Following an increase in febrile convulsions associated with influenza vaccine in children in 2010, Professor John Horvath AO was commissioned by the Australian Government to conduct an independent review of the national response to the reported adverse events following immunisation (AEFI) with the purpose of identifying improvements that could be made to the current Australian system. Professor Horvath commenced his work on the Review in mid-November 2010.

In March 2011 the Review of the management of adverse events associated with Panvax and Fluvax (the Horvath Review), by Professor Horvath, was finalised. The Horvath Review found that the Australian system of AEFI surveillance has a number of strengths. It is similar to passive adverse event surveillance systems in comparable countries and was able to detect the safety signal associated with the use of the 2010 seasonal influenza vaccine, take appropriate action and undertake a rigorous investigation.

The Horvath Review also included recommendations to improve the vaccine safety system in Australia in the following areas:

1) the governance of the vaccine safety system;
2) defining surveillance objectives and establishing protocols and procedures for managing adverse events following immunisation;
3) improving the national system for timely reporting of adverse events following immunisation;
4) raising community and health professional awareness of vaccine safety monitoring to ensure more complete reporting of adverse events following immunisation;
5) nationally agreed protocols for program action and communication;
6) transparency and the functions of the Therapeutic Goods Administration (TGA) to ensure better access to vaccine safety information for consumers and health professionals; and
7) vaccine usage and safety monitoring data.

The Government accepted all recommendations of the Horvath Review and agreed to a two year timeframe for implementation. The implementation of recommendations arising from the Horvath Review has been managed by the Office of Health Protection (OHP) and the TGA, under the leadership of the Chief Medical Officer (CMO). The implementation of the recommendations was overseen by an Implementation Steering Committee (ISC) with advice from a Working Party of Experts (WPOE). The ISC held its final meeting on 20 June 2013.
and acknowledged that implementation of this important body of work has seen the AEFI surveillance system in Australia strengthened and that further work was required to fully implement the recommendations.

This report provides an overview on the implementation of the recommendations of the Horvath Review and identifies further work to be progressed.

SUMMARY OF OUTCOMES OF RECOMMENDATIONS

RECOMMENDATION 1 – THE GOVERNANCE OF THE VACCINE SAFETY SYSTEM.

In 2010, the Horvath Review found that Australia’s governance arrangements for the National Immunisation Program (NIP) had worked well in the past, however the governance and reporting arrangements for vaccine safety issues were not clear. It was recommended that the Department of Health (Health) establish a Working Party to consider the current governance arrangements for monitoring and responding to vaccine safety issues in Australia and make recommendations for an improved system of governance for vaccine safety monitoring.

The Implementation Steering Committee (ISC), chaired by the Chief Medical Officer Professor Chris Baggoley, was established and held its inaugural meeting on 9 August 2011. The ISC supported establishing and resourcing a vaccine safety committee, a new body with responsibility for advising on vaccine safety in Australia as part of improved governance.

Subsequently the Advisory Committee on the Safety of Vaccines (ACSOV) was established under the Therapeutic Goods Regulations 1990 (the regulations). The ACSOV held its inaugural meeting on 13 March 2013.

The role of the ACSOV, as outlined in regulation 39G, is:

(1) The committee’s functions are, at the request of the Minister or Secretary, to provide advice and to make recommendations to the Minister or Secretary about one or more of the following matters:
   a) safety of vaccines;
   b) risk assessment and risk management of vaccines;
   c) any other matter (whether or not related to vaccine safety).

(2) The Minister or Secretary may require the committee to give its advice to other persons or bodies.
More specifically, the role of the ACSOV is to, when requested, provide expert advice:

- to officers of the TGA and the OHP on:
  1. effective and appropriate mechanisms for ensuring the ongoing safety of vaccines, including:
     a. mechanisms to improve the effectiveness of post-market passive surveillance
     b. advising on the most appropriate mechanisms for active surveillance.
  2. potential and/or already identified vaccine safety signals.
  3. the need for, and scope of, additional investigation of vaccine safety signals and the effectiveness of proposed activities to monitor and mitigate any identified risks.
  4. the appropriateness of proposed communication strategies to advise stakeholders of identified vaccine safety issues.

- to officers of the TGA on:
  1. vaccine safety issues that may impact on regulatory decisions made by TGA delegates.
  2. specific Risk Management Plans (RMPs) with respect to the adequacy of proposed post-marketing pharmacovigilance and risk minimisation activities.

- to officers of the OHP on issues related to vaccine safety which impact on the National Immunisation Program.

The ACSOV is chaired by Dr Nicole Gilroy, a consultant physician in infectious diseases, and comprises a broad membership of experts with knowledge of vaccines, vaccine safety, pharmacoepidemiology, vaccine program implementation and consumer issues.

**RECOMMENDATION 2 – DEFINING SURVEILLANCE OBJECTIVES AND ESTABLISHING PROTOCOLS AND PROCEDURES FOR MANAGING ADVERSE EVENTS FOLLOWING IMMUNISATION.**

The Horvath Review found that the national passive AEFI reporting system was able to detect the safety signal associated with the use of the 2010 seasonal influenza vaccine, take appropriate action and undertake a rigorous investigation. However, to clearly articulate its purpose, objectives and key principles of the AEFI surveillance system needed to be developed. These needed to encompass the monitoring of AEFI through passive reporting as well as where more active surveillance may be required, and investigation to be undertaken once a potential signal is identified.
A document describing the Principles and Objectives of the National Adverse Event Following Immunisation (AEFI) Surveillance System has been developed (Appendix 1). The National AEFI Surveillance System is the national system for spontaneous adverse events reporting and monitoring for all vaccines registered and used in Australia and is just one component of a national framework to ensure vaccine safety.

The Horvath Review noted that case definitions for AEFIs varied across jurisdictions and considered the development of national consistency a priority for improving analysis and classification of cases. A consolidated set of AEFI case definitions, for reporting, collating and analysing AEFI, has been developed and agreed by the ISC. The case definitions have been provided to the TGA for consideration.

The essential components of signal detection for AEFI and the elements that should optimally be included in a vaccine safety signal management system for Australia have been identified and will inform standard operating procedures for the identification and management of vaccine safety signals. To allow analysis of AEFI data in relation to vaccine doses administered, information on the number of doses of vaccines administered in Australia from the Australian Childhood Immunisation Register (ACIR) is made available routinely to the TGA for regular reporting of AEFI. An annual report is prepared by the National Centre for Immunisation Research and Surveillance (NCIRS) and the TGA using this AEFI data. This report is published in the Communicable Disease Intelligence (CDI) and is available at the Department of Health website.

The TGA is considering the advice of the ISC with a view to further informing its standard operating procedures specific to identification of vaccine safety signals and management of such signals when identified.

The OHP and TGA will investigate opportunities to access high level epidemiological and biostatistical support to assist in assessment of suspected vaccine safety signals.

**RECOMMENDATION 3 – IMPROVING THE NATIONAL SYSTEM FOR TIMELY REPORTING OF ADVERSE EVENTS FOLLOWING IMMUNISATION.**

To assist with the implementation of the Horvath Review, a joint Therapeutic Goods Administration (TGA)/National Immunisation Committee (NIC) working group was established in December 2011 to develop mechanisms for improved and more timely information flows between the TGA and the jurisdictions; and agreed templates for nationally consistent reporting of AEFI. The work undertaken by this working group has involved a number of steps and subprojects.
A national core data set for reporting of AEFI, developed in consultation with the states and territories and the TGA, was endorsed by the Australian Health Protection Principal Committee (AHPPC) at its August 2013 meeting. AHPPC members agreed that jurisdictions would commence implementation by January 2014. The core data set is an agreed set of data elements to be reported to the TGA following a suspected AEFI. Based on the core data set, a national AEFI reporting form has been developed, which can replace the existing individual forms used by jurisdictions. The TGA, OHP and jurisdictions will continue to work together to develop communication materials to support and promote the use of the AEFI core data set.

A workshop to discuss specific state and territory issues, which may impact on reporting of AEFIs, and how these could be overcome, was held between the TGA, OHP and states and territories. The outcomes of this workshop will be progressed to continue to strengthen improvements in reporting of AEFIs. The OHP will continue to work with the TGA and jurisdictions to consider the development of a national online reporting system.

Monthly teleconferences have been established between the TGA, OHP, and states and territories to discuss AEFI reports received by the TGA, any signals detected through the analysis of these reports and any other potential vaccine safety issues identified by the TGA or the jurisdictions.

**RECOMMENDATION 4 – RAISING COMMUNITY AND HEALTH PROFESSIONAL AWARENESS OF VACCINE SAFETY MONITORING TO ENSURE MORE COMPLETE REPORTING OF ADVERSE EVENTS FOLLOWING IMMUNISATION.**

The Horvath Review provided recommendations to improve not only the way AEFI are identified, monitored, reported and responded to but also how best to communicate the improved system to all stakeholders to improve awareness of, and confidence in, the vaccine safety assessment and monitoring system. The Horvath Review recommended that Department of Health (Health) consider the development of a communications strategy to inform jurisdictions, health professionals and consumers of the vaccine safety monitoring processes in Australia.

As part of the response to the *Transparency Review, TGA reforms: A blueprint for TGA’s future* (the TGA Blueprint for Reform), the TGA is developing a strategy to more effectively facilitate the recognition and reporting of adverse events to all types of therapeutic products by health practitioners and consumers, and promote the adverse event reporting system.

---

**SUMMARY OF OUTCOMES OF RECOMMENDATIONS**

Review of the management of adverse effects associated with Panvax and Fluvax (Horvath Review)
The TGA has provided an overview of the draft *Adverse Event Reporting Strategy* to peak industry, health professional and consumer bodies. The implementation phase of the strategy will involve liaison with stakeholders to inform development and delivery of activities to: improve access to reporting methods; raise awareness of adverse event reporting; and provide education about adverse event reporting.

The TGA has had preliminary discussions with key stakeholders and feedback on the draft strategy has been, and will continue to be, sought from jurisdictions and the TGA’s Advisory Committees on the safety of medicines, vaccines, and medical devices (ACSOM, ACSOV and ACSMD).

The OHP has updated its NIP communication strategy to include information specific to vaccine safety and the importance of AEFI reporting in the immunisation publications and promotional materials. This information is included in the campaign material developed to support the launch of new vaccines under the NIP, for example, the Human Papillomavirus (HPV) for boys and measles-mumps-rubella-varicella (MMRV) vaccination programs.

**RECOMMENDATION 5 – NATIONALLY AGREED PROTOCOLS FOR NATIONAL IMMUNISATION PROGRAM ACTION AND COMMUNICATION.**

The Horvath Review noted there are significant challenges in determining how to communicate with health professionals and the community during the early stages of an investigation of an adverse event signal, when there is a level of doubt about the significance of the events. The Horvath Review considered that a protocol for taking program action, including informing health professionals, consumers and the media, in the event a possible safety signal affecting a NIP vaccine is detected, should be developed and agreed by Health and the state and territory health authorities.

A document describing the *Protocols for National Immunisation Program Action and Communication* (the Protocols) has been developed. These are nationally agreed protocols for program action and communication in the event a safety signal is detected affecting a NIP vaccine.

To develop these Protocols, the OHP has consulted extensively with the TGA as the regulatory authority for all vaccines used in Australia, including those on the NIP. Consultation was also sought from the states and territories. The Protocols have been endorsed by the AHPPC and will be distributed to the OHP, TGA, ACSOV, and jurisdictions.
RECOMMENDATION 6 – TRANSPARENCY AND THE FUNCTIONS OF THE TGA TO ENSURE BETTER ACCESS TO VACCINE SAFETY INFORMATION FOR CONSUMERS AND HEALTH PROFESSIONALS.

As part of the TGA Blueprint for Reform, the TGA has developed the *Database of Adverse Event Notifications (DAEN) – medicines*, a searchable database of adverse event notifications which is now available on the TGA website. The database contains information from reports of adverse events that the TGA has received in relation to medicines, including vaccines, used in Australia. The TGA will provide information on the regulation of vaccines on its website. Further improvements are being explored under the TGA Blueprint for Reform and in the directions of the *National Immunisation Strategy for Australia 2013-2018* (National Immunisation Strategy).

RECOMMENDATION 7 – VACCINE USAGE AND SAFETY MONITORING DATA

The Horvath Review identified that future developments in e-health provide an opportunity to improve the capacity for vaccine surveillance across all age groups, including the capacity to collect data on vaccine administration and adverse events. The Horvath Review considered that the collection of vaccine usage and safety monitoring data should be a key priority for future e-health planning and development.

The Horvath Review considered that the Australian Childhood Immunisation Register (ACIR) dataset can be very useful in signal investigations. Since 2011, communications for the influenza season encourage all immunisation providers to notify any influenza vaccine given to a child under the age of 7 years to the ACIR, regardless of the funding source for the vaccine.

One of the areas for action in the National Immunisation Strategy is for OHP to enhance vaccine safety monitoring systems. This could be achieved by investigating linkages between the existing ACIR, the HPV Register, and other data collections to better assess vaccine safety and vaccine efficacy. Work is underway on a review of the ACIR and HPV Registers to assess their potential for expansion to include other vaccines and provide immunisation coverage data for other age groups.

SUMMARY OF OUTCOMES OF RECOMMENDATIONS

Review of the management of adverse effects associated with Panvax and Fluvax (Horvath Review)
The Working Party of Experts explored potential sources of data for vaccine safety analyses and systems which could be adapted to suit vaccine safety investigations. The development of a system that analyses linked data across a population cohort for monitoring adverse events, such as the United States Vaccine Safety Datalink (VSD), is currently not feasible in Australia. However, it will be important for the TGA to continue to monitor information provided by the VSD and other systems.

The Working Party of Experts explored options for improved understanding of vaccine safety through linkage of relevant data sets including making data readily available for linkage studies. Further work is required to better utilise Australia’s existing healthcare data sets for vaccine safety studies. The OHP will continue to work towards a streamlined mechanism for improved access to relevant data for vaccine safety studies.

SAFETY PLANS FOR NEW VACCINES UNDER THE NATIONAL IMMUNISATION PROGRAM (NIP)

The OHP in conjunction with the TGA has developed specific vaccine safety plans to support the recent introduction of new vaccines, and the extension of an existing vaccine to a new cohort, on the NIP. The feasibility of various methods for enhanced vaccine safety monitoring will need to be considered as part of each individual vaccine safety plan developed for new vaccines added to the NIP. Technical input into the vaccine safety plans will be sought as needed and advice on the proposed plan will be sought from ACSOV.

In developing the safety plan for measles-mumps-rubella-varicella (MMRV) vaccine, recently launched under the NIP, the feasibility of various methods to monitor the safety of MMRV vaccines was considered. The adverse events surveillance following administration of measles containing vaccine is undertaken within the existing Paediatric Active Enhanced Disease Surveillance (PAEDS) system which has been extended to include febrile seizures (FS) in children under 5 years of age. New South Wales is also undertaking active surveillance of FS related to Measles-Mumps-Rubella (MMR) and MMRV vaccination through its Public Health Real-Time Emergency Department Surveillance System (PHREDDS). Enhanced communication and information sharing between the TGA and the jurisdictions through the weekly collation and distribution of MMRV AEFI data and the monthly teleconferences between the TGA, OHP and jurisdictions is also proving beneficial.
To support the extension of the National Human Papillomavirus (HPV) Vaccination Program to include males, a number of enhancements to the existing adverse event surveillance system have been implemented. These include:

- communication activities targeted at immunisation providers, the public and media on the safety of the HPV vaccine and the importance of timely reporting of AEFI;
- rapid school-based reporting of four acute significant AEFI following HPV vaccination to the TGA in all jurisdictions and the weekly collation and distribution of HPV AEFI data which are discussed at regular teleconferences (initially weekly and now monthly) between the TGA, OHP and jurisdictions;
- active surveillance of presentations to emergency departments following HPV vaccination (in NSW); and
- the Adverse Events Following Immunisation – Clinical Assessment Network (AEFI-CAN) HPV Pilot - a pilot project aimed at increasing collaboration and linkage between vaccine safety clinics across Australia to facilitate provision of more standardised information on significant/unexpected HPV AEFI following the expansion of the National HPV Vaccination Program to males.

In the 2013 influenza season a number of projects for enhanced safety monitoring of influenza vaccine in children were funded. The outcomes of these projects and approaches for the 2014 are currently being considered.

**SUMMARY OF FURTHER WORK**

Australia’s adverse event following immunisation surveillance system has been strengthened as a result of implementation of the recommendations from the Horvath Review. There remains some work still to be progressed:

- The consolidated set of AEFI case definitions is being considered by the TGA with a view to implementing a national set of case definitions.
- The TGA may consider the advice of the ISC with a view to further informing its standard operating procedures specific to identification of vaccine safety signals and management of such signals when identified.
- The OHP and the TGA are considering opportunities to access high level epidemiological and biostatistical support to assist in investigation and assessment of vaccine safety signals as required.
- The national core data set for reporting of AEFI will be implemented by January 2014.
• Further enhancements to the reporting mechanisms which will underpin the National AEFI Surveillance System, including the development of: protocols and standard operating procedures to support the national reporting form; and a national online reporting system and communication materials to support and promote the use of AEFI core data set.

• The TGA is developing an *Adverse Event Reporting Strategy* to: improve access to reporting methods; raise awareness of adverse event reporting; and provide education about adverse event reporting for all medicines, including vaccines.

• Planning for safety surveillance in advance of the introduction of new vaccines under the NIP will continue.

• Work to enhance understanding of vaccine safety by improving opportunities for data linkage between existing vaccine registers, AEFI and other relevant data sets, will be further investigated.
Principles and Objectives of the National Adverse Event Following Immunisation Surveillance System

Context

The National Adverse Event Following Immunisation Surveillance System is the national system for passive adverse events reporting and monitoring for all vaccines registered and used in Australia and is just one component of a national framework to ensure vaccine safety.

The safety profile of vaccines is initially determined through clinical trials which are evaluated by the Therapeutic Goods Administration (TGA) prior to the decision to approve the vaccine for use in Australia. Trials are generally undertaken in selected populations and, even when extensive, may not be able to identify rare adverse effects of the vaccine. Post-market monitoring of vaccines is undertaken to identify any change in the safety profile of the vaccine and ensure the continuing safety of the vaccine when in use.

Post-licensure/marketing monitoring encompasses a number of activities which aim to detect, assess, understand and prevent adverse events or any other vaccine-related problem. These activities include those that sponsors are required to undertake as part of their Risk Management Plan (RMP) for the vaccine. Other activities include the analysis of reports of adverse events and the monitoring of literature reports and studies, and in some instances specific active surveillance.

A national adverse event reporting database is maintained by the TGA. Reports are received from many sources including manufacturers, health professionals, state and territory health authorities and consumers. Close liaison between the TGA, the National Immunisation Program (NIP) and state and territory health authorities is required to ensure the effective operation of this database.

The National AEFI Surveillance System is a passive system which may be supplemented by enhanced passive surveillance, sentinel surveillance, active surveillance or post-marketing studies in certain circumstances e.g. the introduction of a new vaccine into the NIP or for the purposes of investigating a possible safety signal.

The National AEFI Surveillance System is designed to detect possible safety signals which require further investigation. The identification and investigation of safety signals is a collaborative process. When determining the appropriate response to a potential vaccine safety signal, safety will be assessed by weighing the net benefit of vaccination as well against the risks.

SUMMARY OF OUTCOMES OF RECOMMENDATIONS

Review of the management of adverse effects associated with Panvax and Fluvax (Horvath Review)
Principles of the National Adverse Event Following Immunisation Surveillance System.

The National AEFI Surveillance System will operate to:

1. Maintain confidence in the safety of immunisation through the implementation of a robust system of surveillance, reporting, investigation and communication.
2. Minimise the risk of harm from immunisation through the detection of AEFIs and program errors.
3. Inform immunisation policy and practice through a consideration of vaccination risks and benefits.
4. Ensure enhanced surveillance is in place when a new program is implemented.
5. Ensure effective governance, decision making action and communication in response to identified safety signals.
6. Ensure that the reporting processes for vaccine safety surveillance are transparent, public and not affected by conflict of interest.

Objectives of the National Adverse Event Following Immunisation Surveillance System

The operation of the National AEFI Surveillance System will aim to ensure community and health-care provider confidence in vaccine safety by delivering the following outcomes:

1. Monitor and compare reported adverse events or reactions with those that are expected for specific vaccines to assess if AEFIs are occurring within expected rates and level of severity.
2. Identify AEFIs not previously reported.
3. Identify and respond to common programmatic oversights or changes in the AEFI profile of different vaccine lots or brands.
4. Identify and respond to safety signals which may require further clinical and/or epidemiologic investigation, a programmatic response or community/health provider education.
5. Proactively enhance general or targeted surveillance when a new immunisation program is implemented to provide:
   - comparison with previously reported adverse event data; and
   - early validation of potential signals raised in trials or other settings.
6. Analyse and report on adverse events and any safety investigations and make such information regularly available in the public domain.
7. Provide timely information that can be made available to potential recipients as well as health care providers and the community to help inform the risks and benefits of immunisation.