® (batch 27901). The child then developed convulsions and was reported to have been rushed to hospital by ambulance and admitted for observation overnight.

- 3 reports from Qld:
  - ADRS No. 267220 is a duplicate of ADRS No. 265563.
  - ADRS Nos 268095 and 268096 were virtually identical reports via Qld Health by a mother of two siblings aged 1 and 3 years, respectively. The initial reports stated that both children developed high temperature within 3 hours of vaccination with Fluvax® (batch 27901) and had "convulsions all day", accompanied by vomiting and in, the son, diarrhoea as well. No medical attention was sought. The completed clinical follow-up forms described a single episode of each child being hot, rolling their eyes back and shaking that lasted a few seconds during which the children were "semi-conscious". These cases have not been medically corroborated and the inconsistent histories cast doubt on the diagnosis. It is more than likely that rigors have been misinterpreted as convulsions in these cases.

- 2 cases from Victoria:
  - ADRS NO. 267233 was a report from a GP via SAEFVIC of a 1-year-old boy who developed a fever of 41°C following his first dose of Fluvax® (batch 27501) and was subsequently admitted to hospital following a febrile convulsion.
  - The second case (ADRS No. 267247) was also a GP report via SAEFVIC. In this case a 3-year-old girl was reported to have had a febrile convulsion during the night and presented to an ED after receiving her first dose of Fluvax® (batch 27901).

  In both these cases there was very little other detail provided, with no other potential causative factors identified.

- 1 case SA. ADRS No. 267229 was a report from SA Health of a 4-year-old girl who developed a fever of 39.9°C, was vomiting and "very flat and dopey" after receiving Fluvax®. The time to onset was not reported. The child had a past history of febrile convulsion and the mother thought she may have had a convulsion because she recognised symptoms from the previous episode. The child was taken to WCH where she was rehydrated and given paracetamol. Of note, WCH was a sentinel hospital and the case does not appear on their spreadsheet as a case of febrile convulsion. It is apparent that no seizure was witnessed and presumably the mother interpreted the listlessness as being post ictal features. However these could be equally explained by the fever and vomiting and therefore this case is considered by this reviewer not to have been medically corroborated.

In the opinion of this reviewer, only 5 of the 19 cases can be considered to have been confirmed with any degree of security – ADRS Nos. 266733, 266788, 267233, 267314 and 267247.

Additionally, on 21 May 2010 WA Health advised by email (TRIM R10/104697) that a further 2 PMH cases (ADRS Nos 265104 and 265879) had been re-classified as <u>not</u> being febrile convulsions following review by paediatricians at PMH:

- ADRS No. 265104 had been already excluded by this reviewer on the basis that the initial AEFI report did not mention a convulsion and the case did not appear on the PMH spreadsheet; and
- ADRS 265879 was considered by this reviewer to be only possibly causally related to seasonal influenza vaccine because the child had developed RSV infection shortly after the presentation to ED. No case notes were submitted for this case by the 19 May 2010 cut-off for this review and so the assessment was based on original AEFI report and a completed clinical follow-up information document submitted by WA Health.

Adding the 5 additional cases (ADRS Nos. 266733, 266788, 267233, 267314 and 267247) to and subtracting ADRS No. 265879 from the 96 confirmed cases as at COB 7 May 2010, gives a final total at the time of completing this report of 100 confirmed cases of febrile convulsion Australia-wide.

Table 1 Summary of demographic characteristics of TGA ADRS database cases

	WA	VIC	QLD	NSW	SA	ACT	TAS	Australia
Number of cases	66	15	11	8	4	2	1	107
Gender								
Male	42 (64%)	9 (60%)	5 (45.5%)	5 (62.5%)	0	1 (50%)	1 (100%)	63 (59%)
Female	23 (35%)	6 (40%)	6 (54.5%)	3 (37.5%)	4 (100%)	1 (50%)		43 (40%)
Unknown	1 (1%)							1 (1%)
Time to onset								
Range	3hr – 72hr	5min – 2wks	10min - 8.5hr	5 – 48hr	5 – 9hr	5 – 12hr	NR	5 min – 2 wks
Mean (hr)	9	7.45 [1]	7.25 [2]	17.75	7.25	8.5	NR	9.0 [3]
Median (hr)	7	7 [1]	8 [2]	11.5	7.5	8.5	NR	7.25 [3]
Distribution								
NR	9 (13.6%)	2 (13.3%)	4 (36.4%)	2 (25%)	0	0	1 (100%)	18 (17.8%) [4]
≤ 6hr	20 (30.3%)	5 (33.3%)	3 (27.2%)	1 (12.5%)	1 (25%)	1 (50%)		31 (28.0%) [4]
>6-12hr	32 (48.5%)	7 (46.4%)	4 (36.4%)	3 (37.5%)	3 (75%)	1 (50%)		50 (46.7%)
>12-24hr	4 (6.1%)			1 (12.5%)				5 (4.7%)
>1d-3d	1 (1.5%)			1 (12.5%)				2 (1.9%)
>3d-7d								
>7d		1 (6.7%)						1 (0.9%)
Previous seasonal influenza vaccination								
Yes	14 (21.2%	2 (13.3%)	0	0	1 (25.0%)	0		17 (15.9%)
No	34 (51.5%)	2 (13.3%)	3 (27.3%)	1 (12.5%)	1 (25.0%)	0		41 (38.3%)
Unknown	18 (27.2%)	11 (73.4%)	8 (72.7%)	7 (87.5%)	2 (50.0%)	2 (100%)	1 (100%)	49 (45.8%)

[1] minus outliers 266280 and 266283

[2] minus outlier 266569

[3] minus all outliers – 26280, 266283 and 266569

[4] these figures differ from those provided in the report for WA – additional information provided for 266564 (received by TGA at that time but not assessed by this reviewer) indicated time to onset was 5.5hr whereas it was previously unreported.

Figure 1 **Age distribution for reports of convulsion on database as at 7 May 2010**

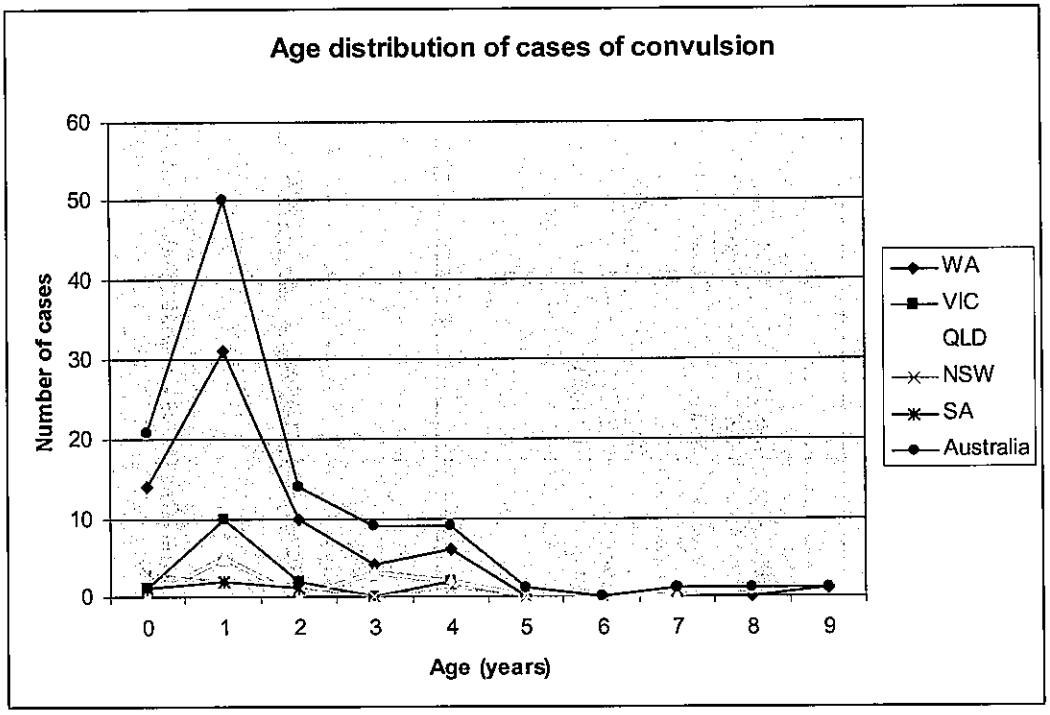


Figure 2 **Distribution of time to onset of convulsion by jurisdiction**

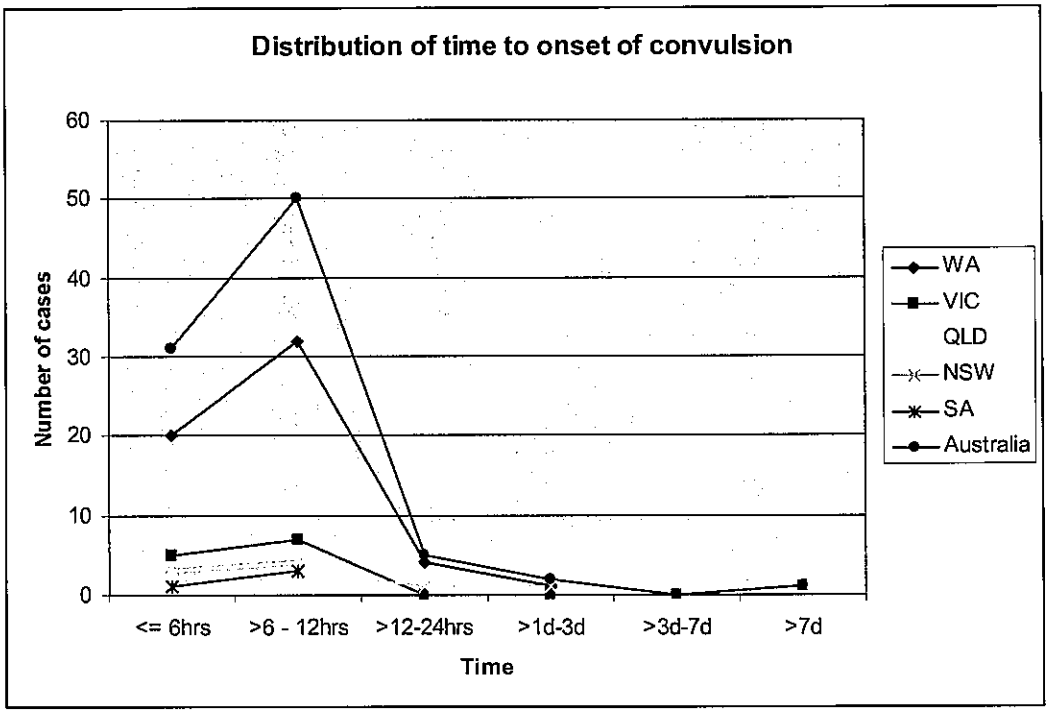


Figure 3 All reports of convulsion across Australia – database plus additional cases submitted by health authorities

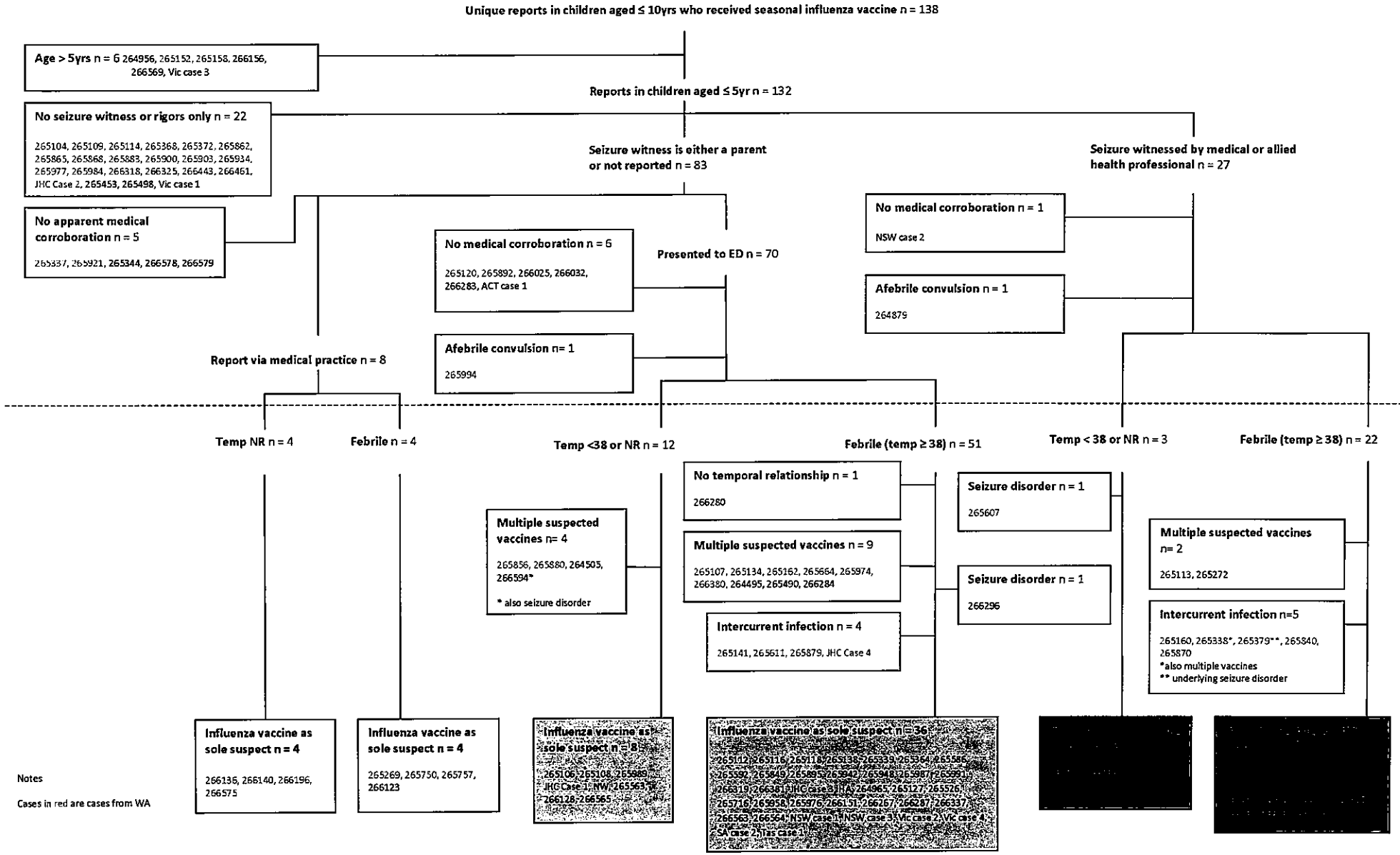


Figure 4 Age distribution of febrile convulsions causally related to seasonal influenza vaccine

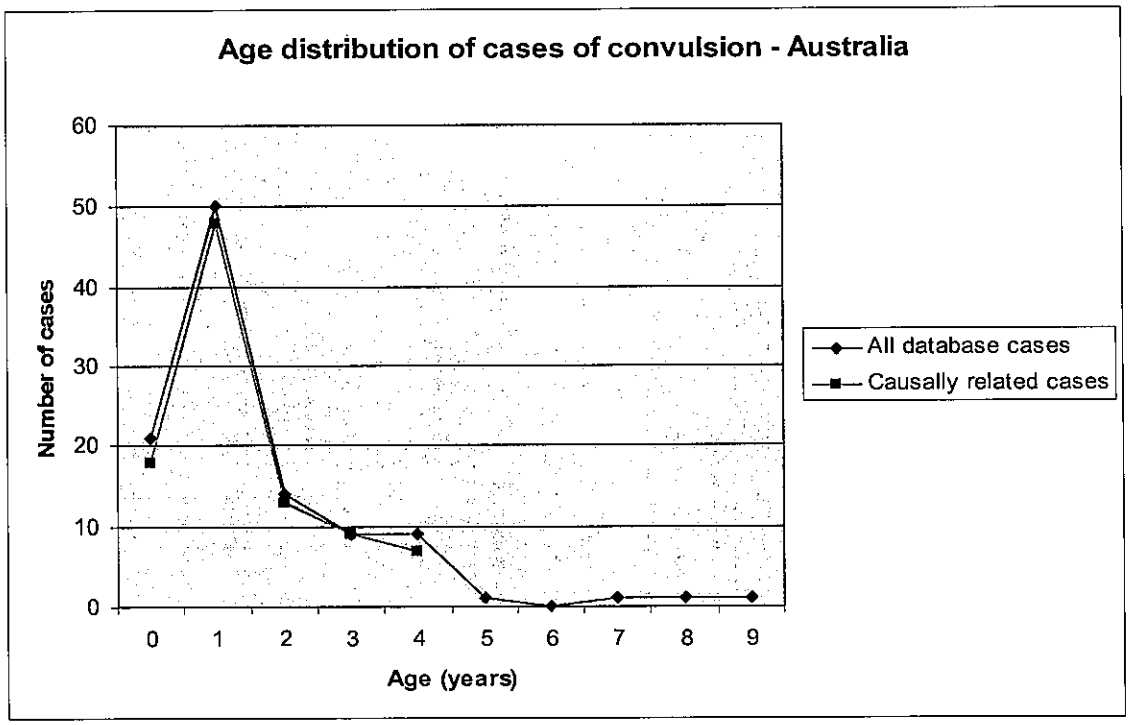
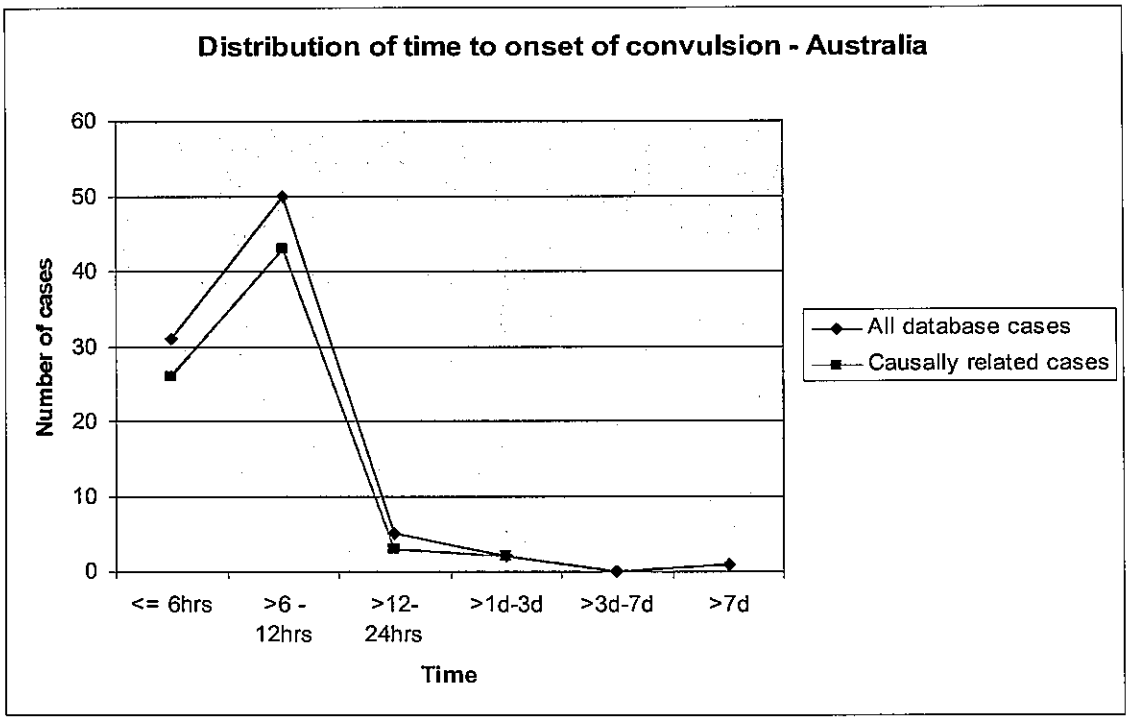


Figure 5 Distribution of time to onset of febrile convulsions causally related to seasonal influenza vaccine



TGA Influenza Seasonal Trivalent Influenza Vaccine Laboratory Investigation Program

Background

Following reports of increased fever, the TGA immediately re-examined batch release data, as well as the results from original compendia testing, carried out by the Office of Laboratories and Scientific Services (OLSS) for batches of Fluvax that had been used in Western Australia.

The TGA planned an investigation that would urgently test for the presence of lipopolysaccharide (LPS) from gram-negative bacteria, which is associated with febrile events, by measuring the endotoxin content of the vaccines. Furthermore, the potency of the batches was tested to check general quality as well as to ensure that the vaccine did not contain an unusually high content of antigen that may trigger a febrile event.

Further to these tests, the TGA has been conducting an investigation and research program to determine whether there is a biological or physicochemical basis to the vaccine product itself that may be contributing to the apparent increase in febrile events related to the 2010 influenza vaccine program.

To assist with this testing, the TGA has sought advice from a panel of experts, chaired by Professor Peter Doherty, and has had discussions with the US Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), as well as the UK's National Institute for Biological Standards and Control (NIBSC), which have offered advice and assistance with the testing program.

1. Vaccine Potency

Rationale

Haemagglutinin is one of the main antigenic determinants of influenza viruses and its content in the vaccine is a principal measure of the quality and efficacy of the vaccine. Furthermore, it is understood that haemagglutinin, amongst other proteins, plays a major role in the pyrogenicity of the influenza vaccine. Therefore the content of haemagglutinin antigen was determined in field samples from WA to check the quality and to determine if there were unusually high amounts of the antigen that may contribute to increased pyrogenicity.

Method

The content of haemagglutinin antigen was determined by immunodiffusion techniques using the Single radial immunodiffusion (SRID) assay. Tests were carried out on field samples of Fluvax from WA. Previous test results from tests carried out by the OLSS at the time of batch release were re-examined for batches of Fluvax, Vaxigrip and Influvac.

Results

All field and retention samples passed the monograph requirements and no unusual values for the content of haemagglutinin antigen were noted.

2. Bacterial Contamination

Rationale

Lipopolysaccharides (LPS) are found in the outer membrane of various gram-negative bacteria and are an important endotoxin that can cause fever. Endotoxins are present during the manufacture of the influenza vaccines and processes are in place to eliminate and test for the presence of these chemicals. Therefore, the content of endotoxin was measured in the final product by the TGA to check that it was not contributing to the increased pyrogenicity. http://en.wikipedia.org/wiki/Endotoxin - cite_note-pmid11948150-1#cite_note-pmid11948150-1

Method

Bacterial endotoxin of gram-negative bacterial origin was quantified using amoebocyte lysate from horseshoe crab (Limulus polyphemus or Tachypleus tridentatus), based on the gel-clot technique whereby the lysate clots in the presence of endotoxins. Tests were carried out on field samples of Fluvax from WA. Previous test results from tests carried out by the OLSS at the time of batch release were re-examined for batches of Fluvax, Vaxigrip and Influvac.

Results

All field samples tested passed the monograph requirements, which is 100EU/dose. All batch release testing passed monograph requirements. Endotoxin content was mostly <1.2EU/mL with the highest sample showing <6EU/mL. Given that the monograph requirement is 100EU/dose, the results indicate that the content of endotoxin is extremely low, with the highest being 1.5EU/dose in children.

3. Contaminants and chemical profile

Rationale

There are a number of processing agents used during the manufacture of the influenza vaccines that are present in trace amounts in the final product. Furthermore, the same production methodology is applied to the same vaccine product from different years. Therefore, chemical profiles of different batches within a given year and between years can be used to determine whether any general abnormalities or contaminants are present. Any significant differences could lead to further inquiries to assist in determining a cause of increase pyrogenicity.

Method

Chromatographic profiling (high performance liquid chromatograph fitted with a photodiode array UV/Vis detector) was used to compare the profile of several batches of the 2010 Fluvax with that of the 2009 Fluvax product. Additionally, two other flu vaccine products (Vaxigrip 2009 and 2010 and Influvac 2009 and 2010) were run for additional comparison. Each of the samples was run without dilution under identical chromatographic conditions in order to observe significant differences, if any, between the profiles of individual samples.

Results

No contaminants or significant differences were noted between batches within a given year or between years for each of the vaccine products. These results did not provide any evidence to pursue other lines of inquiry related to pyrogenicity.

4. Vaccine Protein Profile

Rationale

It is understood that proteins such as haemagglutinin, with a molecular weight (MW) of 77,000 Da, and neuraminidase (60,000 Da) can play a major role in the pyrogenicity of the influenza virus. These are surface membrane glycoproteins that exist in oligomeric forms with the haemagglutinin found as a trimer (230,000 Da) and the neuraminidase as a tetramer 240,000 Da. Monomeric haemagglutinin is itself a heterodimer composed of two subunits – around 50,000 and 30,000 Da. Other protein constituents include matrix proteins (28,000 and 12,000 Da) and nucleoprotein (55,000 Da). Along with several minor components origination from the membrane lipid matrix, these proteins are found at varying levels in vaccine preparations.

Studies reported in the literature suggest that a vaccine manufactured by the same method by the same manufacturer should have a particular chromatographic profile that can be used as a signature for that particular vaccine product. Therefore, any significant changes to the profile for batches of vaccine from the same manufacturer may suggest that the properties of the vaccine are different and may indicate where further investigation is required. Further, differences in the oligomeric forms of the proteins may in some way be related to their potential to be pyrogenic. For example, if there is an increase in the portion of monomers of haemagglutinin, does this influence the pyrogenicity of the vaccine? More generally, chromatographic profiling of the protein can provides evidence of a 'point of difference' for the purposes of further investigation.

Method

A suitable size exclusion high performance liquid chromatography (SE-HPLC) technique was adopted from a study by Garcia-Canas et al (2010). Samples from 2010 and 2009 vaccine batches were injected in triplicate (for Fluvax samples) and duplicate (for Vaxigrip and Influvac samples). Molecular weight reference standard preparation for SE-HPLC analysis (BioRad) was injected for molecular size estimation.

Mass spectrometry techniques are being used to assess and gain a greater understanding of the content, form and distribution of each protein within the different vaccines.

Results

Protein characterisation using size exclusion HPLC has shown different characteristic profiles for the different vaccines, which is expected given differences in the manufacture of each product. For each of the vaccines, there appears to be greater protein aggregation in the 2009 samples compared with 2010 samples, which may reflect increased protein aggregation occurring during the life of the vaccine. Nevertheless, the profiles suggested that the content of one of the proteins in the 2010 seasonal influenza vaccine may be higher than in previous years (see Fig 1 below).

Initial results from mass spectrometry studies indicate that the neuraminidase content of the H1N1 component of this year's seasonal influenza vaccine is higher than previous influenza vaccines.

5. Presence of viral particles and viable virus

Rationale

The influenza vaccines are either split virion (Fluvax and Vaxigrip) or subunit (Influvac) products. The pharmacopoeial requirement for split virion inactivated influenza vaccine requires that the vaccine consists predominantly of disrupted virus particles. Tests must be carried out by the manufacturer to demonstrate that the virus is inactivated. Therefore the presence of whole virus particles and live virus in the finished product was determined by the TGA to check whether this may contribute to increased pyrogenicity.

Method

Transmission electron microscopy and cell culture assays were carried out by the OLSS at the Department of Anatomical Pathology, and the Virology Department, at the Institute of Clinical Pathology and Medical Research, Westmead Hospital. Samples from the following vaccines were examined: Fluvax, Fluxax Junior, Panvax, Panvax Junior, Vaxigrip, Intanza and Influvac. Influenza virus infectivity for all the vaccines was examined in Madin-Darby canine kidney (MDCK) cells. All samples were looked at directly by electron microscopy (EM) and samples of vaccine were also concentrated by ultracentifugation and the sensitivity of Electron microscopy was further enhanced with the use of polylysine coated grids.

Results

No intact viral particles or live virus was detected in the final products. Moreover, no intact viral particles were detected in ultracentrifuged samples or with the use of more sensitive polylysine coated grids.

It is acknowledged that the final product is a very dilute form of the vaccine and it was unlikely that whole particles would be found by direct EM. However, whole virus particles were also not detected using more concentrated samples of vaccine and more sensitive EM techniques. Nevertheless, a significant presence of intact virus particles would have been of concern with regard to potential pyrogenicity from whole virus particles.

6. Cytokine studies

Rationale

Particular cytokines (IL-1, IL-6, TNFα and IFNα) can be associated with febrile events. Therefore, the capacity of the vaccines to induce cytokine expression is being investigated, using in-vitro pyrogenicity studies, to determine if there are differences between vaccines and differences with vaccines from different years.

Method

TGA study

Samples of vaccine were tested in vitro for their ability to stimulate transfected human peripheral blood mononuclear cells (PBMCs). Supernatants from the cells (collected from one individual) were measured for the expression of cytokines TNF-α and IFN-α using ELISA assays. The experiment was conducted in the laboratory of Prof. Bryan Williams, Faculty of Medicine, Nursing and Health Sciences at the Monash Institute of Medical Research. The assay is routinely used in this laboratory to investigate the ability of RNA molecules to stimulate the innate immune response, and was used to test whether the different vaccines had differential stimulation of this response, with TNF-α particularly linked to pyrogenicity. Appropriate controls were included to examine the impact of the vaccine formulations on the cell transfection process.

NIBSC study

Samples of vaccine were sent to NIBSC to investigate TNF-α stimulation in a monocyte activation test using blood from four adult donors.

Results

TGA Study

The different vaccines appear to have a different capacity to inhibit the assay and any results must be interpreted with great caution. In particular, Vaxigrip seem to totally inhibit the assay, with Influvac appearing to have a greater inhibitory capacity compared with Fluvax or Panvax. Nevertheless, Fluvax samples did seem to stimulate relatively greater levels of TNFα expression than Panvax, Influvac and Vaxigrip, but the 2010 Fluvax samples were no more stimulatory than the 2009 Fluvax samples. No differential pattern of IFNα expression between the vaccine samples was observed, except the lack of expression induced by Vaxigrip samples consistent with its apparent inhibition of the assay.

NIBSC Study

Results showed that there was a greater percentage of TNF-α positive lymphocytes following stimulation with Fluvax 2010 and Fluvax 2009 compared with stimulation with Influvac 2010 and 2009. However, there was no difference in the percentage of TNF-α positive lymphocytes following stimulation by Fluvax 2010 compared with Fluvax 2009.

Other studies

The TGA has been advised of results from studies in other laboratories that indicate IFNα and IL-6 expression appears to be greater with Fluvax compared to Panvax and Vaxigrip, but there is not a clear difference in the expression between Fluvax 2009 and 2010. Results from studies by CSL hint that Fluvax 2010 stimulates greater expression of IL-1, IL-6 and TNF-α than Fluvax 2009. However, the expression levels are extremely low and difficult to interpret.

7. Presence of RNA

Rationale

The possibility has been raised that the presence of RNA, particularly in the Fluvax, may be causing pyrogenicity. Therefore, the OLSS is seeking to determine whether RNA is present in the vaccine.

Method

RNA quantification using an Agilant Bioassay Kit – Bioanalyser.

Results

Initial tests have not detected the presence of RNA in Fluvax, however more sensitive tests are planned to try to detect and quantify any presence of RNA.

8. In-vivo pyrogenicity

Rationale

Given the reports of febrile events, the capacity of the vaccines to produce pyrogenicity in animal models is being investigated.

Method

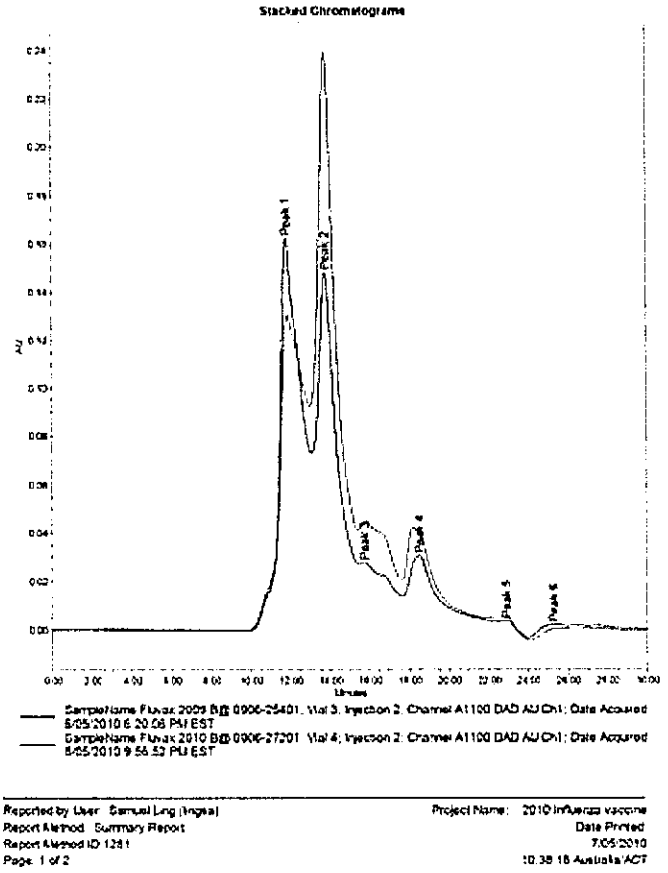
Samples of Fluvax, Fluxax Junior, Panvax, Panvax Junior, Vaxigrip, and Influvac are being tested in standard ferret and rabbit pyrogenicity models, with associated weight loss and cytokine measurements.

Results

Testing by CSL indicates that Fluvax 2010 passes pharmacopoeial requirements for rabbit pyrogenicity tests and there was no difference between 2009 and 2010 Fluvax. The company concluded that none of the formulations tested induced pyrogenic reactions in the rabbits of a magnitude that would indicate that a pyrogen may be the causative agent of the febrile responses in children under 5.

Analysis of results from pyrogenicity studies in ferrets suggests that there may be significant differences in changes to body temperature following inoculation with Fluvax compared to other vaccines. These studies are on-going in an effort to obtain more detailed information.

Fig 1: Protein chromatograms of Fluvax 2010 and 2009 vaccines



SampleName: Fluvax 2009 B@ 0906-25401

	SampleName	Peak Name	Retention Time (min)	Area	% Area	Height
1	Fluvax 2009 B@ 0906-25401	Peak 1	11.801	12486994	38.11	163001
2	Fluvax 2009 B@ 0906-25401	Peak 2	13.771	11246779	34.33	149389
3	Fluvax 2009 B@ 0906-25401	Peak 3	15.726	3054682	9.32	29450
4	Fluvax 2009 B@ 0906-25401	Peak 4	18.494	4196833	12.81	32790
5	Fluvax 2009 B@ 0906-25401	Peak 5	22.876	439238	1.34	6737
6	Fluvax 2009 B@ 0906-25401	Peak 6	25.258	417341	1.27	5014
7	Fluvax 2009 B@ 0906-25401		26.428	248397	0.76	4378
8	Fluvax 2009 B@ 0906-25401		27.376	367129	1.12	3858
9	Fluvax 2009 B@ 0906-25401		29.017	304725	0.93	2296

SampleName: Fluvax 2010 B@ 0906-27201

	SampleName	Peak Name	Retention Time (min)	Area	% Area	Height
1	Fluvax 2010 B@ 0906-27201	Peak 1	11.867	11763197	27.86	131581
2	Fluvax 2010 B@ 0906-27201	Peak 2	13.774	17690160	41.90	240896
3	Fluvax 2010 B@ 0906-27201	Peak 3	15.782	5203542	12.32	47171
4	Fluvax 2010 B@ 0906-27201	Peak 4	18.175	5417385	12.83	45496
5	Fluvax 2010 B@ 0906-27201	Peak 5	22.583	882700	2.09	9371
6	Fluvax 2010 B@ 0906-27201	Peak 6	25.431	316305	0.75	4247
7	Fluvax 2010 B@ 0906-27201		26.448	308837	0.73	4321
8	Fluvax 2010 B@ 0906-27201		27.226	640170	1.52	3751