Postmarketing Vaccine Safety Passive Surveillance: An exploratory study of parent and healthcare provider reporting of Adverse Events following Immunisation (AEFI)

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Abstract

Monitoring the safety of new and exisiting vaccines following licensure is a critical component of maintaining public confidence in immunisation and is an integral part of national immunisation programs. In Australia the process relies predominantly on the passive surveillance of adverse events following immunisation (AEFI) via spontaneous voluntary reports of AEFI by healthcare professionals, vaccine manufacturers and the public to state or federal health authorities. The aim of this thesis was to investigate factors that promote or inhibit parental and healthcare professional reporting of AEFI.

A mixed-methods sequential study design was employed, with three separate studies conducted: two quantitative and one qualitative. The first quantitative study involved telephone interviews of a representative sample of 469 South Australian parents, recruited from the general population about the previous occurrence of children's AEFI, safety opinions, awareness of surveillance and reporting AEFI to healthcare professionals and surveillance authorities. The second quantitative study interviewed 179 parents whose children had experienced an AEFI and had reported the events to the South Australian Immunisation Section, Department of Health. This study was conducted following the national suspension of a seasonal trivalent influenza (STIV) vaccine in 2010. Parental vaccine safety attitudes, reasons for reporting and impact on future vaccination intent were assessed. The qualitative study involved in-depth interviews with 29 healthcare professionals working in general practice, council immunisation clinics and a paediatric hospital emergency department (ED). The interviews sought to examine the experiences, knowledge and training of general practitioners (GPs), nurses and ED consultants in detecting AEFI and of reporting to surveillance authorities. The study was planned using a

social constructionist perspective and thematic analysis was used to analyse the interview data.

In the first study, 95% of all parents were confident in vaccine safety in general. Parental confidence in vaccine safety was significantly associated with higher levels of education (OR:2.58, p = 0.01) and being born in Australia, (OR:2.30, p = 0.004). Mothers, when compared with fathers, were less accepting of two vaccine risks: febrile convulsion (OR:0.57, p = 0.04) and anaphylaxis, (OR:0.55, p = 0.04). One in four parents stated that at least one of their children had previously experienced an AEFI: one third of these parents reported the symptoms to either a healthcare professional or the Department of Health. Parents of children who had experienced an AEFI were less likely to believe vaccines were safe (OR:0.53, $p \leq 0.01$) compared with parents of children who did not experience an AEFI.

In the second study, 88% of all parents were confident in the safety of vaccines in general. Parents reporting an AEFI to the 2010 STIV were more likely to state the event had influenced future vaccination intent than the National Immunisation Program (NIP) vaccine parent AEFI reporters (65% vs 14%, $p<0.001$), with 63% stating refusal or hesitance to re-vaccinate their children against influenza. Concern for their children's symptoms and media reports of the 2010 STIV program suspension were the most common reasons for reporting.

The qualitative study revealed that interpretations of a "serious" or "unexpected" AEFI and what would constitute a reportable AEFI varied according to the professional group. Common barriers to reporting included time constraints and unsatisfactory reporting processes. Nurses were more likely to have received formal training in vaccine safety and reporting than medical practitioners.

Collectively, these studies should inform future strategies aimed at improving AEFI reporting. These need to incorporate ongoing education and enhancing existing reporting processes for health professionals and investigation of alternate surveillance approaches that consumers will use.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other institution and affirms that to the best of my knowledge, the thesis contains no material previously published or written by another person, except where due reference is made in the text of thesis. In addition I certify that no part of this work will, in the future be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Signed .....

Adriana Parrella (Candidate)

Date.....

Publications contributing to this thesis

- Parrella A, Gold M, Marshall H, Braunack-Mayer A, Watson M, Baghurst P. Parental views on vaccine safety and future vaccinations of children who experienced an adverse event following routine or seasonal influenza vaccination in 2010. Human Vaccines & Immunotherapeutics May 2012, 8:5, 662–667

- Parrella A, Gold M, Marshall H, Braunack-Mayer A, Baghurst P. Parental perspectives of vaccine safety and experience of adverse events following immunisation. Vaccine April 2013, 31:16, 2067-2074

- Parrella A, Braunack-Mayer A, Gold M, Marshall H, Baghurst P. Healthcare providers' knowledge, experience and challenges of reporting adverse events following immunisation: A qualitative study. BMC Health Services Research. 2013 Aug 15;13(1):313

- Parrella A, Gold M, Braunack-Mayer A, Baghurst P, Marshall H. Consumer reporting of adverse events following immunisation (AEFI): identifying predictors of reporting an AEFI. Human Vaccines & Immunotherapeutics. [Published online ahead of print] 2014 Jan 09;10(3)

Conference presentations during candidature

- Public Health Association of Australia (PHAA) 12th National Immunisation Conference; 2010 Aug 17-19; Adelaide.

- Public Health Association of Australia (PHAA) 13th National Immunisation Conference; 2012 June 18; Darwin

Poster presentations:

- The University of Adelaide, Faculty of Health Sciences Postgraduate Research Conference; 2011 Aug 25; Adelaide, Australia.

- PHAA (SA branch) Conference 'Population Health: Working across sectors, settings and ages'; 2011 Oct 29; Adelaide, Australia.

Coverage of findings arising from this thesis in the media

- "Doctors urge jab as flu spreads" in The Advertiser, Adelaide, 28 February 2013, pg 5
- ABC local (Adelaide) radio interview, 27 February, 2013
- "University of Adelaide research finds most South Australian parents believe vaccines are safe for their children", Adelaidenow, 27 February, 2013
- Interview, VaxiPlace , 01 March, 2013

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Abbreviations

ABS	Australian Bureau of Statistics
ACSOM	Advisory Committee on the Safety of Medicines
ACSOV	Advisory Committee on the Safety of Vaccines
AEFI	Adverse Event(s) Following Immunisation
CATI	Computer-Assisted Telephone Interviewing
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CYWHS	Children, Youth and Women's Health Service
ED	Emergency Department
GP	General Practitioner
IQR	Interquartile range
IRSD	Index of Relative Socio-economic Disadvantage
NCIRS	National Centre for Immunisation Research and Surveillance
NIP	National Immunisation Program
OR	Odds Ratio
PHAA	Public Health Association of Australia
SA	South Australia
SAEFVic	Surveillance of Adverse Events Following Vaccination in Victoria
SAIS	South Australian Immunisation Section
SEIFA	Socio-Economic Indexes For Areas
STIV	Seasonal Trivalent influenza vaccine
TGA	Therapeutic Goods Administration
UK	United Kingdom of Great Britain and Northern Ireland
US	United States of America

VPD	Vaccine Preventable Disease
WA	Western Australia
WCH	Women’s and Children’s Hospital

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1 Background and rationale for research

Public health surveillance is often referred to as the on-going systematic collection, analysis, and interpretation of health data essential for planning, implementing and evaluating public health activities, linked with the timely dissemination of data.[1] A vaccine safety surveillance system is one form of public health surveillance that aims to monitor all aspects of immunisation programs and ensure the safety of all vaccines administered to the public. A rigorous surveillance system that detects safety issues as they occur during the early and continued use of vaccines is critical to the acceptability of public health immunisation programs and their success in eliminating vaccine preventable diseases (VPD). The importance of post-licensure vaccine safety monitoring cannot be understated. As vaccines are given to mainly healthy individuals, most often children, in order to prevent, rather than treat disease, public expectation of vaccine safety is high.[2]

All medications, including vaccines, carry the risk of adverse reactions. For example, it is well established that the oral polio vaccine, on rare occasions, causes paralytic polio and that vaccines sometimes lead to anaphylactic shock.[3] As immunisation programs aim to achieve and maintain high coverage rates by ensuring the target populations are vaccinated, there is an obligation for health authorities to ensure the rigorous surveillance of all adverse events associated with vaccines and ensure a timely response to any safety signals.[4]

It is frequently acknowledged in the immunisation field that the success of immunisation programs in eliminating VPD such as poliomyelitis, diphtheria and measles, has paradoxically resulted in less public concern for the diseases, but increased public

expectation of vaccine safety.[5-9] Monitoring the continued safety of vaccines aims to identify early safety signals and maintains public confidence in immunisation.[10, 11]

This thesis examines aspects of vaccine pharmacovigilance, defined by the working group on vaccine pharmacovigliance of the Council for International Organizations of Medical Sciences (CIOMS), and the World Health Organization as:

"the science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine or immunization related issues, and to the prevention of untoward effects of the vaccine or immunization."[12]

Specifically, the focus of this thesis concerns the passive surveillance of adverse events following immunization (AEFI), a component of pharmacovigilance. An AEFI is defined as:

"any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease."[12]

The implication of an adverse event may be quite different in scale for a vaccine, which is given to an entire cohort of the population, such as the schedule of recommended childhood vaccines administered via the Australian National Immunisation Program (NIP), compared with a drug, which may be used in a relatively small number of individuals. Hence, the detection, response and communication about AEFI are of great importance to the health of the population and public health practice.

In Australia, the passive reporting of an AEFI is the primary mechanism used for post-marketing surveillance (PMS) of licensed vaccines.[11] This process relies primarily on

health professionals, vaccine manufacturers and the community voluntarily submitting reports of an AEFI to health and regulatory authorities for further investigation.

Parents and healthcare professionals are the key individuals in the detection and reporting of children's AEFI, as the initial detection of a child's AEFI will begin with a report by parents and/or health professionals. There are few published studies that have examined parental and/or health professional AEFI reporting, all of which have occurred outside Australia.[13-17]

Undertaking this study of parental and healthcare professional reporting of AEFI via the passive surveillance system is of relevance as it was conducted shortly after the national, temporary suspension of the seasonal trivalent influenza (STIV) vaccine, Fluvax (CSL), on 23rd April 2010, due to an increase in febrile convulsions among young children, first reported in Western Australia.[18, 19] Raising community and health professional awareness of vaccine safety monitoring to ensure more complete and timely reporting of AEFI were two key recommendations noted in a national review of AEFI surveillance following the STIV safety signal.[19] The studies presented in this thesis evolved within the context of this highly publicised safety signal, and thus provided a novel opportunity to examine factors associated with AEFI reporting.

This chapter provides a brief outline of the purpose of this thesis with an explanation of the chosen framework of studies and outline of the thesis chapters.

1.1 The purpose of this thesis

The overall objective of this thesis was to examine the issue of AEFI reporting within the Australian passive surveillance system from the perspectives of those who are in the position to report children's AEFI in Australia, parents and healthcare professionals, in order to gain an understanding of predictors of and barriers to AEFI reporting.

1.1.1 The Research Questions

The research questions addressed in this thesis are as follows:

1. Do parental attitudes towards vaccine safety differ according to whether their children have experienced an AEFI with parents whose children did not experience an AEFI?

2. Are parents aware of a surveillance system for AEFI reporting?

3. Do safety attitudes and awareness of surveillance differ according to whether parents report their children's AEFI to a healthcare provider or surveillance authority or do not report their children's AEFI?

4. What are the factors associated with parental reporting of AEFIs?

5. What is the impact for parents of experiencing an AEFI on future immunisation decisions?

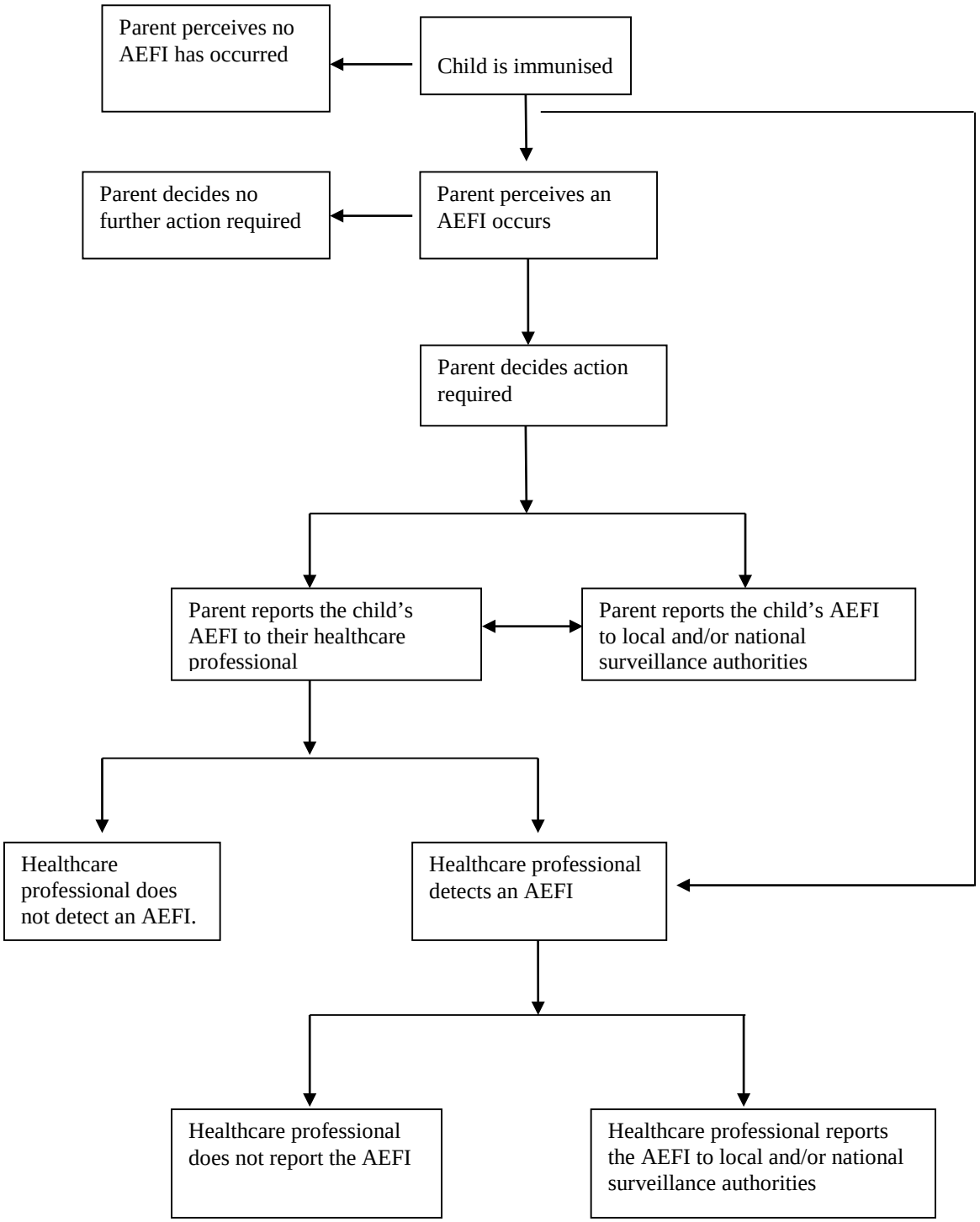
6. What are the experiences, awareness and knowledge of healthcare providers in AEFI reporting and surveillance?

7. How do healthcare providers conceptualise a reportable AEFI?

1.2 Outline of studies in this thesis

This thesis presents the results of three separate studies I conducted regarding parent and healthcare professional AEFI reporting. The research questions and studies that were conducted for this thesis serve to address the complex nature of how reporting can occur or not occur, at various stages, following a child's vaccination. Figure 1.1 depicts the possible flow of events that may occur, from vaccination, the experience of an AEFI, through to parental action following the event, interactions with healthcare professionals and the points at which reporting of an AEFI to surveillance authorities may take place.

Figure 1.1: Detecting and reporting an AEFI



The research consisted of three phases and adopted a mixed methods approach. The first three research questions (section 1.1.1) are addressed in the first study that examines the opinions of parents, sampled from the general public, about their views on vaccine safety and awareness of vaccine safety surveillance. In this study, entitled "General Population Parent Study", two components are examined. The first compared parental views by whether their children had previously experienced an AEFI as stated by parents with parents of children who did not experience an AEFI, and the second, by whether parents reported the AEFI symptoms or not. This study presents results that examine predictors of reporting.

The fourth and fifth research questions (section 1.1.1) are addressed in the second study presented in this thesis. This study surveyed parents of children who had experienced an AEFI and reported the event to the South Australian Immunisation Section (SAIS), South Australian Department of Health. This study, entitled "AEFI Parent Reporter Study," recorded the children's AEFI symptoms that were reported, vaccine safety views, reasons for reporting, impact of an AEFI on future vaccination decisions, and awareness of vaccine safety surveillance.

The vaccine safety attitudes of the two groups of AEFI parent reporters from both the AEFI Parent Reporter Study and the General Population Parent Study are also compared in order to examine similarities and/or differences between the two groups.

The sixth and seventh research questions (section 1.1.1) are addressed in the third study, entitled the Healthcare Provider Study. This qualitative study involved interviewing general practitioners (GPs), paediatric hospital Emergency Department (ED) consultants, general practice and local council immunisation nurses about their experiences of detecting an AEFI in clinical practice, reporting to AEFI monitoring systems in Australia and previous training in vaccine safety.

This research and the studies presented in this thesis provide an understanding of the factors that promote or inhibit parental and healthcare provider reporting of vaccine adverse events.

General Population Parent Study: a study of parental views regarding vaccine safety

A computer-assisted telephone interview (CATI) of 469 South Australians, randomly sampled from the Electronic White Pages (EWS), was conducted. In this study I sought to capture and compare the perspectives of four parent sub-groups:

- Parents who stated that their child had experienced a previous AEFI, referred to as "AEFI parents" in this thesis, were compared with those who stated that their child had not experienced an AEFI, referred to as "no-AEFI parents"; and
- Parents who reported their children's AEFI symptoms to a healthcare professional or surveillance authority, the "AEFI parent reporters" were compared with those who did not report their children's AEFI, "AEFI parent non-reporters".

Specifically, the aims of the General Population Parent Study were:

- To determine the frequency of parental perceptions of children's AEFI in the general population;
- To examine parental beliefs and socio-demographic predictors regarding vaccine safety views and perceptions of AEFI;
- To measure the extent and nature of parental reporting of AEFI to health professionals and/or surveillance authorities; and
- To determine predictors of parental reporting of AEFI.

AEFI Parent Reporter Study:a cross-sectional survey of AEFI parent reporters

This study of AEFI parent reporters examined the demographics, vaccine safety attitudes, awareness of surveillance, reasons for reporting an AEFI and impact on future vaccination decisions of parents of children who had experienced an AEFI and who had reported it to the South Australian Immunisation Section, (SAIS), South Australian Department of Health, either direct to the SAIS or via a healthcare professional.

The primary aim of the AEFI Parent Reporter study was:

- To examine parental beliefs regarding vaccine safety and perceptions of experiencing an AEFI.

The secondary aims were:

- To describe socio-demographics of AEFI parent reporters;
- To examine reasons for reporting an AEFI to a surveillance authority or a health professional; and
- To assess the impact of their children's AEFI to a vaccine/s, as measured by attitudes towards revaccination.

Healthcare Provider Study: a qualitative study of healthcare providers' knowledge, experiences and challenges of AEFI reporting

To explore the perspectives of healthcare professional AEFI reporting, a qualitative study was conducted involving face-to-face interviews with three health professional groups: paediatric hospital emergency department (ED) consultants, general practitioners (GPs) and nurses. Specifically the aims of this study were:

- To gain an understanding of the experiences of healthcare providers of detecting AEFI; and
- To examine healthcare provider experience and attitudes towards reporting AEFI.

1.3 Thesis outline

The remainder of the thesis is organised as follows. In Chapter 2, I review the relevant literature that provides the context for the thesis objectives, as described in this chapter. In Chapter 3, I present an overview of the research methods and study design for each of the three studies described earlier in section 1.2. The results of the studies are presented as manuscripts in Chapters 4, 5 and 6. Chapter four presents the results of the General Population Parent Study, a random sample of South Australian parents, from which I sought to ascertain the occurrence of children's previous AEFI, the prevalence of reporting of AEFI to a surveillance authority or healthcare professional and vaccine safety attitudes. This study compares differences in safety attitudes by whether respondents' children had ever experienced an AEFI and by whether the AEFIs were reported or not. Chapter 4 also includes results that examine predictors of vaccine safety views. Chapter 5 presents the key results of the AEFI Parent Reporter Study, where I examine the type of adverse events reported, reasons for reporting an AEFI and vaccine safety attitudes of parent AEFI reporters. A comparison of the results of the common survey questions included in the two parent studies is also included in Chapter 5, in order to assess similarities/differences in demographics and safety attitudes of parent AEFI reporters. Chapter 6 presents the results of the third study, the Healthcare Provider Study and addresses the gap in understanding healthcare professionals' experience of an AEFI.

Finally, Chapter 7 follows with a general discussion of the results, potential areas requiring future research, and concluding remarks concerning the translation of findings to improve passive surveillance.

This thesis is a combination of written text (Chapters 1-3, and Chapter 7) and peer-reviewed journal papers that have either been published (Chapters 4 and 5) or are currently in press (Chapter 6).

2 Literature review

The aim of the review presented in this chapter is two-fold. Firstly, I present the underlying principles of passive AEFI surveillance reporting systems. The major aspects underlying the public health importance of monitoring adverse events following immunisation, the purpose of post-licensure surveillance, and limitations of passive surveillance are described. Secondly, this chapter examines the available literature on the issue of consumer, parent and healthcare professional AEFI reporting, with some discussion of parallels with relevant studies regarding consumer and healthcare professional adverse drug reaction (ADR) reporting.

The articles presented in this chapter were sourced via searches of the Medline databases, initially devised in conjunction with the University of Adelaide research librarian. The primary search strategy relating to published studies concerning AEFI and safety surveillance was first conducted in September 2009 with the following search terms:

(vaccination[mh] OR vaccin*[tiab] OR mass immunization[mh] OR immuni*[tiab]) AND (adverse effects[sh] OR adverse[tiab] OR adverse events following immunisation) AND (post-marketing surveillance OR safety surveillance OR safety vaccine OR Phase IV clinical trials AND (impact*[tiab] OR complain*[tiab] OR attitudes [mh]) AND (parent)

From this search that resulted in 230 articles, title and abstract review were conducted in order to cull studies concerning topics and/or outcomes not directly relevant to the research questions 1 to 5 of this thesis, presented in section 1.1.1.

For the literature regarding healthcare professional AEFI and ADR reporting relevant to research questions 6 and 7, the following search terms were used:

(adverse drug reaction [mh]) AND (adverse effects[sh] OR adverse events following immunization) AND (post-marketing surveillance [mh] OR safety surveillance OR safety vaccine) AND (healthcare professional [mh] OR healthcare provider [mh] or healthcare worker [mh])

Although the literature review searches were not designed as a systematic review, with strict a priori study inclusion criteria, specific criteria were applied in selecting relevant articles. Full-text articles published between 1990 and 2013 and in English were selected. This time-frame was chosen as appropriate to sourcing all relevant studies. References from selected articles were also reviewed in order to capture studies not identified in initial literature searches (snowballing). Additional searches were conducted to November 2013 in order to update recently published studies.

2.1 Vaccine safety surveillance

Of all public health measures adopted worldwide, vaccination is frequently acknowledged as having produced the most public health impact by reducing the burden of disease and mortality from vaccine preventable diseases (VPD), especially in childhood. It is estimated that with the introduction of vaccines 5 million small pox deaths, 2.7 million cases of measles, 2 million cases of neonatal tetanus, 1 million cases of pertussis, 600,000 cases of paralytic poliomyelitis and 300,000 cases of diphtheria have been prevented annually.[20] Childhood vaccination has been described as one of society's best cost-effective healthcare investments.[21]

Achieving and maintaining high levels of vaccination coverage in a population relies, in part, on the delivery of safe immunisations. The safety of a vaccine is inferred by the relative absence or presence of adverse events following immunization (AEFI). [22] An AEFI is defined as:

"any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease."[12]

An AEFI is generally classified into five categories:

- Vaccine product-related reaction: An AEFI that is caused by a vaccine due to one or more of the inherent properties of the vaccine product (known vaccine side effects);
- Vaccine quality defect related reaction: An AEFI caused by a vaccine that is due to one or more quality defects of the vaccine product as provided by the manufacturer;
- Program errors caused by errors in vaccine handling, prescribing or administration;
- Coincidental event unrelated to immunisation, occurring at or soon after immunisation; and
- Anxiety-related reaction: An AEFI arising from anxiety about the immunisation.[12]

The assessment of a vaccine's safety occurs both before and after a vaccine has been licensed for public use. In Australia, the quality, safety and efficacy of all vaccines are regulated by the Therapeutic Goods Administration (TGA), in accordance with the provisions of the *Therapeutic Goods Act 1989*.[23]

2.1.1 Pre-licensure vaccine safety surveillance

Prior to licensure, all vaccines are tested for safety and efficacy in phased (phase 1-3) human clinical trials.[24] Although the experimental trial design of pre-licensure trials (randomised, placebo-controlled, blinded) allows for rigorous assessment of a vaccine's safety, they do have a number of important limitations.[25] Phase 1 trials usually include

fewer than 20 participants and can detect only extremely common adverse events. Phase 2 trials generally include only 50 to several hundred people. The sample size for phase 3 trials, although ranging from 1,000 to 10,000, are based primarily on efficacy rather than safety considerations, with the duration of observation often less than 30 days. [25, 26] Hence, pre-licensure trials are generally not large enough to provide adequate safety data for potential adverse reactions that are rare, for example occurring less than 1 per 1,000 doses; reactions with delayed onset, for example, occurring 30 days or more after immunisation; reactions that occur with the administration of vaccine combinations; and for reactions that occur in sub-populations who have associated co-morbid conditions and are excluded from pre-licensure trials.[24, 27-29]

2.1.2 Post-marketing passive vaccine safety surveillance

The primary method of post-marketing vaccine safety surveillance in Australia is via passive surveillance.[11] This process is reliant on health care professionals, vaccine manufacturers and the community voluntarily submitting spontaneous reports of AEFI to health authorities regarding an adverse event which has occurred after the administration of a vaccine. A spontaneous AEFI report is defined as

"an unsolicited communication by a health-care professional or consumer to a manufacturer, regulatory authority or other organisation that describes one or more adverse events in a patient who was given one or more vaccine products and that does not derive from a study or any organised data collection scheme."[12]

The purpose of post-marketing surveillance is to identify adverse events not detected in pre-licensure clinical trials and monitor trends in AEFI reporting, in order to serve as an early warning system for further investigation.[30] The main limitations of a passive vaccine surveillance system include:

- Under-reporting of events. The system relies on consumers and health professionals being aware of an AEFI, reporting pathways and actually reporting the event;
- Variablity in report quality and completeness. The information notified in AEFI reports frequently lack sufficient detail, for example about the symptoms, and the vaccine/s associated with the event;
- Reporting bias. For example, events with a close temporal relationship with immunisation and events that are publically rumored to occur as a result of immunisation are more likely to be reported;
- Inability to establish a causal relationship between an AEFI and a vaccine. That is, not being able to distinguish between a true AEFI from coincidental events that may occur not related to vaccination; and
- The inability to determine accurate AEFI incidence rates because of a lack of a precise numerator (adverse events) and, often, denominator, when there is a lack of reliable information on the number of administered vaccine doses.[27, 30-34]

Currently in Australia there are multiple pathways for reporting an AEFI. At a national level up until 2013, AEFI reports could be notified by healthcare professionals or the public via the Therapeutic Goods Association (TGA), and were assessed by the Advisory Committee for Safety of Medicines (ACSOM), formerly known as the Adverse Drug Reaction Advisory Committee, (ADRAC). The ACSOM reviewed reports of adverse events associated with all medicines, not just vaccines. Following the STIV signal in 2010 and subsequent recommendations for a committee dedicated to providing advice to the Minister of Health and the TGA on the safety, risk assessment and risk management of vaccines only, AEFI reports are currently managed by the Advisory Committee for Safety of Vaccines (ACSOV). [35] Formats for reporting an AEFI to the TGA include: telephone,

by pre-paid reporting form (commonly known as the "blue card") or online. Any medical events occurring after vaccination, that are regarded as "serious" and/or "unexpected" should be reported.[36] An established causal association with vaccination is not a pre-requisite for reporting. As of August 2012, the adverse events recorded are publically accessible online via the Database of Adverse Event Notifications (DAEN), at http://www.tga.gov.au/safety/daen.htm.

At a jurisdictional level, other than Tasmania and Victoria, AEFI reports can be notified to state and territory Departments of Health.[19] In Victoria, AEFIs are notified to the Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC), an integrated surveillance and clinical support service, funded by the Victorian Department of Health.[37] In Tasmania, health professionals report directly to the TGA. The format for AEFI reporting is not standardised across Australia as each jurisdiction has its own reporting form and collects different data.[19]

AEFI reporting is mandatory for vaccine manufacturers. The *Therapeutic Goods Act 1989* (the Act) requires manufacturers to submit reports of serious AEFIs within 15 days of becoming aware of the event. For healthcare professionals, reporting to the relevant health authority is mandated by jurisdictional legislation except in Tasmania, South Australia and Victoria.

Currently, consumers may report AEFIs to the relevant health authority in most jurisdictions (South Australia, Victoria, New South Wales, ACT and Western Australia). Nationally, consumers can also report an AEFI by phoning the Adverse Medicine Events Line (AMEL), a service funded through the National Prescribing Service and based at the Mater Hospital in Brisbane, which forwards reports to the TGA. Information about how consumers can make a report to the TGA is available on the TGA website.

In South Australia, the South Australian Immunisation Service (SAIS), SA Department of Health, is responsible for receiving AEFI reports, collating AEFI data, and providing follow-up to individuals requiring advice and/or further information regarding continuing immunisation. Since 1996, medical practitioners, immunisation providers and members of the public have been encouraged to report any serious and/or unexpected AEFI to the SAIS. Information collected in AEFI reports includes demographic details, the suspected vaccine, concomitant vaccines administered, details of the event, including time to recovery and subsequent treatment administered/required.[38]

At a national level, de-identified AEFI data is analysed by the National Centre for Immunisation Research and Surveillance (NCIRS) and annual reports summarising national AEFI surveillance data have been published regularly since 2003 in the Department of Health and Ageing journal, Communicable Diseases Intelligence.[39] State-based AEFI reporting rates for the same vaccines in Australia are highly variable. For example, the annual reporting rate in 2011 ranged from 6.2 per 100,000 in New South Wales to 27.7 per 100,000 in the Northern Territory.[39] In 2010, Western Australia, South Australia and the Australian Capital Territory had the highest overall reporting rates (42.1, 34.9 and 32.6 per 100,000 population, respectively) while New South Wales had the lowest rate of 5.9 per 100,000 population.[40]

It is known that AEFI reporting rates are highest for the infant vaccines and increase in incidence following the introduction of a new vaccine.[41]

2.1.3 The importance of post-marketing surveillance

Post-marketing passive vaccine safety surveillance involves implementing specific pharmacovigilance plans that are "timely, efficient, sufficiently large and in place for the life of the vaccine"[30] To ensure the public's trust in immunisation, it is essential that the risks and benefits of each vaccine are evaluated. [4, 10, 42] Effective PMS is critical for a

number of reasons. Firstly, as described in section 2.1, pre-licensure vaccine trials (phase 1-3) do not provide adequate safety data for potential adverse reactions which are rare, delayed, occur with vaccine combinations, or occur in individuals who have associated co-morbid conditions. Hence, post-marketing surveillance of vaccine safety is crucial as the detection of new, rare or delayed events may only become apparent with widespread use in populations, much larger than those observed in pre-licensure clinical trials.[32, 43]

Secondly, for established vaccines, PMS aims to monitor trends in known adverse reactions and, if the observed rate exceeds the expected rate, further investigation is required. Finally, PMS aims to detect program errors, such as incorrect vaccine administration or manufacture.[30, 44] In summary, the primary function of passive PMS is to provide an early warning system about possible new AEFI or a change in frequency of known ones and generate hypotheses, not test causality, which requires additional investigation.[33]

2.1.4 Post-marketing surveillance use and impact

There are several examples of how passive PMS has demonstrated its ability to detect rare adverse events that were either not detected or incompletely understood during pre-licensure clinical trials. One example of the importance of spontaneous reporting of a newly described AEFI was demonstrated by the detection of the association between intussusception and Rotashield, which subsequently led to the withdrawal of the Rotashield vaccine in the United States in 1999. In 1998 RotaShield was the first licensed vaccine for prevention of rotavirus gastroenteritis.[32] Rotaviruses are the most common cause of severe infant and childhood gastroenteritis worldwide, responsible for an estimated 23 million outpatient visits, 2.3 million hospitalisations, and over half a million deaths annually among children under 5 years of age.[45] Within ten months following licensure of RotaShield® (Wyeth Lederle Vaccines), passive surveillance via the Vaccine Adverse

Reporting System (VAERS) in the United States detected 15 reported cases of intussusception following 1.5 million doses administered, a rate of 1 case per 10,000 infants, occurring primarily after the first dose, which signalled the need for suspension of RotaShield and further evaluation of the vaccine.[46-48] Since then, two different rotavirus vaccines have been developed and licensed, RotaTeq® (Merck and Company, Inc.) and Rotarix® (GSK Biologicals). No observed risk of intussusception comparable to the Rotashield® vaccine was observed during large pre-licensure safety trials for either of both currently licensed vaccines. However, post-marketing assessment using active hospital-based surveillance has observed an increased risk in an Australian birth cohort in the first seven days following the first and second dose of both vaccines compared to age-matched controls.[49]

In 1976, an association with Guillan-Barre Syndrome (GBS) and a H1N1 influenza vaccine in the United States, first detected via increased reports notified to VAERS, resulted in its withdrawal from use.[50, 51] Guillain-Barré syndrome (GBS) is an acute, immune-mediated paralytic disorder of the peripheral nervous system. In the three months following release of the vaccine, 45 million people were immunised. During this time, VAERS received over 500 reports of GBS, including 25 deaths.[52]

Post-marketing surveillance is also important for monitoring the safety profile of vaccines over their lifetime on the market. This is demonstrated with changes in polio vaccination schedules globally, implemented after years of experience following approval and use of the oral vaccine. The changes in polio immunisation policies that have been adopted worldwide first beginning in 1998 in the United States is an example of this. Polio vaccination schedules have progressively withdrawn the use of oral poliovirus vaccines (OPV) and replaced them with inactivated poliovirus vaccines (IPV) because of the observed rare risk of vaccine-associated paralytic poliomyelitis (VAPP) associated with

the OPV.[53-55] The Australian government replaced the use of OPV with IPV in 2005 in vaccination schedules.

2.1.5 The influenza safety signal in 2010

In Australia the importance of post-licensure vaccine safety surveillance was highlighted in 2010, with the occurrence of higher than expected numbers of febrile convulsions and febrile reactions to a paediatric seasonal trivalent influenza vaccine (STIV), first observed in Western Australia.[56, 57] On 23 April 2010, all seasonal influenza vaccinations were suspended in children less than 5 years of age by Australia's Chief Medical Officer.[18, 40] Two subsequent, independent reviews on the management and response to the STIV issue criticised both Commonwealth and state health authorities for deficiencies in AEFI surveillance.[19, 58] In particular, the reviews noted delays in sending AEFI reports to the TGA and significant under-reporting of febrile convulsions by healthcare professionals.

The challenges in post-marketing surveillance, as illustrated by the 2010 STIV safety signal, are in receiving adequate information (AEFI reports) from all available sources, acting promptly upon safety concerns as they arise to avoid further occurrence of the AEFI and potential harm, whilst also reviewing the available data and assessing whether the risk of the event under investigation outweighs the benefits of continuing vaccination. How public health authorities respond in such scenarios can impact on the public's confidence in vaccination. Vaccine safety controversies can be further fuelled by allegations of public health officials failing to respond to suspected and unconfirmed risks.[59]

2.1.6 The value of consumer involvement in pharmacovigilance

Direct reporting of adverse drug reactions (ADRs) by consumers is increasingly viewed as an important component of pharmacovigilance. Most reporting systems world-wide until recently relied on health professionals and vaccine manufacturers to notify adverse events. Previously ADR reports from consumers were not sought from surveillance authorities,

possibly due to debate around what consumer reporting would contribute to health professional reporting in terms of quality of information.[60-62] The most common resistance by health authorities and healthcare professionals to include consumer reports in ADR systems was often based on the assumption that patient/consumer reporting would result in biased/selective reporting such as the influence of media coverage of problems with controversial drugs or that consumer reports might inundate the system with information about minor or well-known ADRs, thereby undermining the ability to detect important safety issues.[63]

However, consumer/patient reporting has important benefits. Consumer/patient reporting in pharmacovigilance strategies seeks to address inherent weaknesses of passive surveillance systems, such as under-reporting by healthcare providers.[64-66] Incorporating direct reporting serves as a recognition of consumers' rights by valuing their unique experiences and perspectives in contributing to patient safety systems.[67, 68] Targeting consumer reporters is also seen as a way for patients to report when healthcare professionals have not acknowledged the association between adverse symptoms and a medication.[64, 69]

A consumer advocacy group in Australia, the Consumers Health Forum, had for numerous years promoted the introduction of consumer reporting of medication ADRs.[70] Direct consumer reporting of ADRs for all medications, including vaccines, was first introduced in Australia at a national level in 2003 via the AMEL.[71] The AMEL (as described in section 2.1.2), operates via the Mater Hospital in Queensland, and collects reports from consumers, before submitting them to the TGA (see section 2.1.2). With regards to adverse events associated with vaccines, currently, direct consumer reporting of AEFI is possible in most jurisdictions. In the other jurisdictions consumers are directed to report an AEFI via a health care professional (eg, their immunisation provider or any other health

provider). At a national level, it is possible for consumers to report an AEFI direct to the TGA; however, the proportion of reports submitted by consumers is small. In 2011, there were 2,327 AEFI reports collected by the TGA and, of these, only 2% were consumer reports.[40] At an international level, the proportion of reports surveillance systems receive from consumers is also small. In a review of the international literature on patient ADR reporting, the total proportion of reports made by patients was shown to comprise 7-15% of total number of reports[62], a much higher proportion compared with the Australian AEFI reporting rates. In 2011, of the 14,400 ADR reports received by the TGA, 3% originated from consumers.[72]

Worldwide, direct consumer reporting of ADRs to regulatory authorities has been possible for a number of years: a recent review of patient ADR reporting reported that 46 countries accept direct patient ADR reports to their national spontaneous reporting schemes.[73] Recent legislative changes in pharmacovigilance in the European Union will expand this total as all European countries were mandated to include consumer reporting to national regulatory authorities as of July 2012.[74, 75] Although direct reporting by consumers is becoming increasingly accepted there is a lack of research examining consumer awareness of reporting systems. In the United Kingdom (UK), a recent study of the general population conducted in 2009 aimed to assess public awareness of the UK Yellow Card Scheme (YCS), the national ADR reporting scheme, following a publicity campaign in 2008 to alert the public of the availability of direct reporting.[65] It found that only 8.5% (172/2028) respondents were aware of the reporting scheme and that respondents who were aware of the YCS were significantly more likely to have completed secondary or tertiary education skilled working and working class, ($p<0.001$).

Few studies have compared consumer/patient reports with reports from healthcare professionals. Of the studies that have compared ADR reporting for medications or

vaccines by consumers and healthcare professionals, it has been shown that consumers can contribute significantly to successful pharmacovigilance, by either identifying new ADRs not previously reported by health professionals, or in providing reports that are of comparable quality with those submitted by healthcare providers.[60, 62, 63, 76-81]

In an unpublished study of AEFIs in South Australian children between 1997-2002 parents submitted the majority of all AEFI reports (60% parents vs 40% health professionals)[82]. The study found that there was no statistically significant difference in the quality of reports between parents and GPs that were regarded as suitable for notification to the national safety committee responsible for safety assessment at the time, ADRAC.

2.1.7 Parent AEFI reporters

There is limited research regarding the characteristics that define parents who report an AEFI to a surveillance system. No studies have occurred to date in the Australian setting with regards to reporting. Two American studies have examined AEFI parent reporters in families with infant children.[14, 83] Only one of these studies included a sample of parents who reported to an AEFI surveillance system.[83]

The study by Gust, Campbell et al. (2006) compared demographics, immunisation attitudes, beliefs and behaviours of 2,286 parents of young children (19 to 35 months) who sought medical attention for an AEFI. Three parent groups were compared: parents of children who experienced an AEFI and sought medical attention (223, 6.9%); parents whose children did not experience an AEFI, (1268, 61.6%); and parents who did not seek any medical advice/treatment for their child's AEFIs, (795, 31.5%).[14] The parent groups were sampled from a previous, national immunisation survey of the general population. This study did not collect information on the type of adverse event children experienced or whether parents reported their children's AEFI to a surveillance authority. The study found that parents who sought medical treatment for their child's AEFI reported greater

concern for vaccine (OR=2.08, [95% CI,1.07,4.05]), and were more likely to have children with incomplete immunisation schedules (OR=2.30,[95% CI, 1.17,4.55]) compared with parents who indicated their children did not experience an adverse event. The study authors proposed that parents who held greater vaccine safety concerns were more "reactive" when their children experienced minor, common vaccine side effects, ie. by seeking medical attention.[14]

The study by Woo et al (2004) compared the vaccine risk perception among 124 parents who had reported that their children had acquired autism or a developmental delay disorder after immunisation to the Vaccine Adverse Event Reporting System (VAERS) in the United States, with results of an immunisation survey of 1600 parents in the general population.[83] Most respondents in this study were the children's mother (91.9%); aged ≥ 30 years, (92.7%), had received at least some college education (91.1%) and annual household incomes of ≥ US$50,000. Only 15% of the VAERS parent AEFI reporters believed immunisation was "extremely" important and 66% had withheld at least one vaccine compared with 87% and 14.3% of parents respectively in the general population study by Gellin et al. (2000).[84] The study authors concluded that parents reporting autism and developmental delay as an AEFI differed significantly in their beliefs about the benefits of immunisation compared with parents in the general population. Both studies demonstrate that parents reporting or seeking medical attention for their children's perceived AEFI do question vaccine safety and the benefits of immunisation. However, neither of the above studies examined factors or reasons related to parental reporting of AEFIs to healthcare or surveillance authorities.

In an unpublished, qualitative study (n=10) conducted in South Australia that examined parental experiences and the impact of an AEFI it was found that, following an AEFI event, parents were initially hesitant about future vaccination decisions.[85] However, with

adequate support and risk communication, all children in this sample continued their immunisation schedules.

2.1.8 Healthcare provider AEFI reporters

Since Australia has a national schedule of recommended immunisations, reactogenicity of particular vaccine brands is unlikely to account for the wide variation in AEFI reporting rates between states. A much more likely explanation is differential reporting rates amongst vaccine and health care providers within individual states. In the majority of vaccine and ADR surveillance systems worldwide, AEFI reports are received from healthcare providers.[17, 86-89] The reporting knowledge, attitudes and practices of healthcare provider AEFI reporting is an under-researched issue and little is known regarding factors which facilitate or impeded healthcare AEFI reporting.

Only four studies that focus on health professional AEFI reporting, all of which were conducted outside of Australia, have occurred to date. The first study examined family physicians' (GPs) awareness of vaccine safety monitoring systems and reporting frequency for vaccine associated adverse events.[13] In this study, a mailed survey was sent to a random sample of 747 family physicians across Canada. The survey aimed to determine GPs' awareness of how and when to report vaccine associated adverse events. Questions included in the survey covered observation of vaccine adverse events; education about vaccine adverse events; knowledge of monitoring systems; awareness of reporting criteria and forms; perception of the obligation to report vaccine events and preferred formats to facilitate reporting. The overall response rate was 32% (226 out of 717 eligible). Of the 226 Canadian GPs, 55% had observed an AEFI and 42% had reported it. Less than 50% were aware of a monitoring system for AEFI, only 28% knew of reporting criteria and 39% had received vaccine adverse event education during medical training. Reporting was significantly associated with knowledge of a vaccine adverse event surveillance system

and reporting criteria. For respondents who did not report, (n=172), the primary reason was that the GP had never observed an AEFI (52%), did not know reporting was expected (16%), the event did not seem serious enough (16%) or did not know the reporting procedure (10%).

The second study that examined health provider AEFI reporting associated with the introduction of a new Meningococcal serogroup C Conjugate (Men C) vaccine, to the Yellow Card System in the United Kingdom.[16] This study included three healthcare provider groups, hospital doctors, GPs and nurses, and aimed to examine rates of reporting, severity of AEFI and completeness of reports by provider type. In order to facilitate the monitoring of a new Men C vaccine, the Yellow Card Scheme was extended to allow nurses for the first time to report. A higher rate of AEFI reporting by nurses (48%) was observed compared with GPs (27%) and hospital doctors (24%). Completeness of the reports varied across the professional group. In this study only 50% of the required information collected on the Yellow Cards (UK reporting forms) were completed with hospital doctors' providing AEFI reports that were more complete (73%), followed by nurses (48%) and GPs (35%).

The third study, conducted in the United States, included a total of 293 respondents, physicians, pharmacists and nurses or nurse practitioners.[15] The response rate was 36%. A 23 question survey was developed in paper and online formats that covered the frequency of AEFI reporting, beliefs and awareness of AEFI reporting, barriers to reporting and strategies to increase reporting rates. Of all respondents, 71% had never reported an AEFI, with 17% indicating they were not aware of how to make a report. Although 82% were aware of the reporting system VAERS, only half (55%) were aware of how to report using the VAERS. The study demonstrated a significant difference ($p<0.01$) by healthcare provider type having ever reported an AEFI. Barriers to reporting included unclear

definitions of a reportable AEFI; time pressures in competing a report; and confusion in whose responsibility it was to report. Reporting was associated with being alerted to look for specific events (87%); discounting other explanations for the event (81%); if the event was seen repeatedly (71%) and if the events occurred in vulnerable patient groups such as pregnant women, infants or patients aged ≥65 years (44%).

The fourth study is the most recent conducted to date. This study included a nationally representative sample of family physicians (GPs), physician assistants, nurse practitioners, practice nurses and nurses working in paediatrics, family medicine and internal medicine.[90] The survey aimed to assessed demographics and professional characteristics; knowledge and attitudes of identifying and reporting an AEFI to VAERS, healthcare provider sources of information about VAERS and how to improve awareness of reporting. The study analyses included predictors of not reporting to VAERS. The response rate was 54.9%. Although 71 % were familiar with VAERS, only 14% were "very" or "extremely" familiar with the paper reporting procedure and approximately one third were not familiar of when it was required to report an AEFI. Approximately 40% of all study participants had identified at least one AEFI, with only 18% indicating they had reported to VAERS. Respondents indicated they would report a serious AEFI regardless of whether they were a known (73%) or unknown (62%) reaction associated with immunisation. Participants who indicated that they were not familiar with submitting a paper report to VAERS were more likely (OR =12.84; $p < 0.001$) not to report an AEFI than those who were very or extremely familiar with that process. Individuals working in internal medicine, family medicine or Obstetrics and Gynaecology were more likely (OR =4.22, 1.76, and 1.74, respectively; $p = 0.0005$) not to report than those working in paediatrics. Those who were not at all familiar with reporting criteria to VAERS tended not to report versus those who were very or extremely familiar with the requirements (OR = 5.52; $p = 0.013$).

2.1.9 Healthcare provider adverse drug reporting

As there is little research regarding healthcare provider AEFI reporting, studies examining reasons why adverse drug reactions (ADRs) are not reported may provide, to some extent, an indication of factors applicable to reasons associated with under-reporting of AEFI. Furthermore, in many pharmacovigilance systems, pathways for reporting an AEFI are identical to ADR reporting. At a national level in Australia, the format for reporting an AEFI is the same for ADRs. As an ADR can occur for many medications, they are very common. In Australia, ADRs are a significant burden. Hospital admissions associated with ADRs range from 6% of all admissions in the general population to 30% of admissions in older Australians.[91, 92] In general practice patients aged over 45 years it is estimated that 12% have experienced an ADR.[93]

Although it is well recognised that passive surveillance requires complete, accurate and timely reporting by healthcare providers and that health professional, rates of reporting are low in ADR systems. Evidence of reporting trends by Australian GPs suggest that rates are declining. In 2011, GPs contributed only 7% of all ADR reports to the TGA[72] compared with 28% of all reports received in 2003.[94] Similarly, in the United Kingdom, a 37% decline in reporting by GPs has occurred between 2003 and 2012.[95]

It is estimated that less than 10% of all ADRs are reported and that only 5% of medical professionals report to ADR systems.[96, 97] A systematic review of 37 studies that included both hospital-based and general practice settings estimated the rate of under-reporting of all ADRs to spontaneous reporting systems from 6% to 100%, with a median under-reporting rate of 94% (Interquartile Range 82–98%).[96] A study conducted in Sweden that focussed on serious and potentially fatal adverse events found the overall rate of under-reporting over a period of 5 years was 86%.[98] In this study, 1349 patient case notes that included a diagnosis of cerebral haemorrhage, venous thrombosis or phlebititis, pulmonary

embolism and other venous thrombosis or embolism were reviewed for causality and drug use at the time of the event. The results showed that between the five hospitals, under-reporting ranged from 75% - 100%.

Although under-reporting may occur due to lack of detecting an ADR, it has also been shown that doctors do not report, even when they do detect an adverse event.[69, 99, 100] Numerous studies in various settings and countries have identified factors associated with under-reporting of ADR by healthcare professionals and all report similar findings.[96, 101-104] A systematic review of 45 studies conducted in Europe, United Kingdom, Asia and the United States examined the influence of personal and professional factors on ADR reporting and summarised the key determinants associated with under-reporting.[101] The attitudes most frequently associated with healthcare professionals not reporting ADRs were: ignorance of what to report or ignorance of a reporting system (38/40 studies, 95%); diffidence in 72% (23/32 studies); lethargy in 77% (27/35 studies); indifference and insecurity regarding causation (not possible to ascertain whether the drug caused the reaction) in 67%, (16/24 studies); a belief that only safe drugs are released into the market in 47% (8/17 studies); and fear of possible involvement in litigation or investigation (24%) (Lopez-Gonzalez, Herdeiro et al. 2009). A qualitative study of 16 community pharmacists also found confusion about ADR reporting and low knowledge of availability of the pharmacovigilance system in Malaysia.[102] Barriers to reporting in this study were similar to findings of quantitative studies of ADR reporting: not seeing an ADR, lack of understanding of the reporting pathway, complexity of the reporting process and lack of feedback from authorities were noted.

2.1.10 Healthcare provider training in vaccine safety

Parents rely primarily on immunisation providers for advice on vaccine safety.[84] GPs, paediatricians, nurses and other health professionals all play an important role in

maximising childhood immunisation coverage, by their attitudes towards immunisation and in adequately communicating immunisation risk and benefits to the public.[105] To effectively engage with parents regarding vaccine safety concerns, providers need to understand the vaccine safety surveillance system.[32] Ensuring healthcare provider training and knowledge of vaccine surveillance processes is an important component of an effective surveillance system.[106, 107] It is reasonable to infer that healthcare providers' knowledge of vaccine safety is obtained via pre/post-service training, and in-field practice. However, few studies regarding the training received by healthcare workers who provide immunisations or provide information on immunisation have been conducted in Australia or internationally to date.

In addition to the Canadian study[13] described in section 2.1.8, a recent European study assessed the pre-service training in immunisation and vaccine safety with students (n=184) and curriculum coordinators (n=92) of medical schools, universities and nursing schools in seven participating countries.[108] Major gaps in knowledge and competences were identified regarding vaccine safety, communication with parents, addressing anti-vaccine arguments and practical skills. Less than 60% of students reported receiving training in safety issues and controversies and only 44% reported they had received training in effectively communicating vaccination issues to parents and public.[108] An Australian cross-sectional survey of health care providers' immunisation knowledge and attitudes, in two regional Area Health Services of NSW, compared the experience of continuing education rates of GPs, midwives and nurses working in various health settings, (general practice, community and hospital departments.[109] It was reported that 93% of community nurses indicated receiving accreditation training, followed by practice nurses (69%) and hospital nurses (26%).[109] Nurses receiving training were more confident in addressing parental concerns regarding immunisation compared with nurses not receiving training.

An unpublished cross-sectional survey (n=452) conducted in Western Sydney in 2004 included GPs, nurses, midwives, paediatric and community nurses (National Centre for Immunisation Research and Surveillance 2004). This study indicated that most nurses and GPs believed vaccination training and education was inadequate and that there was need for improved training for healthcare providers.

Studies of training in ADR reporting in medical and pharmacy schools also reveal low levels of training with approximately fewer than half of the respondents being taught about ADR reporting during their undergraduate teaching.[110, 111] A recent cross-sectional study of 13 pharmacy schools in the United Kingdom reported that the amount of time devoted to teaching pharmacists about their role in pharmacovigilance was: less than 4 hours, (7/13 respondents); between 4 and 8 hours, (5/13 respondents) and over 20 hours (1/13).[112]

In the United Kingdom and Japan, increasing pharmacovigilance teaching in undergraduate programs and providing training opportunities within clinical settings have been recommended and adopted in response to inadequate training. [112, 113]

2.1.11 Interventions aimed at improving ADR reporting by healthcare professionals

Numerous intervention studies designed to reduce under-reporting and improve the quality of reports in various healthcare settings have occurred internationally, as evidenced by a sytematic review of 43 studies that were published to 2010.[114] The types of interventions included in the review by Gonzalez-Gonzalez et al. 2013 and in more recently published studies that demonstrated increased ADR reporting include:

- educational, such as workshops about reporting, and/or reminders to report via email, letters or posters;[115-125]
- modification of reporting forms;[126, 127]

- modification of reporting procedures;[127-130]
- improving access to reporting forms; [120, 124, 131];
- improving feedback to reporters;[127]
- providing incentives to report;[122, 123]
- and providing assistance from another professional the time of reporting.[122, 126]

A brief description of these intervention studies published since 2010 is shown in Table 2.1.

Table 2.1: Examples of intervention studies to improve healthcare professional spontaneous ADR reporting

Author, year of publication, country	Study design	Study period (months), target population, sample size	Intervention, study outcome	Increase in reporting observed
Biagi et al. 2013 [131] Italy	Non-randomised controlled trial	36 GPs N=168	Monthly email updates of drug safety with a report form attached, over 10 month period Reporting rates from three local health areas before and following intervention	Reports from participating local health areas rose by 49% in the first year (2010) compared to previous year, while the number of ADR reports submitted by GPs in control areas increased by 8.8%. In the second year post-intervention (2011), the number of reports from the intervention and control group local health areas decreased by 6.8% and 4.3% respectively compared to 2010.
Herdeiro et al. 2012 [117] Portugal	Cluster randomised controlled trial	12 Hospital and outpatient centre physicians N=6,579	1. 1-hour workshop involving presentation of a clinical case 2. Telephone interview on previous ADR reporting experience and awareness. Reporting rates and quality of reports	Workshop intervention increased reporting rates by an average of four-fold across the 20 month follow-up period compared with control group. RR=3.97; 95% CI 3.86, 4.08, p <0.001. The telephone intervention resulted in a non-statistically significant increase. RR =1.02, 95% CI 1.00, 1.04 compared with control group. The workshop intervention increased quantity and quality of reporting for more than one year compared to an increase in the first 4 months of follow-up only in the telephone group.
Ribeiro-vaz et al. 2012 130 Portugal	Pre-post experimental design	45 Hospital nurses, physicians, pharmacists N=27 hospitals	The inclusion of hyperlinks to an online ADR reporting form and/or in electronic patient records. The number of spontaneous ADR reports reports per month pre- and post intervention	The median ADR reports per month significantly increased, from two (range 0-12) to five reports (range 1-17) in hospitals with hyperlink access to the EPRs, p=.043 The median of ADR reports per month using the online form increased from one (range 0-5) before the intervention to four (range 1-17) after, p=.009. The reporting of serious ADRs increased 3-fold, and non-previously described ADRs increased 4.5-fold. Daily website visits to the regional pharmacovigilance centre increased from ten before the intervention to 27 after , p< 0.001.

Table 2.1 cont.

Author, year of publication, country	Study design	Study period (months), target population, sample size	Intervention, study outcome	Increase in reporting observed
Johansson et al 2011 [119] Sweden	Randomised controlled trial	12 Primary healthcare physicians and nurses N=845 physicians N=1,423 nurses	One page ADR information letters sent quarterly, including updates of ADR information, a current case report and instructions on what and how to report. Phase two involved a follow-up questionnaire asking whether the letter had been received and read. The number and quality of ADR reports submitted to the regional pharmacovigilance centre in 2008.	No significant differences in reporting rates were observed between the two groups in the year prior to the intervention. During the year of intervention, control group units submitted more ADR (37) reports (52) than the intervention units (p=0.34). Intervention units submitted greater total of high quality reports than the control group (37 vs 15 reports, p =0.048). More respondents in the intervention than in the control group received (29% vs 19%, p=0<0.0001) and read (31% vs 26%, p<0.0001) the ADR letter.
Gerritsen et al 2011 [118] Netherlands	Retrospective cohort Education Intervention	58 GP registrars in 3rd year of training N=259	A practice-based ADR training method was introduced in 3rd year of training Compared number and quality of ADR reports made by GPs following practice-based pharmacovigilance training method to the standard, lecture-based training method	Practice-based training resulted in 6.8 reports per 1000 months of follow-up compared to standard lecture-based training method of 2.1 reports per 1000 months of follow-up. ADR report quality was higher from GPs who received practise-based training and included more off-label events than lecture-based method

2.2 Research justification

The limitations of passive PMS in monitoring AEFI can lead to delays in and identifying at-risk persons in the unvaccinated population, as well as patients suffering from undetected adverse reactions in the vaccinated population. The recent example in Australia with the STIV in 2010 illustrates this point. Two independent, commissioned reviews of the AEFI system in Australia highlighted deficiencies in healthcare provider AEFI reporting which resulted in delayed signal detection of the febrile convulsions following STIV in 2010.[19, 58] Both reviews included recommendations that asserted the need to improve timely detection and reporting of AEFI, by increasing awareness of national reporting by both consumers and healthcare providers. In 2013,a key priority of the work of the ACSOV was to design strategies aimed at improving reporting by health professionals.

Despite their limitations, spontaneous reporting schemes continue to be the foundation of most pharmacovigilance systems. Furthermore, passive surveillance is not likely to be replaced by alternate methods that do not rely on healthcare provider awareness or readiness to report.[132-134] This is because passive surveillance should be able to monitor vaccine safety and detect safety signals in real time or near-real time. This also means it can be used to generate hypotheses regarding causation which can then be tested using alternate methods of safety surveillance. Alternate methods, such as data linkage, predominantly use retrospective data and are usually used to detect pre-specified AEFI and to test hypotheses for associations between a vaccine and an AEFI.[135] Additionally, in practice, introducing data linkage for vaccine safety surveillance in Australia to date has been hampered by difficulties and complexity of the federal and state/territory legislative frameworks, requirements and concerns from data custodians and Human Research Ethics

Committees (HRECs) regarding issues of privacy and consent for linkage studies to occur.[136]

2.3 Conclusion

The studies reviewed in this chapter have highlighted the gap in knowledge with respect to parental/consumer and health professional AEFI reporting. The example of the STIV safety signal in 2010 provided a timely reminder of the challenges of passive surveillance systems and illustrates an ongoing need for robust passive AEFI reporting systems. The AEFI reporter, whether it be a health professional or member of the public, is central to the effectiveness of passive surveillance. As the rates of reporting are important to the reliability of passive surveillance to adequately detect AEFI, it is important to understand the factors that lead to AEFI reporting. To improve the system it is crucial to understand who reports (and why) to the AEFI surveillance system in order to identify factors that lead to reporting by either a consumer or health professional.

This literature review has demonstrated that there are no or very few studies to date that have provided a description of the characteristics of AEFI parent or health professional reporters and factors that may lead to reporting to surveillance authorities. Furthermore, there is a paucity of research that compares consumer AEFI reporters with non-reporters.

This thesis addresses this gap, through the design, conduct and results of three studies of parents and healthcare professionals. The two parent interviews explore:

- Vaccine safety beliefs of parent AEFI reporters;
- The types of adverse events parents reported to surveillance authorities and healthcare professionals;
- Reasons for reporting an AEFI;
- Awareness of a vaccine safety surveillance system; and

- Socio-demographic characteristics of AEFI reporters and non-reporters.

The generalisability of parental opinions will be compared using selected questions common to both parent surveys.

The health professional study, using a qualitative methodology, explores the experiences of general practitioners, ED consultants and nurses in AEFI detection and reporting. It examines their views about:

- Occurrence of an AEFI in practice;
- Frequency of reporting to a surveillance system;
- Definitions of a reportable AEFI;
- Barriers to reporting; and
- Training in vaccine safety

The findings of this thesis should fill a gap in knowledge about parent and healthcare professionals reporting to passive surveillance systems.

3 Methods

In chapters 1 and 2 the aims, research questions, justification and a review of the literature relevant to AEFI reporting were presented. In this chapter I describe the study rationale, methods and design used for data collection and analysis of each of the three research phases that make up this study. The aim is to provide an overview of how the research was conceptualised and demonstrate how and why a mixed methods approach was important to the design and conduct of this study. It also includes a brief description of the ethical considerations and strategies employed to ensure research quality.

3.1 Rationale for mixed methods design

This study has sought to use both qualitative and quantitative methods to help understand the issue of AEFI reporting by parents and healthcare providers within the Australian passive vaccine safety surveillance system. The rationale for using a mixed methods design in this study is grounded in the principle that neither quantitative nor qualitative methods alone were sufficient to answer the research questions.[137] While each of the two research methods may be based on different epistemological premises, the strengths and weaknesses of both provided a sound rationale for their integration.[138, 139] I considered that, when used in combination in the one program of study for the purposes of this thesis, the two approaches would be complementary, rather than competitive. In this section I address the more theoretical questions about the use of mixed methods research followed by the more practical ones in section 3.2.

It is often stated in the literature that most quantitative methods are based on the positivist paradigm of enquiry, while the constructivist or interpretivist paradigm underlies qualitative methods. [140, 141] Epistemologically, these two approaches are very different. In

brief, quantitative purists regard scientific knowledge as based on pure observation that is free of interests, values, purposes, and psychological make-up of individuals. They believe that social observations should be treated as entities in much the same way that physical scientists treat physical phenomena, (ie, cause and effect thinking) and should be objective. On the other hand, qualitative purists[142, 143] claim knowledge is based on multiply-constructed realities that are socially and historically constructed, that time- and context-free generalisations are neither desirable nor possible, that research is value-bound, and that it is impossible to differentiate fully between causes and effects.

Despite these theoretical differences, the emergence of mixed research methods over the past thirty years in the health and social sciences indicates that strategies to combine these approaches can be found. Mixed research methods have developed in response to the limitations of the sole use of quantitative or qualitative methods and are now considered a legitimate alternative to each of these two traditions alone. From an epistemological perspective, the philosophy of pragmatism offers one approach to accommodate the differing theoretical orientations of qualitative and quantitative methods.[139, 144] Pragmatists do not commit/confine their beliefs to any one system of philosophy and reality.[139] They argue that both quantitative and qualitative methods are useful and decisions about the use of either will depend on the research question(s) and phase of the research cycle.[140] They also argue that, by mixing the design throughout the planning, data collection, analysis and inference stages, the overall study becomes rich in multiple sources of data and allows for richness in interpretation.

Despite the appeal of pragmatism as a foundation for mixed methods, debate remains about its acceptability. For example, Hall (2013) suggests paradigm issues are a major concern in mixed methods research and that pragmatism does not justify the use of mixed methods.[145] A widely held premise for claiming pragmatism as the basis for mixed

methods is that researchers should be free to choose "what works". This debate, commonly known as the "paradigm wars" originated in the 1970s and 1980s between quantitative and qualitative researchers, and stemmed from the idea of incompatibility between the differing philosophical world- views underpinning quantitative or qualitative approaches.[146] The argument was that mixed method studies cannot and should not be conducted because quantitative and qualitative researchers use different and opposing philosophies and methods to study research problems. This idea conveyed by both sets of research purists, that a positivist philosophical worldview could be combined only with quantitative methods and that a naturalistic worldview, could be combined only with qualitative methods is also known as the *"incompatibility thesis"*.[147] Howe asserts that although the two research methods are linked to specific paradigms, this should be neither sacrosanct nor compulsory. [147] What is critical to either methodology and to how a research piece should be judged by is not by how well it matches a set of conventions, but rather by how well it fits with the purpose of the research. The standards that should be applied, proposed by Howe and Eisenhardt (1990) include:

- Choosing appropriate methods that provide data that can answer the research questions;
- Ensuring the background assumptions to the research are coherent; and
- Ensuring that the methods and data analyses are applied effectively, or well enough so that the results are credible.[148]

Within the context of the overall design of this thesis , in agreement with Cresswell and Plano (2011), I believe that mixed methods research assumes or rather,

"encourages the use of multiple worldviews or paradigms rather than the typical association of certain paradigms for quantitative researchers and others for qualitative researchers." [149]

In essence, mixed methods as a research design, is inclusive, pluralistic and complementary. It has allowed me the freedom to adopt an appropriate method for the three separate studies included in this thesis and for the collection of data that would not be attainable if the research had relied on one method alone.

Both quantitative and qualitative components of the studies included in this thesis evolved from discussions with my supervisors and other academics at the University of Adelaide whom I consulted at various stages of the project. My desire to strengthen my quantitative research skills and to undertake for the first time a piece of qualitative research work led to the research studies detailed in this thesis and the eventual expansion of the project from a Masters program with progression to a PhD. When planning the content of this thesis, I considered that the first two studies of parental AEFI reporting would require a quantitative approach as they sought results that would categorise and compare the characteristics, (such as socio-demographics) and opinions of AEFI parents with no-AEFI parents, and AEFI parent reporters with AEFI parent non-reporters. The advantages of a quantitative approach for the parent studies enabled the collection of data and the identification of attributes from a large population sample rather than a small group of individuals that would be achieved using a qualitative method.[139] Furthermore, these results could be applied not only for the purposes of answering the research questions within this study, but also to other published research that employed quantitative methods to measure parental immunisation opinions and characteristics.

In contrast, I considered that the study of health care professionals required a qualitative approach as the research questions sought to explore and understand each individual's experiences, rather than construct a measure of their reporting experience. A qualitative method for this phase of the research was most appropriate in order to understand how an AEFI is interpreted or conceptualised by health professionals. Secondly, as described in

the literature review (section 2.1.8), when I conducted the initial literature review in 2009, I had identified two published studies to date [13, 16] about healthcare professional reporting that had both employed quantitative methods. Both studies demonstrated low levels of awareness of AEFI reporting. Therefore, adopting a qualitative approach for this phase of the study provided an opportunity to examine the experiences of healthcare professionals in AEFI reporting, aiming to gain an understanding of *why* reporting was infrequent. Together with my PhD supervisors, I decided that integrating quantitative and qualitative data, rather than choosing from one research method only would best suit the over-arching objective of examining parental and healthcare professional perspectives of AEFI reporting within the Australian passive surveillance system.

3.2 Mixed methods designs in practice

A mixed methods study starts with a strong mixed methods research question, that is, one which demands the use and integration of both qualitative and quantitative methods.[150] There are differing views regarding the definition of mixed methods design. These definitions, in turn, have shaped debate about how to incorporate mixed methods in health and social sciences research. Interpretations of mixed methods design have evolved over time, and are still evolving.[140, 151-155] Johnson, Onwuegbuzie and Turner (2007) described 19 definitions from social science researchers in the literature.[155] Some distinguished between mixing methods within a single phase/strand of a study.[140] For example, Tashakkori and Teddlie (1998) defined mixed methods as the combination of "*qualitative and quantitative approaches in the methodology of a study"* while other definitions describe mixing as incorporating quantitative and qualitative components across separate phases/strands.[139] Mixing across two complete research projects within the same study has also been defined as a "multiple methods" study.[156] Tashakkori and Creswell (2007) assert it is necessary for researchers to distinguish between a definition of mixed methods as the

collection and analysis of the two types of data (qualitative and quantitative) and mixed methods as the *integration* of the two approaches to research. They argue that the first definition is more focussed on ‘‘methods’’ and the latter on ‘‘methodology.’’ The first uses the two types of data without integrating the results, whilst the second integrates the findings of the two arms. Methods refer to the specific details of the techniques or procedures used within a study for the collection and analysis of data, such as questionnaires, interviews, or participant observation. Methodology, by contrast, refers to the philosophical assumptions that guide the overall strategy or plan of action underlying the choice and use of methods, for example ethnography, survey research or phenomenological research including the mixture of the two approaches.[157]

The following definition adopted by Cresswell and Tashakkori encompasses both aspects: [139,151]

“mixed methods research is defined as research in which the investigator collects and analyzes data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study or a program of inquiry.” [139, 151]

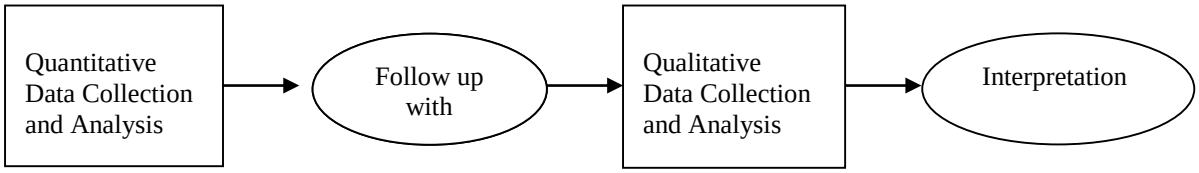
By 2011, Creswell and Plano’s definition had evolved to one which considered the core features of a mixed methods study as one where a researcher:

- *“collects and analyzes persuasively and rigorously both qualitative and quantitative data (based on research questions);*
- *mixes (or integrates or links) the two forms of data concurrently by combining them (or merging them), sequentially by having one build on the other, or embedding one within the other;*
- *gives priority to one or to both forms of data (in terms of what the research emphasizes);*
- *uses these procedures in a single study or in multiple phases of a program of study;*
- *frames these procedures within philosophical worldviews and theoretical lenses; and*
- *combines the procedures into specific research designs that direct the plan for conducting the study.”* [149]

As can be inferred from the above definition, there are various approaches and decisions to be made in the application of mixed methods designs. A mixed design may use quantitative and qualitative techniques together, either in parallel or in sequential phases.[138] Creswell, Plano Clark, Gutmann, and Hanson (2003) classified these techniques into two major categories, *sequential* and *concurrent*, with three variations of both.[158] In sequential designs, either the qualitative or quantitative data are collected in two distinct phases. This involves an initial stage, followed by the collection of the other data type during a second stage. In contrast, concurrent designs are characterised by the collection of both types of data during the same stage/phase. Within each of these two categories, the specific design plans are based on: the priority given to the qualitative and quantitative data (equal or unequal), the methods used to analyse and integrate the data, and the theoretical basis underlying the study methodology.[137, 158]

I considered that, as the results of each study conducted in this research of AEFI reporting for this thesis would be used to synthesise the final discussion, a sequential explanatory mixed methods design would be most appropriate as the overall study design. The sequential explanatory design, as described by Creswell and Plano[149] is shown schematically in Figure 3.1. This design starts with the collection and analysis of quantitative data followed by the subsequent collection and analysis of the qualitative data. The second, qualitative phase of the study is designed so that it follows from the results of the first quantitative phase. As an explanatory sequential design begins quantitatively, the researcher typically places greater emphasis on the quantitative methods than the qualitative methods.

Figure 3.1: The explanatory sequential design

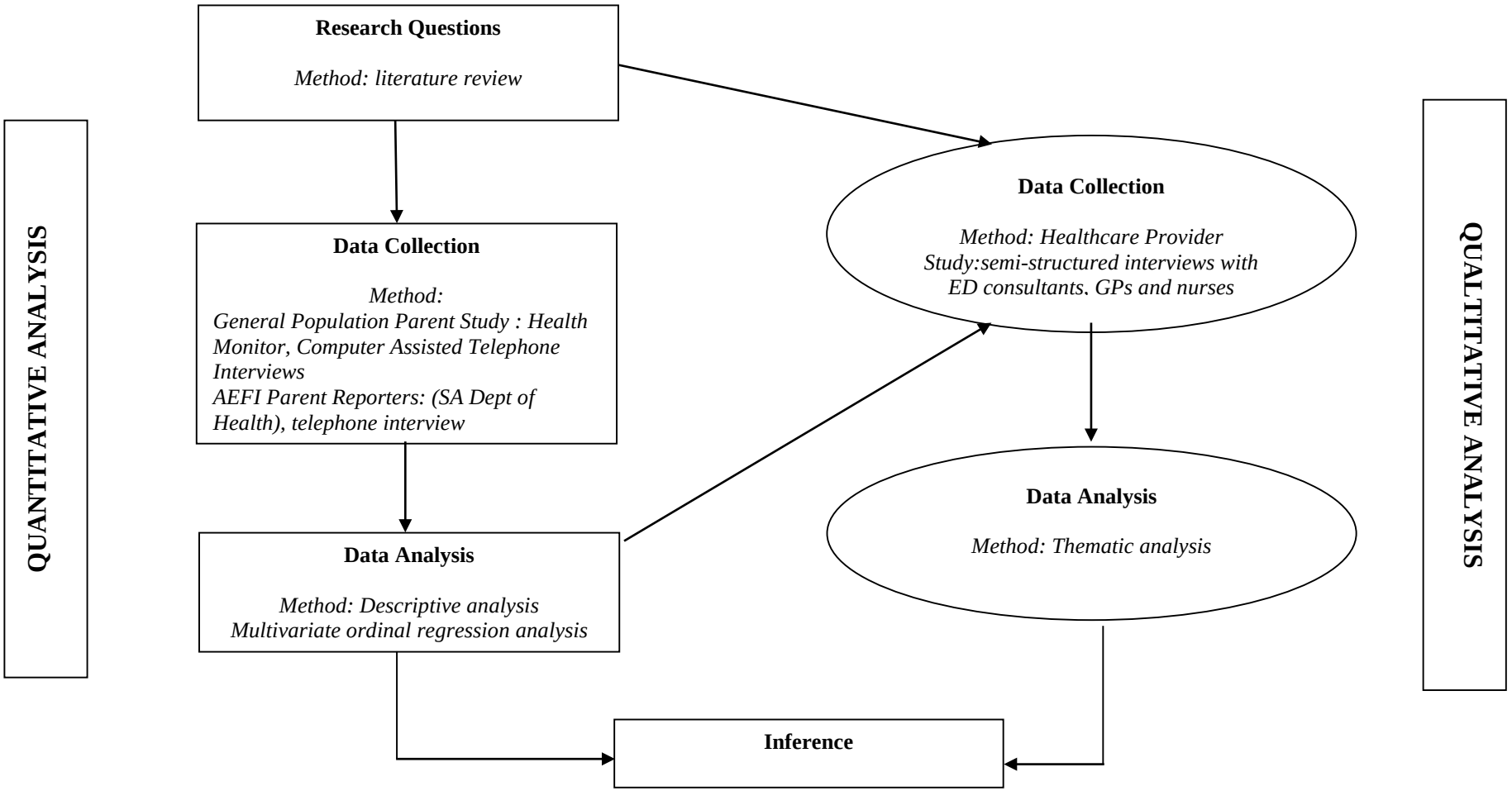


The different phases of the three research studies presented in this thesis were planned so that the parent studies (quantitative phase) were to be conducted first, followed by the healthcare professionals' study (qualitative phase). Each of the three studies was intended to be completed as a stand-alone piece of research with findings informing the next phase. However, in practice, the reality of lengthy holdups in accessing, collecting and analysing the quantitative data for the two parent studies, combined with the need to recruit participants, conduct interviews and begin to familiarise myself with the data for the qualitative healthcare provider study meant that undertaking the research was somewhat different. In effect, the AEFI Parent Reporter study (see section 1.2) preceded both the General Population Parent and Healthcare Provider studies, whilst the General Population Parent study data was collected and analysed in parallel with the Healthcare Provider study. Nevertheless, each phase of the research contributed to the overall understanding of AEFI reporting by parents and healthcare providers. In particular, findings from both parent studies highlighted the importance of healthcare providers' interactions with parents. In the General Population Parent Study, parents mainly reported their children's AEFI symptoms to health-care professionals (see Chapter 4, Figure 4.1). In the AEFI Parent Reporter study most parents sought some help for their children's AEFI by attending their local hospitals and general practice clinics (see Chapter 5, Table 5.4). The findings from the two studies helped to confirm the need to examine healthcare providers'

understandings of an AEFI in clinical practice and experiences of reporting. These results also informed the questions I needed to include in the qualitative interviews.

The overall study design and research methods used are shown schematically in Figure 3.2. First, a literature review was undertaken in order to develop the research questions and provide the context for the research and inform the qualitative and quantitative parts of the study. The following sections of this chapter describe the processes I used for the conduct and analyses of each study.

Figure 3.2: The study design



3.3 Quantitative data

3.3.1 Recruitment

General Population Parent Study

In this study, the aim was to recruit a random sample of parents from the general population and compare children's experience of an AEFI as described by parents, vaccine safety views and awareness of surveillance. It was considered a random sample of parents from the general population would be best suited in providing a representative sample of community opinion and would minimise selection bias. A Health Monitor survey was decided as an appropriate tool to source participants. The Health Monitor surveys are computer assisted telephone interview (CATI) surveys undertaken tri-annually and administered by the Population Research and Outcome Studies (PROS) Unit, University of Adelaide.[159] Data obtained from the Health Monitor population health surveys have been used to "*inform policy, programs and health services that will promote the health and well-being of the South Australian population*." The sample group of respondents for the Health Monitor Survey is derived from a random selection of households detailed in the Electronic White Pages (EWP) for nominated localities. Approximately 4,100 households are sampled with the aim of attaining approximately 2,000 completed interviews. The survey was conducted between March and May 2011. Prior to conducting interviews the sampled households are mailed an invitation letter detailing their selection and broad purpose of the Health Monitor with instructions for opting out of the survey. Screening of eligible adults is undertaken by the CATI staff administering the survey (Harrisons Research) when calling eligible households. As per the Health Monitor protocol, within each household, adults aged at least 18 years who last had their birthday were selected for participation in the interview. Only one person per household was interviewed, with no replacement sought for non-contactable persons. At least 10 call-backs were made to each

household before the selected individual was classified as a non-contact. In order to sample parents for this study, each selected adult was asked if he or she was a parent or legal guardian and, if so, further questions were asked about the vaccination status and experience of each child in his or her care, enabling classification of the respondent as having a child or children who had received a previous immunisation. Respondents with poor or no English were excluded from participating and no incentive was offered for participation. A pilot survey of 50 respondents was conducted to check question format and sequence.

In addition to the questions that were included for the purposes of this study, three separate studies were also conducted as part of the Health Monitor survey. The organisations involved were the Children's and Women's Youth Health Service, Department of Recreation and Sport and the Cancer Council, South Australia. The questions submitted from these organisations covered topics regarding public opinion on privacy and data linkage for vaccine safety surveillance, awareness of a physical activity guidelines campaign and smoking.

The recruitment results for the General Population Parent Study are presented in Chapter 4, (see section 4.3.5).

AEFI parent reporter Study

For this study, parents or guardians of children ≤7 years of age who directly telephoned the SAIS to report or seek advice for their child's AEFI symptoms and parents identified in AEFI reports received by the SAIS via the Child Health Parent Help line or their health care provider (HCP) were eligible to participate. During the recruitment period, the SAIS nurses sought verbal approval from parents who were being followed up with regards to their children's AEFI to receive the study information materials from a university study researcher (myself). At the end of each week during the recruitment phase, a SAIS nurse

would email me a spread-sheet with the names and addresses of parents who had consented to receive the study invitation materials. The spread-sheet contained the names, addresses and information regarding the child's immunisation and AEFI event. In order to be able to record a response rate for the study it was agreed with SAIS that I would also receive a de-identified line listing of children's AEFI symptoms, associated vaccine(s) and postcode for each parent who had declined to participate. One week after sending out the study information, I contacted parents by telephone to obtain verbal consent to participate in the study and a convenient time for the survey was scheduled. Prior to commencing interviews, I re-confirmed verbal consent with each parent on the day of the telephone interview. The recruitment results for the AEFI Parent Reporter Study are presented in Chapter 5 section 5.5.2.

3.3.2 Ethics, consent and confidentiality

The research protocol I adopted for the parent studies follow standard ethical guidelines including voluntary participation, seeking informed consent, confidential treatment of information, and the right to withdraw at any point of the project.[160] Here I provide a description of the measures adopted while planning and conducting the two parent studies. Together, they ensured that the rights and welfare of each research participant would be protected and that harm to participants was minimised:

- In the General Population Parent Study, participants were recruited by the CATI staff associated with the PROS unit, SA Department of Health Information, and employed an established protocol when engaging with each person. All personal information obtained from respondents by the CATI staff remained confidential. I did not receive any identifying details of eligible participants and actual respondents. All survey data was de-identified prior to receiving the dataset.

- I received informed consent from every respondent before conducting the interviews for the AEFI Parent Reporter Study. As described above parents were first asked for consent by the SAIS nurse. I sent parents a detailed study information sheet enclosed with the study invitation (see Appendix 6), which explained what they would be consenting to, should they decide to participate along, with the opportunity to withdraw consent. At the beginning of each scheduled telephone interview, I reconfirmed consent using a verbal checklist (see Appendix 7). This demonstrated and acknowledged my understanding of the need for continuous consent throughout the research process.

- All data collected and/or received for both parent studies remained private and securely protected. The data was stored on secure servers managed by the University of Adelaide. The servers are fire-walled, with files accessible only to authorised personnel, with computers protected by secure password. The paper forms used for recording the AEFI Parent Reporter study telephone interview data were stored in a locked cupboard in the Discipline of Paediatrics, University of Adelaide for which only I had access. All data from both studies will be stored for 7 years and then deleted.

- As described in section 3.3.1, I received only de-identified data of non-consenters in the AEFI Parent Reporter Study, in order to ascertain the study response rate. I received de-identified interview data only from PROS for the General Population Parent Study.

- The nature of the research for both parent studies was assessed as low/minimal risk to participants. In the AEFI Parent Reporter study, the research protocol allowed for parents who indicated concern regarding their children's immunisations or the AEFI experienced the opportunity to discuss their concern with a SAIS nurse

consultant to determine appropriate support and to A/Prof Mike Gold, the principal supervisor for this thesis, who is a vaccine safety expert. Of the 179 parents interviewed one parent expressed a desire for more information about how vaccine safety is monitored in Australia. A/Prof Gold emailed the parent about current mechanisms in place for assessing vaccine safety in Australia. No further communication/concern was received from this parent.

Documentation of approval for both parent studies from the appropriate HRECs is included in Appendix 1,(General Population Parent Study) and Appendix 4,(AEFI Parent Reporter Study). The invitation letter and study information sent to eligible participants in the AEFI Reporter Study are included in Appendix 5 and Appendix 6. The verbal consent checklist that was used on the day of telephone interview in included in Appendix 7.

3.3.3 Parent studies' questionnaires

General Population Parent Study

In addition to the standard demographic questions included in all Health Monitor surveys, a total of seven selected questions were included in the survey that would be repeated in the AEFI Parent Reporter study, in order to be able to compare results across the two parent studies. In order to be able to sample parents or legal guardians of children from all adult respondents participating in the survey, questions were included in the Health Monitor that identified whether there were children residing in respondents' household (question A5) and whether the respondent was a parent/legal guardian (question D.0). If the respondent identified as a parent/legal guardian, further questions were asked to: attain vaccination status of each child in the respondent's care (questions D.1-D.4); acquire information from parents about children's previous occurrence and experiences of an AEFI (questions D.7 and D.8); and for information related to parents' reporting of AEFI symptoms to healthcare professionals and surveillance authorities (question D.9). These

questions enabled the classification of the Health Monitor respondents, referred to throughout this thesis as, “AEFI parents”, “no-AEFI parents”, “AEFI parent reporters” and “AEFI parent non-reporters”. The Health Monitor survey used for this component of the thesis is included in Appendix 3.

AEFI Parent Reporter Study

The questionnaire (see Appendix 8) I used in the AEFI Parent Reporter Study was designed by myself in conjunction with my supervisors and with some input from the South Australian Immunisation Service (SAIS), SA Dept. of Health. The structured interview was made up of five main parts: general questions regarding acceptability of immunisation; vaccine safety opinion questions; the child’s AEFI event; awareness of vaccine safety surveillance; hypothetical AEFI reporting scenarios; and parent demographics. The immunisation and vaccine safety questions in the first two sections aimed to be consistent with previous immunisation research questions in order to be able to compare results and increase external validity.[5, 7, 83, 84, 161-163] However, because there were few studies published on parents’ beliefs about the likelihood of their children experiencing serious and/or mild adverse events, and no studies regarding parental awareness of surveillance, specific interview items were tailored to the research questions of my study. In particular, the questions that clearly defined a serious and mild AEFI and those that asked parents to respond to the acceptability of a stated numeric risk of anaphylaxis and febrile convulsion were designed to assess parents’ perceptions about the risks associated with vaccines (see Appendix 8, questions B8 and B9).

I piloted the questionnaire with a group of 10 mothers sourced from my personal and university contacts, who were not involved in the study in order to gain practice in conducting the telephone interviews, assess the time it would take to complete an interview, and to test the sequencing and format of the questions. After each interview I

asked respondents to provide some initial feedback regarding the format of the survey and to gauge whether there were any issues relating to the comprehension of the wording.

3.3.4 Analysis

Here I provide a brief overview of the methods of analysis for the parent studies. This is also described in detail within each of the published manuscripts in Chapter 4.

General Population Parent Study

The data analysed was obtained from the 469/2002 interviewed adults, who identified themselves as parents or legal guardians of 929 children aged 18 years and under. Two separate analyses were conducted with the data obtained from the Health Monitor. The first compared the safety views, awareness of surveillance, perceptions of AEFI and vaccine risks by whether parents stated that their children had previously experienced an AEFI, the AEFI parents", or that their children had not previously experienced an AEFI, the "no-AEFI parents". These results are presented in Chapter 4, (see section 4.2.5). The second component of the General Population Parent study was to analyse the results by whether the AEFI parents reported their children's AEFI to a healthcare professional or surveillance authority, the "AEFI reporters" in this thesis or did not report, the "AEFI non-reporters". These results are also presented in Chapter 4, (see section 4.3.5).

As the recruitment for the General Population Study was conducted by an external organisation described above, which recruited participants according to their standard protocol, i.e a fixed random sample of 2000 adults, it was not possible to recruit a targeted number of parents into the four sub-groups of interest for the purposes of this study: AEFI parents, no-AEFI parent, AEFI parent reporters and AEFI non-reporters. Although the underlying hypothesis to comparing differences in safety opinion between the two sets of parents, ie, that AEFI parents would have greater concern for vaccine safety than no-AEFI parents and that AEFI reporters would also hold greater concern for vaccine safety, it was

not necessary or appropriate to conduct sample size calculations. Essentially, the results of parental safety concern in the General Population Study in this thesis provide an indication of differences in proportions that could be applied to sample size estimates in future Australian AEFI safety opinion studies (ie. it is a pilot study). However, had it been possible to have recruited parents into the groups of interest, the estimated difference in proportions reported by the study conducted in the United States by Gust, Campbell et al. (2006) could have been applied.[14] In this study an approximate difference of 10% between AEFI parents (which included parents who sought medical treatment and those who didn't for their children's AEFI) and no–AEFI parents, whose children did not experience an AEFI was observed.[14] To detect an effect size difference of 10% between two proportions using a two-tailed test at the 5% level with power of 80% a sample size of n=199 would be required in both groups.

Univariate and multivariate ordinal logistic regression analyses were performed to compare differences in safety opinions between the "AEFI parents" and "no-AEFI parents".

The demographic variables included in the regression analyses included: parent age, gender, total children (1, 2, 3 and >3), parent respondents' education , income and country of birth (Australia or other). The Index of Relative Socioeconomic Disadvantage (IRSD) as a measure of socio-economic status.[164] All variables were included in the final multiple regression model regardless of significance in the univariate analyses.

Odds ratios were calculated when comparing variables to measure:

- the association between AEFI parent status and safety opinions and;
- to measure the association between reporting an AEFI to health professionals or surveillance authorities with safety opinion.

A p-value less than .05 was considered statistically significant. The two publications included in this thesis of the General Population Parent Study results report on data that was weighted to the gender, age and geographical area profile of the South Australian population and the probability of selection within a household. In doing so, the survey findings are applicable or representative to that population as a whole. The most recent Australian Bureau of Statistics (ABS) Estimated Residential Population (ERP) data, 2009 was used for the weighting process.

AEFI Parent Reporter Study

Descriptive statistical analyses were performed using the STATA statistical program Stata, version 11.0 (StataCorp, College Station, Tex, USA). As this study was conducted shortly after the suspension of the seasonal trivalent influenza vaccine program in 2010 and the data was over-represented by parents reporting an AEFI to seasonal influenza vaccination, in addition to reporting results on the overall sample, the response proportions and $\chi 2$ tests comparing National Immunisation Program (NIP) parent reporters with influenza parent reporters were used in the study analyses. Parents reporting an AEFI from both NIP and either pandemic or seasonal influenza vaccines together were included in the influenza reporting group for the $\chi 2$ analyses. For tables with less than 5 respondents in any one cell, the Fisher's exact test p value was calculated.

3.4 Qualitative study

The remaining sections in this chapter provide an overview of the conduct and analysis of the third component of this thesis, the Healthcare Provider Study.

3.4.1 Rationale for the interviews

The qualitative component of this thesis provided an important and necessary augmentation to the quantitative data collected in the parent studies. As I argued earlier in

section 3.1, a qualitative approach was ideally suited to the description and analysis of explanations and experiences of healthcare professionals' AEFI reporting. Qualitative data collection methods include, for example, observation, unstructured or semi-structured interviews, and analyses of document texts, focus groups and open-ended surveys. This project required an investigation of the practices and experiences around detecting and reporting vaccine adverse events that, as yet, had not been described. It would involve probing the study participants about what they considered were reportable AEFIs, challenges to detecting and reporting an AEFI in their workplace, and for suggestions to improve passive surveillance. Individual, face to face semi-structured interviews were selected as the appropriate method for data collection, as it was considered that participants would more freely discuss their experiences and opinions with no influence from their peers, that might occur if they were to participate in focus groups.[165] Furthermore, the use of interviews is especially useful for obtaining participants' meanings for events and behaviours, and because of this, avoids an over-simplification in the description and analysis of the data.[166] I considered in-depth interviews the best method as I wanted to gather information from individuals rather than obtain collective views as occurs in the use of focus groups, although I acknowledge that observing the divergence or convergence in views amongst participants' peers could well reveal information not possible with one-to-one interviews. I considered another advantage of conducting interviews was that each individual could be probed for clarity or further information following their initial answer to a greater degree than if they were interviewed in a group situation. Finally, conducting interviews with each participant was also most convenient to their work schedules and would facilitate study recruitment.

3.4.2 Selection of interview participants

To create a meaningful representative sample of participants, with a diverse range of experience the data collection methodology was built upon a strategic choice of *purposive sampling*, where potential respondents were selected because they met specific contextual characteristics of interest to the study objectives.[167] The main goal of purposive sampling is to focus on particular characteristics of a population that are of interest, which best enables the researcher to answer the research questions. The participants in this study were selected because they had the requisite knowledge or experience to speak to the research topic. The ED consultants were selected as eligible and necessary participants because I knew from news items in the media and accounts of families presenting to hospitals with children's suspected AEFI to the seasonal influenza vaccine that they were important potential reporters of an AEFI.[168] I had also learnt from the findings of the AEFI Parent Reporter Study, that numerous parents had sought medical advice at their local hospital's ED for their children's AEFI. Furthermore, I learnt from anecdotal accounts during the telephone interview that, for some parents who had presented to an Emergency Department in South Australia, there was a level of dissatisfaction with the attending doctor concerning the discussion regarding their children's AEFI symptoms, especially in relation to the influenza vaccine. Parents recalled some doctors discounting the significance of the AEFI; other doctors were not sure the symptoms were related to their child's immunisation, in contrast to parents' belief that they were. Secondly, I also knew that the South Australian Department of Health had asked hospitals via internal memos to check their attendance and admission records for occurrence of febrile convulsions following suspension of 2010 STIV. Therefore, the ED consultants were important informants to interview about detecting reportable AEFIs. Similarly, parents in the General Population Study had also sought advice from their general practitioner by either attending a consult or calling the practice to advise and discuss their child's symptoms.

I had initially planned to interview only doctors, that is, ED consultants and GPs. However, following the initial interviews with ED consultants and GPs, nurses were often mentioned as important providers of immunisation and advice to parents, and that they could also play a role in detecting and reporting an AEFI. Therefore, nurses would be an important addition to the study.

3.4.3 Recruitment

ED consultants

Following ethics approval from the Human Research Ethics Committees (University of Adelaide and Children's, Youth and Women's Health Service), I began recruitment of the ED consultants. This was first initiated by meeting with the Department's Director to discuss the research project and confirm his support for himself and ED consultant staff to be involved in the study. In order to facilitate recruitment, he agreed to provide each consultant with a copy of the study information sheet (see Appendix 11) via the hospital's internal staff email and to inform them of the project in a departmental meeting. The ED consultants were also advised of his support for the study and approval for individuals to be interviewed onsite during their non-clinical work days. Individual staff members who were willing to be interviewed were told to advise the department's administration officer, whom I was to contact to arrange the interview appointments. Prior to the scheduled appointments I emailed participants to confirm their participation with the study and included a copy of the information sheet. Of the 14 ED consultants who were employed at the time, 13 agreed to be involved. The person who refused participation did so because she only worked one day per week in the ED and did not have any non-clinical days at the hospital.

General Practitioners

Two strategies were used to recruit GPs into the study. The first was to contact potential participants via mine and my supervisors' professional networks of university research academics and clinical peers. Of these contacts, a colleague associated with the University of Adelaide and involved within an academic organisation in training general practitioners, sought permission to advertise the study via her organisation's internal email. Following approval from the organisation's Board the email was sent to 50 GP Registrars and 93 GP Supervisors which resulted in one GP expressing interest and subsequently participating. Of the 17 GPs who were contacted either via myself or supervisors, eight GPs were interviewed.

Secondly, the study was advertised via an electronic distribution mail list of the local branch of the Royal Australian College of General Practitioners (South Australia & Northern Territory) which is distributed to approximately 2700 GPs, of which 1900 are based in South Australia. This resulted in one GP contacting me and subsequently being interviewed. The advertisement is included in Appendix 10.

Nurses

The general practice study nurses were also recruited via academic contacts at the University of Adelaide: this resulted in two nurses agreeing to be interviewed. In addition, I asked the general practitioners I interviewed to forward on the study information to nurses who would be involved in immunisation at their practices. As I did not receive any queries from nurses in these practices after conducting all of GP interviews, it was decided that I should contact a nurse consultant via the South Australian Immunisation Section (SAIS) , SA Department of Health, who was aware of the first parent study via my collaboration with the unit. I asked if she could contact any of her nurse colleagues who were working in general practices and local council clinics. She emailed four nurses (two general practice and two local immunisation nurses) advising of a research project about

AEFI and forwarded my contact details. All four nurses agreed to be involved. I provided each person with the study information sheet and subsequently arranged for a time to conduct the interview in their workplace.

3.4.4 Ethics, consent and confidentiality

As I mention earlier in section 3.3.2, I followed standard ethical guidelines for voluntary participation, seeking informed consent, confidential treatment of information, and the right to withdraw at any point of the project.[160] The participant information sheets (see Appendix 11) and consent forms (see Appendix 12) were distributed to participants prior to conducting the interviews. The forms were modified slightly for each professional group recruited, but all contained clear statements about the nature of the study, what their participation would involve, and the right to withdraw at any time without consequence. In addition, participants were provided the contact details of my PhD supervisor, A/Prof Mike Gold and relevant ethics committee liaison personnel in case they had any questions, concerns or complaints during the study.

Prior to beginning the interviews I asked each participant to read and sign two copies of the consent form. I collected one of the signed consent forms and the second copy was left with the research participant to keep as a record of their consent to participate. All signed consent forms were stored in a locked cupboard in the Discipline of Paediatrics.

This research was considered of low/minimal risk to participants. In the event that a study participant would raise any concerns or queries about their AEFI practice or knowledge, we had decided that it would be appropriate to refer them on to A/Prof Mike Gold, who is the Head of Immunology at the Children Youth and Women's Health Service (CYWHS). None of the participants in the different settings interviewed expressed concern for their knowledge of AEFI or previous experience in clinical practice.

As detailed earlier in section 3.4.3, prior to the submission of ethics applications for this study I met with the director of the ED department to provide a brief of the research project as a whole. This allowed me to build rapport with the appropriate person who would in part authorise agreement for the study. It also allowed me to familiarise myself with the hospital ED environment.

During the study I began each interview with the GPs, nurses and ED consultants by reviewing the purpose of the study and I briefly discussed my research interests in the project and professional background with them. This helped to build initial rapport with each participant and facilitate a relaxed atmosphere for both myself and the participant. Not being a health professional also helped participants to not be threatened by what I knew or did not know about detecting and reporting AEFIs.

The interview data were transcribed and stored electronically on password protected files. Participants' confidentiality was assured by de-identifying the transcripts: I replaced the participants' identity with a numeric ID, such as ED 1, GP 1 and Nurse 1.

3.4.5 The interview guide

The semi-structured, open-ended interviews were based around a topic guide (see Appendix 13), which was made up of a series of open-ended questions. It was designed to engage each participant in talking about their experiences. The questions were developed from a review of key findings of literature surrounding AEFI and ADR reporting as described in Chapter 2. Each interview sought to explore:

- Participants' knowledge and experience of detecting, managing and reporting an AEFI;
- Factors that would facilitate or impede AEFI reporting;
- Understanding of AEFI surveillance; and

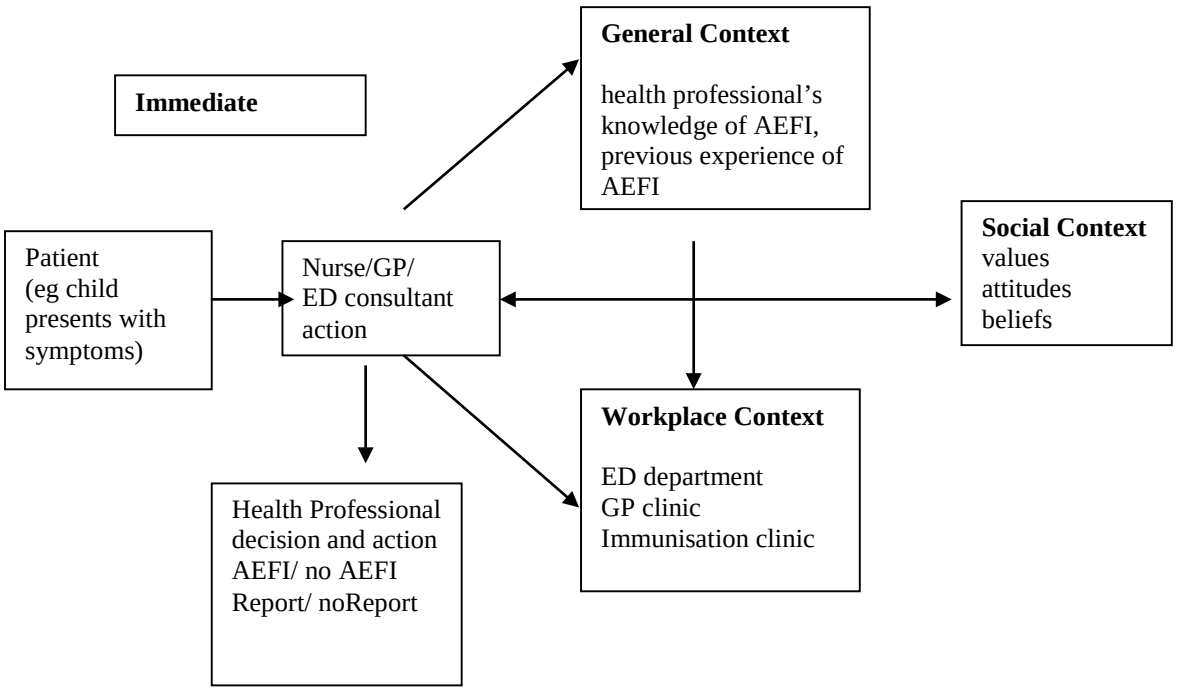
- Previous training in vaccine safety.

I was able to deviate from the guide if a participant raised an important issue or provided an unusual response by following up with question probes such as: “Can you tell me more about that?” or “This is an interesting point. Could you clarify what you mean about ..?”

3.4.6 Analytical Approach

Taking into account the purpose of this research study arm and the questions posed, I decided to approach my data analysis within a social constructionist epistemological framework.[157, 169] Social constructionism is a sociological theory of knowledge that considers how social phenomena develop in social contexts. That is, it is theory that explains how people make meaning or produce knowledge within the world in which they live and work.[139] The philosophical underpinning of social constructionism as described by Burr (2003) is that it denies that knowledge is a direct result of reality, in essence, questioning the notion of ‘truth’.[169] A person’s beliefs or conceptual frameworks are acquired by interactions between culture, language and social practices. As a researcher, the social constructionist approach allowed me to recognise that the individual perspectives of the health professionals I interviewed and the meanings they constructed from their interpretations and experiences of AEFI all occurred within a context that was shaped by their organisational environment and broader social structures. Hence, I approached my analysis from the perspective that the clinical decision-making and reporting of AEFI by ED consultants, GPs and nurses would be influenced by their previous clinical experience, nature of their workplace environments and social interactions. Figure 3.3 depicts an illustrative conceptual model of these contextual layers/factors that I adopted as the framework for analysing health professional AEFI reporting, from a social constructionist perspective.

Figure 3.3: AEFI detection and reporting: contextual factors that influence health professionals' actions and decisions



The immediate context includes: the child presenting with symptoms to an ED department, council clinic or general practice; child and parent interaction with the doctor/nurse and the specific actions taken by the relevant health professional. The health professional's actions and decisions in response to a child's AEFI symptoms are influenced by contextual layers/factors as shown in the conceptual model that influences his/her decision-making process. The specific context includes a number of factors that may influence decision-making such as the physical setting. For example, if it were an Emergency Department (ED), factors that would influence clinical decision-making could include: staffing patterns (for example rotation of personnel); availability of resources and technology; and the volume of patient visits to the ED. The general context relates to each professional's unique system of knowing such as the knowledge base of the professional, education, years of experience and previous experience of an AEFI.

3.4.7 Thematic analysis

There are differing views on the use of thematic analysis in qualitative research. It has been characterised as a data analysis tool to use across different qualitative research methods, rather than a specific method/approach in its own right.[170] However, Braun and Clark argue that thematic analysis should be considered a method in its own right.[171] The process involves the identification of themes through "careful reading and re-reading of the data."[172] Boyatzis defines a theme as "a pattern in the information that at minimum describes and organises the possible observations and at maximum interprets aspects of the phenomenon."[170] A theme can be constructed as a statement or a concept that captures and brings meaning to a pattern of responses within a data set.[171]

I undertook analysis of the interview data according to the guidelines suggested by Braun and Clarke. The six phases of thematic analysis they propose are illustrated in Table 3.1. Although I mainly used an inductive approach to identify key themes and categories that were common in the experiences of participants, I had also anticipated some themes as a result of the literature review regarding healthcare provider reporting and by using the interview guide. For example, I suspected reporting would be infrequent as I knew from the literature, but did not anticipate that the conceptualisation of a "serious" or "unexpected" AEFI would differ by professional group.

I audio-recorded all interviews and transcribed them for data analysis. N-Vivo (QSR International), version 9 software was used for data analysis. Before generating the initial codes I read the transcripts several times in order to become familiar with their content and confirm my thoughts about the key messages each participant was conveying.

Table 3.1: The six phases of thematic analysis

Phase	Description of the process
1. Familiarising yourself with your data	Transcribing data, reading and re-reading the data, noting down initial ideas.
2. Generating initial codes	Coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code.
3. Searching for themes	Collating codes into potential themes, gathering all data relevant to each potential theme.
4. Reviewing themes	Checking if the themes work in relation to the coded extracts (Level 1) and the entire data set (Level 2), generating a thematic 'map' of the analysis.
5. Defining and naming themes	Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme.
6. Producing the report	The final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a scholarly report of the analysis.

The primary themes that I identified addressed:

1. Conceptualising an AEFI: descriptions of participants' experience of an AEFI in clinical practice, how an AEFI was categorised, expectations of an AEFI and thoughts on what would be reported or not.
2. Types of AEFI: how participants described an AEFI in clinical practice.
3. Reporting an AEFI: this related to what participants had reported previously, how they had reported, formats for reporting, challenges to reporting but also what they would not report.

4. Attitude to surveillance: how and whether participants described the importance of surveillance and their role as reporters.
5. Vaccine safety knowledge: descriptions of training in vaccine safety, sources of information and participants' methods for maintaining/updating knowledge

The themes and how I came to define them were reviewed by one of my supervisors Annette Braunack-Mayer, who is an experienced qualitative researcher. We met several times throughout the data collection and analysis phase to review transcripts and codes. Together with these meetings and supervisory meetings with A/Prof Mike Gold and A/Prof Helen Marshall, we discussed key findings and issues in order to ensure that I accurately reflected the interview data. The final thematic structure was arranged according to the model of social construction I describe above, whereby reporting is broadly described within the contexts of the workplace, personal knowledge, clinical experience and attitudes to surveillance. De-identified extracts from the data were selected as representative examples that reflected participants' meanings. The results of the thematic analysis are presented in Chapter 6 in the published journal article. Figures 3.4 and 3.5 below provide illustrative examples of the overall process of code development and content of sub-codes for the first two themes. The names of the codes reflected the focus and purpose of the study. I developed three child nodes to sit under the parent node of "Conceptualising an AEFI" (Figure 3.4) which reflect and encompass evidence of this node in the data. The child nodes were:

- AEFIs seen in practice - included talk of actual AEFI events participants had dealt with either directly or indirectly during participants' clinical practice.
- Categories of AEFI - included talk demonstrating participants' ideas/beliefs of the degrees of severity of an AEFI.

- Anticipation of an AEFI – described participants' expectancy of the occurrence of an AEFI.

The parent node "Reporting an AEFI" (Figure 3.4) consisted of the following child codes:

- Previous experience of reporting – involved participants' descriptions of previous reporting of an AEFI;
- Awareness of reporting processes – included talk of participants knowledge of reporting processes, formats and existence of workplace reporting policies/protocol; and
- Attitude towards reporting-included talk revealing participants attitudes towards reporting, challenges to reporting and preferred formats of reporting.

Figure 3.4: Code development for "Conceptualising an AEFI"

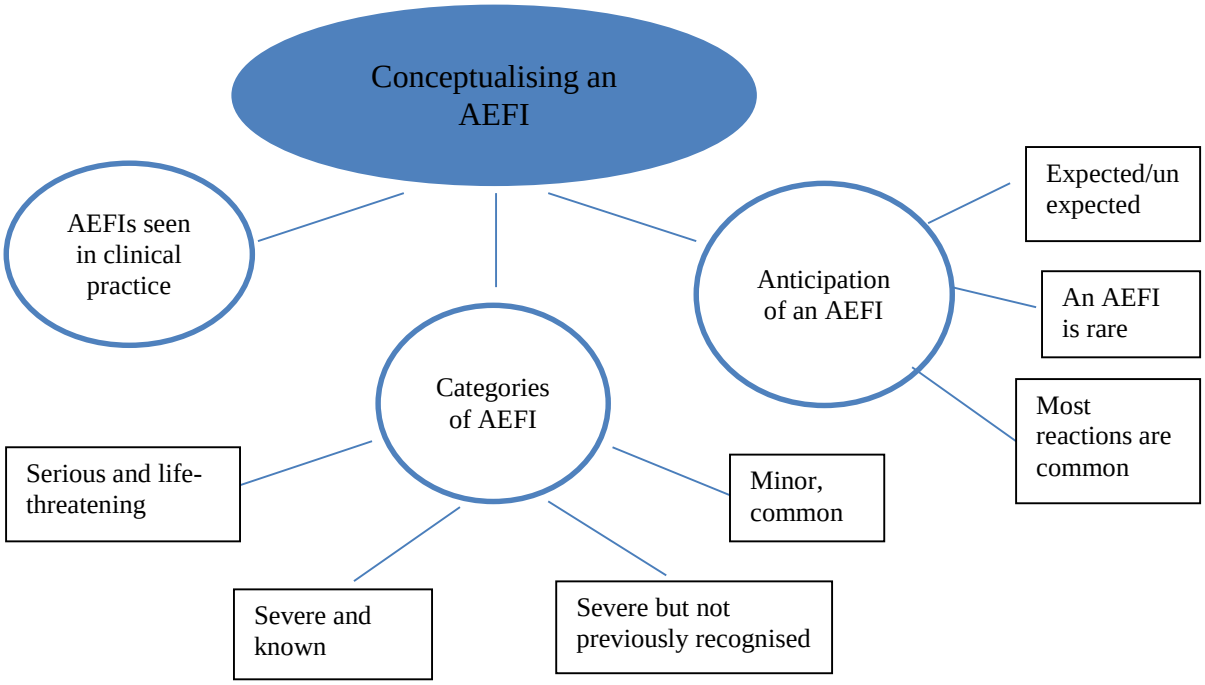
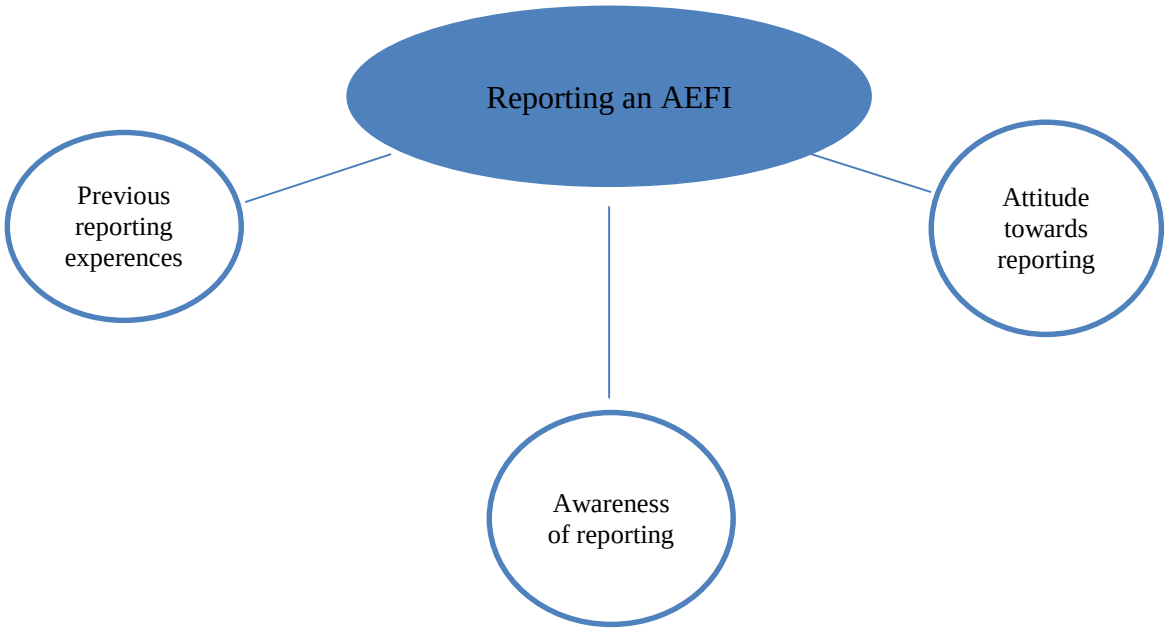


Figure 3.5: Code development for "Reporting an AEFI"



3.4.8 Rigour and quality

The term rigour is often used in qualitative research. It refers to assessing the thoroughness and conceptual appropriateness of the research processes employed in answering a study's research questions.[172, 173] What constitutes a rigorous and valid qualitative study has been the subject of considerable debate over the past two decades.[141] Different qualitative approaches are based on fundamentally different principles or assumptions[174] and, as such, the criteria for assessing rigour and quality must be chosen to fit the adopted approach. As a novice qualitative researcher, selecting appropriate criteria was daunting. For example Cohen and Crabtree present 13 evaluation frameworks one could adopt.[174] When reviewing the literature regarding the concept of rigour in qualitative research, there are a number of common elements I found worthy to note and applicable to all qualitative research, regardless of the different methodological approaches. These include: the need for a clear theoretical framework; agreement or congruence between the chosen methodology and the research question; and a clear decision trail that allows the reader to see the analytical processes used by the researcher. I believe these key features can be analysed to assess the integrity and competence of a research piece, regardless of the research paradigm. These elements have also been expressed by some researchers as "goodness" to the concept of rigour as an overarching principle of qualitative inquiry and an interactive process that takes place throughout the study.[175, 176] In this respect, the "goodness" of a study's essence must be reflected in the entire study and can be demonstrated in the following six elements.

- Foundation. This provides the philosophical stance and gives context to and informs the study. I have clearly stated the social constructionist perspective from which the health care provider study was conducted. .

- Approach. The methodology or specific grounding of the study's logic and criteria. I attempt to represent the approach in the sections above detailing the rationale for the study and methodology adopted.
- Collection of data. Explicitness about data collection and management. I have clearly stated the methods employed of data collection and management.
- Representation of voice. The researcher's reflection on their relationship with participants and the phenomena under exploration.
- The art of meaning. The process of interpreting and presenting new insights through the data and chosen methodology. I have been careful to employ research methods and an interpretive style that are consistent with a social constructionist perspective. The examples of participants' extracts from the interviews serve as illustrations of my interpretations.
- Implication for professional practice. Recommendations arising from the study results. These are discussed in the published journal paper (Chapter 6) and further in the final discussion of this thesis in Chapter 7.

In deciding on a set of criteria for this study, I believe the various ways of ensuring rigour as implied by the "goodness" elements were helpful to maximising rigour to the qualitative component in this thesis. In addition, the following specific criteria for assessing qualitative research, as proposed by Mays and Pope were also relevant.[177] Although they suggest a number of ways to ensure or improve rigour in qualitative research, they also suggest that not all will be appropriate for every study design and research question and should be used with discretion.

Triangulation

Triangulation in qualitative research involves using multiple data sources in an investigation through which the researcher looks for patterns of convergence to develop the overall interpretation. I achieved source triangulation whereby I collected and compared data from the three different professional groups who worked in different settings and different roles to enhance the richness of the data. A modified form of analyst triangulation was used in that my interpretations of the data and findings were discussed with both Prof. Annette Braunack-Mayer who had expertise in supervising the qualitative component and my supervisors A/Prof Mike Gold and A/Prof Helen Marshall, both clinicians in the field of vaccine safety, in order to understand different or multiple ways of understanding participants' experiences and perspectives in the data collected.

Negative or Deviant Case Analysis

Attention to negative cases involves searching for alternate explanations or views in the data that appear to contradict or differ from the general consensus. It ensures that any findings generated from data explain a wide range of observations. The results I present in the Chapter 6 journal publication show that I sought contradictory cases from the data in participants' views regarding attitudes to surveillance and in how participants conceptualised a reportable AEFI.

Relevance

Relevance in part refers to the extent to which findings can be generalised beyond the settings in which they are generated. A major criticism of qualitative research is lack of representativeness and generalisability. I recognise that the small sample of participants interviewed in South Australia may not be applicable to the views of all health professionals, or those working in other locations or other professions we did not include such as pharmacists and other medical specialists. However, the aim of including a range

of professional groups and work settings in the study was an attempt to provide a description of participants' accounts that would represent views comprehensible to others in such settings.

Respondent validation

Respondent validation refers to asking participants to provide feedback upon the researcher's interpretations of the data in order to establish concordance. This was partially achieved in the study. I did not specifically ask each participant to validate the ideas and themes I had constructed. All participants were informed that they could view the transcripts if they were interested to check accuracy of the interviews. None of the participants requested to review their interview data. One way I found of validating the themes after the initial interviews was to confirm with some participants during interviews that I was finding some of their views/experiences were common to other participants.

Reflexivity

Reflexivity refers to the researcher's critically assessing how the research process and the researcher may have influenced the findings generated. It involves a constant and self-critical examination of one's personal opinions, past experiences and socio-cultural influences that is brought to the research process throughout all stages of the research and how this may influence interaction with participants and subsequent presentation of the research findings.[178] I attempted to maintain a high degree of reflexivity throughout the conduct of this study through various means. First, I acknowledged the influence of my own experience and the goals I aimed to achieve as a researcher, recognising my role as a novice in being responsible for conducting all aspects of this piece of qualitative research. Second, I aimed to reflect and be aware of my interactions with participants during interviews, my interpretations and understandings of participants' meanings, and finally as a mother of three young children I considered how my previous encounters with healthcare

professionals in the same clinical settings that the study participants worked in might have influenced the research processes.

I carefully thought about my interview style before beginning each interview and reviewed my thoughts on how each went throughout this phase of the study. My aim was to convey to each person my curiosity and interest in their experiences. Although I wanted the conversations to proceed with a sense of informality to facilitate the flow of discussion and to be able to deviate to where participants would take the conversation, at the same time, I also needed to convey a clear, professional understanding of the issues discussed as my role as the researcher. These aspects allowed for a reflexive approach to both data collection and analysis and resulted in the meanings I present in this thesis as honest and transparent.

3.5 Conclusion

In this chapter I have outlined the approach of each phase of the three studies that were conducted for this thesis. I have described the rationale for the use of a mixed methods approach and theoretical perspectives that were used to guide the methods, analysis and interpretation of the results. The ethical considerations taken into account are also described. The specific steps employed for recruitment, data collection and analysing the data for the two parent studies and the healthcare provider study were presented.

In the following chapters (Chapters 4-6), I present the results of the three studies that comprise this thesis as manuscripts that were accepted for publication. Each chapter addresses the research questions for each phase of the research, as described in section 1.1.1.

4 General Population Parent Study Results

4.1 Preface

This chapter contains the first two of four publications contributing to this thesis. The two publications present the results of the analyses of the General Population Parent Study, using the data obtained from Health Monitor survey, conducted between March and May 2011. The complete list of questions is included in Appendix 3.

The first, published in *Vaccine*, "Parental perspectives of vaccine safety and experience of adverse events following immunisation" focuses on the AEFI parent and no-AEFI parent sub-groups. The results address the first two research questions for this thesis:

- Do parental attitudes towards vaccine safety differ according to whether their children have experienced an AEFI with parents whose children did not experience an AEFI?
- Are parents aware of a surveillance system for AEFI reporting?

The article investigates the previous occurrence of an AEFI, parental reporting to healthcare professionals and surveillance authorities. Factors which may be associated with perceiving a child has experienced an AEFI such as demographics and safety opinions are examined.

The second publication, "Consumer reporting of adverse events following immunisation (AEFI): identifying predictors of reporting an AEFI," presents the survey results comparing the AEFI parent reporters with the AEFI parent non-reporters. It has been published in *Human Vaccines and Immunotherapeutics* and addresses the third and fourth research questions of this thesis:

- Do safety attitudes and awareness of surveillance differ according to whether parents report their children's AEFI to a healthcare provider or surveillance authority or do not report their children's AEFI?
- What are the factors associated with parental reporting of AEFIs?

The analyses presented in this publication aimed to assess demographic factors associated with reporting and the association with reporting and safety opinion.

4.2 Publication: Parental perspectives of vaccine safety and experience of adverse events following immunisation"

4.2.1 Statement of authorship

Parrella A, Gold M, Marshall H, Braunack-Mayer A, Baghurst P. Parental perspectives of vaccine safety and experience of adverse events following immunisation. Vaccine April 2013, 31:16, 2067-2074

By signing below, the authors declare that they give consent for this paper to be presented by Adriana Parrella towards examination for the Doctor of Philosophy.

Adriana Parrella (Candidate)

Developed the trial protocol, authored the study invitation material, designed the telephone survey questions, conducted interviews, collected the data, performed data analyses, reviewed the literature and drafted the manuscript.

Signed: …… Date: ….25/02/2014……

Michael Gold

Contributed to the conception and design of the study, helped design the study invitation material and telephone survey questions, helped interpret the results and reviewed the manuscript.

Signed: …… Date: 25/02/2014……

Helen Marshall

Contributed to the conception and design of the study, helped design the study invitation material and telephone survey questions, helped interpret the results and reviewed the manuscript.

Signed: …… Date: 25/02/2014

Annette Braunack-Mayer

Contributed to the conception and design of the study, helped design the study invitation material and telephone survey questions, helped interpret the results and reviewed the manuscript.

Signed: …….. Date: 25/02/2014

Peter Baghurst

Contributed to the design of the statistical analysis of the study data, provided statistical advice, and reviewed the manuscript.

Signed: …… Date: 25/02/2014……

4.2.2 Abstract

Introduction

We aimed to determine demographic predictors of parental vaccine safety and risk perceptions, and assess the relationship between the occurrence of children's perceived adverse events following immunisation (AEFI) on parents' opinions.

Methods

Computer-assisted telephone interviews (CATI) were conducted in 2011 with a cross-sectional, random general population sample of rural and metropolitan residents in South Australia. Multivariate ordinal logistic regression analyses examined associations between parental vaccine safety attitudes and socio-demographic factors, adjusting for whether children had ever experienced a previous suspected AEFI.

Results

Of 469 parents interviewed, 95% were confident in vaccine safety in general, but almost half expressed concern for pre-licensure testing of vaccines. Of all parents, 41% responded that at least one of their children had experienced an AEFI. Almost one third of the AEFI parent group indicated they reported their children's symptoms to either a healthcare professional or the Department of Health. Parental acceptability of the risks of febrile convulsion and anaphylaxis were 73% and 76% respectively. Ordinal logistic regression analyses showed parents of children who had experienced a suspected AEFI were associated with greater concern for vaccine safety (OR:0.53, $p \leq 0.01$) and more were likely to expect either a mild or a serious AEFI. After adjusting for demographics, parental confidence in vaccine safety was significantly associated with higher levels of education (OR:2.58, $p = 0.01$) and being born in Australia, OR:2.30, $p = 0.004$. Mothers, when compared with fathers, were less accepting of the two vaccine risks presented: febrile convulsion (OR:0.57, $p = 0.04$) and anaphylaxis, (OR:0.55, $p = 0.04$).

Conclusions

Parents commonly perceive and report that their child has experienced an AEFI. In this group of parents the subsequent expectation of an AEFI and vaccine safety concerns may be heightened. Further research should investigate parental understandings of differentiating an expected event from an adverse event, as this could inform immunization risk communication and consumer AEFI reporting strategies.

4.2.3 Introduction

It is widely acknowledged that the success of immunization programs in eliminating vaccine preventable diseases (VPD) has resulted in less public fear of disease but increased concerns for vaccine safety. [6, 179, 180] Community acceptance of both the benefits of immunization and potential vaccine risks is crucial to achieving high immunization coverage rates.[181] As immunizations are administered to healthy individuals to prevent illness, expectations of vaccine safety are high. Several factors have contributed to heightened concerns for vaccine safety, including the increasing number of vaccines in immunization schedules, limited or no experience of VPD, and the increasing presence and influence of conflicting safety information in online or news media.[179, 180, 182, 183] Parental concerns such as the fear of potential adverse effects, refusal of recommended vaccines, concern for safety of new vaccines, misconceptions such as vaccines causing autism or too many vaccines weaken the immune system have been reported in published research.[5, 7, 8, 84, 184]

An adverse event following immunization (AEFI) is defined as 'any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine."[12] Although most vaccine reactions are common and usually mild, the occurrence of an AEFI can negatively influence attitudes towards revaccination and impact on vaccine coverage. In Australia, increased concerns

about influenza vaccination have been identified in parents notifying an AEFI to surveillance authorities[185] following the temporary suspension of seasonal trivalent influenza vaccination (STIV) on 23rd April 2010, due to an increase in expected rates of febrile convulsion.[19] Decreased paediatric uptake of influenza vaccination has been observed as a result of the safety signal.[186] Studies elsewhere have also reported negative parental attitudes towards vaccine safety and immunization associated with the experience of a child's AEFI.[14, 83] Although AEFI staus has been shown to influence safety views, other determinants may be associated with vaccine safety attitudes.

Monitoring parental confidence in vaccine safety and safety concerns are important to inform immunization strategies and maintain high coverage rates. Although our study of parents reporting an AEFI to surveillance authorities found concerns for a specific vaccine as a result of a real safety signal[185], in order to better understand parental vaccine safety perceptions, it is necessary to examine the views of parents in the general population. The purpose of the present study was to examine (1) vaccine safety attitudes, (2) perceptions of experiencing mild and serious AEFI, (3) differences in attitudes according to whether a child had experienced a perceived AEFI and (4) demographic predictors associated with concern, from a random community sample of parents residing in South Australia (SA).

4.2.4 Methods

We conducted a cross-sectional telephone survey of adults randomly selected from electronic residential telephone listings, between March and May 2011, from metropolitan and rural SA (population 1.6 million). The study was part of the Health Monitor program of the Population Research and Outcomes Studies Unit, University of Adelaide.[159] The Health Monitor program conducts surveys of 2000 South Australian households three times a year. It is used by health professionals and policy makers for research and policy

planning. In addition to the vaccination questions, other health-related topics were also included in the survey.

Selected households were sent a letter introducing the survey. Following initial telephone contact, the adult in the household (aged ≥18 years) who most recently had a birthday was identified. The Computer Aided Telephone Interviews (CATI) were conducted by trained marketing researchers, with up to 10 call-backs made to interview the selected adult. Respondents with poor or no English were excluded from participating. A pilot survey of 50 respondents was conducted in order to refine survey question format and sequence.

Respondents who identified as a parent or legal guardian of children aged birth–18 years were asked their views on vaccine safety; pre-licensure safety testing ; acceptability of two vaccine safety risks, anaphylaxis and febrile convulsion; and awareness of a system for vaccine safety surveillance. Parents were asked whether an AEFI had ever occurred for each child and if so, to describe the symptoms experienced. To examine vaccine safety risk perceptions and assess parental expectations of potential adverse reactions, we asked parents to recall their beliefs regarding the likelihood of their youngest child experiencing a mild AEFI (described as fever, irritability and injection site swelling) and a serious AEFI (requiring medical attention), at their last immunization.

We compared the responses of two subgroups: parents who indicated any of their children had previously experienced an AEFI ("AEFI parents") and parents for whom all children had not experienced AEFI symptoms ("no-AEFI parents"). In this study, the term "AEFI" does not imply causality, but only a temporal relationship to an immunization that the parent judged to be vaccine related.

Statistical analyses were performed using data weighted to the age, gender, probability of selection within a household and geographical area profile of the South Australian population. Individual data were weighted by the inverse of the individual's probability of

selection and then reweighted by age, gender and area, derived from the Australian Bureau of Statistics estimated resident population for 30 June, 2009.[159, 187] Survey response frequencies were tabulated with analyses for clustered, weighted survey data. Differences in survey response proportions between AEFI- and no-AEFI parent sub-groups were examined with χ^2 tests. Ordinal logistic regression analyses were used to examine the association between AEFI-parent status and response to survey questions, adjusting for evidence of any potential confounders among the demographic variables collected in the survey. Preliminary checks confirmed the proportional odds assumption was not violated.[188] The demographic covariates included: parent age, gender, total children (1, 2, 3 and >3), education (secondary school, certificate/trade and university), income and country of birth (Australia or other). We used the Index of Relative Socioeconomic Disadvantage (IRSD) as a measure of socio-economic status.[164] All variables of interest, regardless of statistical significance in univariate analysis were included in the multivariate regression analyses. Statistical tests were two-tailed, with a significance level of 5%. The study was approved by the Human Research Ethics Committees of the South Australian Department of Health and the University of Adelaide.

4.2.5 Results

Description of study sample

The sample (n=469) in this study comprised parents or legal guardians of 929 children aged ≤ 18 years and was a sub-group of respondents identified in a household community sample of 2002 randomly selected adults, in which the response rate was 55.6% [189]. Table 4.1 summarises the demographics of all respondents and two sub-groups of parents: AEFI parents (n=191, 40.7%), and no-AEFI parents (n=278, 59.3%), weighted for both numbers and proportions. Of all parents, 165 (35.2%) were males and 304 (64.8%) were females. The mean age of the parent interviewee was 40.2 years (95% confidence interval (CI): 39.4

to 41) and a range of 18 to 66 years. The median number of children per parent was two, with a range of one to seven children. The respondents' households were situated in both metropolitan (n=345, 73.6%) and rural Adelaide (n=124, 26.4%).

Parental demographic differences

There were no statistically significant differences in age, gender, income, total children, employment, education and marital status between the AEFI parent and the no-AEFI parent sub-groups. Significant differences were found by gender in the AEFI parent group (p=<0.01), with a greater proportion of mothers stating their children had experienced an AEFI (68%) compared to the no-AEFI parents (46%).

Previous AEFI and reporting

Of all children, 97.6% (n=913) were fully or partially immunized compared to coverage estimates of 89% for South Australian children up to 5 years of age.[190] Of all parents, 41% (n=191) stated 28.8% of all children (n=269) had previously experienced an AEFI (Figure 4.1). The children's age at time of interview who had experienced an AEFI was 0-2 years (18.9%), 3-5years (21.4%), 6-10 years (26.7%) and >10 years (33.0%). Fever was the most commonly experienced AEFI (59%), followed by injection site swelling (36%); injection site rash (24%); other, described as fatigue, irritability (17%), rash over part or whole body (6%); diarrhea (3.%); vomit (2%); convulsion (0.4%) and anaphylaxis (0.4%) (Table 4.2).

One third of the AEFI parent group (32%, n=62) reported their children's symptoms to either a healthcare professional or the Department of Health (Figure 4.1). Of the 66 children who had an AEFI reported, 59 children's AEFI were reported to one person only, and 7 were reported to more than one person.

General Practitioners (family physicians) received the majority of reports (53%). Fever was the most common symptom reported (Table 4.2).

Table 4.1: Household demographics of survey respondents (n=469): South Australia, 2011

Respondent characteristics	All Parents raw N (weighted N)	All Parents weighted %	AEFI Parents[a] weighted N (weighted %)	No AEFI Parents[b] weighted N (weighted %)	SA population[c]
Age (years)					
18–34	89 (125)	26.8	55 (28.9)	70 (25.3)	21.5
35–44	220 (217)	46.2	98 (51.3)	119 (42.7)	14.5
45+	160 (127)	27.0	38 (19.8)	89 (32.0)	33.6
Sex					
Male	165 (209)	44.6	61 (31.7)	149 (53.6)	48.6
Female	304 (260))	55.4	131(68.3)	129 (46.4)	51.4
Residence					
Metropolitan	345 (350)	74.6	139 (72.5)	211 (76.1)	73.7
Rural	124 (119)	25.4	53 (27.5)	66 (23.9)	26.3
Country of birth					
Australia	382 (386)	82.2	155 (81.1)	230 (83.0)	69.2
Other	87 (83)	17.8	36 (18.9)	47 (17.0)	24.7
Main language spoken at home					
English	453 (450)	96.1	184 (96.3)	266 (95.9)	82.5
Other	16 (19)	3.9	7 (3.7)	11 (4.1)	13.0
Educational attainment					
Secondary school/studying	141(134)	28.5	49 (25.7)	85 (30.5)	52.8
Trade/certificate/diploma	190 (187)	40.0	79 (41.5)	108 (38.9)	24.8
Bachelor degree or higher	138 (148)	31.5	63 (32.8)	85 (30.5)	13.6
Annual household income ($AU)[d]					
≤ 20 000 (<18 148)	21 (15)	3.3	5 (2.8)	10 (3.6)	20.3
20 001–40 000 (18 200–41 548)	37 (30)	6.4	12 (6.4)	18 (6.4)	18.7
40 001–60 000 (41 600–62 348)	70 (69)	14.7	26 (13.7)	43 (15.4)	19.5
60 001–80 000 (62 400– 88 348)	75 (76)	16.2	37 (19.6)	39 (14.0)	17.4
80 001-100 000 (88 400 - 103 948)	86 (87)	18.6	39 (20.6)	48 (17.2)	7.3
>100 000 (>104 000)	141(151)	32.2	50 (26.1)	101 (36.5)	16.7
Not stated	39 (40)	8.6	21 (10.9)	19 (7.0)	1.8

Table 4.1 cont

Respondent characteristics	All Parents raw N (weighted N)	All Parents weighted %	AEFI Parents[a] weighted N (weighted %)	No AEFI Parents[b] weighted N (weighted %)	SA population[c]
Employment					
Full or part time	388 (396)	84.4	157 (82.0)	239 (86.1)	57.2
Not in workforce	81 (73)	15.6	34 (18.0)	39 (13.9)	37.6
Socioeconomic quintile[e]	93 (88)	18.9	32 (16.5)	57 (20.5)	17.7
1 (Least disadvantaged)					
2	79 (78)	16.7	35 (18.1)	44 (15.8)	18.2
3	98 (99)	21.1	47 (24.6)	52 (18.8)	18.3
4	114 (110)	23.4	41 (21.4)	69 (24.8)	21.4
5 (Most disadvantaged)	85 (93)	19.8	37 (19.4)	56 (20.2)	24.4

[a] AEFI parent subgroup are parents who indicated any of their children aged ≤18 years had previously experienced a suspected adverse event following immunization (AEFI)

[b] no-AEFI parent subgroup are parents who indicated any of their children aged ≤18 years had not previously experienced a suspected AEFI

[c] Australian Population Census, 2006, persons aged ≥18 years, Australian Bureau of Statistics (ABS), http://www.abs.gov.au/cdataonline.

[d].The 2006 ABS Census income categories are not directlycomparable in terms of income ranges. The SA population income category percentages relate to income of family households with one or more children. (Cat.(No. 2068.0 - 2006 Census Tables). Percentages do not equal 100 due to rounding

[e] Socio-Economic Indexes for Areas (SEIFA) area-based index of relative socioeconomic disadvantage (IRSD) derived from residential postcode and based on the Australian census data

Figure 4.1: Children's experience of AEFI and total parental AEFI reports

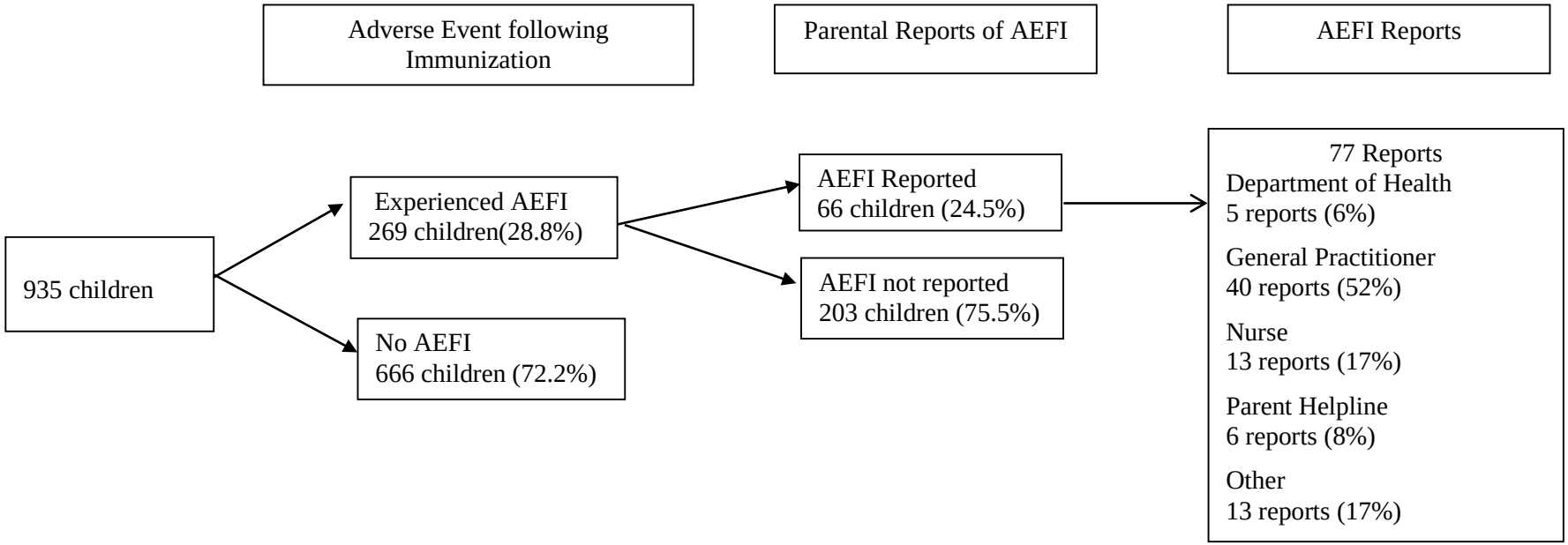


Table 4.2: Children's AEFI Symptoms and AEFI Reported

Symptom	Total AEFI	AEFI reported N (%)	AEFI not reported N (%)	(P value)[a]
Fever	158	44 (28)	114 (72)	0.14
Injection Site Swell	97	17 (18)	80 (82)	0.06
Injection Site rash	64	17 (28)	47 (72)	0.27
Rash over body	15	13 (87)	2 (3)	<0.01
Diarrhea	9	4 (44)	5 (55)	0.34
Vomit	6	5 (83)	1 (17)	<0.01
Convulsion	1	1 (100)	0	0.04
Anaphylaxis	1	1 (100)	0	0.08
Other	45	13 (29)	32 (71)	0.12
Total	396	115	281	

[a] p value compares proportion of AEFI symptoms reported with those not reported

Vaccine Safety Opinion

The majority (95%) of all parents stated that vaccines given to children in general were "safe" or "very safe", although half stated concern for the adequacy of pre-licensure safety safety testing (Table 4.3). The AEFI parents were more likely to expect a mild (fever, irritability or injection site reaction, p=<0.01) and serious AEFI (requiring medical treatment, p=0.03) at their children's last immunization.

Predictors of Survey Response

Table 4.4 presents the regression results. The adjusted analyses show that the AEFI parents were significantly more concerned for vaccine safety in general than the no-AEFI parents, and were more likely to expect a mild or serious AEFI at their youngest child's last immunization, (although the result for the serious AEFI was not significant, p=0.09). The odds of stating confidence in vaccine safety, compared to the no-AEFI parents were lower, OR=0.53 [p<0.01, 95% CI(0.34, 0.84)]. The odds of stating mild reactions were unlikely to occur at their children's last immunization were OR=0.18, [p=<0.01, 95% CI, (0.12, 0.28)].

There were few demographic predictors that were significant in the adjusted models. Of those that were, mothers, Australian born and university qualified respondents expressed

greater confidence in vaccine safety in general, OR=1.59 [p=0.05, 95% CI (1.00, 2.51)], OR=2.31 [p=<0.01, 95% CI,(1.31, 4.06)], and OR=2.28 [p=0.01, 95% CI,(1.24, 4.19)] respectively. Likewise, mothers, compared with fathers, were less accepting of febrile convulsion, OR=0.57 [p=0.04, 95% CI,(0.33, 0.97)] and anaphylaxis risk, OR=0.55 [p=0.04, 95% CI,(0.31, 0.97)].

Parents of two and three children, compared with parents of one child, were less concerned about pre-licensure safety testing but the results showed marginal significance, OR=1.63 [p=0.05, 95% CI,(0.99, 2.67)] and OR=1.85 [p=0.05, 95% CI,(1.00, 3.42)] respectively. Similarly, parents of two and three children believed a serious AEFI at their youngest child's last immunization was unlikely, OR=1.80 [p=0.03, 95% CI,(1.05, 3.07)] and OR=2.48 [p=0.01, 95% CI,(1.28, 4.83)] respectively.

Household incomes of (AUD) 20,001-40,000 and 80,001–100,000, compared with the lowest income category were associated with the belief that a mild AEFI was unlikely, OR=4.81 [p=0.03, 95% CI,(1.96, 19.98)] and OR=4.13 [p=0.04, 95% CI,(1.09, 15.58)] respectively.

Parents aged 35-44 and 45+ years, compared with parents aged 18-34 years, were most likely to not expect a serious AEFI at the time of their children's last immunization, OR=1.72 [p=0.05, 95% CI,(0.99, 2.98)] and OR=2.22 [p=0.01, 95% CI,(1.23, 4.04)] respectively.

Awareness of vaccine safety surveillance

Of all parents, 55% were aware of the existence of a surveillance system for vaccine safety (Table 4.3). There was greater awareness of a surveillance system among the AEFI parents (57.5%) than no-AEFI parents (53.4%), p=0.03. Of all demographic variables, mothers were more aware of a surveillance system, (OR=1.77, p=0.01, 95% CI,(1.14, 2.76).

Table 4.3: Parental opinions on vaccine safety and the probability of experiencing an adverse event following immunization (n=469).

Respondents	N					
AEFI Parents	191					
No AEFI Parents	278					
Total Parents	469					
Survey Question	Response, weighted N (%)					(P) [a]
In general, how safe would you say the vaccines given to children are?	Very unsafe	Unsafe	Undecided	Safe	Very safe	
AEFI parent	2 (1.3)	3 (1.8)	5 (2.8)	83 (43.6)	97 (50.6)	
No AEFI parent	2 (0.05)	8 (2.8)	2 (0.05)	95 (34.1)	172 (62.1)	0.08
Total Parents	4 (0.8)	11 (2.4)	7 (1.5)	178 (38)	269 (57.4)	
How concerned are you that new vaccines have been adequately tested for safety before they are released to the public in Australia?	Very concerned	Somewhat concerned	Undecided	Not too concerned	Not at all concerned	
AEFI parent	46 (23.8)		1 (0.4)	52 (27.4)	38 (19.9)	
No AEFI parent	76 (27.2)	54 (28.4)	4 (1.5)	84 (30.4)	53 (19.1)	0.48
Total Parents	121 (25.8)	61 (21.8)	5 (1.0)	137 (29.2)	91 (19.5)	
		115 (24.5)				
How likely did you think he/she would experience a reaction such as fever, irritability or redness at the injection site? [b]	Very likely	Somewhat likely	Undecided	Not too likely	Not at all likely	
AEFI parent	61 (32.8)	77 (41.8)	0 (0)	33 (17.9)	14 (7.5)	
No AEFI parent	14 (5.5)	72 (27.7)	6 (2.2)	114 (44.3)	52 (20.3)	<0.01
Total Parents	75 (16.9)	149 (33.6)	6 (1.3)	148 (33.3)	66 (15.0)	
How likely did you think he/she would experience a reaction that would need medical treatment from a hospital or GP? [c]	Very likely	Somewhat likely	Undecided	Not too likely	Not at all likely	
AEFI parent	7 (3.7)	18 (10.2)	0	75 (41.6)	80 (44.5)	
No AEFI parent	1 (0.5)	13 (5.0)	1 (0.6)	95 (37.2)	145 (56.7)	0.03
Total Parents	8 (1.8)	31 (7.2)	1 (0.3)	170 (39.0)	225 (51.7)	
Acceptability of febrile convulsion risk [d e]	Not acceptable		Undecided	Acceptable		
AEFI parent	39(20.3)		12 (6.3)	140 (73.4)		
No AEFI parent	68 (24.5)		9 (3.1)	200 (72.4)		0.20
Total Parents	106 (22.8)		21 (4.4)	340 (72.8)		

Table 4.3 cont.

Acceptability of Anaphylaxis risk[f]		Not acceptable	Undecided	Acceptable	
	AEFI parent	31 (16.4)	14 (7.3)	146 (76.3)	
	No AEFI parent	47 (17.1)	18 (6.4)	213(76.5)	0.93
	Total Parents	79 (16.8)	32 (6.8)	359 (76.4)	
Are you aware that a system for checking and assessing vaccine safety exists in Australia?		No	Undecided	Yes	
	AEFI parent	67 (34.8)	15 (7.7)	110 (57.5)	
	No AEFI parent	121 (43.7)	8 (2.9)	148 (53.4)	0.03
	Total Parents	188 (40.1)	23 (4.9)	258 (55.0)	

Table Notes

a: χ^2 P value compared AEFI parents with no-AEFI parents

b: 21 (4.4%) missing cases, excludes 5 (1.2%) "did not consider"

c: 21 (4.4%) missing cases, excludes 12 (2.5%) "did not consider"

d: 2 refusal

e: The risk of febrile convulsion was stated as 1 per 12,000

f: The risk of anaphylaxis was stated as 1 to10 per 1,000,000

Table 4.4: Odds ratios for the association between socio-demographic, AEFI status variables and vaccine safety opinions

	Vaccine safety in general	Concern about safety testing	Likelihood of a mild reaction	Likelihood of a serious reaction	Acceptability of Anaphylaxis Risk	Acceptability of febrile convulsion Risk	Awareness of a surveillance system
	Univariate OR (95% CI) Adjusted OR (95% CI)	Univariate OR (95% CI) Adjusted OR (95% CI)	Univariate OR (95% CI) Adjusted OR (95% CI)	Univariate OR (95% CI) Adjusted OR (95% CI)	Univariate OR (95% CI) Adjusted OR (95% CI)	Univariate OR (95% CI) Adjusted OR (95% CI)	Univariate OR (95% CI) Adjusted OR (95% CI)
Sex							
Male [a]	referent	referent	referent	referent	referent	referent	referent
Female	1.15 [0.77, 1.73]	1.05 [0.73, 1.52]	0.64 [0.45, 0.90]**a**	0.68 [0.44 ,1.04]	0.50 [0.30 , 0.84]**a**	0.59 [0.36 ,0.95]**a**	1.61 [1.07, 2.42]**a**
	1.59 [1.00, 2.51]**a**	1.20 [0.79, 1.85]	0.88 [0.58, 1.38]	0.79 [0.47 ,1.32]	0.55 [0.31, 0.97]**a**	0.57 [0.33, 0.97]**a**	1.77 [1.14, 2.76]**a**
Age							
18-34	referent	referent	referent	referent	referent	referent	referent
35-44	1.19 [0.71, 1.99]	0.46 [0.30, 0.70]**a**	1.25 [0.80, 1.95]	1.61 [0.95, 2.70]	1.45 [0.81, 2.60]	1.23 [0.70, 2.14]	0.83 [0.50, 1.40]
	1.09 [0.61, 1.95]	0.42 [0.26, 0.69]**a**	1.32 [0.81, 2.14]	1.72 [1.00, 2.98]**a**	1.29 [0.70, 2.39]	1.10 [0.60, 2.02]	0.74 [0.42, 1.31]
45+	1.23 [0.73, 2.07]	0.66 [0.41, 1.09]	1.73 [1.09, 2.73]**a**	1.97 [1.15, 3.38]**a**	1.88 [0.98, 3.60]	1.97 [1.06, 3.70]**a**	1.16 [0.66, 2.03]
	1.36 [0.75, 2.48]	0.78 [0.46, 1.34]	1.59 [0.96, 2.62]	1.22 [1.23, 4.04]a	1.89 [0.89, 4.01]	1.93 [0.93, 4.10]	1.19 [0.62, 2.27]
Country of Birth							
Overseas Born	referent	referent	referent	referent	referent	referent	referent
Australian Born	1.87 [1.16, 3.02]**a**	1.25 [0.78, 1.99]	1.06 [0.65, 1.73]	1.59 [0.91, 2.78]	1.33 [0.74, 2.39]	1.15 [0.67 ,2.00]	0.78 [0.46, 1.33]
	2.30 [1.31, 4.06]**a**	1.36 [0.80, 2.33]	1.11 [0.59, 2.11]	1.61 [0.84, 3.09]	1.73 [0.93, 3.25]	1.40 [0.78, 2.52]	0.92 [0.50, 1.69]
Total Children							
1 child [a]	referent	referent	referent	referent	referent	referent	referent
2 children	1.27 [0.79 , 2.03]	1.36 [0.91, 2.01]	1.13 [0.75, 1.70]	1.64 [1.04, 2.57]**a**	1.16 [0.67 ,1.99]	0.81 [0.49, 1.35]	0.97 [0.60 ,1.56]
	1.20 [0.71, 2.03]	1.63 [0.99, 2.67]**a**	1.50 [0.90, 2.47]	1.80 [1.05, 3.07]**a**	0.96 [0.51, 1.81]	0.73 [0.40, 1.32]	1.08 [0.63, 1.86]
3 children	1.11 [0.62, 1.96]	1.45 [0.82, 2.58]	1.28 [0.76, 2.14]	1.93 [1.07, 3.49]**a**	1.63 [0.76, 3.50]	2.37 [1.09, 5.11]**a**	1.22 [0.67, 2.24]
	1.02 [0.54, 1.94]	1.85 [1.00, 3.42]**a**	1.73 [0.95, 3.14]	2.48 [1.28, 4.83]**a**	1.23 [0.53, 2.86]	2.31 [0.97, 5.52]	1.25 [0.65, 2.44]
>3 children	1.03 [0.44, 2.43]	0.99 [0.52, 1.92]	0.75 [0.25, 2.26]	0.59 [0.19, 1.85]	1.06 [0.43, 2.66]	0.99 [0.40, 2.48]	0.90 [0.42 ,1.94]
	1.16 [0.43, 3.15]	1.42 [0.60, 3.35]	0.94 [0.29, 3.10]	0.69 [0.20, 2.44]	1.33 [0.41, 4.33]	1.05 [0.38, 2.90]	0.86 [0.36, 2.05]
Education							
Secondary School	referent	referent	referent	referent	referent	referent	referent
Trade/certificate/diploma	1.21 [0.76, 1.90]	1.12 [0.72, 1.74]	1.04 [0.65, 1.64]	1.22 [0.75, 1.97]	1.46 [0.85 ,2.52]	1.04 [0.65, 1.64]	1.17 [0.72 ,1.89]
	1.50 [0.90, 2.50]	1.28 [0.79, 2.06]	0.98 [0.58, 1.64]	1.17 [0.70, 1.97]	1.47 [0.79, 2.73]	1.46 [0.80, 2.67]	1.45 [0.84, 2.51]
Bachelor degree/higher	1.60 [0.93, 2.70]	1.64 [1.04, 2.59]**a**	0.98 [0.63, 1.52]	1.20 [0.73, 1.98]	1.69 [0.92 ,3.10]	0.98 [0.63, 1.52]	1.48 [0.88 ,2.49]
	2.58 [1.24, 4.19]**a**	1.68 [0.99, 2.86]	0.99 [0.57, 1.70]	1.20 [0.67, 2.14]	1.70 [0.82, 3.53]	1.77 [0.90, 3.47]	1.76 [0.96, 3.24]
Household Income							
≤20000	referent	referent	referent	referent	referent	referent	referent
20001 - 40000	1.04 [0.30, 3.66]	0.97 [0.22, 4.25]	3.20 [0.96, 10.63]	0.90 [0.19, 4.30]	1.25 [0.37, 4.22]	3.20 [0.96, 10.63]	1.64 [0.46, 5.89]
	1.01 [0.28, 3.66]	0.89 [0.22, 3.72]	4.81 [1.96, 19.98]**a**	1.32 [0.25, 6.94]	1.04 [0.31, 3.56]	0.54 [0.14, 2.02]	1.38 [0.33, 5.00]
40001 - 60000	1.86 [0.59, 5.94]	0.94 [0.24, 3.72]	3.11 [0.91, 10.65]	0.97 [0.23, 4.10]	1.17 [0.41 ,3.35]	3.11 [0.91, 10.65]	0.99 [0.31, 3.15]
	1.50 [0.47, 4.82]	0.84 [0.26, 3.38]	3.78 [0.93, 15.25]	1.01 [0.22, 4.66]	0.96 [0.34, 2.68]	1.06 [0.31, 3.65]	0.84 [0.25, 2.85]
60001 - 80000	1.23 [0.38, 3.92]	1.04 [0.26, 4.21]	2.08 [0.62, 6.93]	1.08 [0.26, 4.26]	3.85 [1.18, 12.55]**a**	2.08 [0.62, 6.93]	1.46 [0.47, 4.53]
	1.10 [0.35, 3.46]	0.89 [0.24, 3.30]	2.84 [0.70, 11.51]	1.00 [0.21, 4.66]	2.78 [0.87, 8.86]	0.82 [0.24, 2.84]	1.13 [0.33, 3.86]
80001 - 100000	1.55 [0.50, 4.79]	0.94 [0.24, 3.65]	3.05 [0.96, 9.68]	1.04 [0.25, 4.26]	1.15 [0.41, 3.24]	3.05 [0.96, 9.68]	1.11 [0.36, 3.48]
	1.23 [0.40, 3.76]	0.84 [0.25, 2.83]	4.13 [1.09, 15.58]**a**	1.00 [0.23, 4.40]	0.80 [0.29, 2.19]	0.57 [0.17, 1.89]	0.87 [0.26, 2.95]
>100000	2.06 [0.68, 6.19]	1.47 [0.39, 5.54]	3.07 [0.98, 9.62]	1.10 [0.27, 4.43]	2.55 [0.89 ,7.31]	3.07 [0.98, 9.62]	1.36 [0.45, 4.10]
	1.43 [0.47, 4.31]	1.30 [0.38, 4.47]	3.48 [0.87, 13.92]	0.91 [0.20, 4.18]	1.48 [0.51, 4.34]	0.83 [0.25, 2.78]	1.00 [0.30, 3.38]

Table 4.4 cont.

IRSD[b]							
Least disadvantaged (tiers1-2)	referent	referent	referent	referent	referent	referent	referent
Middle (tier3)	0.95 [0.58, 1.55]	0.77 [0.47, 1.26]	0.77 [0.50, 1.18]	0.65 [0.39, 1.07]	0.60 [0.31, 1.18]	0.77 [0.50, 1.18]	0.79 [0.47, 1.35]
	1.04 [0.62, 1.76]	0.93 [0.54, 1.60]	0.93 [0.56, 1.54]	0.73 [0.41, 1.28]	0.63 [0.30, 1.32]	0.85 [0.44, 1.63]	0.73 [0.40 ,1.32]
Most disadvantaged (tiers 4-5)	0.64 [0.33, 1.23]	0.72 [0.39, 1.31]	1.03 [0.57, 1.84]	0.71 [0.35, 1.47]	0.46 [0.21, 0.99]**a**	1.03 [0.57, 1.84]	0.65 [0.34, 1.28]
	0.79 [0.39, 1.62]	0.79 [0.42, 1.69]	1.14 [0.58, 2.23]	0.72 [0.32, 1.61]	0.53 [0.22 ,1.23]	0.59 [0.27, 1.31]	0.66 [0.31, 1.40]
AEFI parent							
No	referent	referent	referent	referent	referent	referent	referent
Yes	0.63 [0.42, 0.94]**a**	1.02 [0.71, 1.46]	0.17 [0.11, 0.26]**a**	0.57 [0.38, 0.85]**a**	1.00 [0.63, 1.60]**a**	1.10 [0.71, 1.72]	1.28 [0.87, 1.90]
	0.53 [0.34, 0.84]**a**	1.04 [0.68, 1.60]	0.18 [0.12, 0.28]**a**	0.67 [0.42, 1.07]	1.07 [0.64, 1.79]	1.39 [0.84, 2.30]	1.21 [0.77, 1.89]

Table Notes
a: significant pvalue
b: SEIFA IRSD quintiles

4.2.6 Discussion

In this representative sample of the South Australian population, the majority (95%) of parents believed that vaccines were safe, indicating high overall confidence in vaccine safety. This finding is encouraging because false claims about vaccine safety are frequently cited in media reports and on the internet.[191, 192] In addition, this study was conducted 12 months following the unprecedented vaccine suspension of an Australian manufactured seasonal influenza vaccine, due to an increase of febrile convulsions, and during a time when media reports regarding the safety of the 2011 influenza vaccines were circulating.[193] There were no consistent socio-demographic predictors of vaccine safety concerns evident from the analyses we conducted, although we did find that mothers, when compared with fathers, expressed greater concerns. This is the first Australian study, to our knowledge, that examined parental perceptions of experiencing a defined mild or a serious AEFI. We found half of all parents expected common vaccine side effects, such as fever or injection site reaction, and 10% thought a serious AEFI would occur at their youngest child's last immunization.

Although vaccines were regarded as safe, half of all parents expressed concern about prior testing of vaccines and one in four was not aware of a system in Australia for monitoring vaccine safety. This may suggest that consumers accept the safety of vaccines without knowledge of or consideration of systems to track their ongoing safety. All parents of vaccinated children in South Australia are meant to be provided with vaccine safety information at the time of immunization which outlines how vaccine safety is monitored and how to report adverse events.[194] Our findings would indicate that either parents are not being provided with this information, or that it is not readily recalled. Thus, it would seem that current community education regarding the measures taken to monitor vaccine safety

and ensuring public awareness of AEFI reporting processes requires comprehensive evaluation by health authorities.

Almost one in four parents indicated that at least one child had an AEFI, a similar rate reported in a study conducted in the United States of America.[195] The majority of the events in our study were expected side effects of vaccination (fever and injection site reactions) and of all AEFI parents, a quarter notified the symptoms to a healthcare provider or health authorities. Of all symptoms described, skin rash and vomiting were most likely to have been reported, as were the two serious events (convulsion and anaphylaxis). We presume this is because parents may have regarded the events as "unexpected". Since up to 10% of children may experience a skin rash after the MMR vaccine,[196] there is a need to educate parents about differentiating expected mild events from adverse events (of any severity) which should be reported.

Parents who perceived that their children had experienced an AEFI were more concerned about vaccine safety in general when compared with those whose children were not perceived as having had an AEFI, which is consistent with the study by Gust et al.[14] This trend towards concern is difficult to interpret, as the regression analyses demonstrated no statistically significant differences when compared with the no-AEFI group for most of the other survey items, (except for perceptions of mild AEFI). The AEFI parents were more likely to expect both mild and serious AEFI than parents of children who did not experience an AEFI, (although the adjusted analyses were not significant for serious AEFI). This may indicate, (but not prove), that the AEFI parents were more concerned about vaccine safety prior to immunization. However, other factors, such as knowledge and experience of expected events following immunization may play a part in the perception of whether these events are adverse or not, and whether they should be reported.

Interestingly, similar proportions of both AEFI and no-AEFI parents believed the risks of a rare AEFI (convulsions) and a very rare AEFI (anaphylaxis) were unacceptable,with almost equal proportions who were undecided about the risks presented. This perhaps reflects the difficulty in understanding the concept of relative risk regarding vaccine reactions and the manner in which they are communicated.[197-199] As the addition of new vaccines to immunization schedules creates the opportunity for an increase in the number of AEFI to occur[200], the relative risk of a vaccine reaction compared to perceptions of VPD may impact further on the confusion.

Immunization providers and healthcare professionals are influential sources of vaccine safety information and advice to parents[84, 180, 184, 201] and are often contacted for medical advice following a suspected AEFI.[195] The parents in this study reported their children's AEFI most commonly to general practitioners, whereas only 6% of all AEFI were notified directly to the Department of Health. We would suggest that it is likely that parents would seek medical advice from their general practitioner, rather than make a formal AEFI notification to health authorities. We did not verify whether reports were made to general practitioners or the Department of Health, as this was out of this study's scope. Similarly we do not know if the healthcare providers subsequently reported the children's AEFI to the local Department of Health or the national surveillance authority.

Our findings are subject to several limitations. The analyses presented are based on cross-sectional data and from a relatively small sample and sample sub-groups, which may have reduced our statistical power to detect differences. This study design cannot measure causality, that is, if the children's AEFI experience negatively influenced parental beliefs about vaccine risk perception, as parents were interviewed after immunizations had occurred, and up to several years following immunization. The children's AEFI were self-reported by parents and not verified through medical records, leading to the possibility of

recall bias. The questions regarding the likelihood of mild and serious AEFI were asked only for the youngest child. It is possible that the vaccination experience of older children, or earlier vaccinations of the youngest child may have influenced parents' response regarding the expectation of a serious/mild AEFI. As we included children aged up to 18 years in the study, it is important to consider that changes in vaccines and immunization schedules may have resulted in differing rates and types of AEFI experienced and that vaccination of older children would have occurred several years ago, which could have affected parents' recollection of AEFI. We did not ask parents to recall specific vaccines associated with their children's AEFI or the timeframe of reporting to health authorities. Furthermore, we could not assess whether parents' concerns or perceptions of an AEFI differed by children's age. The generalisability of these findings is limited also to the beliefs of parents fluent in English, as interviews were conducted only in English. The timing of this study, 12 months after a major, highly publicised safety signal and vaccine suspension may affect generalisability of results. Finally, we did not collect information on children's health status or parents' beliefs about specific vaccines, although these factors have been associated with parents reporting that their children have experienced an AEFI.[202]

Although our results cannot determine whether the experience of an AEFI caused higher vaccine safety concerns or whether parents with higher vaccine safety concerns were more likely to believe their children experienced an AEFI, we believe that our findings provide useful information about Australian parental vaccine safety views, perceptions of children's AEFI and reporting to healthcare providers. Further research should investigate parental understandings of reportable events to inform immunization risk communication education and consumer AEFI reporting strategies.

End of published article

4.3 Publication: "Consumer reporting of adverse events following immunisation (AEFI): identifying predictors of reporting an AEFI"

4.3.1 Statement of authorship

Parrella A, Gold M, Braunack-Mayer A, Baghurst P, Marshall H. Consumer reporting of adverse events following immunisation (AEFI): identifying predictors of reporting an AEFI. [Published online ahead of print] 2014 Jan 09;10(3)

By signing below, the authors declare that they give consent for this paper to be presented by Adriana Parrella towards examination for the Doctor of Philosophy.

Adriana Parrella (Candidate)

Designed the telephone survey questions, performed data analyses, interpreted results, reviewed the literature and drafted the manuscript.

Signed: …… Date: 25/02/2014

Michael Gold

Contributed to the conception and design of the study, procured funding, helped design the telephone survey, assisted in the interpretation of results, and reviewed the manuscript.

Signed: Date: 25/02/2014

Helen Marshall

Contributed to the design of the telephone survey, assisted in the interpretation of results, and reviewed the manuscript.

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Annette Braunack-Mayer

Contributed to the design of the telephone survey, assisted in the interpretation of results, and reviewed the manuscript.

Signed: Date: 25/02/2014

Peter Baghurst

Contributed to the design of the statistical analysis of the study data, provided statistical advice, and reviewed the manuscript.

Signed: Date: 25/02/2014

4.3.2 Abstract

Passive reporting of adverse events following immunisation (AEFI) by consumers or healthcare professionals is the primary mechanism for post-marketing surveillance of vaccine safety. Although recent initiatives have promoted consumer reporting, there is a lack of research concerning consumer reporters. Computer assisted telephone interviews (CATI) were conducted in 2011 of a cross-sectional, random, general population sample of 191 South Australian parents who stated that their children had previously experienced an AEFI. We compared awareness of surveillance, vaccine safety opinions and demographics of parents reporting an AEFI to either healthcare professionals or surveillance authorities with those who did not report their children's AEFI. Multivariate regression analyses measured: the association between reporting and safety views; and demographic predictors of reporting an AEFI. Reporting an AEFI to a healthcare professional or a surveillance authority was not significantly associated with awareness of a surveillance system. AEFI reporters, when compared with non-reporters ,were more likely to be Australian-born (OR =4.58, [1.64, 12.78], p=0.004); were associated with the perception that a serious reaction was more likely to occur at their children's last immunization (OR=2.54 [95%CI 1.22, 5.30], p=0.013); and were less accepting of the risk of febrile convulsion, (OR=3.59 [95%CI 1.50, 8.57], p=0.004).

Although reporting an AEFI was not associated with awareness of surveillance or most socio-demographics, the results suggest some difference in safety opinions. Further studies are required to ascertain if these differences pre-date the occurrence of an AEFI or are a consequence of the AEFI and how consumers can contribute further to vaccine safety surveillance.

4.3.3 Introduction

Post-marketing safety surveillance (PMS) is a crucial component of pharmacovigilance for all medications and vaccines.[30, 203] Passive surveillance is considered essential for PMS and is recommended by the World Health Organisation (WHO) in all countries to provide a minimal capacity for vaccine safety monitoring and build national strategies dedicated to vaccine pharmacovigilance.[42] This mechanism of surveillance involves consumers (vaccinees or their parents) and/or healthcare professionals recognising and spontaneously submitting reports of suspected AEFI to health authorities for subsequent investigation and response when required. It is widely acknowledged that this method of safety surveillance is limited by incomplete reporting information, under-reporting, biased reporting, the inability to distinguish coincidental from causal events and delayed notifications.[27, 30-33] The reasons for this are multifactorial but include a poor understanding of safety surveillance by healthcare providers, limitations on provider time and unclear interpretations of what constitutes a reportable AEFI.[15, 90] In a recent study we investigated the experience of AEFI reporting and found that healthcare professionals' definitions of a reportable AEFI varied across professional groups and work settings.[204]

Consumer involvement is important for effective pharmacovigilance, with an increasing recognition of the benefits of consumer reporting of adverse events following the administration of medications or vaccines.[62, 73] Until recently, most PMS systems worldwide have restricted reporting of adverse events to healthcare professionals.[205] As under-reporting by healthcare professionals is a known, major limitation of passive reporting systems, it is becoming more common to incorporate consumer reporting into PMS. Recent measures to strengthen pharmacovigilance in Europe include new legislation introduced by the European Medicines Agency (EMA), that as of July 2012, requires all member states to incorporate direct consumer reporting of adverse events to their national medicine authority.[74]

In Australia, consumer reporting of adverse drug reactions, (ADRs) for all medications, including vaccines, was introduced at a national level in 2003.[71] Currently, direct consumer reporting of ADRs is promoted through the Adverse Medicine Events Line, a telephone reporting facility.[206] In addition, consumers can report directly to the Australian national regulatory authority, the Therapeutics Goods Administration (TGA), by submitting a web based report.[36] In 2011, there were 2,327 AEFI reports collected by the TGA and of these, only 2% were consumer reports.[39] In addition to reporting at a national level, most jurisdictions in Australia accept consumer reports[19], with some jurisdictions actively promoting consumer reporting. For example, in Western Australia during the past two years, approximately 20% of all AEFI reports were notified by consumers.[207]

The need for a rigorous and timely vaccine safety surveillance has received much attention in recent years in Australia, as a result of the suspension of a paediatric seasonal trivalent influenza vaccine, (STIV), Fluvax, CSL in 2010, due to increased rates of febrile convulsion in children aged ≤ 5years.[19] One of the key recommendations of a national review of the Australian AEFI surveillance system commissioned as a result of the STIV safety signal, was that consumer knowledge and awareness of the surveillance system for AEFI reporting required improvement.[19] Although consumer reporting is encouraged as a strategy to complement healthcare professional reporting, little is known about consumers who report an AEFI. For example, identifying who is likely to report or not report an AEFI and an understanding of the reasons for doing so could inform strategies aimed at improving consumer reporting. We have previously found that parents reporting their children's AEFIs was primarily related to media attention within the context of a known vaccine safety signal and that parents frequently report their children's AEFIs to healthcare professionals, rather than direct to a surveillance authority.[185] There is limited research on factors such as socio-demographics or vaccine safety opinions that may be associated with parental reporting of their children's AEFI symptoms to healthcare professionals and/or

surveillance authorities. Since the detection of an AEFI may commence with a parent's concern and report, it is critical to understand these factors.

In this study, the primary aim was to examine the vaccine safety opinions and socio-demographic characteristics of parent AEFI reporters and non-reporters in the general population. Our second aim was to test for predictors of reporting a child's AEFI to a surveillance authority or healthcare professional.

4.3.4 Methods

Study population

The study was conducted as part of the Health Monitor programme of the Population Research and Outcomes Studies Unit, (PROS) University of Adelaide.[159] The Health Monitor survey is a commissioned computer aided telephone interview (CATI) survey of a randomly selected household community sample of approximately 2000 adults, conducted three times per year. It is used by government and non-government health professionals and policy makers for research and policy planning, with the main focus being population health surveillance. Each participating organisation contributes towards the cost of their survey questions. The study was conducted as part of a multi-study survey (one of four separate studies) between March and May 2011. In addition to the present study's questions , other immunisation topic questions regarding public opinion on data linkage for vaccine safety surveillance and safety attitudes,[189] and other health-related topics related to physical activity and smoking were included. Households in both urban and rural areas were randomly selected from the South Australian (population 1.6 million) electronic white pages directory and an invitation letter was sent introducing the survey. Adults in each household who were aged 18 years or over, and who had the most recent birthday were selected for interview. There was no replacement for non-contactable persons. Each respondent was asked if he or she was a parent or legal guardian and, if so, further

questions were asked about the vaccination experience of each child in his or her care, enabling classification of the respondent as having a child or children who had received a previous immunisation. Further questions were asked to establish whether the children had ever experienced an AEFI. The scripted interview surveys were conducted by trained researchers on each day of the week and at different times of the day. Respondents with poor or no English were excluded from participating. No incentive was offered for participation. A pilot survey of 50 respondents was conducted to check question format and sequence.

The term "AEFI" was defined as "any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the useage of the vaccine".[12] Hence an AEFI does not imply causality, but only a temporal relationship to an immunization that was judged to be vaccine related. We defined a parent "AEFI reporter" as a parent who indicated that they presented their child's AEFI symptoms to a healthcare professional or reported their child's AEFI to a surveillance authority. An "AEFI non-reporter" was defined as a parent who stated that they did not report their children's symptoms to a healthcare professional or surveillance authority.

The survey included seven questions that sought to examine parents' views of vaccine safety in general; pre-licensure safety testing of vaccines; acceptability of two vaccine safety risks, anaphylaxis and febrile convulsion; and awareness of a system for vaccine safety surveillance. In order to examine vaccine safety risk perceptions, respondents were asked to recall their opinion of the likelihood of their children experiencing a mild AEFI (described as fever, irritability and injection site swelling) and a serious AEFI (defined as requiring medical attention), at their youngest child's last immunization. Ethical approval to conduct the study was granted by the University of Adelaide and South Australian Department of Health ethics committees.

Statistical Analysis

We compared differences in parental safety opinion response proportions of parent AEFI reporters with the non-reporters, using the $\chi 2$ test. Multivariate ordinal logistic regression analyses were conducted to determine: the socio-demographic predictors of reporting an AEFI to a health professional or surveillance authority; and to measure the association between reporting a child's AEFI and parental views on vaccine safety. The analyses were adjusted for potential confounders among the socio-demographic variables collected. Preliminary checks confirmed the proportional odds assumption was not violated.[188] The demographic covariates included: parent age, gender, total children; education (secondary school, certificate/trade and university), income and country of birth (Australia or other). We used the Index of Relative Socioeconomic Disadvantage (IRSD) as a measure of socio-economic status.[164] Statistical tests were two-tailed, with a significance level of 5%. Odds Ratios and 95% confidence intervals were used to examine the strength and precision between sociodemographic predictors of reporting and the association with reporting and vaccine safety opinions. Statistical analyses were conducted using STATA 11.2 (StataCorp, College Station, Tx, USA). All statistical analyses were performed using data weighted to the age, gender, probability of selection within a household and geographical area profile of the South Australian population. Individual data were weighted by the inverse of the individual's probability of selection and then reweighted by age, gender and area, derived from the Australian Bureau of Statistics estimated resident population for 30 June, 2009.[159, 187] All results presented are weighted for both numbers and proportions.

4.3.5 Results

To complete the 2002 interviews, a total of 4700 telephone listings were selected. Of these, 3600 were eligible numbers: 1100 were ineligible either because they were not residential numbers, were disconnected, were fax/modem numbers or corresponded to

households located outside of SA. Of the remaining households, 993 refused to be interviewed, 275 were not contactable after six attempts, 229 were either not available or unwell and 101 spoke no English, a participation rate of all eligible households of 55.6%.

Of the total adult sample of 2002, 469 (23.4%) were parents or legal guardians of one or more children aged < 18years of age (n=929). Of these 469 parents 191 (41%) reported that one or more of their children (n=269) had previously experienced an AEFI. [208] At the time of interview approximately 60% of all children who had experienced the AEFI were aged ≥6years.[209] The type of symptoms described by parents has been previously described, with the majority being common and expected reactions associated with childhood immunizations.[209]

Parents were asked "Were any of the symptoms ever reported to any of the following?" with the response options recorded as: the "Department of Health," a "GP" (family physician), "Parent Helpline" (a South Australian parent telephone information service funded by the Women's and Children's Health Network), "Immunisation nurse," "other" or "did not report." Of the 191 parents, 32% (n=62) stated they had reported their child's AEFI. Most (96%) AEFI symptoms were reported to healthcare professionals.

Parent demographics

The mean age of the parents interviewed was 38.8 years (95% CI: 37.7 to 39.9) and a range of 19 to 62 years. When comparing demographics, a greater proportion of AEFI non-reporters were born outside Australia (24%) compared with the AEFI reporters (9%), (p=0.007). No other statistically significant difference in demographics was observed between the parent AEFI reporters and AEFI non-reporters (Table 4.5).

Table 4.5:Household demographics of survey respondents (n=191).

	AEFI reporters N/62 (%)	AEFI non-reporters N/129 (%)
Sex		
Male	15 (23.2)	46 (35.7)
Female	47 (76.8)	83 (64.3)
Age		
18-34 yrs	19 (30.7)	36 (28.0)
35-34yrs	32 (52.6)	66 (50.7)
≥45 yrs	10 (16.7)	28 (21.3)
Total Children		
1 child	16 (26.0)	35 (26.8)
2 children	25 (41.2)	65 (49.8)
3 children	10 (16.7)	21 (16.1)
>3 children	10 (16.1)	9 (7.3)
Education		
Secondary School	21 (34.8)	28 (21.4)
Trade/certificate/diploma	23 (37.7)	56 (43.3)
Bachelor degree or higher	17 (27.5)	46 (35.3)
Annual household income ($AU)		
≤ 20 000	2 (4.0)	3 (2.2)
20 001–40 000	3 (5.0)	9 (7.1)
40 001–60 000	8 (13.0)	18 (14.1)
60 001–80 000	12 (18.7)	26 (20.0)
80 001-100 000	12 (19.6)	27 (21.1)
>100 000	18 (28.7)	32 (24.8)
Not stated	7 (11.0)	14 (10.8)
Country of birth		
Australian born	57 (91.5)	98 (23.9)
Born elsewhere	5 (8.5)	31 (76.1)
IRSD		
Least disadvantaged (IRSD 1)	10 (15.8)	22 (16.9)
Middle (IRSD 2-4)	39 (63.7)	83 (64.3)
Most disadvantaged (5)	13 (20.5)	24 (18.8)

Table Notes

Proportions for each household characteristic may not add up to 100% due to rounding of figures to one decimal place
AEFI reporters are parents who indicated that they had previously reported any of their children's AEFI symptoms to either a healthcare professional or surveillance authority
AEFI non-reporter are parents who indicated that they had not previously reported any of their children's AEFI to either a healthcare professional or surveillance authority
Socio-Economic Indexes for Areas (SEIFA) area-based index of relative socioeconomic disadvantage (IRSD) derived from residential postcode and based on the Australian census data

Safety views

The majority of parents surveyed (91% of reporters and 96% of non-reporters) believed vaccines were safe (Table 4.6). Almost double the proportion of AEFI reporters compared with non-reporters believed a serious AEFI was "very" or "somewhat likely" at their youngest child's last immunization (21% vs 11%, p=0.004). The AEFI non-reporters stated lower levels of concern for vaccine safety for nearly all survey items, although most of the differences observed in response proportions were not statistically significant (Table 4.6). Approximately two thirds of respondents in both groups stated they were aware of a surveillance system for vaccine safety.

In both univariate and multivariate regression analyses that tested for demographic predictors of reporting, of all the variables, Australian-born parents were significantly associated with reporting an AEFI, unadjusted OR= 3.38 [1.34, 8.53], p=0.01, adjusted OR =4.58, [95%CI 1.64, 12.78], p=.004, compared to parents born elsewhere (Table 4.7).

After adjusting for all possible demographic confounders in the multivariate analyses, AEFI reporters when compared with non-reporters, were associated with more concern for vaccine safety on two survey items. They perceived a serious reaction was more likely to occur at their children's last immunization OR=2.54 [95%CI 1.22, 5.30], p=0.013, (Table 4.8). AEFI reporters were less accepting of the febrile convulsion risk of vaccines when compared with the non-reporters, OR=3.59 [95%CI 1.50, 8.57], p=0.004, (Table 4.8).

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Table 4.6: Parental safety opinion by AEFI reporting status

Respondents	N					
AEFI reporters	62					
AEFI non-reporters	129					
	Response, N (%)					χ^2 (P)
In general, how safe would you say the vaccines given to children are?						
	Very unsafe	Unsafe	Undecided	Safe	Very safe	
AEFI reporters	2 (2.7)	2 (2.5)	3 (4.3)	27 (43.3)	29 (47.2)	
AEFI non-reporters	1 (0.6)	2 (1.5)	3 (2.1)	57 (43.7)	68 (52.3)	3.0 (0.60)
How concerned are you that new vaccines have been adequately tested for safety before they are released to the public in Australia?						
	Very concerned	Somewhat concerned	Undecided	Not too concerned	Not at all concerned	
AEFI reporters	18 (28.8)	10 (17.0) 44 (33.8)	1 (1.4)	18 (28.5)	15 (24.4) 23 (17.8)	
AEFI non-reporters	28 (21.5)		0 (0)	35 (26.9)		8.2 (0.12)
How likely did you think he/she would experience a reaction such as fever, irritability or redness at the injection site?[b]						
	Very likely	Somewhat likely	Undecided[a]	Not too likely	Not at all likely	
AEFI reporters[c]	23 (39.2)	21 (35.9)	0 (0)	10 (17.5)	4 (7.4)	1.9 (0.64)
AEFI non-reporters[d]	38 (29.8)	56 (44.5)	0 (0)	23 (18.1)	10 (7.6)	
How likely did you think your child would experience a reaction that would need medical treatment from a hospital or GP?[e]						
	Very likely	Somewhat likely	Undecided	Not too likely	Not at all likely	
AEFI reporters [f]	4 (6.6)	8 (13.9)	0 (0)	29 (50.5)	17 (29.0)	9.9 (0.04)
AEFI non- reporters[g]	3 (2.3)	10 (8.4)	0 (0)	46 (37.3)	63 (51.9)	

Table 4.6 cont.

Acceptability of febrile convulsion risk [h]				
	Not acceptable	Undecided	Acceptable	
AEFI reporters	18 (29.9)	4 (6.5)	39 (63.7)	5.6 (0.09)
AEFI non-reporters	20 (15.7)	8 (6.2)	101 (78.0)	
Acceptability of Anaphylaxis risk[i]				
	Not acceptable	Undecided	Acceptable	
AEFI reporters	10 (16.4)	7 (11.6)	44 (72.0)	2.7 (0.29)
AEFI non-reporters	21 (16.3)	7 (5.3)	104 (78.4)	
Are you aware that a system for checking and assessing vaccine safety exists in Australia?				
	No	Undecided	Yes	
AEFI reporters	19 (31.1)	5 (8.0)	38 (60.9)	0.6 (0.79)
AEFI non-reporters	47 (36.6)	10 (7.6)	72 (55.8)	

Table Notes

Totals and proportions may not add up to sample totals and 100% due to rounding of figures.

[a] Category "undecided" was omitted from question 3 and question 4 analyses.

[b] The question: Thinking back to when your youngest child was last immunised, how likely did you think it would be that (s)he would experience a reaction, such as fever, irritability or redness at the injection site? Would you say this type of reaction was: "very likely", "somewhat likely", "not too likely", "not at all likely".
The response categories, "Did not consider it at the time", and "Don't know" were recorded if stated by parent respondent

[c] excludes 3 missing

[d] excludes 1 "did not consider", 1 missing

[e]. The question: And again, thinking back to your youngest child's last immunisation, how likely did you think it would be that (s)he would experience a reaction that would need medical treatment from a hospital or GP. Would you say: "very likely", "somewhat likely", "not too likely", "not at all likely".

[f] 3 missing

[g] excludes 6 "did not consider", 1 missing

[h] The question: "Young children who develop a fever after immunisation may sometimes go on to have a fit or seizure, known as a febrile convulsion. The risk of a febrile convulsion is approximately one in every 12,000 children immunised. When considering whether to vaccinate your child would you say this risk of febrile convulsion is: acceptable, not acceptable".
A response of "undecided" was recorded if parents stated they did not know.

[i]. The question: "Anaphylaxis is a severe, allergic reaction that can occur after immunisation. It requires immediate, medical treatment. The risk of experiencing an anaphylactic reaction to any vaccine ranges from approximately 1 to 10 for every 1 million doses of vaccine. When considering whether to vaccinate your child would you say this risk of anaphylaxis is: acceptable, not acceptable. A response of "undecided" was recorded if parents stated they did not know.

Table 4.7: Socio-demographic predictors of parental reporting of children's AEFI, n=191

Predictor Variable	% [95%CI]	Unadjusted Odds Ratio, [95%CI]	P	Adjusted Odds Ratio, [95% CI]	P
Sex					
Male	31.7 [24.4, 39.9]	referent		referent	
Female	68.3 [60.1, 75.6]	1.83 [0.81, 4.19]	0.147	1.93 [0.78, 4.75]	0.153
Country of Birth					
Overseas Born	18.9 [13.8, 25.3]	referent		referent	
Australian Born	81.1 [74.7, 86.2]	3.38 [1.34, 8.53]	0.010	4.58 [1.64, 12.78]	0.004
Parent Age					
18–24	28.9 [21.9, 37.0]	referent		referent	
35–44	51.3 [43.6, 58.9]	0.95 [0.42, 2.13]	0.898	1.13 [0.46, 2.79]	0.792
45+	19.8 [15.0, 25.7]	0.72 [0.28, 1.82]	0.482	0.78 [0.25, 2.41]	0.662
Total Children					
1 child	26.5 [20.4, 33.7]	referent		referent	
2 children	47.0 [39.5, 54.7]	0.85 [0.38, 1.90]	0.696	0.88 [0.32, 2.18]	0.711
3 children	16.3 [11.4, 22.7]	1.07 [0.39, 2.88]	0.893	1.06 [0.33, 3.36]	0.927
>3 children	10.1 [6.2, 16.2]	2.27 [0.68, 7.60]	0.182	2.12 [0.51, 8.72]	0.296
Education					
Secondary School	25.7 [19.7, 32.8]	referent		referent	
Trade/certificate/diploma	41.5 [34.2, 49.2]	0.54 [0.25, 1.17]	0.116	0.54 [0.22, 1.33]	0.178
Bachelor degree/higher	32.8 [25.9, 40.4]	0.48 [0.20, 1.14]	0.095	0.59 [0.22, 1.63]	0.307
Household Income *					
≤20000	3.1 [1.5, 6.4]	referent		referent	
20001 - 40000	7.2 [3.9, 12.9]	0.39 [0.05, 2.78]	0.344	0.59 [0.06, 5.62]	0.644
40000 - 60000	15.4[10.4, 22.2]	0.51 [0.10, 2.76]	0.433	0.72[0.08, 6.15]	0.762
60000 - 80000	21.9 [15.7, 29.9]	0.52 [0.10, 2.71]	0.432	0.93 [0.12, 7.14]	0.943
80000 - 100000	23.1 [17.1, 30.4]	0.51 [0.10, 2.55]	0.413	0.95 [0.13, 7.11]	0.957
>100000	29.2 [22.4, 37.2]	0.64 [0.13, 3.13]	0.578	1.52 [0.20, 11.47]	0.683
IRSD					
Least disadvantaged **	16.5 [11.8, 22.6]	referent		referent	
Middle	64.1 [56.4, 71.1]	1.06 [0.45, 2.51]	0.900	1.08 [0.41, 2.85]	0.883
Most disadvantaged	19.4 [13.7, 26.6]	1.16 [0.39, 3.45]	0.785	0.85 [0.25, 2.91]	0.793

Table Notes
*****21 Refused/don't know** Socio-Economic Indexes for Areas (SEIFA) area-based index of relative socioeconomic disadvantage (IRSD) derived from residential postcode and based on the Australian census data

Table 4.8: Association between reporting an AEFI and vaccine safety views, n=191

	Unadjusted OR (95% CI)	P	Adjusted OR[a] (95% CI)	P
Vaccine safety in general	1.34 [0.39, 1.43]	0.380	2.00 [0.89, 4.51]	0.095
Concern about safety testing	0.86 [0.45, 1.64]	0.651	1.05 [0.52, 2.12]	0.896
Likelihood of a mild reaction	1.30 [0.69, 2.43]	0.405	1.35 [0.67, 2.70]	0.401
Likelihood of a serious reaction	2.49 [1.33, 4.67]	0.005	2.54 [1.22, 5.30]	0.013
Acceptability of febrile convulsion risk	2.09 [1.04, 4.20]	0.038	3.59 [1.50, 8.57]	0.004
Acceptability of anaphylaxis risk	1.32 [0.65, 2.68]	0.434	1.36 [0.57, 3.3]	0.483
Awareness of a surveillance system	0.80 [0.42, 1.52]	0.496	0.69 [0.33, 1.45]	0.325

Table Notes

[a]adjusted for gender, country of birth, age, total children, education, income and IRSD

4.3.6 Discussion

In this study we examined and compared the socio-demographics and vaccine safety views of parents who had previously reported their children's AEFI symptoms to either health professionals or surveillance authorities with those who did not report their children's AEFI. The study results demonstrate that reporting an AEFI was not related to most parental socio and other demographics and that having previously reported to a healthcare professional or surveillance authority was not associated with greater awareness of a surveillance system. Our study shows that the reason parents report an AEFI was mostly independent of socio-demographic factors.

The aim of the general population survey analyses presented in this paper was to examine if safety views and/or socio-demographics differed according to whether parents reported their children's AEFI to a health professional or surveillance authority. Although the reporters' safety opinion results indicated greater concern (Table 4.6) on most survey items, only one was statistically significant. This may suggest parent reporters and non-reporters did not differ greatly in safety opinions. Furthermore, the types of AEFI parents

described were common and expected effects of immunisation[209], which may also explain why safety opinions did not differ greatly.

With regards to predicting characteristics of parents who will report an AEFI to a surveillance authority or health professionals, of all demographic data collected, we found no significant predictors of reporting other than country of birth, with Australian parents more likely to report, than those born outside Australia. We cannot attribute reporting to parents' language as nearly all reporters and non-reporters had indicated English was the main language spoken at home. This may also be explained by the exclusion of survey sample respondents who were not fluent in English, as the interviews were conducted in English only. However, reporting an AEFI in this general population study to either surveillance or health professionals was significantly associated with a greater expectation of a serious AEFI occurring and less acceptance of the risks of febrile convulsion (Table 4.8).

In a previous analysis of all 469 parents in the initial study sample, we found that parents who stated their children had experienced an AEFI ("AEFI parents") were significantly more concerned for vaccine safety in general and were more likely to expect a mild AEFI, than those whose children who did not experience an AEFI ("no-AEFI parents").[208] The present analyses that compare the opinion results by whether parents reported their children's AEFI to a health professional or surveillance authority or not demonstrated statistical significance on two different survey items. The AEFI reporters were more likely to perceive a serious AEFI could occur and were more concerned about febrile convulsion risk.

The study results should be considered with potential limitations. The analyses presented are based on cross-sectional data and from a relatively small sample, which may have reduced our statistical power to detect differences. However, the more powerful tests of association, ordinal logistic regressions did detect statistical significance on two of the

survey items. Due to the sampling methodology of the Health Monitor it was not possible to attain the proportion of non-responders who were parents of children aged <18 years from the 3600 total eligible households sampled. Parents were identified after the selected adult had agreed to participate in the interview via the survey questions. The study participants were asked to recall the occurrence and description of their children's AEFI (self-reports), in addition to whether the symptoms were reported to health professionals or a surveillance authority, the Department of Health. Given that almost two-thirds of the children who had experienced an AEFI in this study were aged ≥6 years, it is likely that the children's previous vaccinations and AEFI may have occurred several years prior to interview and as such, may have influenced respondents' recall of AEFI and reporting. We did not verify parents' reports with health providers as it was not within the scope of this study and because of the potentially long period since the event occurred and was reported. Similarly, we did not collect information regarding the timing of children's onset of AEFI, the associated vaccine(s), the circumstances and timing of reporting their children's AEFI were also not known and not elicited due to potential for inaccuracy in details collected retrospectively. However, the nature of the AEFI in the study sample was similar in both reporter and non- reporter groups and therefore likely to be valid. The results regarding the likelihood of experiencing a mild/serious AEFI at their last immunization should be interpreted with caution as these questions were asked for only the youngest child. It may be possible that parents' perceptions were influenced by the youngest child's earlier vaccinations and/or vaccination experiences of older children. A further limitation is that responses to the survey questions were not validated independently with specific validation methods/tools, which suggest it is difficult to assess respondents' understandings of each question. However, it is likely that the use of clearly defined questions regarding the type of AEFI and presenting the febrile convulsion and anaphylaxis risks numerically to

respondents (Table 4.6) would have minimised the potential risk of misunderstanding of the questions' meanings.

The framing of the safety opinion questions, whereby respondents were asked for a fixed response, did not allow for a more in-depth exploration of respondents' views. For example, a qualitative research method approach may be useful in understanding parental acceptability of vaccination risks. One approach could be to explore understandings of the risks we presented with perceptions of the potential risks of vaccine preventable diseases. In particular, as parents indicated awareness of surveillance, but chose to report to health professionals, a qualitative approach may provide a deeper understanding of parent motivation to reporting[209] and further examine parent knowledge of reporting channels other than health professionals. We did not ascertain reasons for parents reporting or not reporting their children's AEFI and this may provide a further distinction in determining factors associated with reporting. Finally, the interpretation of reporting as a predictor of safety opinion in the general population cannot be interpreted as causative, because of the cross-sectional study design. Having reported may have biased their responses to how likely they thought their children would be to experience an AEFI. In order to address the limitations of such bias and that of using retrospective data, a larger, prospective study examining opinions before or at the time of immunisation, and then obtaining information on subsequently reported AEFIs to surveillance and medical providers, together with reasons for reporting or not would be required.

Studies in countries with existing patient reporting schemes comparing ADR reporting for medications or vaccines by consumers and healthcare professionals have demonstrated that consumers can contribute significantly to successful pharmacovigilance, identifying new ADRs not previously reported by health professionals, and in providing relevant reports.[60, 76-80, 210]

Blenkinsopp (2007) proposes that patients will report an ADR if they believe their doctors will not.[62] Not reporting an ADR or an AEFI may relate to consumers accepting an adverse event in a trade-off for the perceived benefits of a medication or vaccine. This would seem a reasonable explanation for parents not reporting an AEFI in this general population study, given the reactions described were known vaccine side-effects.

The results in this study suggest that generally, there was no difference in vaccine safety opinion between reporters and non-reporters. Reporters were however, more concerned about the likelihood of a serious AEFI occurring and less accepting of febrile convulsion risk. Although the majority of parents stated they were aware of the existence of a system for vaccine safety surveillance, this study cannot explain why they chose to report to health professionals on the whole. As the majority of reports in this study were notified to healthcare professionals,[208] it is not surprising that knowledge of a system was not a factor associated with reporting. This could relate to parental preference towards medical professionals as sources of vaccine safety. [84, 180, 184, 201] It may also suggest that parents in this study had a general sense or trust that of there is a safety system, yet were not actually aware that an AEFI could be reported directly to local immunization authorities or of the national reporting scheme operated by the TGA. This should be investigated further in future research.

The strengths of this study were that parents were selected from a random sample of the general South Australian population. Parents were asked to respond to clearly defined questions regarding perception of the likelihood of an AEFI occurring. The study results showed that direct parent reporting to a surveillance authority was low. Preference towards reporting to healthcare professionals was also noted in a recent Australian study of public awareness of consumer ADR reporting, in which 85% of all respondents who had previously experienced an ADR stated they reported to healthcare professionals and only 10% stating awareness of the Australian national reporting scheme.[211] The low levels of

reporting to relevant surveillance authorities in both studies implies a need to introduce communication strategies to the public about channels of reporting.

Australian federal health authorities are currently investigating strategies for improved communication with consumers about vaccine safety monitoring and raising awareness of reporting systems. Future research and public awareness-raising campaigns should aim to address the provision of information about reporting schemes to people of non-Australian-born background. In particular, ensuring that relevant information was available at the time of immunisation in a range of languages would help to meet the needs of the non-English speaking population. Finally, in order to better understand factors associated with direct reporting to a surveillance authority, rather than via a healthcare professional, further research with consumers who report direct to surveillance authorities is required.

End of published article

4.4 Postcript

As mentioned in above in section 4.3.6, as the the General Population Parent study did not collect data on reasons for parents not reporting to the Department of Health, it is difficult to determine the motivators to reporting directly to a surveillance authority rather than via a health-care professional. However, following the acceptance of this publication and just prior to concluding this thesis, two studies relevant to consumer reporting have been published. The first is an Australian study on consumer awareness and reporting of ADR of 4981 respondents.[211] Only 10% of all respondents were aware of the national reporting scheme operated by the TGA. This low rate of consumer awareness of direct reporting in this Australian study is similar to the 8% level of awareness reported in the UK study by Fortnum (2012).[65] Similar to the General Population Parent Study findings I presented in section 4.2.5 the study authors reported that 85% of respondents who experienced an ADR reported the event to a healthcare professional, mainly their GP.[211]

The second study to be published since the parent studies in this thesis were conducted in 2010 and 2011, is a qualitative study of direct reporting to the UK Yellow Card Scheme (YCS) by parents of children who had experienced suspected ADRs. [209] It assessed awareness of the YCS and motivators to reporting in a group of 44 parents of children aged 16 years or under. The parent non-reporters were recruited via two separate observational studies as part of an adverse drug reaction in children program that investigated the type and prevalence of suspected ADRs in a tertiary paediatric hospital setting. Non-reporters in the first study were parents whose children required an unplanned hospital admission and in the second, parents of hospital in-patients who had experienced suspected ADRs. Of all the ADRs experienced by the children, an AEFI had occurred in nine children of the parent reporters (9/17) and in two children of the non-reporters (2/27). The study found limited awareness of the YCS in both parent groups. Over half of the parent reporters indicated that they became aware of the YCS either through their training or work as a health professional or through friends or relatives who had connections with the medical or pharmaceutical profession.[209] Only a small number (not stated) of reporting parents discovered the availability of direct reporting via the Internet or through publicity materials and only one parent was informed of the Scheme via the health professional caring for the child. In the non-reporting parents, two had heard of the Scheme and were both nurses. The reasons parents gave for reporting their children's ADRs were: altruistic, wanting to prevent harm in other children; emotional, needing to feel that their concerns were acknowledged and recorded; contributing towards pharmacovigilance, ensuring the safety of medications and a belief that their healthcare providers had not taken parents' concerns about the ADR seriously.[209] Of those who knew of the Scheme via their work, a sense of professional obligation to report was also a reason to report. Reasons for not reporting included: uncertainity about whose role it was to report and confusion about parents' role, by either assuming their healthcare provider would/should do so or that their healthcare

provider would disapprove. The non-reporters also described uncertainity about whether an ADR had occurred by healthcare professionals or not having sufficient medical knowledge to decide whether one had occurred as further reasons for not reporting.

4.5 Conclusion

The General Population Parent Study results presented in this chapter indicate that AEFI parents do consider that vaccines are safe in general. Among the subset of AEFI parents in the survey, it was shown that parental reporting of an AEFI occurred primarily to healthcare professionals and almost 60% of all parents stated awareness of a surveillance system. No significant differences in demographics were found between the AEFI reporters and AEFI non-reporters. With regards to safety opinions, the AEFI reporters were more concerned about the likelihood of a serious reaction and were not comfortable with the stated risk of febrile convulsions. Hence, it can be concluded that these results, taking into account the limitations as stated in each publication, suggest that demographics are not factors associated with reporting but there may be some differences in acceptability of vaccine risks. In Chapter 5, the issue of factors associated with reporting is further explored.

5 AEFI Parent Reporter Study Results

5.1 Preface

This chapter contains the third publication contributing to this thesis. This article has been published in *Human Vaccines and Immunotherapeutics* and outlines the study design and key results of the AEFI Parent Reporter Study. The complete list of questions is included in Appendix 8.

The results address the first two research questions for this thesis:

- What are the factors associated with parental reporting of AEFIs?
- What is the impact for parents of experiencing an AEFI on future immunisation decisions?

In addition to the publication results, this chapter also includes a comparison of the vaccine safety opinions of the General Population Parent Study and the AEFI Parent Reporter Study, to further examine the two AEFI parent groups in this thesis.

5.2 Publication: Parental views on vaccine safety and future vaccinations of children who experienced an adverse event following routine or seasonal influenza vaccination in 2010.

5.2.1 Statement of authorship

Parrella A, Gold M, Marshall H, Braunack-Mayer A, Watson M, Baghurst P. Parental views on vaccine safety and future vaccinations of children who experienced an adverse event following routine or seasonal influenza vaccination in 2010. Human Vaccines & Immunotherapeutics May 2012, 8:5, 662–667

By signing below, the authors declare that they give consent for this paper to be presented by Adriana Parrella towards examination for the Doctor of Philosophy.

Adriana Parrella (Candidate)

Developed the trial protocol, authored the study invitation material, designed the telephone survey questions, conducted interviews, collected the data, analysed the data, reviewed the literature and drafted the manuscript.

Signed: ……. Date: 25/02/2014

Michael Gold

Contributed to the conception and design of the study, helped design the study invitation material and telephone survey questions, helped interpret the results and reviewed the manuscript.

Signed: Date: 25/02/2014

Helen Marshall

Contributed to the conception and design of the study, helped design the study invitation material and telephone survey questions, helped interpret the results and reviewed the manuscript.

Signed: …… Date: 25/02/2014

Annette Braunack-Mayer

Contributed to the conception and design of the study, helped design the study invitation material and telephone survey questions, helped interpret the results and reviewed the manuscript.

Signed: …….. Date: 25/02/2014

Maureen Watson

Contributed to the conception and design of the study, helped design the study invitation material and telephone survey questions, supervised study recruitment and reviewed the manuscript.

Signed:…… Date: 02/12/2013

Peter Baghurst

Contributed to the design of the statistical analysis of the study data, provided statistical advice, and reviewed the manuscript.

Signed: D Date: 25/02/2014

5.2.2 Abstract

Objective

To assess parental vaccine safety views and future vaccination decisions after an adverse event following immunisation (AEFI) experienced by their child.

Methods

A cross-sectional telephone survey was conducted of parents of children aged 0-7 years, identified in AEFI reports submitted to the South Australian Immunisation Section, Department Health. The reports included childhood National Immunisation Program (NIP), seasonal or pandemic influenza vaccines. Interviews were conducted following a national suspension of the 2010 seasonal trivalent influenza (STIV) vaccine. Parental attitudes towards vaccine safety, reasons for reporting the AEFI and impact on future vaccination intent were assessed.

Results

Of 179 parents interviewed, 88% were confident in the safety of vaccines in general. Parents reporting an AEFI to the STIV were more likely to state the event had influenced future vaccination decisions than the NIP vaccine reporters (65% vs 14%, $p<0.001$), with 63% stating refusal or hesitance to re-vaccinate their children against influenza. Media reports of the 2010 STIV program suspension was the most common reason for reporting an AEFI for parents of children who received an influenza vaccination.

Conclusions

The AEFI experience did not impact on parental decision to continue with routine childhood NIP schedules, regardless of whether children received influenza or NIP vaccines. In contrast, most parents whose child experienced an AEFI to the 2010 STIV stated decreased confidence in the safety of influenza vaccines, which is likely to have

impacted on the uptake of seasonal influenza vaccination in 2011. Addressing influenza vaccine safety concerns to promote influenza vaccination in the community is required.

5.2.3 Introduction

On March 15th 2010, a funded seasonal trivalent influenza vaccine (STIV) was introduced into the Australian National Immunisation Program (NIP) for children aged from 6 months with specified medical at risk conditions. On April 23rd 2010, the program was suspended nationally, due to increased reports of fever and febrile convulsions observed in children aged ≤5 years.[18] This event was accompanied by an increase in reports of adverse events following immunisation (AEFI) to influenza vaccination to surveillance authorities. Given the potential for decreased public confidence in influenza vaccination as a result of the program suspension, this paper presents a comparison of the vaccine safety views and future vaccination decisions of parents reporting an AEFI to influenza vaccines with parents reporting an AEFI to other NIP childhood vaccine/s.

In Australia, the primary mechanism of post-licensure monitoring is via passive surveillance, whereby immunisation providers, other healthcare professionals, vaccine manufacturers and the public voluntarily submit AEFI reports to health authorities. Reports may be submitted to local state and territory health authorities, each with different systems for reporting (paper, online, fax and/or telephone) and data collection, or via the national Advisory Committee for Safety of Medicines (ACSOM), a subcommittee of the Therapeutic Goods Association (TGA) or both. The responsibility for monitoring is shared across the local and national jurisdictions. In South Australia, an AEFI is reported to the South Australian Immunisation Section (SAIS) of the Department of Health.

There is no published Australian research examining the impact of an AEFI on future vaccination intentions or vaccine safety views of parent AEFI reporters. Examining the

experiences and views of parent AEFI reporters is important in assessing whether an AEFI influences parental perceptions of vaccine safety and future vaccination decisions.

5.2.4 Participants and Methods

A telephone survey was conducted from 17 May – 13 September 2010 with parents of children aged ≤7years who reported an AEFI to SAIS, between 01 January and 30 June 2010. Parents who reported directly to SAIS, or had their children's AEFI reported to SAIS by a healthcare provider were included in the study. An AEFI was defined as "a medical incident that takes place after an immunisation, causes concern, and is believed to be caused by immunisation."[212] The term "AEFI" implies a temporal relationship to an immunisation that parents or a healthcare professional believe to be vaccine related.

Parents entered the study initially after providing consent to a SAIS nurse to receive the research study information. Consent to complete the telephone interview was confirmed after the researcher (AP) contacted parents, one week after they received the study information.

The survey included questions on vaccine safety, details of the AEFI, reasons for reporting, future vaccination intent and socioeconomic details. Several survey items were adapted from other published immunisation surveys.[5, 83, 84, 161-163] To assess vaccine safety attitudes, parents were asked to indicate level of concern for vaccine safety, pre-licensure testing of new vaccines, the use of combination vaccines and the increase in the number of vaccines included in the NIP schedule, using a five point Likert scale.

Descriptive statistics, response proportions and chi-square tests comparing NIP with influenza AEFI reporters were performed using Stata, version 11.0 (StataCorp, USA). Parents reporting an AEFI to both NIP and either pandemic or seasonal influenza vaccines together were included in the influenza reporting group for the chi-square analyses. The

Fisher's exact test p value was calculated for tables with less than five respondents in any one cell.

Ethics approval to conduct the study was granted by the University of Adelaide and SA Department of Health Research Ethics Committees.

5.2.5 Results

Participant Recruitment

Of the 219 parents eligible for inclusion, 179 (82%) completed the interview. Interviews were conducted at a range of 13 to 220 days (median 70 days) following the AEFI report dates.

Household Demographics

The total number of children per participant household ranged from 1 (30%) to 7 (0.5%), with 90% having less than four children. The median age of all children in respondents' households was four years (interquartile range [IQR], 2.3 - 7years). Approximately one quarter of all respondents (28%) reported total household income greater than $AU 100,000 ($US 99,810). Higher household income was reported for parents reporting an AEFI to influenza vaccines compared with parents reporting following NIP vaccines (p=0.04).

AEFI Reports

A total of 210 AEFI reports were included in the study (Table 5.1). Most reports were made for vaccinations received in 2010 (209), with one report of an AEFI to measles, mumps and rubella (MMR) vaccination received in 2006. The seasonal influenza vaccine was the most frequently reported vaccine, included in 76% of all reports. The Fluvax^{R} vaccine (CSL Melbourne) was associated with 159 of the 160 STIV AEFI reports.

Of all vaccines reported by the 179 parents, 120 reported an AEFI to seasonal influenza, 43 reported NIP vaccines, 10 reported NIP and seasonal influenza vaccines administered

together, five parents reported pandemic influenza and one parent reported an AEFI to NIP and pandemic influenza vaccines.

Table 5.1:Vaccines associated with AEFI reports*

Vaccine	Number of Reports (% of all reports)
Australian National Immunisation Program (NIP)**	44 (21%)
Measles-Mumps-Rubella	33
DTPa-IPV	29
7v Pneumococcal conjugate	12
DTPa-IPV-HepB-Hib	11
Rotavirus	11
Monovalent Hib	9
Meningococcal C conjugate	8
Varicella	6
23v Pnuemococcal polysaccharide	1
2010 Seasonal Trivalent Influenza***	160 (76%)
2009 Pandemic Influenza****	6 (3%)
Total Reports	210

* AEFIs are not linked to individual vaccines when administered simultaneously at immunisation encounters.

** Reports of NIP vaccines only

*** includes 12 reports of NIP and 2010 Seasonal Influenza

**** includes 1 report of NIP and Pandemic Influenza

Of all parents reporting an AEFI, 152 reported an AEFI for one child, 23 parents reported for two and four parents reported for three children. Of all ages recorded in the 210 reports, 74% of the children (155) were aged 2 - 7 years, 18 % (37) 1 to <2 years and 9% (18) aged <1 year, with the median age for all children being 3.5 years. The majority of reports occurred in females (F:M ratio = 1.91).

The reports were submitted by 89 parents and 88 healthcare providers including: family physicians (42), nurses (27), the Parent Helpline, a South Australian parent telephone information service funded by the Women's and Children's Health Network, (13) and hospitals (6). Two reports were notified by both a parent and a healthcare provider.

Figure 5.1 shows the distribution of AEFI reports received per week from January to June 2010. Increased reports of AEFIs following a STIV were observed from the week ending

16th April and continued to rise for two weeks. The reporting of AEFIs associated with NIP vaccines remained stable throughout the study period. Of the 166 reports that included influenza vaccines, 74% were submitted to SAIS following the program suspension date (23rd April, 2010).

Figure 5.1: Influenza and NIP vaccine AEFI reports, by week January-June 2010

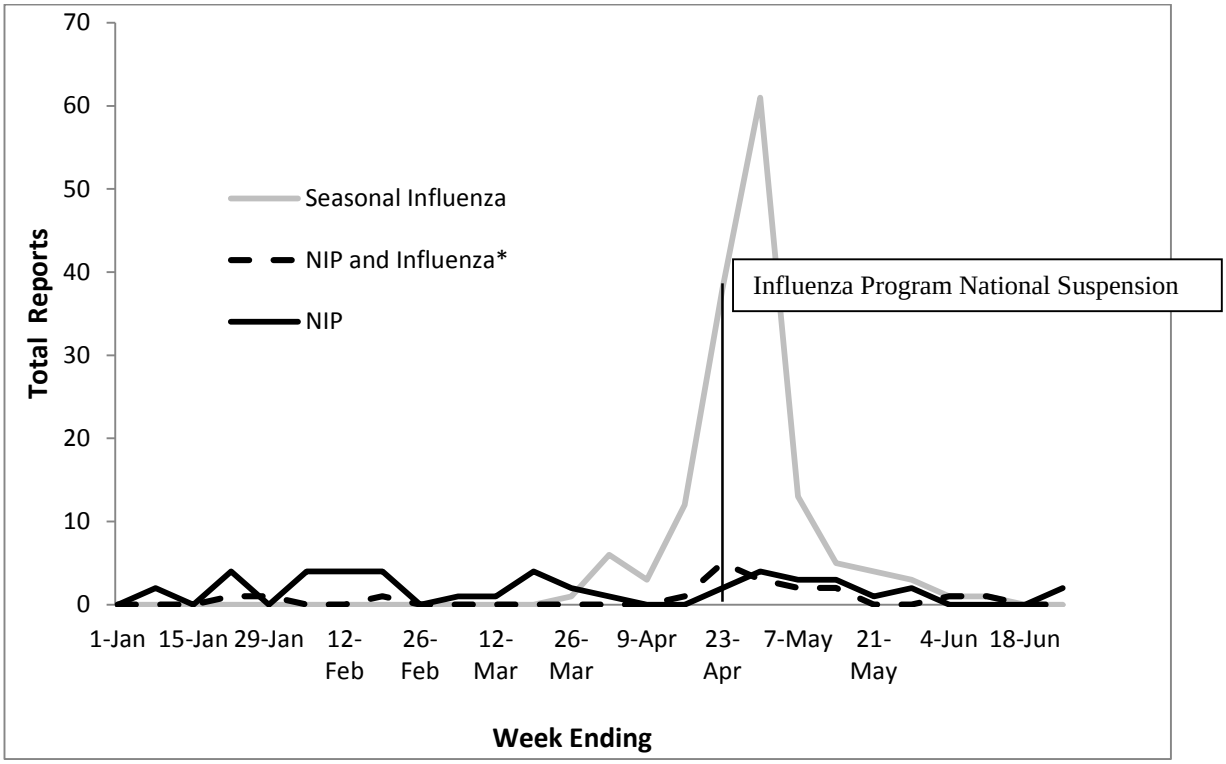
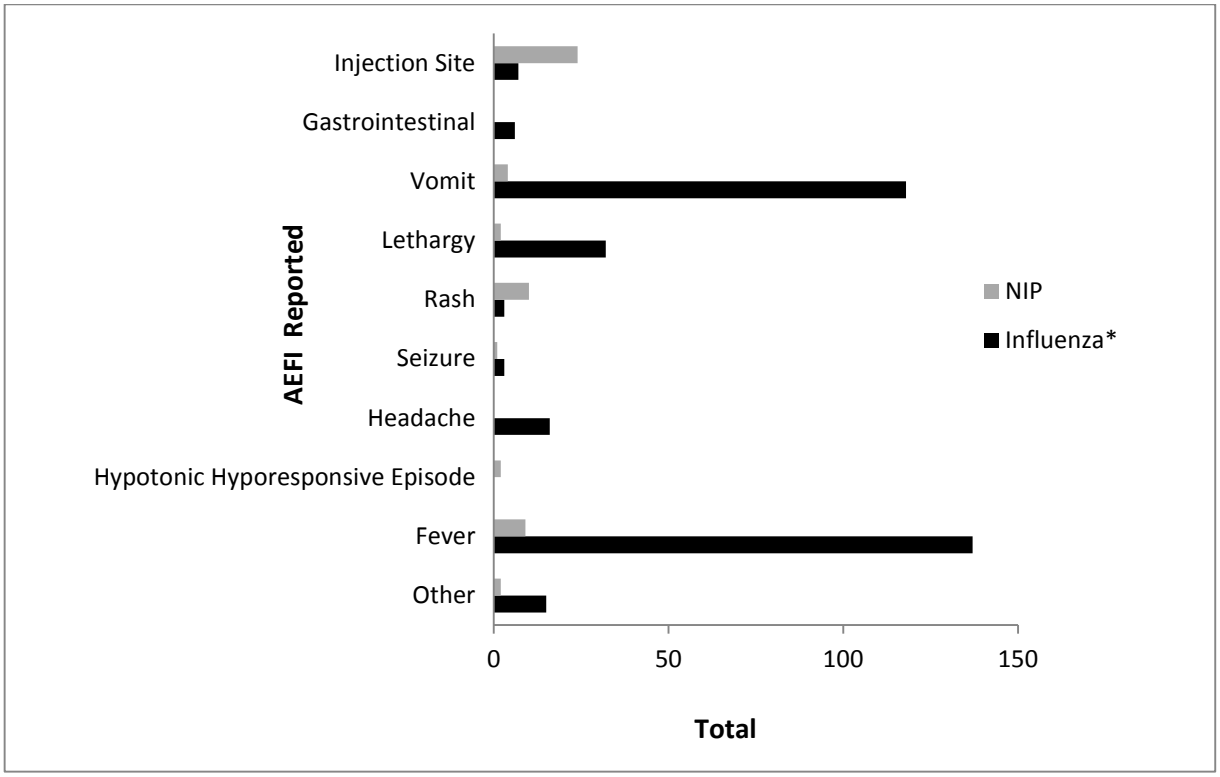


Figure 5.2 shows the adverse events reported. The most common event was fever, which was reported in a greater proportion of children receiving influenza vaccines compared with the NIP vaccines (94% vs 19%, p <0.001). For the NIP vaccines, injection site reaction was the most frequently reported AEFI, recorded in 56% of all NIP reports, compared with 5% of influenza vaccine reports (p<0.001). Serious reactions reported included four febrile convulsions, three following a STIV and 1 following MMR, Men C and Hib vaccination. Two Hypotonic Hyporesponsive Episodes (HHE) following NIP (HHE level 1)[213] vaccination were recorded.

Figure 5.2: Adverse events recorded in AEFI reports



* Influenza reaction totals include: 120 seasonal influenza, 5 pandemic influenza, 12 NIP and seasonal influenza, 1 NIP and pandemic influenza reports

Vaccine Safety Opinion

The vaccine safety opinions of the parent AEFI reporters are presented in Table 5.2. Overall, 88% (157) of all parents stated the safety of vaccines in general as either “very safe”/”safe” and 12% (21) responded “don’t know” with no statiscally significant difference between the NIP and influenza vaccine reporters. When asked for opinions on the adequacy of pre-licensure testing of new vaccines 58% (25) of the NIP and 77% (105) of the influenza vaccine reporters responded “very/somewhat concerned” but this was not statistically significant. Forty-two percent (18) of NIP vs 30% (41) of influenza vaccine reporters responded they were “very/somewhat” concerned about increased number of vaccines included in the NIP schedule (p=0.005). Forty-seven percent (20) of NIP vs 43% (58) of influenza reporters stated “very/somewhat” concerned about the use of combination vaccines (p=0.007).

Table 5.2: Vaccine Safety Opinion

In general, how safe do you think the vaccines that are given to children are?

	Very safe N (%)	Safe N (%)	Unsafe N (%)	Don't know N (%)	p value
NIP Program AEFI Reporter	8 (19)	31 (72)	0	4 (9)	
Influenza AEFI Reporter	43 (32)	75 (55)	1 (1)	17 (12)	0.236
Total	51 (28)	106 (59)	1 (1)	21 (12)	

How concerned are you that new vaccines have been adequately tested for safety before they are released to the public in Australia?

	Very concerned	Somewhat concerned	Not too concerned	Not at all concerned	Don't know	
NIP Program AEFI Reporter	8 (19)	17 (40)	13 (30)	4 (9)	1 (2)	0.108
Influenza AEFI Reporter	41 (30)	64 (47)	24 (18)	6 (4)	1 (1)	
Total	49 (27)	81 (45)	37 (21)	10 (6)	2 (1)	

How concerned are you about the increase in the number of vaccines included in the Schedule?

NIP Program AEFI Reporter	8 (19)	10 (23)	12 (28)	12 (28)	1 (2)	
Influenza AEFI Reporter	3 (2)	38 (28)	49 (36)	45 (33)	1 (1)	0.005
Total	11 (6)	48 (27)	61 (34)	57 (32)	2 (1)	

How concerned are you about the use of combination vaccines?*

NIP Program AEFI Reporter	7 (16)	13 (30)	18 (42)	5 (12)	0	
Influenza AEFI Reporter	7 (5)	51 (37)	34 (25)	39 (29)	5 (4)	0.007
Total*	14 (8)	64 (36)	52 (29)	44 (25)	5 (3)	

Table Notes
NIP = National Immunisation Program
*proportions do not total 100 due to rounding of figures

To assess the impact of the seasonal influenza program suspension, we asked parents to consider the acceptability of an influenza vaccination if it were available to all children, as per the NIP funded program. Parents reporting an AEFI to influenza vaccines were less likely to accept an influenza vaccination compared with NIP reporters but this was not statistically significant. Of all influenza reporters (n=136), 27% (37) and 15% (20) responded "no" and "don't know" respectively, compared with 19% (8) and 9% (4) of NIP reporters.

Reasons for reporting an AEFI

Parents were asked why they contacted a medical professional or SAIS. Multiple responses were recorded. The reasons stated in order of frequency were to provide a formal notification of the AEFI, 49% (87); concern for their children's symptoms 41% (73); media attention 32% (57); to seek advice 27% (49); and because a healthcare provider advised the parent to contact SAIS 5%, (10). For parents reporting an AEFI to influenza vaccination after the program suspension, (n=101), the most common reason was a wish to notify health authorities of the adverse event 65%, (66), followed by awareness of media reports regarding the STIV program suspension and/or reports of increased adverse events following STIV vaccination 56%, (56).

Impact of an AEFI

We asked parents if and how the AEFI had impacted on future vaccination decisions (Table 5.3). The NIP vaccine reporters were more likely to state the AEFI would not impact on future vaccination decisions than the STIV reporters ($p<0.001$). Of all STIV reporters, 74 (62%), responded they would vaccinate their children with routine NIP schedules only and 75 (63%) stating they were either hesitant towards or would not continue vaccinating their children against influenza.

Table 5.3: Impact of the AEFI on future vaccination decision

Impact	NIP N /43 parents (%)	Seasonal Influenza N /120 parents (%)*	NIP & Influenza N /11 parents (%)	p value
No impact	37 (86)	46 (38)	3 (27)	0.000
Would not accept future immunisation	0	32 (27)	0	0.000
Hesitant to accept future immunisation	6 (14)	43 (36)	0	0.000
Would continue with NIP immunisation only	*not applicable*	74 (62)	8 (73)	0.000

* percentage does not total 100 as multiple responses were recorded

5.2.6 Discussion

The timing of this study, following the national STIV program suspension in children less than 5 years of age, provided an opportunity to survey parents about vaccine safety within the context of an identified vaccine safety issue. All parents were interviewed following the suspension but prior to any outcome of two commissioned reviews.[19, 58] The majority of parents stated confidence in the safety of vaccines in general with all influenza and NIP vaccine reporters stating they intended continuing with their children's NIP schedules. This suggests that experiencing an AEFI to either influenza or an NIP vaccine should not impact on NIP vaccination coverage in this group of children who have been reported to have experienced an AEFI. Whilst it is difficult to extrapolate this to the wider parent population, these results are encouraging, as they suggest that despite a significant influenza vaccine safety issue, parents are able to understand the specific nature of the safety signal and maintain trust in the routine vaccination program.

This contrasts with parental concern about influenza vaccination safety expressed by both influenza and NIP vaccine reporters. Sixty-three percent of STIV vaccine reporters would either not accept or were uncertain about a future influenza vaccination (Table 4.2). This

suggests that the experience of their children's adverse event to the influenza vaccine was of sufficient concern for these parents to not accept a further influenza vaccination. It may also reflect response to the widely publicised safety signal. The low level of support for influenza vaccination expressed by parents in our study is in contrast with an Australian study conducted in 2006, of 169 mothers, conducted prior to the STIV program suspension, in that only six percent of all respondents were opposed to influenza vaccination[214] and an American study [215] in which 78% of parents intended to vaccinate their children against influenza. It is likely that the negative views regarding influenza vaccination expressed by the NIP vaccine parents were influenced by awareness of the STIV program suspension, as noted during interviews with parents. Further research is required to ascertain if this view is shared by the wider community of parents and in particular parents of children within the medical at risk category. Clearly if these parents share similar views then specific strategies will need to be developed to regain trust in the safety of influenza vaccination.

End of published article

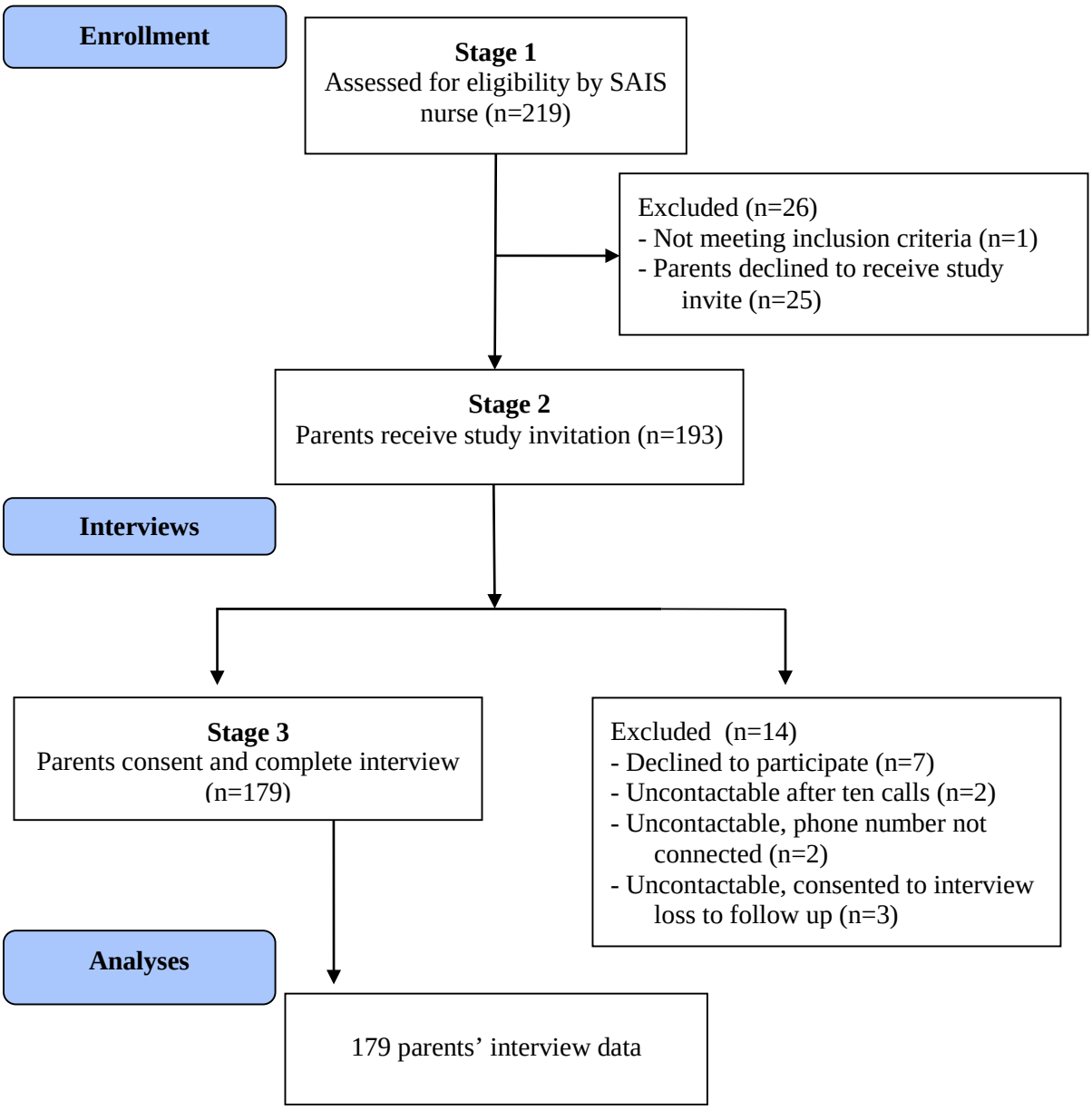
5.3 Additional results and discussion

Here, I provide additional results that were not included in the publication above.

5.3.1 Study 1 recruitment result

The recruitment results for the three stages of study recruitment are shown in Figure 4.3 An overall participation rate of 82% was achieved. Of the 219 elgibile parents at Stage 1, 26 parents were excluded. Of these 26, 25 declined to receive the study information and invitation. The one parent excluded at Stage 1 by the SAIS study nurse was due to personal circumstances that the nurse assessed would make this parent inappropriate for participation. At stage 3, a further 14 parents were excluded.

Figure 5.3: Study 1 Recruitment and Analysis Flowchart



5.3.2 Parental action following an AEFI

Table 4.5 illustrates the type of actions parents took following their children's AEFI. Of all 179 parents, 154 (87%) sought medical advice or attention from one or more healthcare professionals. Of those who sought help, 114 parents (74%) contacted one healthcare professional only, 37 (24%) contacted two and 3 (2%) contacted three healthcare professionals.

Table 5.4: Parental action following children's AEFI, n=179

Parent Action	n (%)
Home observation only	25 (14)
Called GP or nurse	67 (37)
Called Parent Helpline	49 (27)
GP visit	49 (27)
Emergency Department visit	32 (18)

* Response not mutually exclusive

5.3.3 Healthcare provider advice to report

In order to gain an understanding of communication that occurred between healthcare providers and parents about reporting an AEFI, the survey included a question about whether a healthcare professional discussed reporting to the Department of Health. Of those who had sought medical advice or attention, 104 (68%) responded that a professional had suggested the AEFI required reporting, 47 (31%) did not suggest and 3 (2%) were undecided. Table 5.5 provides the responses to this question by the type of help parents sought. Of all the professionals, less than half of the hospital emergency department professionals discussed or mentioned reporting with parents.

Table 5.5: Parental action and healthcare provider advice, n=154

Parent action	Did a healthcare provider mention reporting the AEFI to the Department of Health?		
	Yes	No	Don't know
Consult GP	31 (63.3)	17 (34.7)	1 (2.0)
Called GP/ Nurse	47 (70)	19 (28)	1 (1.5)
Called Parent Helpline/Health Direct	37 (75.5)	11 (22.5)	1 (2.0)
Attended Accident & Emergency	15 (47%)	17 (53%)	0 (0)

5.3.4 Vaccine safety opinion and awareness of surveillance survey results

Table 5.6 presents the vaccine safety opinions of both AEFI parent group samples from the General Population Parent Study and the AEFI Parent Reporter Study. The majority of AEFI reporters in both studies stated the safety of vaccines in general as "very safe"/"safe." However, the AEFI Reporter Parent Study sample expressed a higher level of concern on several survey items. Almost three quarters, (73%) of the AEFI Reporter Parent Study parents were concerned for safety testing compared with 42% of the General Population AEFI parent reporters (p=0.000). A smaller proportion of SAIS parents expected a mild AEFI, (58% vs 69%, p=<0.001) and a serious AEFI (9.8% vs 18.2%) at their children's last immunizations (P=<0.001).

Table 5.6: Vaccine Safety Opinion, AEFI Parent Reporters

Respondents	N					
AEFI Reporter Study	179					
General population AEFI Reporters	66					
	Response, N (%)					χ^2 (P)
In general, how safe would you say the vaccines given to children are?						
	Very unsafe	Unsafe	Undecided	Safe	Very safe	
AEFI Reporter Study	0	1 (0.6)	21 (11.7)	106 (59.2)	51 (28.5)	17.1 (0.001)
General population AEFI reporters	1 (1.5)	2 (3.0)	3 (4.6)	27 (41.0)	33 (50.0)	
How concerned are you that new vaccines have been adequately tested for safety before they are released to the public in Australia?						
	Very concerned	Somewhat concerned	Undecided	Not too concerned	Not at all concerned	
AEFI Reporter Study	49 (27.4)	81 (45.3)	2 (1.1)	37 (20.7)	10 (5.6)	26.6 (0.000)
General population AEFI reporters	18 (27.3)	13 (19.7)	1 (1.5)	17 (25.8)	17 (25.8)	
How likely did you think he/she would experience a reaction such as fever, irritability or redness at the injection site?						
	Very likely	Somewhat likely	Undecided	Not too likely	Not at all likely	
AEFI Reporter Study[a]	23 (13.0)	80 (45.2)	1 (0.6)	39 (22.2)	34 (19.2)	22.3 (0.000)
General population AEFI reporters[b]	25 (37.9)	21 (31.8)	0 (0)	11 (16.7)	5 (7.6)	
How likely did you think your child would experience a reaction that would need medical treatment from a hospital or GP?						
	Very likely	Somewhat likely	Undecided	Not too likely	Not at all likely	
AEFI Reporter Study[c]	2 (1.2)	14 (8.6)	0 (0)	44 (27.0)	103 (63.2)	18.3 (0.000)
General population AEFI reporters[d]	3 (4.6)	9 (13.6)	0 (0)	30 (45.5)	20 (30.3)	

Table 5.6 cont.

Acceptability of febrile convulsion risk				
	Not acceptable	Undecided	Acceptable	
AEFI Reporter Study	35 (19.5)	16 (8.9)	128 (71.5)	3.4 (0.196)
General population AEFI reporters	20 (30.3)	4 (6.1)	42 (63.6)	
Acceptability of Anaphylaxis risk				
	Not acceptable	Undecided	Acceptable	
AEFI Reporter Study	17 (9.5)	26 (14.5)	136 (76.0)	3.5 (0.174)
General population AEFI reporters	12 (18.2)	9 (13.6)	45 (65.2)	
Are you aware that a system for checking and assessing vaccine safety exists in Australia?				
	No	Undecided	Yes	
AEFI Reporter Study	59 (33.0)	9 (5.0)	111 (62.0)	1.5 (0.482)
General population AEFI reporters	22 (33.3)	6 (9.1)	38 (57.6)	

Table Notes
General Population Study data presented are the raw data
Category "undecided" was omitted from question 3 and question 4 analyses.
a: excludes 2 did not consider
b: excludes 2 did not consider, 4 missing
c: excludes 16 did not consider
d: 4 missing

5.4 Conclusion

In this chapter I have presented the results of the AEFI Parent Reporter Study. The findings demonstrated that parents sought medical advice from healthcare professionals when dealing with their children's AEFI. The context of the safety signal regarding the STIV in 2010 provided a timely opportunity to examine AEFI reporting by both parents and healthcare professionals. The majority of reporting to the South Australian Department of Health Immunisation Section by healthcare professionals occurred after the vaccine was suspended from use. It was also noted in a review of the AEFI system that most of the STIV AEFI reports were received by the Therapeutic Goods Association (TGA) after all seasonal influenza vaccinations in children aged <5years were suspended nationally.[19] This occurred in response to the call by the expert scientific advisory panel committee convened by the TGA to investigate the safety signal to health professionals for data. All jurisdictions were asked to collect and provided data on febrile convulsion presentations to emergency department, vaccine distribution, along with clinical data from immunisation providers.

On the whole, the parent studies presented in Chapters 4 and 5 showed that confidence in vaccine safety is high, regardless of whether a child has experienced an AEFI. However, parents' response to the 2010 influenza safety signal showed that confidence in vaccine safety can be relatively fragile. Similarly, loss of confidence and subsequent decline in vaccine coverage has occurred with other vaccines. The example of the MMR scare in the United Kingdom resulted in a decline in vaccine coverage following the now discredited 1998 study suggesting a link between the MMR vaccine and autism. The MMR coverage rates have now recovered to 89% following the lowest coverage rates in 2004 of less than 80%, but still less than the 95% recommended by the World Health Organization.[216, 217]

The two parent studies showed that parents on the whole reported their children's AEFI to healthcare professionals. The results from the AEFI Parent Reporter study presented in this chapter suggest that the low level of health professionals' reporting of AEFI before the national suspension requires investigation into how and why this might have occurred. In the next chapter, I further examine the issue of healthcare professional reporting and present results of the qualitative component of this thesis.

6 Healthcare Provider Study Results

6.1 Preface

In Chapters 4 and 5 the importance of AEFI reporting by healthcare professionals was evident in the results. Parents from both studies indicated they sought advice or reported their children's AEFI to healthcare professionals. The AEFI Parent Reporter Study also revealed that healthcare professionals did not report the AEFIs associated with the seasonal influenza vaccine prior to the suspension of the vaccine. This provided further evidence to the already known issue of under-reporting by healthcare professionals.

In this chapter I present the fourth publication contributing to this thesis. It has been published in *BMC Health Services Research* and addresses the final two research questions:

- What are the experiences, awareness and knowledge of healthcare providers in AEFI reporting and surveillance?
- How do healthcare providers conceptualise a reportable AEFI?

6.2 Publication: Healthcare Provider knowledge, experience and challenges of reporting adverse events following immunisation: a qualitative study

6.2.1 Statement of authorship

Parrella A, Braunack-Mayer A, Gold M, Marshall H, Baghurst P. Healthcare providers' knowledge, experience and challenges of reporting adverse events following immunisation: A qualitative study. BMC Health Services Research. 2013 Aug 15;13(1):313

By signing below, the authors declare that they give consent for this paper to be presented by Adriana Parrella towards examination for the Doctor of Philosophy.

Adriana Parrella (Candidate)

Contributed to the conception of the study, designed the interview questions, performed data analyses, interpreted results, reviewed the literature and drafted the manuscript.

Signed: …… Date: 25/02/2014……

Annette Braunack-Mayer

Contributed to the conception of the study , helped design the interview questions, assisted in the analysis and interpretation of results, and reviewed the manuscript.

Signed: …….. Date: 25/02/2014

Michael Gold

Contributed to the conception of the study, helped design the interview questions, assisted in the interpretation of results, and reviewed the manuscript.

Signed: Date: 25/02/2014

Helen Marshall

Helped design the interview questions, assisted in the interpretation of results, and reviewed the manuscript.

Signed: Date: 25/02/2014

Peter Baghurst

Assisted in the interpretation of results, and reviewed the manuscript.

Signed: Date: 25/02/2014

6.2.2 Abstract

Background

Healthcare provider spontaneous reporting of suspected adverse events following immunisation (AEFI) is central to monitoring post-licensure vaccine safety, but little is known about how healthcare professionals recognise and report to surveillance systems. The aim of this study was explore the knowledge, experience and attitudes of medical and nursing professionals towards detecting and reporting AEFI.

Methods

We conducted a qualitative study, using semi-structured, face to face interviews with 13 Paediatric Emergency Department consultants from a tertiary paediatric hospital, 10 General Practitioners, 2 local council immunisation and 4 General Practice nurses, recruited using purposive sampling in Adelaide, South Australia, between December 2010 and September 2011. We identified emergent themes related to previous experience of an AEFI in practice, awareness and experience of AEFI reporting, factors that would facilitate or impede reporting and previous training in vaccine safety. Thematic analysis was used to analyse the data.

Results

AEFI reporting was infrequent across all groups, despite most participants having reviewed an AEFI. We found confusion about how to report an AEFI and variability, according to the provider group, as to the type of events that would constitute a reportable AEFI. Participants' interpretation of a "serious" or "unexpected" AEFI varied across the three groups. Common barriers to reporting included time constraints and unsatisfactory reporting processes. Nurses were more likely to have received formal training in vaccine safety and reporting than medical practitioners.

Conclusions

This study provides an overview of the experience and beliefs of three healthcare professional groups in relation to identifying and reporting AEFI. The qualitative assessment reveals differences in experience and awareness of AEFI reporting across the three professional groups. Most participants appreciated the importance of their role in AEFI surveillance and monitoring the ongoing safety of vaccines. Future initiatives to improve education, such as increased training to health care providers, particularly, medical professionals, are required and should be included in both undergraduate curricula and ongoing, professional development.

6.2.3 Background

In Australia, the spontaneous reporting of adverse events following immunisation (AEFI) is the primary mechanism used for post-marketing passive surveillance (PMS) of licensed vaccines. Passive AEFI surveillance is common in many countries, worldwide [29, 218-220]. The process relies on immunisation providers, health professionals, and consumers voluntarily submitting ad-hoc reports to jurisdictional public health and/or federal regulatory authorities.[221] Vaccine manufactures are mandated to report to the federal authority, the Therapeutic Goods Administration (TGA), and in four of the eight Australian states/territories, but not South Australia, health professionals are mandated by jurisdictional legislation to report to the local public health authority. At the federal level up until 2013, the Advisory Committee for Safety of Medicines (ACSOM), a subcommittee of the TGA was responsible for the ongoing evaluation of all drug and vaccine safety. As of 2013, in response to recommendations for an improved system of governance for vaccine safety monitoring[19], a new statutory Advisory Committee on the Safety of Vaccines (ACSOV) has been established to evaluate vaccine safety. Any medical events occurring after vaccination, that are regarded as “serious” and/or

"unexpected" should be reported.[36, 222] An established causal association with vaccination is not a pre-requisite for reporting.[12]

Effective PMS is critical for a number of reasons. First, for new vaccines, pre-licensure clinical trials are not powered to detect rare adverse events that occur with a frequency of less than 1 in 1,000, or with delayed onset, and they are usually tested in homogeneous, healthy study populations.[28, 29] Thus, PMS aims to identify potential safety signals which may require further investigation not identified in pre-licensure trials and that may become apparent outside the controlled conditions of clinical trials. Secondly, for established vaccines, PMS aims to monitor known adverse reactions and if the observed rate exceeds the expected rate, further investigation is required. Finally, PMS should detect program errors, such as incorrect vaccine administration or manufacture.[30, 44] Hence, all licensed vaccines require specific pharmacovigilance plans that incorporate post-licensure passive surveillance and are "timely, efficient, sufficiently large and in place for the life of the vaccine."[30] An example of the importance of voluntary reporting of suspected AEFI was demonstrated by the withdrawal of the Rotashield vaccine in the United States in 1999. Ten months post-licensure and following 1.5 million doses administered, 15 reported cases of intussusception, higher than expected to occur, signalled the need for suspension of its use and further evaluation of the vaccine.[46]

Under-reporting is a known limitation of passive vaccine and adverse drug reaction (ADR) surveillance systems.[44, 96] In Australia this is demonstrated by the marked variation of AEFI reporting rates across jurisdictions for the same vaccines.[37, 39] The importance of and need for timely healthcare provider reporting of AEFI as they occur was highlighted by a recent Australian experience of a vaccine safety signal. On the 23rd April 2010, a seasonal trivalent influenza vaccine (STIV) for children aged less than 5 years was suspended nationally for three months due to an increased incidence of fever and febrile

convulsions,[18] associated with the vaccine brand, Fluvax (CSL). In an analysis of AEFI reports submitted to the South Australian Department of Health in the first six months in 2010, the majority (71%) of influenza AEFI reports submitted by healthcare providers were received after the STIV program was suspended.[223] Subsequent reviews of AEFI surveillance in Australia following the STIV suspension have suggested that under-reporting and delayed reporting of febrile convulsions, contributed to delays in signal detection.[19, 58]

Healthcare professional AEFI reporting is an under-researched area, with only four studies conducted elsewhere, published to date.[13, 15, 16, 90] All four studies employed quantitative methods to either measure awareness of surveillance, reasons for reporting or to compare actual AEFI reports by health professionals. The first examined Canadian family physicians' awareness of vaccine safety monitoring systems and reporting frequency for vaccine associated adverse events.[13] Less than half of the study respondents were aware of a monitoring system for AEFI, only one third knew of reporting criteria and only one in four had received vaccine adverse event education during medical training. The primary reason for not reporting was that an AEFI was never observed, the respondents did not know reporting was expected, the event did not seem serious enough or respondents were not aware of reporting procedures. Ranganathan et al. (2003) examined AEFI reports of Meningococcal serogroup C Conjugate (Men C) vaccine submitted to the Yellow Card Scheme (United Kingdom) by hospital doctors, General Practitioners (GPs) and nurses.[16] This study found nurses reported AEFI more frequently compared with GPs and hospital doctors and that completeness of the reports varied across the professional group. The third study of health professional AEFI reporting conducted in the United States included physicians, pharmacists, and nurses [15] and examined the frequency of reporting to the Vaccine Adverse Event Reporting System (VAERS), beliefs and awareness of AEFI reporting, barriers to reporting and strategies to increase reporting rates. Of all

respondents, 71% had never reported an AEFI, with 17% indicating they were not aware of how to report. The study demonstrated significant differences in having ever reported an AEFI by health professional type. Barriers to reporting included unclear definitions of a reportable AEFI, time pressures in completing a report, and confusion in whose responsibility it was to report. Reporting was associated with being alerted to look for specific events, discounting other explanations for the adverse event; observing the same AEFI repeatedly and whether the events occurred in vulnerable patient groups such as pregnant women, infants or patients aged ≥65 years. The fourth study is the most recent conducted to date and included family physicians, physician assistants, nurse practitioners, practice nurses and nurses working in paediatrics, family medicine and internal medicine.[17] The survey assessed demographics and professional characteristics and knowledge and attitudes toward identifying and reporting an AEFI to the Vaccine Adverse Event Reporting System (VAERS) in the United States. Although nearly three quarters of study participants were familiar with VAERS, only 14% were "very" or "extremely" familiar with the paper reporting procedure and approximately one third were not familiar when it was required to report an AEFI. Approximately 40% of all study participants had identified at least one AEFI, with only 18% indicating they had reported to VAERS. Respondents indicated they would report serious AEFI regardless of whether they were known (73%) or unknown (62%) to be associated with immunisation. Those who indicated that they were not familiar with submitting a paper report to VAERS were more likely not to report than those who were familiar with the process. Similarly, respondents who were not at all familiar with reporting criteria to VAERS tended not to report compared with those who were familiar with the requirements.

Studies of adverse drug reaction (ADR) reporting by health professionals have identified several factors that are common to under-reporting of AEFI. Ignorance of reportable events, lack of awareness of a reporting system, insecurity regarding causation (not

possible to ascertain whether the drug caused the reaction) and lack of time are common reasons associated with lack of reporting.[96, 97, 101-104] Other factors not demonstrated in previous AEFI studies that have been associated with under-reporting of ADR include fear of litigation; indifference; lack of financial incentives to report and a belief that only safe drugs are released into the market.[97, 101] Some parallels exist in adverse medical incident reporting studies. These studies reveal parallel differences in reporting behaviour between medical specialties where nurses are more likely to report to internal incident reporting systems than doctors and 'the fear of blame' as a common barrier to reporting by doctors.[224-226]

Consumer perceptions and experience of health professional ADR reporting have demonstrated concern that health professionals' lack of clarity in recognising adverse medicine events prevents reporting of potential adverse events.[64, 69] Two recommendations arising from a meeting of the Consumers Health Forum of Australia (CHF) in June 2011 were to improve and encourage adverse event reporting processes through training and education for health professionals.[227] These recommendations are echoed in a national review of Australian AEFI surveillance following the 2010 STIV safety signal to increase both consumer and health professional awareness of AEFI reporting and to improve communication and notification of AEFI between jurisdictional and federal health authorities.[19]

It is likely that differences in healthcare provider AEFI knowledge and practice of reporting results in inconsistent adverse event data collection and, ultimately, inaccurate measurement of the incidence of vaccine adverse events, by delaying or missing important vaccine safety concerns.[228] Since spontaneous reporting is central to passive vaccine PMS and given that health professionals provide the majority of AEFI reports to surveillance systems [86], it is important to understand not only the factors such as awareness of and

frequency of reporting, but also how health professionals identify/conceptualise a reportable AEFI. This paper presents results of a qualitative study that aimed to determine how healthcare providers identify and report AEFI within the South Australian context.

6.2.4 Methods

Design

Following a review of key findings from existing literature on AEFI and ADR reporting as described above and information obtained from a study of parent AEFI reporters we had previously conducted [185], we chose to adopt in-depth qualitative interviews for the study design as it was most suited to our research questions: What are the experiences, awareness and knowledge of healthcare providers in AEFI reporting and how do healthcare providers conceptualise a reportable AEFI? These questions and the associated study design are consistent with a social constructionist paradigm in qualitative research, enabling the interviewer to make meaning of each participant's "world", their individual perspectives and meanings in a context that is shaped by their organisational environment and broader social structures.[157]

We chose to conduct individual, face to face interviews as appropriate to examine each participant's specific experience and understandings of AEFI and because it was most suited to participants' work schedules. The interviews were conducted with the General Practioners (GPs) and Paediatric Emergency Department (PED) consultants, between December 2010 and February 2011. Based on preliminary analysis of the interview data, it was recognised that nurses also played an important role in AEFI reporting, and a further six interviews were conducted with two local council immunisation and four general practice nurses in September 2011.

Recruitment

We recruited twenty-nine healthcare professionals from an Emergency Department of a tertiary, paediatric hospital, GP clinics, and local council immunisation clinics in Adelaide, capital city of South Australia (population 1.6 million). Characteristics of participants are presented in Table 6.1. Purposive sampling was used to identify participants for the study.[229] The participants recruited in each category (see Table 6.1) represented a range of health professionals who were in a position to detect, manage and/or report an AEFI. The PED consultants were recruited via the Emergency Department with initial information about the study communicated to participants via the head of Emergency. All consultants except one agreed to participate. We used three strategies to recruit the GPs including contacting potential participants via professional (university research academics and clinical) contacts of the authors, advertising via an electronic distribution mail list of the local branch of the Royal Australian College of General Practitioners and finally via electronic communication within an academic organisation involved in training general practitioners. The study nurses were recruited via contacts of the authors, the general practice clinics involved in the study, and via the local Department of Health Immunisation Section.

Table 6.1: Study Participants

Professional group	Female	Male	Age range (years)	Mean number of years worked in professional group
Nurse	6	0	31-53	19
Paediatric Emergency Department specialist	6	7	35-57	15
General Practitioner	8	2	40-57	21

Topic Guide

The semi-structured, open-ended interviews were conducted using a topic guide (see Table 6.2). The original interview schedule was developed from a review of key findings of literature surrounding AEFI and ADR reporting as described earlier. Each interview sought to explore participants' knowledge and experience of detecting, managing and reporting an AEFI; factors that would facilitate or impede AEFI reporting; understanding of AEFI surveillance and previous training in vaccine safety. All interviews were conducted at participants' workplace, ranging from 25 to 65 minutes.

Table 6.2: Interview Topic Guide

Theme	Guiding question
Experience of an AEFI	1. Could you tell me about an AEFI you have seen during the course of your work? 2. How often have you seen an AEFI in this workplace or during your career? 3. How did you respond to the AEFI? 4. How did the event turn out?
Reporting an AEFI	1. Have you ever reported an AEFI? Why? 2. How have you reported? 3. Was it an easy/difficult process? Could you explain? 4. If you talked to an authority about the event what was the response from the person? 5. If you needed to report an AEFI today how would you do it? 6. What do you think are the main factors that would lead you to report an AEFI? 7. Why would you report an AEFI? 8. What would you not report as an AEFI? 9. What would be your preferred format for reporting? Why?

Table 6.2 cont.

Workplace	1. Can you tell me about whether AEFI are discussed with your colleagues? 2. Could you describe any policy/protocol for reporting an AEFI in your workplace?
Surveillance	1. Could you describe your understanding of how vaccines are monitored for safety after they are released to the public? 2. Who do you think should be responsible for monitoring vaccine safety in Australia? 3. How do you access communication regarding vaccine safety issues? 4. Is there sufficient information available to you from surveillance authorities or other sources? Explain. 5. In your opinion, who should be responsible for monitoring the ongoing safety of vaccines? 6. What do you think happens after an AEFI report is made? 7. What is your impression of how safety is monitored?
Training	1. Could you tell me about any training you have had in vaccine safety either during your career or as a student? 2. How do you update your knowledge in vaccine safety? 3. What would be an ideal way to update or provide training? 4. Do you think doctors and nurses have sufficient training and knowledge in current vaccine safety issues? Why?

Ethical considerations

Participation was voluntary and signed, informed consent was obtained before conducting the interviews. The study was approved by the University of Adelaide and Children Youth and Women's Health Service (CYWHS) Human Research Ethics Committees. This study adhered to the qualitative research review guidelines (RATS). [230]

Analysis

Each interview was audio-taped and data transcribed verbatim by AP. Thematic analysis was used to structure analysis of the transcripts [231] with NVivo, version 9 (QSR International, UK). Initially, open coding of interview data was undertaken. These codes

were generated inductively from participants' descriptions of their experiences in responding to and reporting an AEFI, and awareness of vaccine safety surveillance. Following initial coding of transcripts, preliminary themes that captured information relevant to the research questions were generated. This process involved identifying patterns in the data: recurring ideas, perspectives and descriptions that depicted each participant's context and perspective. The final analysis for this study focussed on key themes, narratives, and professional histories emerging from the interviews. Data concordance was verified by AP and ABM, a trained qualitative researcher with extensive experience in medical and public health qualitative research. Key themes were discussed with the research team that included two clinicians with expertise in vaccine safety and surveillance (HM and MG) at regular team meetings. We achieved topical saturation as similar themes emerged from various participants from each professional group after preliminary analysis of initial interviews. Quotes that best illustrate important representation of participants' views and experiences identified through our iterative process of review and discussion are presented in the following section.

6.2.5 Results

Previous experience of an AEFI and reporting

Most participants (27/29) reported seeing or being involved in the care of children or adults with a suspected AEFI, in their current or previous workplace. The cases included children presenting with suspected hypotonic hypo-responsive events, anaphylaxis, febrile convulsion, non-febrile convulsions, extensive limb swelling, high fevers and skin rashes (reported as allergic events). Although participants described experience of at least one AEFI throughout their career, most stated they were "rare" or "not that common", and occurred "years" prior to the interview. The most recent events recalled were febrile

convulsions following STIV vaccination in 2010 and a "severe local swelling" in the week prior to the study interview.

> *"I haven't had a lot of adverse reactions at all. They're quite rare actually. If you think of the number of kids we vaccinate. I've had lots of local reactions but I don't recall off the top of my head any significant."* GP 9

> *"We'd still be seeing the reactions rather than but no, not very common at all. Even less since we've used the acellular vaccine, even less."* GP 7

Of all participants, 19/29, (7 GPs, 5 nurses and 5 PED consultants), indicated they had reported an AEFI to a surveillance system at some point in their career, either in Australia or overseas. Only two participants stated they had reported more than once, despite the fact that most had worked for many years in the health system (a mean of 18 years for all three groups). When asked to recall when they had reported, a common response was in the distant past, with some as far back as "fifteen or twenty years ago."

> *"That one with the measles I would have reported. I think there was a couple of others too but it's going back a long way."* GP 7

Awareness of reporting

All nurses were familiar with paper and telephone reporting procedures to the local Department of Health and also described their workplace reporting processes, such as having the report forms on hand and/or an existing protocol for reporting adverse events (Table 6.3). Six of the thirteen PED consultants (46%) stated they were not aware of a system for reporting or how to report an AEFI.

> *"I would probably have to ask my colleagues how to do it."* ED 4

> *"I'd have to ask one of the other consultants what the procedure was, because I don't currently know."* ED 9

Two GPs were not aware of how to make a report, even though one stated having reported previously. The second GP had previously diagnosed an AEFI which would have been reported, had she known of a reporting system.

> *"I found it difficult to try and find out where I was meant to report and then due to competing demands didn't seek further information."* GP 5

For those who indicated awareness, reporting was thought to occur generally either via the national adverse drug reporting system or the local Department of Health. Few participants indicated awareness of both national and local reporting systems. We found participants were generally confused about the various reporting options and unaware that reports could be notified via phone, postal, fax, electronic or online submission.

> *"It would be helpful if the practice nurses could report on my behalf."* GP 10

> *"It would be nice to have a number, a telephone number with who to go to. That's the sort of thing we probably need with adverse events to vaccines."* GP 6

When describing awareness of workplace policies participants were also prompted to describe whether AEFIs were discussed during the course of their work. If an AEFI was discussed in the various workplace settings, it would usually occur informally with colleagues if a patient presented with symptoms that were unusual or serious. For example, in the hospital setting, around the time of the influenza safety signal in 2010, the ED consultants recalled informal discussions with colleagues of febrile convulsion cases presenting to the ED. The nurses would discuss cases that were "out of the norm."

> *"We do discuss it between us quite a lot if you get something quite a bit different. You know such and such happened have you had that happen with yours or are you aware of that being anything? So we do usually discuss it amongst ourselves."* GP 6

"We tend to talk about things that happen. If it was something serious I think generally we would discuss those things." GP 7

Table 6.3: Participants' awareness of AEFI reporting protocol or policy in their work setting

Nurses	General Practitioners	ED consultants
If we see an adverse event, then we do report. We have the forms for reporting. (General Practice nurse)	I think I would say that you know the majority that would be 99%, is done by our nurse and would probably only get reported from the nurse	I'd have to double-check. I'd have to ask a colleague
I would say there's one in the policy manual. (General Practice nurse)	No I don't know that there is one here actually.	We can just click on forms, adverse events reporting form and just print it out, so that's what we do.
The forms are in our filing cabinet. But I know you can get it from SAICU and I know it's on their website. We're actually in the process of doing a procedure, protocol. (General Practice nurse)	I would say there wouldn't be anything completely formal that we've ever discussed at a meeting or anything. I don't think there's ever been a formal policy. No.	*Not answered*
Not actually in writing but because I'm the only one here generally, anything that's out of the normal goes past me anyway. We always keep a copy of them (the adverse event reporting form) at the clinics. (Council immunisation nurse)	Not that I'm aware of. There may be, but not sure.	I don't really know because I've never had to do it because obviously it's quite rare.
I do the reporting and advise the doctors that I've done that as well. If we do any written documentation it's always scanned into the notes too. (General Practice nurse)	No actually we don't as far as I know have a policy. Probably we should, but no we don't.	I would have to look at information on our intranet that has information about reporting adverse reactions to vaccines and remind myself how to do it.
It is in our standard operation procedure that we do have that, if an adverse event occurred, it just says fill in a form. (Council immunisation nurse).	Well our practice nurse looks after all these things and she would report.	I remember looking up a number probably from the Immunisation Handbook.

Table 6.3 cont.

Nurses	General Practitioners	ED consultants
	No not specifically. There hasn't been a designated discussion about what we do about these things when they occur.	I don't think so. I'm not familiar with a documented protocol as such.
	There's those blue forms.	I'd have to ask one of the other consultants what the procedure was, because I don't currently know.
	Not formal, but we know to report to ADRAC.	We've got it on our web on our intranet there's links to it. The numbers there or you make the notification or you just fill it in and send it off.
	I'd have to see what the protocol was, but we haven't had one for so long	Reporting would not be protocolised.
		We've got the blue forms. We fill in the blue forms and send them off.
		No, there is no protocol

Recognition of a reportable AEFI

Participants were asked to describe the types of events they would consider necessary to report. All stated that a reportable AEFI was an event characterised as "serious" and/or "unexpected." Reactions were generally considered serious if they were life-threatening (such as anaphylaxis); clinically significant or severe (for example, convulsions); and/or relevant to the patient's future vaccinations, because of the potential impact on future vaccination decisions.

"I've never seen an anaphylaxis. I've never seen a hypotonic reaction. I've never seen anything I would classify as serious. Ever. I've never seen an AEFI that I've had to report" GP 3

"Most of the cases that present actually aren't significant events. So, that would be the usual fevers following vaccinations or localised reactions. Few actually meeting the criteria for being significant. I've not seen anyone with an anaphylaxis." ED 9

Two underlying interpretations were evident when participants described an "unexpected" AEFI. In the first instance, "unexpected" referred to an event that was rare, but with a known (but low) probability of occurring, such as anaphylaxis. These were regarded as unexpected because they were more severe and less common than the "normal" vaccine reactions.

"Beyond the reasonable in terms of you know what you would expect. It's obviously more severe." Nurse 3

When compared by professional group, all GPs and nurses would report this type of unexpected AEFI, (severe or rare, but previously recognised), whereas only half of the PED consultants explicitly stated or implied this. Discussion regarding febrile convulsions illustrated a difference in interpretation of "unexpected" across the groups. Most PED consultants stated that they had managed children who had experienced febrile convulsions in relation to influenza vaccination in 2010; however, only three could recall reporting this as an AEFI. When discussing the 2010 safety signal and opinions of why febrile convulsions were not reported, several reasoned that they are a known AEFI, that the children had experienced relatively minor convulsions, and that only prolonged convulsions that were "clinically significant" should be reported.

"I guess you know we saw a number of children not long after the vaccine was released with febrile, apparent febrile reactions to the vaccine who didn't appear to be particularly otherwise unwell. I guess febrile reactions to vaccines are relatively

common, that we weren't particularly perturbed about it at all until there were reports of children becoming quite unwell and having prolonged convulsions and there is significant morbidity associated with those, particularly interstate. I'm not sure whether there were terribly many in Adelaide." ED 5

The PED consultants tended to describe as reportable only those events that were very severe or life-threatening, often referred to as "clinically significant" or "dangerous."

"I think it has to be a very significant event... where it's well above the normal thing and potentially quite dangerous." ED 6

The second meaning attributed to "unexpected," was a reaction that was not known to occur following vaccination. This type of AEFI would be reported because there was no established scientific evidence available that connected it to a vaccination.

"If a child came back the next day or a week later and had an illness or an event that I couldn't in my mind relate necessarily to the vaccine then yes I would." GP 3

In addition to serious and unexpected reactions, some participants considered all adverse events occurring following newly released vaccines should be reported. Three participants stated all reactions, regardless of severity, should be reported.

"Well I guess theoretically any reaction to a vaccine should be notified, even if it's a minor reaction. The flu vaccine was a good case in that although we saw the children as having relatively minor febrile reactions to the vaccine there was obviously children who were having more severe end of the spectrum reactions associated with fever, so it's a good illustration that probably any reaction to a vaccine should probably be notified." ED 1

"I think any adverse event no matter how little or large needs to be reported." Nurse 2

Barriers to reporting

When discussing vaccine safety surveillance, most participants stated the critical role of healthcare providers in reporting AEFI but also recognised the limitation of passive surveillance of relying on healthcare providers to report.

> *"If you don't have reports you don't know how it's going out there in the arena, do you?"* Nurse 6

> *"Well I think everyone involved in administering vaccines which includes GPs and nurses and anybody seeing people. So, it's really, all of us have to play a role."* GP 4

> *"It seems to be more clinical adverse reactions are heavily dependent on the clinician reporting them."* ED 10

> *"There's a lot of assumptions made. We're assuming someone's going to tell us and then we're assuming that we're going to notify someone else when we find out."* GP 9

Although reporting by health professionals and the public was understood as key to monitoring AEFI, two participants did not believe they shared responsibility for AEFI surveillance.

> *"Not me. I don't know. There's probably some immunisation body.*
> *The only way you're going to know that there's some problem with a vaccine is if people are going to report significant events post –vaccine. And then someone else can sort it out."* ED 3

> *"I think it should be a government department because it's a public health issue."* GP 5

The amount of information required in completing a report, time constraints, competing workplace priorities in the workplace and dissatisfaction with reporting methods were identified as barriers to reporting by the GPs and PED consultants. By contrast, the nurses did not describe any of these barriers.

"Busy clinicians really don't have time to sit down and fill out several pages of report form." ED 1

"The reporting system is too difficult. The only way I want to report anything is automatically through my software." GP 4

Preferred Format for Reporting

Participants' preferences for a preferred format for reporting an AEFI varied across the three professional groups, and covered the current options for paper, phone, fax and electronic reporting. The nurses preferred either the phone or paper reporting, the GPs, phone or web-based reporting and the PED consultants varied in their opinions, stating paper/fax, phone and electronic formats. The phone was often stated as a convenient method for communicating and receiving immediate feedback/response with an immunisation professional. Paper reporting was believed useful to have a record or "trail" of communication with the local Department of Health and for the purpose of having patients' events recorded with their medical history.

"I prefer phone because I can ask questions for myself, as for if there was any correlation. So I'm reporting the incident but also following-up the information for myself or for the patient." Nurse 3

When discussing ideal electronic formats, GPs and PED consultants suggested creating systems that were linked to their workplace systems/practice management software and allowed for automatic submission.

"With electronic, particularly if there is a system built into your database using emergency as an example, if there is a reporting form built into the system so that it's prepopulated with demographic data and all you need to do is click some boxes, the form would be sent in automatically." ED 5

Training

All nurses had received some formal training in vaccine safety and AEFI reporting, such as Division of General Practice, Department of Health workshops, or post-graduate university training for immunisation providers. Most of the GPs and PED consultants could not recall specific training either pre- or post-graduation. All GPs and most PED consultants believed that, in general, doctors' pre-service education in vaccine safety and adverse event reporting was inadequate.

> *"I can't remember having any specific training on immunisations or reporting and adverse reactions. It's just assumed that we have obtained that knowledge somewhere rather than actually having a specific study or certification in vaccine."* ED 8

> *"I would have to say I don't think I had any training as a student at all. Or at least can't recall it. I can't remember hearing anything about vaccinations in medical school apart from sick people with COPD need vaccinations but nothing about the vaccines or safety."* GP 5

All participants supported strategies for updating knowledge via the continuing medical education programs of their relevant professional accreditation organisations.

6.2.6 Discussion

This is the first qualitative study, to our knowledge, that explores healthcare provider AEFI reporting awareness, practices and attitudes. We found reporting was infrequent across the three groups interviewed and conflicting views between groups as to what events would constitute an AEFI. Potential reasons for this could be that an AEFI occurs infrequently; that an AEFI is not recognised as such; and/or that an AEFI is recognised, but not reported. Our results show events which were either completely unexpected (that are not known to occur following vaccination), or which might represent an increase in expected reactions were less likely to be reported.

This study has shown that the requirement for all "serious" events to be reported to authorities, regardless of whether they were causally related to the vaccination, was interpreted differently amongst participants and by professional group. All participants would report the most severe events, often termed "life-threatening," or "dangerous." However, we found from the PED consultant interviews that, on the whole, they would only report events that were perceived as "life threatening." Compared with the nurses and GPs, they were less likely to report other events that were not as severe and those that are a known AEFI. The under-reporting of febrile convulsions following STIV in April 2010, could possibly be an illustrative example. Based on these interviews, we could reason that the PED consultants did not report febrile convulsions because this is a known complication of immunisation associated with fever. Taken together with the belief that most of the children they treated had experienced minor, (or not clinically significant) convulsions illustrates their differing interpretation of "serious" compared with GPs and nurses. Possibly, working in an environment in which one regularly sees serious and life-threatening presentations, compared with other settings, such as an immunisation clinic or family physician's workplace, increases a hospital emergency doctor's threshold for the definition of "severe" or "serious" and, therefore, what would be reported. Viewed in this light, under-reporting can be explained partly by the varied interpretation of what constitutes an AEFI.

The context of the workplace setting in this study is important to consider in relation to understanding factors that might influence a health professional's decision to report an AEFI. We did not seek information from each work setting involved about whether in fact there was an established policy or protocol for reporting. However, from the interviews we conducted, it was apparent that reporting was an established norm for immunisation nurses in local council clinics, as a council nurse's core work is providing immunisations to the public. Having report forms at hand and documented protocols for AEFI reporting

facilitated reporting in such settings. We suggest there are three possible explanations for the variations in awareness of participants from the general practice and hospital settings (Table 6.3). First, it may be that there was no current policy in place. Second, if a policy existed, it had not been introduced or established effectively within the workplace. For example, in the hospital setting, the ED consultants did have access to the local Department of Health reporting form via the internal intranet; however, few indicated awareness of it during interviews. This would suggest a need to ensure staff are informed and updated about accessing the reporting link. Given that the study occurred less than 12 months after the safety signal associated with the seasonal influenza vaccine and subsequent relay of public health alerts to hospitals and primary healthcare settings regarding the occurrence of febrile convulsions and need to report, it was surprising that there were such low levels of awareness. A third explanation for low levels of awareness amongst the GPs and ED consultants could be that reporting was not seen as a prime function of medical staff and might be delegated to nursing or administrative staff. Apart from one GP who indicated that the nurse at his practice would be responsible for reporting as part of her role in immunising patients, we found no evidence of delegated reporting amongst the GPs. In the ED setting, delegating the reporting to a registrar who was undertaking an ED rotation was described by some consultants and hence could explain their unfamiliarity with the actual processes of reporting, regardless of whether it was to local or national surveillance authorities. In this context one could speculate that reporting was not seen as a primary function of the clinician, but rather an administrative function to be performed by non-medical staff or, as in the ED setting, junior medical staff.

Despite the limitations of passive surveillance, it is not likely to be replaced by alternate methods of surveillance that do not rely on healthcare professionals' awareness or readiness to report, such as data linkage.[132-134] Passive surveillance should monitor vaccine safety and detect safety signals in real time or near-real time. Alternate methods of

surveillance such as data linkage or sentinel surveillance are usually used to detect known events and to test hypotheses for associations between a vaccine and an AEFI [135] but are limited by timeliness of reporting. Thus, there is an ongoing need for robust passive AEFI reporting systems. From this study it is clear that, even if an AEFI is recognised, there are significant barriers to reporting by health care providers. These barriers are consistent with factors identified in previous studies of AEFI and ADR reporting [13, 15, 101] and include a lack of awareness or confusion about reporting systems, a lack of time to report and differing perceptions of a reportable AEFI. Unlike other studies, we did not find evidence about fear of litigation, or that vaccine adverse events are not reported because of inherent trust that licensed vaccines are all safe.[101]

Few participants in this study were aware of both local and national reporting processes. Future research should explore whether a single pathway for AEFI reporting may be preferred by healthcare providers, rather than the existing system which provides a choice between reporting to the local Department of Health within each Australian jurisdiction or the national body (TGA). We also found differing preferences for the varied methods of reporting. In addition to these barriers, under-reporting may in part be attributed to the administration of less reactogenic vaccines in more recent years that has resulted in lower occurrence of some reactions. This would result in less awareness of reporting, as practitioners are less likely to be familiar with a system if they do not need to use it. However, this would not explain the differences in awareness across the three professional groups, as nurses were more familiar with both reporting processes and specific workplace protocols for reporting.

We found the nurses were more likely than the doctors to have received formal training in vaccine safety surveillance, which generally occurred as professional development training. This finding is consistent with previous published studies that reported low levels of vaccine safety education during medical training in Europe and Canada [13, 232] and an

unpublished, cross-sectional survey of 452 GPs, GP nurses, midwives, paediatric and community nurses, conducted in Sydney, Australia.[233] Our study confirms a need to provide adequate education across healthcare providers' training, both pre- and in-service, which has been recognised internationally.[232, 234] Adverse event reporting should be incorporated in continuing medical education programs.

The strength of this study lies in its qualitative approach. This format allowed participants to provide detailed accounts of their experiences and understanding of AEFI and reporting system. We were also able to sample participants from different work settings and professions. However, there were some limitations that may affect the generalisability of our findings beyond this study. Firstly, our participants all came from the one jurisdiction, and their responses may have been shaped by the organisational context for reporting of AEFI in that jurisdiction. Second, we acknowledge that participants in this study self-selected to participate and may provide an element of responder bias, since more motivated individuals or those with an interest in immunisation may have participated. However, we expected that responder bias would have been associated with greater familiarity with AEFIs and reporting systems than was evidenced in our study. Third, most participants had completed undergraduate training decades previously and this may have influenced their recall of adverse event training.

Our findings support the recommendations of the two reviews into AEFI surveillance in Australia, which were initiated because of the occurrence and delayed detection of febrile convulsions post STIV in 2010. Both reviews highlighted deficiencies in healthcare provider reporting [19, 58] and recommend a need to improve AEFI detection and reporting by introducing strategies aimed at increasing awareness of national reporting and strengthening communication within the surveillance system. Future research that would inform strategies to improve AEFI reporting should aim to include the perspectives of workplace managers and surveillance authorities as key informants.

6.2.7 Conclusion

Although the majority of participants had observed an AEFI in clinical practice and understood the importance of their role in AEFI reporting for post-marketing safety surveillance, we found reporting was infrequent. Reporting was related to the perceived interpretation of a reportable AEFI. The current guideline of reporting "serious" and "unexpected" events was interpreted differently in the three work settings and this would suggest there needs to be clearer definition and guidelines about reportable adverse events. Barriers to reporting included lack of time and knowledge of reporting processes. To test the magnitude of these factors, further research should be conducted among a larger representative group of healthcare professionals across Australia.

The participants' recall of training in vaccine safety suggests that there is a need to increase education and training in vaccine and drug adverse events and current reporting methods, at both undergraduate and postgraduate levels, particularly for medical professionals. Specific strategies for updating knowledge should be implemented via the professional relevant accreditation bodies and continuing medical education programs. The surveillance system and its methods for reporting should be easy to access, widely promoted and "user friendly" to both health professionals and consumers with formats for reporting designed so that the system is accessed effectively in different work settings. The limitation of any passive surveillance system is the submission of reports and the barriers identified in this study should be addressed as the Australian system is strengthened.

Competing interests

The authors declare that they have no competing interests

Authors' contributions

AP with the supervision of MG, ABM and HM developed the study design, performed the data collection, data analysis and wrote a draft manuscript. ABM assisted in data analysis.

The drafts of this article were revised critically by all authors. All authors have contributed to the draft and approved the final version of the manuscript.

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6.3 Conclusion

The results of the Healthcare Provider study, conducted in 2010-2011, are similar to those of the two studies from the United States I described in Chapter 2, regarding awareness and experience in AEFI reporting, published in 2012 and 2013.[15, 90] Some of the findings are echoed in the study by Meranus et al (2012), that found very similar categories of what healthcare providers would report: namely, serious reactions that are "known" AEFI symptoms and unknown reactions whether serious or minor. These studies, together with the results of the Healthcare Provider Study, confirm that more serious events are more likely to be reported and that reporting is related to health professionals' knowledge of reporting criteria and awareness of reporting pathways.

The results presented in this chapter add to the exisiting knowledge of AEFI reporting by providing evidence of the variation in the interpretation of AEFI by professional group

7 Findings and conclusion

Although vaccine safety surveillance relies on reporting of AEFI by the public and healthcare providers, there have been few studies to date that aimed to predict factors that lead to reporting or the barriers that inhibit it. This thesis sought to gain an understanding of these predictors and barriers of the Australian passive vaccine safety surveillance system, by examining the perceptions, understanding and experiences of those who are in the position to report an AEFI – that is, healthcare professionals and parents.

A mixed methods approach was adopted to address these knowledge gaps. In the quantitative components parents were interviewed about their children's experience of a previous AEFI, their vaccine safety opinions, their awareness of surveillance, and their experience of reporting an AEFI. The qualitative component of this thesis aimed to draw out how healthcare providers detect and perceive a "reportable" AEFI within their workplace. Three professional groups were interviewed: ED consultants, general practitioners and nurses.

This concluding chapter draws together the findings and implications for improving AEFI surveillance arising from the series of studies presented in this thesis. Although the findings do hold implications regarding parental vaccine safety education, such as perceptions of an AEFI risks and distinguishing common vaccine side effects from an AEFI, this conclusion will be restricted to the implications and recommendations for improving AEFI reporting. I conclude this thesis with recommendations that both address the current system and also look to alternative strategies for vaccine safety surveillance.

7.1 Key findings

The specific research questions addressed in this thesis and the key findings were:

1. Do parental attitudes towards vaccine safety differ according to whether their children have experienced an AEFI with parents whose children did not experience an AEFI?

The General Population Study findings presented in Chapter 4 demonstrated that parents of children who had experienced an AEFI held greater concern for vaccine safety in general and were more likely to expect an AEFI when compared with parents of children who had not experienced an AEFI. In this study sample, the regression results showed parental confidence in vaccine safety was significantly associated with higher levels of education and being Australian-born.

2. Are parents aware of a surveillance system for AEFI?

Of all parents interviewed in the General Population Study, 55% stated awareness of the existence of a surveillance system. Although a greater proportion of AEFI parent reporters (61%) indicated awareness of a system compared with the parent non-reporters (56%), the difference was not statistically significant. Similarly, 62% of the parents interviewed in the AEFI Reporter Study, (Chapter 5) stated awareness of a system for surveillance.

3. Do safety attitudes and awareness of surveillance differ according to whether parents report their children's AEFI to a healthcare provider or surveillance authority or do not report their children's AEFI?

The ordinal logistic regression results presented in Chapter 4 showed no significant difference in safety opinions for most of the survey items except for two. The AEFI reporters, when compared with non-reporters, perceived that a serious reaction was more likely to occur at their children's last immunisation and were more concerned about the stated risk of febrile convulsion. There was no significant difference in awareness of surveillance between reporters and non-reporters.

4. What are the factors associated with parental reporting of an AEFI?

This question was addressed in both parent studies. In the General Population Study, after adjusting for all socio-demographics, the only predicting factor associated with reporting an AEFI was that Australian-born parents were more likely to report. On the whole, there were no major differences in safety opinions that one could expect would predict reporting. Even though two of the vaccine safety opinion question results were significant (serious AEFI and febrile convulsion risk), the retrospective nature of the study makes it impossible to interpret whether these opinions determined reporting.

In the AEFI Parent Reporter Study, when asked why parents reported their children's AEFI to the South Australian Department of Health Immunisation Section or a healthcare professional, the most common reason was that they were worried, followed by wanting to make a notification, that is "report" the adverse event. For parents reporting an AEFI to the influenza vaccine in 2010, media reports of the safety issue was the second most common reason for reporting.

5. What is the impact for parents of experiencing an AEFI on future immunisation decisions?

The AEFI Parent Reporter Study results demonstrated that the experience of an AEFI did not impact on intentions to continue with the childhood schedule of immunisations available via the National Immunisation Program (NIP). However, parents whose children experienced an AEFI to the 2010 seasonal influenza vaccine expressed decreased confidence to continue with future influenza vaccinations,

6. What are the experiences, awareness and knowledge of healthcare providers in AEFI reporting and surveillance?

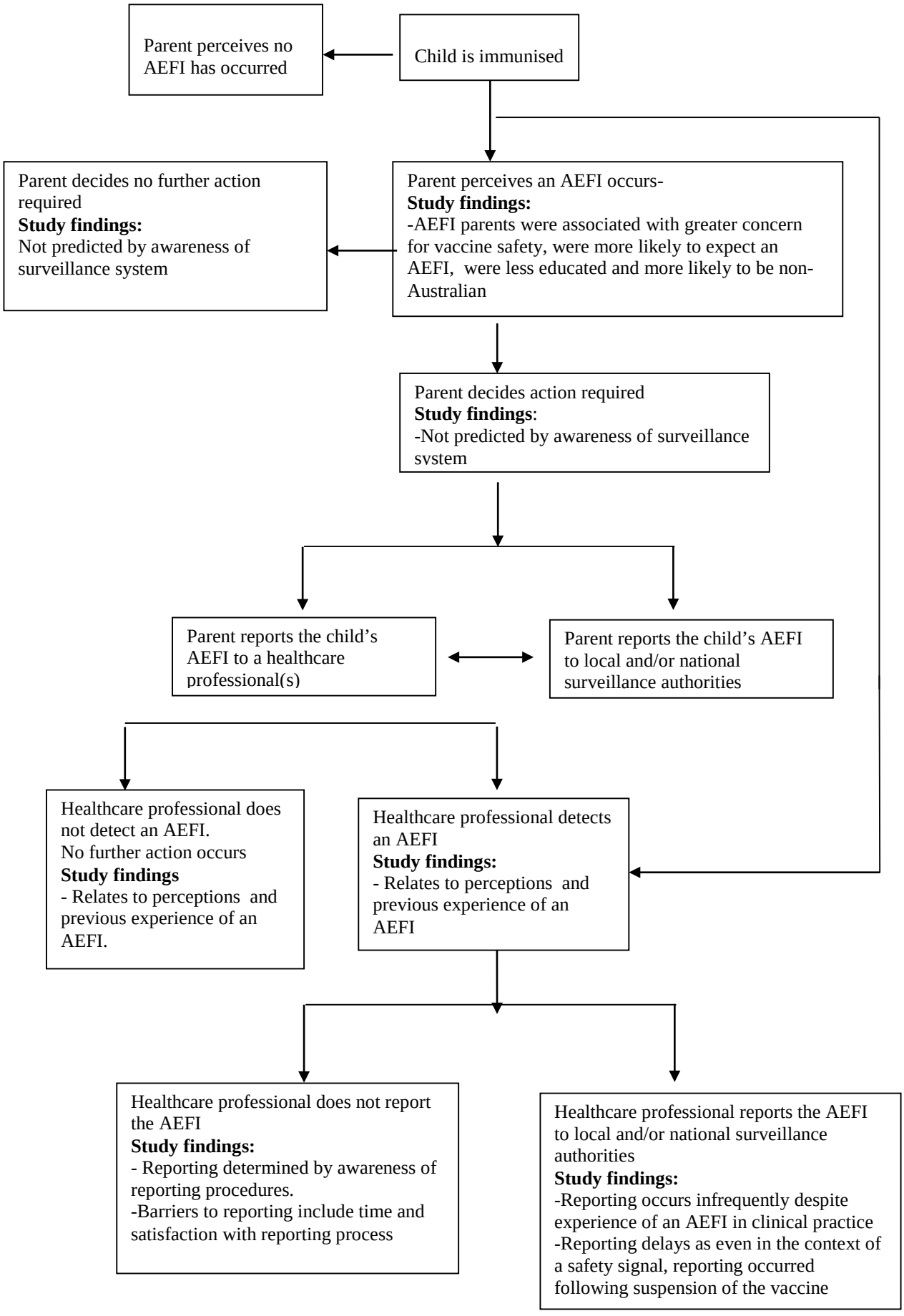
The qualitative interviews with the healthcare professionals demonstrated that although most participants had previously dealt with an AEFI during clinical practice, reporting was infrequent and that the experience and awareness of reporting differed across the three professional groups. Common barriers to reporting included time constraints and dis-satisfication with reporting processes. The participants, apart from the nurses, indicated low levels of training in vaccine safety training.

7. How do healthcare providers conceptualise a reportable AEFI?

The Healthcare Provider study results revealed differing interpretations of the type of events that would constitute a reportable AEFI. The requirement for all "serious" or "unexpected" events to be reported to authorities, regardless of whether they were possibly causally related to the vaccination, was interpreted differently amongst the three professional groups. In particular, the ED consultants interpretations of a reportable AEFI implied a "higher" threshold for reporting, whereby only the most extreme or severe events would be reported.

In Figure 7.1 the flow of the possible outcomes that follow a child's immunisation with regards to whether an AEFI is reported or not, as described in Chapter 1, is revisited with the addition of the above key research findings of this thesis.

Figure 7.1: Detecting and reporting an AEFI



7.2 Implications of the findings and recommendations for improving AEFI reporting

Since the 2010 seasonal influenza safety signal there has been continued interest in vaccine safety and improving AEFI reporting. Two reviews have been conducted investigating the AEFI system and how the safety signal was managed by the relevant Australian health authorities: the first concentrating on Western Australia[58] (the Stokes report) and the second, commissioned by the Federal Government to invetigate the national response[19] (the Horvath review). Two key recommendations were proposed by Horvath relating to improving AEFI reporting. These were to raise public and healthcare professional awareness of safety monitoring (recommendation 4) and for the Department of Health to develop communication strategies to inform health professionals and consumers of AEFI monitoring processes (recommendation 6). The Horvath review also recommended that the recording of vaccine useage and safety monitoring data should be a key priority for future e-health planning and development (recommendation 7), which also hold implications for improving reporting.

In this section I consider how the key findings of this thesis relate to these recommendations.

7.2.1 Consumer reporting

This thesis has demonstrated that parents were aware of a surveillance system, regardless of whether their children experienced an AEFI or not and regardless of whether parents reported an AEFI. I also found that the majority of parents contacted health professionals about their children's AEFI. Seeking medical advice is a logical and reasonable action for parents concerned about their children's well-being and, generally, parents are informed at the time of immunisation to contact their health provider with any concerns. However, the low level of reporting to surveillance authorities indicates that, in essence, parents know a

system for reporting exists but do not actually use it. By reporting their children's AEFI mainly to healthcare providers it may be implied that parents assume that their healthcare provider will report to the system or they believe that, in going to a health care provider, they have "reported" the AEFI. A reasonable explanation in these scenarios would be that parents hold an underlying expectation or trust that healthcare professionals would actually take further action if required.

Thus, although increasing consumer awareness of direct reporting as suggested by the Horvath report may have a role in alerting the public to the existence of a system, the findings of this thesis suggest parents would primarily communicate the AEFI to their healthcare provider. Thus, any focus on improving reporting should involve improving healthcare provers' awareness, in particular immunisation providers' reporting.

7.2.2 Healthcare professional reporting

The findings of the studies in this thesis have highlighted how healthcare professionals are central to passive surveillance by being the major recipients of reports of children's AEFI by parents, however in practice, they fail to report to surveillance authorities. The healthcare professionals' experience of AEFI reporting presented in this thesis provide a clear picture of how healthcare professional reporting is a very weak, if not, the weakest link in the current Australian passive surveillance system. This was evidenced by the under-reporting of AEFI to surveillance systems, the inconsistent interpretations of an AEFI in practice and in the varied understandings of the reporting system processes. Furthermore, the availability of training in vaccine safety and reporting is limited, especially for the medical professionals.

This thesis did not analyse or test specific interventions aimed at improving healthcare professional reporting, or assess the effectiveness of the surveillance system processes, such as flow of information between jurisdictional and national authorities, but, rather,

with regards to the healthcare professional reporting, it aimed to examine how the current system worked from the perspectives of healthcare professionals. It is clear, as was demonstrated by the 2010 influenza safety signal, that if we are to continue to rely on passive surveillance as the main method of vaccine safety surveillance, it will be necessary to introduce specific strategies in order to improve healthcare reporting.

In deciding on further directions, it would be reasonable not only to consider strategies that aim to strengthen the current system as it stands now, but to also investigate new approaches that would complement and/or replace aspects of the existing passive system. In particular, new systems would need to over-ride the vouluntary nature of passive surveillance and automate the detection and reporting processes.

The recommendations I propose below are two-fold: first, addressing the weaknesses of the current system and second, proposing alternative strategies. The first two proposals aim to strengthen the existing system via education and workplace strategies for professionals in clinical practice. The third proposes the development of technology that automates reporting by healthcare professionals and the final recommendation supports a potential alternative enhanced surveillance approach that incorporates both cosumer and healthcare provider.

Recommendation 1

Establish the provision of brief vaccine safety training activities tailored to the specific workplace and professional group, such as general practice and hospital settings that include content on AEFI reporting to healthcare professionals. Such training activities should be provided and coordinated via their relevant accreditation bodies or professional colleges.

Recommendation 2

Promote the establishment of workplace protocols for AEFI detection and reporting and that delegate responsibility for reporting to a dedicated person or personnel in the workplace.

Recommendation 3

Introduce reporting processes that encapsulate automated reporting to the relevant authorities. Such processes would require systems that automatically link to a report form when recording patient encounters in electronic patient systems. This technology is already available in some GP and ED clinical settings.

Recommendation 4

Establish alternative enhanced passive safety surveillance systems, for example using e-technology to capture real-time AEFI data. The recent approval by the National Health and Medical Research Council (NHMRC) for The Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS) research project[235] is an example of a novel approach to safety surveillance. It aims to investigate whether a short message service (SMS) text prompt to consumers following immunisation is more effective than the current practice of passive reporting to detect an AEFI. The SMS will detect any medical event following immunisation and subsequent AEFI identification will be evaluated by either a nurse-led computer assisted telephone interview or a web-based consumer report.

7.3 Limitations of the study

The limitations of each individual study were discussed in the relevant chapter discussions. Here, I discuss the limitations of the study overall. The overall purpose of this thesis was to address the gaps between the experience of and subsequent reporting of an AEFI by consumers, in this case parents, and by healthcare professionals. I aimed to investigate

consumer reporting by examining parents who had reported to a surveillance authority (Parent Reporter Study) and parents in the general community, (General Population Study). Initially, to examine predictors of reporting, I had considered the possibility of comparing the AEFI reporters from both studies with the AEFI non-reporters in the General Population Study. However, given the context of the highly publicised influenza safety signal in 2010, and the very different nature of the studies (the first a non-random sample of AEFI parents, the second a random sample of general population parents), it became evident that it would not be appropriate to combine the demographic and safety opinion data from both surveys to do this. The only option was to compare the AEFI reporters with the non-reporters in the General Population Study. This resulted in a relatively small sample of respondents for the regression analyses and hence may have affected the precision in detecting differences in response between the two groups.

As stated in the discussion in Chapter 5, the General Population Study was not designed to obtain detailed experiences of the children's previous AEFIs, nor were these experiences verified, because it was not feasible. Including a range of questions in the study about reasons for reporting or not would have been useful to further examine determinants of reporting, but was not possible due to the length of the Health Monitor survey and additional cost of including further questions. As most parents stated that the reactions were reported to health professionals and not a surveillance authority, the inability to draw conclusions or generalise from the data about predictors of reporting or not reporting to surveillance authorities is an inherent limitation to this study.

As I have stated previously in this thesis, the results of the parent studies are difficult to interpret because they were conducted retrospectively. In order to further examine predictors of reporting an AEFI, prospective studies would address the limitiations of using retrospective data and recall bias. Sampling general practice and immunisation council

parent cohorts at the time of children's immunisations, rather than a general population sample would yield more detailed information about the experience of an AEFI. Such studies, using both quantitative and qualitative methods would address limitations of the parent studies in this thesis and would provide a more accurate predictor of reporting, such as reasons for reporting and safety opinions. A prospective study would also identify parents who would be eligible to report to a surveillance authority but do not.

Despite these limitations, this is an important exploratory study that draws attention to the need to improve AEFI reporting and the passive surveillance system.

7.4 Concluding remarks

Adverse event reporting systems are critical for maintaining quality and safety in health care. The need for robust post-marketing vaccine safety surveillance will continue to grow as new vaccines are introduced in the near future. The findings of this thesis have highlighted important aspects of parental and healthcare professional AEFI reporting. The studies provide a foundation to inform future studies and relevant immunisation and safety surveillance policy strategies.

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Appendix 1 Ethical approval for General Population Parent Study

THE UNIVERSITY OF ADELAIDE
AUSTRALIA

RESEARCH BRANCH
RESEARCH ETHICS AND COMPLIANCE UNIT

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CRICOS Provider Number 00123M

13 October 2010

Dr MS Gold
Discipline of Paediatrics

Dear Dr Gold

PROJECT NO: H-166-2010 *Community perceptions of vaccine safety and surveillance including attitudes to data linkage*

I write to advise you that I have approved the above project on behalf of the the Human Research Ethics Committee. Please refer to the enclosed endorsement sheet for further details and conditions that may be applicable to this approval.

Approval is current for one year. The expiry date for this project is: 31 October 2011

Where possible, participants taking part in the study should be given a copy of the Information Sheet and the signed Consent Form to retain.

Please note that any changes to the project which might affect its continued ethical acceptability will invalidate the project's approval. In such cases an amended protocol must be submitted to the Committee for further approval. It is a condition of approval that you immediately report anything which might warrant review of ethical approval including (a) serious or unexpected adverse effects on participants (b) proposed changes in the protocol; and (c) unforeseen events that might affect continued ethical acceptability of the project. It is also a condition of approval that you inform the Committee, giving reasons, if the project is discontinued before the expected date of completion.

A reporting form is available from the Committee's website. This may be used to renew ethical approval or report on project status including completion.

per Professor Garrett Cullity
Convenor
Human Research Ethics Committee

Appendix 2 General Population Parent Study invitation

THE UNIVERSITY OF ADELAIDE AUSTRALIA

POPULATION RESEARCH AND OUTCOME STUDIES
1.1.1.1.1.1 FACULTY OF HEALTH SCIENCES
SCHOOL OF MEDICINE
DIVISION OF MEDICINE

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March 2011

Dear Householder,

Your household has been invited to take part in an important health and wellbeing survey being conducted by the University of Adelaide on behalf of a number of organisations interested in public health issues. This survey addresses a range of physical health and wellbeing issues. The feedback you provide will help us to improve the health of South Australians and inform planning of services in our community. Your participation in the survey is very important.

One of our interviewers will be contacting your household in the next few weeks to interview the adult in the household aged 18 years and over in the household who had the last birthday. The interview will be conducted over the telephone and will take around 15 minutes. Your phone number has been selected randomly from all telephone listings in the state. **All information collected will be confidential.**

Participation in the survey is voluntary and you are free not to answer any questions if you feel uncomfortable; however it is important to the success of this study that everyone selected takes part. If you do not wish to participate, or if you have any concerns, questions or complaints about the survey, please contact the Health Study Hotline on (free-call telephone) 1800 420 445. If you have a complaint that you wish to discuss with an independent person you can contact the University of Adelaide's Human Research Ethics Committee's Secretary on (08) 8303 6028.

Yours sincerely

Anne Taylor

Associate Professor

Appendix 3 Health Monitor 2011

HM Survey
[2011 – March]

INTRODUCTION

Good ..... My name is ..... I'm calling on behalf of The University of Adelaide. We are conducting a survey on a range of health issues. We recently sent you a letter about the survey on behalf of the University. Did you receive the letter?

(Single response)

1. Yes
2. No
3. Don't know

Interviewer note: If respondent did not receive letter, offer to read the following:
'**The survey will be conducted by The University of Adelaide, on behalf of organisations interested in public health issues. This particular survey will address a number of topics relevant to the health of the South Australians. The feedback that you provide will help us to improve the health of South Australians and inform planning of services in our community**.'

Intro1 Records prior to survey are randomly allocated into three aged groups:

1. 16 to 24 years Go to Intro2A
2. 25 to 34 years Go to Intro2B
3. 35 to 44 years Go to Intro2C

Intro2A To ensure that we get a good representation of the community, could you please tell me if there is anyone in your household aged <u>between 18 to 24 years</u>.

(Single Response)

1. Yes Go to Intro4A
2. No / Not stated Go to Intro3

Intro2B To ensure that we get a good representation of the community can you please tell me if there is anyone in your household who is aged <u>between 25 to 34 years</u>.

(Single Response)

1. Yes Go to Intro4B
2. No / Not stated Go to Intro3

Intro2C To ensure that we get a good representation of the community can you please tell me if there is anyone in your household who is aged <u>between 35 to 44 years</u>.

(Single Response)

1. Yes Go to Intro4C
2. No / Not stated Go to Intro3

Intro3 Since there is no-one in this age group, can I please speak to the person in the household who was the last to have a birthday.

(Interviewer note: some of the questions are only asked of people in certain age groups.)

Sequence guide: go to A1

Intro4A Can I please speak to the person aged between 18 and 24 years in the household who was last to have a birthday.

(Interviewer note: some of the questions are only asked of people in certain age groups.)

Sequence guide: go to A1

Intro4B Can I please speak to the person aged between 25 and 34 years in the household who was last to have a birthday.

(Interviewer note: some of the questions are only asked of people in certain age groups.)

Sequence guide: go to A1

Intro4C Can I please speak to the person aged between 35 and 44 years in the household who was last to have a birthday.

(Interviewer note: some of the questions are only asked of people in certain age groups.)

Sequence guide: go to A1

Your phone number has been selected randomly from all telephone listings in the State.
I can assure you that all information given will remain confidential. The answers from all people interviewed will be gathered together and presented in a report.
No individual answers will be passed on.
The questionnaire will take approximately 15 minutes to complete, but may take longer depending on the number of questions that are relevant to you.
Whilst your input to the survey is very important to us, participation is voluntary and you can choose not to answer any particular question or any section. You are free to withdraw from the survey at any time.
Please be aware that this phone call may be listened to by my Supervisor for quality control and training purposes.

A. DEMOGRAPHICS SCREEN

As some of the next questions relate to certain groups of people only, could you please tell me…

A.1 How old you are?

(Single Response. *Interviewer note enter 998 Don't know, 999 refused*)

1. Enter age
2. Not stated
3. Don't know

Sequence Guide: If A1 <998 Go to A3

A.2 Which age group are you in? Would it be...

(Read options, single response)

1. 18 to 24 years
2. 25 to 34 years
3. 35 to 44 years
4. 45 to 54 years
5. 55 to 64 years
6. 65 years and over
7. Refused (End interview)

A.3 Voice (ask if unsure)

(Single response)

1. Male
2. Female

A.4 Including yourself, how many people aged 18 years and over live in this household?

(Single response. *Enter number of people 18 years and over.*)

1. Enter number
2. Not stated [999]

A.5 How many children under 18 years live in your household?

(Single Response. *Enter number of people under 18 years. Enter 0 if none*.)

1. Enter number
2. Not stated [999]

A.6 What is your postcode?

(Single response. *Enter 5999 if postcode is not known.*)

1. Enter number
2. Not stated [5999]

Sequence Guide: If A.6 $\neq$ 5999 Go to NS

A.7 What town or suburb do you live in?

(Single Response. *Enter town/suburb*)

1. Enter town/suburb

B VACCINE SAFETY & EFFECTIVENESS

[Discipline of Paediatrics, CYWHS]

The next few questions are about the vaccination of children in Australia.

B.1 In general, how safe would you say the vaccines given to children are?
(Single response)
1. Very safe
2. Safe
3. Unsafe
4. Very unsafe
5. Don't know/ Can't say
6. Refusal

D. CHILDHOOD VACCINATIONS

Sequence Guide: If A.5= 0 or 999, go to NS

D.0 The next few questions ask specifically about vaccinations relating to children in the household. Are you a parent or legal guardian of the children?
(Single response.)
1. Yes
2. No
3. Don't know
4. Refusal

Sequence Guide: If D.0>1 Go to NS

D.1 What is the age of the (next (for 2nd and subsequent children) **) youngest child in the house for whom you are the parent or legal guardian?**
(Single response. Interviewer note: if child is under 13 months, specify months)
1. Specify years _____
2. Specify months_____
3. No other children
4. Don't know
5. Refusal

Sequence Guide: If D.1=3 Go to D.10

D.2 Are they male or female?
(Single response)
1. Male
2. Female
3. Refusal

D.3 Is the child up to date with their immunisations, according to the recommended childhood immunisation schedule?
(Single response)
1. Yes
2. No
3. Don't know
4. Refusal

Sequence Guide: If D.3=1 Go to D.5

D.4 Has the child ever received an immunisation?
(Single response)
1. Yes
2. No
3. Don't know
4. Refusal

Sequence Guide: If D.4>1 Go to D.1

Sequence Guide: If D.4=1 and first child Go to D.5,
All subsequent children Go to D.7

D.5 Thinking back to when your youngest child was last immunised how likely did you think it would be that (s)he would experience a reaction, such as fever, irritability or redness at the injection site? Would you say this type of reaction was:
(Read options. Single response)
1. Very likely
2. Somewhat likely
3. Not too likely
4. Not at all likely
5. Did not consider it at the time
6. Don't know
7. Refusal

D.6 And again, thinking back to your youngest child's last immunisation, how likely did you think it would be that (s)he would experience a reaction that would need medical treatment from a hospital or GP. Would you say:
(Read options. Single response)
1. Very likely
2. Somewhat likely
3. Not too likely
4. Not at all likely
5. Did not consider it at the time
6. Don't know
7. Refusal

D.7 Has/have your child(ren) ever experienced a reaction following immunisation*?*
1. Yes
2. No
3. Don't know
4. Refusal

Sequence Guide: If D.7>1 Go to D.1

Can you describe the reaction signs and symptoms they experienced?
(Multiple response)
1. Fever
2. Vomiting
3. Swelling at the injection site
4. Diarrhoea
5. Rash at the injection site
6. Rash over part of or whole body
7. Collapse
8. Convulsion
9. Severe allergic reaction affecting breathing and blood pressure (anaphylaxis)
10. Other (specify)
11. Don't know
12. Refusal

D.9 Were any of the symptoms reported to any of the following?
(Read Options. Multiple response)
1. Department of Health
2. GP
3. Parent Helpline
4. Immunisation nurse
5. Other (specify)
6. Did not report
7. Don't know
8. Refusal

D.10 Anaphylaxis is a severe, allergic reaction that can occur after immunisation. It requires immediate, medical treatment. The risk of experiencing an anaphylactic reaction to any vaccine ranges from approximately 1 to 10 for every 1 million doses of vaccine. When considering whether to vaccinate your child would you say this risk of anaphylaxis is:
(Read options. Single response)
1. Acceptable
2. Not acceptable
3. Don't know
4. Refusal

D.11 Young children who develop a fever after immunisation may sometimes go on to have a fit or seizure, known as a febrile convulsion. The risk of a febrile convulsion is approximately one in every 12,000 children immunised. When considering whether to vaccinate your child would you say this risk of febrile convulsion is:

(Single response)

1. Acceptable
2. Not acceptable
3. Don't know
4. Refusal

D.12 Are you aware that a system for checking and assessing vaccine safety exists in Australia?

(Single response)

1. Yes
2. No
3. Don't know
4. Refusal

Z. DEMOGRAPHICS

Now to finish with some general questions.

Z.1 Which of the following best describes your current marital status?

(Read options. Single response. *Interviewer note: 'De facto' equals 'Living with partner'*)

1. Married
2. Living with a partner
3. Widowed
4. Divorced
5. Separated
6. Never married
7. Not stated / inadequately described

Z.2 What is your work status?

(Read options if necessary. Single response. *Interviewer note: Self-employed is either full or part time*)

1. Full time employed
2. Part time / casual employment
3. Unemployed
4. Home duties
5. Retired
6. Student
7. Unable to work because of disability / Workcover / invalid
8. Other (specify)

(Sequence guide: If Z.2 = 1 or 2, go to Z.4)

Z.3 Do you receive any of the following pension benefits?

(Read options. Multiple response)

1. Disability Support Pension
2. Unemployment Benefits
3. Sickness Benefits
4. Aged /widow's pension
5. Service or defence/ War widow's/ Repatriation Pension
6. Supporting parents benefit
7. AUSTUDY/student allowance
8. Other (specify)
9. None
10. Refused

Z.4 In which country were you born?

(Single response)

1. Australia
2. Austria
3. Bosnia-Herzegovina
4. Canada
5. China

6. Croatia
7. France
8. Germany
9. Greece
10. Holland/Netherlands
11. Hong Kong
12. Iran
13. Italy
14. Japan
15. Malaysia
16. New Zealand
17. Philippines
18. Poland
19. Slovenia
20. Spain
21. U.K. and Ireland
22. USA
23. Vietnam
24. Former Yugoslav Republic of Macedonia
25. Former Yugoslav Republics of Serbia & Montenegro
26. Other country (specify)
27. Refused

(Sequence guide: If Z.4 = 1, go to Z.6)

Z.5 What year did you arrive in Australia?
(Single response)
1. Enter year
2. Don't know

(Sequence guide: go to Z.7)

Z.6 Are you of Aboriginal or Torres Strait Islander origin?
(Single response)
1. Yes
2. No
3. Refused

Z.7 What is the main language you speak at home?
(Single response)
1. English
2. Cambodian
3. Cantonese
4. Chinese
5. Croatian
6. Dutch
7. Filipino
8. German
9. Greek
10. Italian
11. Polish
12. Serbian
13. Spanish
14. Vietnamese
15. Other (specify)

Z.8 Which best describes the highest educational qualification you have obtained?
(Read options. Single response)
1. Still at school
2. Left school at 16 years or less
3. Left school after age 16
4. Left school after age 16 but still studying
5. Trade / Apprenticeship
6. Certificate / Diploma
7. Bachelor degree or higher
8. Refused

Z.9 The next question is about housing. Is your dwelling ….
(Read options. Single response)
1. Owned or being purchased by the occupants
2. Rented from the Housing Trust
3. Rented privately
4. Retirement village
5. Other (specify)
6. Refused

Z.10 I would now like to ask you about your household's income. We are interested in how income relates to lifestyle and access to health services. Before tax is taken out, which of the following ranges best describes your household's income, from all sources, over the last 12 months?

(Read options. Single response)

1. **Up to $12,000**
2. **$12,001 - $20,000**
3. **$20,001 - $30,000**
4. **$30,001 - $40,000**
5. **$40,001 - $50,000**
6. **$50,001 - $60,000**
7. **$60,001 - $80,000**
8. **$80,001 - $100,000**
9. **$100,001 - $150,000**
10. **$150,001 - $200,000**
11. **More than $200,000**
12. Not stated/refused
13. Don't know

That concludes the survey. On behalf of The University of Adelaide, thank you very much for taking part in this survey.

Please record what language this interview was conducted in. (Single response)

1. English
2. Italian
3. Greek
4. Vietnamese
5. Other (specify)

Date of interview
Day of week interview undertaken
Time of day interview undertaken

Appendix 4 Ethical approval for AEFI Parent Reporter Study

Government of South Australia
SA Health

Human Research Ethics Committee

ABN 97 643 356 590

Level 10, CitiCentre
11 Hindmarsh Square
Adelaide SA 5000

PO Box 287
Rundle Mall
Adelaide 5000
Telephone (08) 8226 6064
Facsimile (08) 8226 7088

Ms Adriana Parrella
Discipline of Paediatrics
The University of Adelaide
Mail Drop DX 650516
ADELAIDE SA 5005

Dear Ms Parrella,

Re: Vaccine Safety Monitoring: A study of passive reporting as a mechanism of post marketing surveillance.

HREC PROTOCOL NO: 334/01/2013

Thank you for responding to the issues raised by the SA Health Human Research Ethics Committee in relation to the above proposal.

I am pleased to advise that ethics approval has been granted to your project subject to the following conditions:

- The research must be conducted in accordance with the 'National Statement on Ethical Conduct in Human Research.'
- When the project is completed, a final report must be provided to the HREC.
- The HREC must be notified of any complaints by participants or of adverse events involving participants.
- The HREC must be notified immediately of any unforeseen events that might affect ethical acceptability of the project.
- Any proposed changes to the original proposal must be submitted to and approved by the HREC before they are implemented.

- If the project is discontinued before its completion, the HREC must be advised immediately and provided with reasons for discontinuing the project

Approval is given for a period of three (3) years only, and if the research is more prolonged than this, a new submission will be required.

Should you have any questions or concerns, please contact Sarah Lawson, Executive Officer of the HREC, Tel 8226 6367 or E-mail hrec@health.sa.gov.au

We wish you well with your project.

Yours sincerely,

Andrew Stanley
CHAIRPERSON
HUMAN RESEARCH ETHICS COMMITTEE

9/3/2010

THE UNIVERSITY OF ADELAIDE
AUSTRALIA

RESEARCH BRANCH
RESEARCH ETHICS AND COMPLIANCE UNIT

SABINE SCHREIBER
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TELEPHONE +61 8 8303 6028
FACSIMILE +61 8 8303 7325
email: sabine.schreiber@adelaide.edu.au
CRICOS Provider Number 00123M

24 February 2010

Dr MS Gold
Discipline of Paediatrics

Dear Dr Gold

PROJECT NO: H-016-2010 *Vaccine safety monitoring? - A study of passive reporting as a mechanism of post marketing surveillance*

I write to advise you that the Human Research Ethics Committee has approved the above project. Please refer to the enclosed endorsement sheet for further details and conditions that may be applicable to this approval.

Approval is current for one year. The expiry date for this project is: 28 February 2011

Where possible, participants taking part in the study should be given a copy of the Information Sheet and the signed Consent Form to retain.

Please note that any changes to the project which might affect its continued ethical acceptability will invalidate the project's approval. In such cases an amended protocol must be submitted to the Committee for further approval. It is a condition of approval that you immediately report anything which might warrant review of ethical approval including (a) serious or unexpected adverse effects on participants (b) proposed changes in the protocol; and (c) unforeseen events that might affect continued ethical acceptability of the project. It is also a condition of approval that you inform the Committee, giving reasons, if the project is discontinued before the expected date of completion.

A reporting form is available from the Committee's website. This may be used to renew ethical approval or report on project status including completion.

Professor Garrett Cullity
Convenor
Human Research Ethics Committee

Appendix 5 AEFI Parent Reporter Study invitation letter

DATE

Dear XXX

Re: Vaccine Safety Monitoring Study

I am writing to you with regards to the above research study. I am contacting parents who have reported vaccine reactions following their children's immunisations to the SA Department of Health Immunisation Service (SAIS). Your contact details were provided to me by SAIS as you have previously indicated consent to receive this information.

The study aims to seek your opinions on immunisation and vaccine safety. Please read the enclosed information sheet which explains the study and what would be involved if you agree to take part.

The University of Adelaide and SA Department of Health Research Ethics Committees have approved this project. All information will be treated in the strictest confidence.

I will be calling you approximately one week after sending this letter and if you are willing to participate, will arrange a convenient time with you for telephone survey. If you have any queries, please do not hesitate to contact me on 8313 1412 or by email.

I look forward to discussing the project with you.

Yours sincerely,

Adriana Parrella
Project Researcher
Vaccine Safety Monitoring Study
Discipline of Paediatrics, University of Adelaide
Tel: 8313 1412, Fax: 8313 1406
Email: adriana.parrella@adelaide.edu.au

Appendix 6 AEFI Parent Reporter Study Information Sheet

Discipline of Paediatrics
School of Paediatrics and Reproductive Health
University of Adelaide, Adelaide, SA, 5005

Chief Investigator: Dr Michael Gold
Email: michael.gold@adelaide.edu.au

Project Researcher: Ms Adriana Parrella
Tel 8313 1412 Fax : 8313 1406
Email: adriana.parrella@adelaide.edu.au

INFORMATION SHEET

Researchers: Dr Michael Gold, Ms Maureen Watson, Dr Helen Marshall, Professor Annette Braunack-Mayer, Ms Pip Rokkas, Ms Adriana Parrella

You are invited to take part in a research project,

"Vaccine Safety Monitoring - A study of passive reporting as a mechanism of post marketing surveillance"

The monitoring of vaccine safety relies on reports from the public and healthcare professionals in order to detect unexpected vaccine reactions. This study will include both parental and healthcare professionals' views on vaccine safety and the process of monitoring vaccine reactions.

The research is being undertaken by a team from the University of Adelaide in collaboration with the South Australian Immunisation Service (SAIS), SA Department of Health. Approval for this research has been obtained from the Human Research Ethics Committees of each participating organisation.

Why is the research being done?
There is a lack of previous research about the experience and views of people who have experienced vaccine side effects and reported it to health authorities. This study will aim to examine whether experiencing a vaccine reaction influences future vaccination decisions. It will also assess factors that lead to parents/caregivers reporting a vaccine reaction to vaccine safety monitoring systems.

Who can participate in this research?
We are seeking parents/caregivers of children aged 7 years and under who have reported a vaccine reaction to any immunisation their child/ren experienced in 2010 to the South Australian Immunisation Service (SAIS), or the Child and Family Health Parent Helpline or their immunisation provider. You have been chosen to participate as you have indicated that you would be interested in receiving this information. We are also seeking families who have not reported any vaccine reactions to participate in this research.

What choice do you have?
Participation in this research is entirely your choice. Only those people who give their informed consent will be included in the project. Whether or not you decide to participate, your decision will not disadvantage you in any way. If you do decide to participate, you may withdraw from the project at any time without giving a reason.

please turn over

What would you be asked to do?
Your participation requires the completion of a telephone survey. This survey will take approximately 15-20 minutes of your time. The project researcher will call you.

You will be asked to:

- Answer questions about the immunisation event you reported to SAIS
- Answer questions about your views on immunisation and vaccine safety
- Answer questions regarding you and your children's previous immunisation experiences

What are the risks and benefits of participating?
There are no known or potential risks to participating in this study and we cannot promise you or your family any benefit from participating in this research.

How will your privacy be protected?
The researchers will not know who you are unless you choose to participate in the study.
Any information collected for the project, remains confidential, that is:

- Any personal details obtained from you will be kept in a locked filing cabinet separate from other study information
- Your details will be de-identified on the survey records by replacing your name with a study ID.
- Your personal details will never be mentioned in the reports or any documentation arising from the study.
- Your answers to the telephone interview will only be accessed by the research team.
- At the completion of the study, data will be stored on password-protected computer disks, and locked securely in the Discipline of Paediatrics, University of Adelaide for a minimum of 15 years.

How will the information collected be used?
Information gathered from this research study will be reported in medical journals and in a thesis by the project researcher. It may also be communicated to health professionals and researchers during conferences. You will not be identified in any publications/presentations arising from the project and you may request a copy of a summary of results.

What do you need to do to participate?
Please read this Information Statement and be sure you understand its contents before you consent to participate. If there is anything you do not understand, or you have questions, please contact the researcher.

One week after sending this information to you, the project researcher will contact you and confirm your participation in the telephone survey. With your permission, the researcher will conduct the survey or arrange a suitable time with you to call back.

Additional information
If you have any questions or would like more information on the research project please contact Dr Michael Gold/Adriana Parrella, whose contact details are at the top of the front page.

This project has been approved by the University of Adelaide's Human Research Ethics Committee, (Approval No.) and the South Australian Department Health Human Research Ethics Committee, (Approval No.). Should you have concerns about the manner in which the research is conducted, it may be given to the researcher, or if an independent person is preferred, to: Secretary, Human Research Ethics Committee, Research Branch, University of Adelaide, 5005. Telephone 08 8303 6028.

We thank you for considering participation in this research project.
Dr Michael Gold

Appendix 7 AEFI Parent Reporter Study verbal consent

This is (Adriana Parrella). I am a researcher from the University of Adelaide. I am calling about the Vaccine Monitoring Study.

I recently sent you a letter about the Vaccine Monitoring Study. I am calling all people who we sent a letter to. We would like to ask your opinions on immunisation and know what you think about the monitoring of vaccine safety. With your permission, would you be willing to be interviewed now?

Yes …proceed with verbal checklist below.

No…call back at arranged time/parent withdraws consent

YES: Before starting the interview could I please read you the following statements to ensure your informed consent?

1. I have read the Information Sheet sent to me.

2. I understand that the privacy and confidentiality of any information I provide will be safeguarded as explained in the Information Sheet

3. I have been informed that, while information gained during the study may be published, I will not be identified and my personal results will not be divulged.

4. I understand that I am free to withdraw from the project at any time and that this will not affect me, now or in the future.

Start Interview.

Appendix 8 AEFI Parent Reporter Study telephone survey

Section A. IMMUNISATION VIEWS

To begin with, I will ask you about your views on vaccination. There are no right or wrong answers. For some of the questions I am interested to know what you think, by asking you to rate your opinion according to a list of options that I will give you.

Would you say you strongly agree (1), agree (2), disagree(3) or strongly disagree (4) with each of the following statements

A1 It is important that my child/children receive all of the recommended childhood vaccines.

Strongly agree..... 1
Agree..... 2
Disagree..... 3
Strongly disagree..... 4
(Don't know)..... 98
(Refused)..... 99

A2 I am going to read you four reasons that parents give for immunising their children. When you had your child immunised how important were each the following reasons to you:

Would you say each reason is: very important (1), somewhat important (2), not too important (3)or not at all important (4).

A2a Vaccination is a good way to protect my children from disease 1_/ 2_/ 3_/ 4_
A2b My GP or other healthcare provider recommended immunisation 1_/ 2_/ 3_/ 4_
A2c Everyone else I know is doing it 1_/ 2_/ 3_/ 4_
A2d It is recommended for childcare or kindy 1_/ 2_/ 3_/ 4_

A3 What do you think about the following statement?

I should have my child/children vaccinated because the more children that are vaccinated, the less likely infectious disease will spread in my community.

Would you say you strongly agree, agree, disagree or strongly disagree?

Strongly agree..... 1
Agree..... 2
Disagree..... 3
Strongly disagree..... 4
(Don't know)..... 98
(Refused)..... 99

A4 In general, how effective do you think vaccines are in preventing diseases such as polio, whooping cough, measles, influenza and chicken pox?

Would you say:

Always effective.....1
Nearly always effective.....2

Sometimes effective.....3
Seldom effective.....4
(Don't know).....98
(Refused).....99

A5 In the past 10 years, four new vaccines have been added to the Australian Immunisation Schedule for children to receive before they are 2 years old. These include the Meningococcal C, Rotavirus, Pnuemococcal and Varicella/ Chicken Pox vaccines. How concerned are you about the increase in the number of vaccines included in the Schedule?

Would you say you are:
Very concerned.....1 (go to question 5a)
Somewhat concerned.....2 (go to question 5a)
Not too concerned.....3
Not all concerned.....4
(Don't know).....98
(Refused).....99

A5a. Why are you concerned about the increase in the number of vaccines?

Response Codes
Immune system overload.....NR_0 / Yes_1
Not all vaccines are necessary.....NR_0 / Yes_1
Vaccine safety concerns.....NR_0 / Yes_1
Other..... NR_0 / Yes_1

A6 How concerned would you be if more vaccines were added to the Schedule for children aged 2 and under?

Would you say you would be:
Very concerned.....1
Somewhat concerned.....2
Not too concerned.....3
Not all concerned.....4
(Don't know).....98
(Refused).....99

A7 Would you agree to your child/ children receiving an influenza vaccination if the vaccine was recommended and made available for free like the current childhood vaccinations ?

YES_1 / NO _2 / DK_98 / REF _99 (NO, go to A7a)

A7a Why?

A8 To reduce the number of injections received, some vaccines are delivered in combination with other vaccines. For example the Infanrix-hexa vaccine given to infants at 2, 4, and 6 months of age includes 6 vaccines in one injection. How concerned are you about the use of these combination vaccines?

Would you say you:
Very concerned.....1. (go to 8a below)
Somewhat concerned.....2 (go to 8abelow)
Not too concerned.....3
Not all concerned.....4

(Don't know).....98
(Refused).....99

A8a. Why are you concerned about the use of combination vaccines?
Response Codes
Immune system overload.....NR_0 / Yes_1
Vaccine safety concerns.....NR_0 / Yes_1
Difficult to determine which vaccine causes reaction... NR_0 / Yes_1
Cannot exclude vaccines .....NR_0 / Yes_1
Other.....NR_0 / Yes_1

A9 Apart from vaccination, do you believe there are alternative ways of protecting your child from getting infected with diseases such as polio, whooping cough, measles, influenza and chicken-pox?

YES_1 / NO _2 / DK_98 / REF _99 (YES, go to question 9a)

A9a. YES, what can you do?

Good diet/healthy lifestyle.....1
Practice good hygiene.....2
Homeopathic vaccination.....3
Herbal , natural or complementary medicines.....4
Other.....96

A10 Is your child/ren up to date with their immunisations, according to the recommended childhood immunisation schedule?

YES_1 / NO _2 / DK_98 / REF _99

Section B. ATTITUDES TO VACCINE SAFETY
The following questions are seeking your opinions about vaccine safety. .

You may be aware that all medicines, including vaccines, carry a risk of adverse reactions. Some reactions can occur frequently and others can occur rarely.

B1 In general, how safe do you think the vaccines that are given to children are?

Would you say vaccines are very safe, safe, unsafe or very unsafe?
Very safe.....1
Safe.....2
Unsafe.....3
Very unsafe.....4
(Don't know).....98
(Refused).....99

B2 What or who of the following options would be your most trusted source of information about vaccine safety? Would you say (*read options*):
Who would be your 2nd most trusted?
GP.....1
Immunisation Nurse.....2
Vaccine manufacturer.....3
Family.....4
Friends.....5
Internet.....6

Media (eg television, magazines).....7
Medical journals.....8
None.....9
Other.....96
(Don't know).....98

B3 I am interested in your views about the safety of new vaccines. How concerned are you that new vaccines have been adequately tested for safety before they are released to the public in Australia?

Would you say:

I am very concerned about the safety new vaccines.....1
I am somewhat concerned about the safety of new vaccines...2
I am not too concerned.....3
Not all concerned.....4
(Don't know).....98
(Refused).....99

B4 Thinking back to when your child was last immunised, how likely did you think he/she would experience a reaction such as fever, irritability or redness at the injection site (could occur at the time he/she was immunised)?

Would you say : very likely, somewhat likely, not too likely or not at all likely to occur?

Very likely to occur.....1
Somewhat likely to occur.....2
Not too likely.....3
Not at all likely to occur.....4
(Did not consider the likelihood of occurring at the time)...5
(Don't know).....98

B 5 How concerned were you that he/she would experience this reaction? (That is, fever, irratibility and redness at the injection site after vaccination)

Would you say you were very concerned, somewhat concerned, not too concerned or not at all concerned?

Very concerned.....1
Somewhat concerned.....2
Not too concerned.....3
Not all concerned.....4
(Don't know).....98
(Refused).....99

B6 Thinking back to when your child was last immunised how likely did you think that he/she would experience a reaction that would need medical treatment from a hospital or GP (could occur at the time your child was immunised?)

Would you say : very likely, somewhat likely, not too likely or not at all likely to occur?

Very likely to occur.....1
Somewhat likely to occur.....2
Not too likely.....3
Not at all likely to occur.....4
(Did not consider the likelihood of occurring at the time)...5
(Don't know)..... 98
(Refused).....99

B7 How concerned were you that he/she would experience this type of reaction? (That is, would require medical treatment from a hospital or GP)

Would you say you were very concerned, somewhat concerned, not too concerned or not at all concerned?

Very concerned.....1
Somewhat concerned.....2
Not too concerned.....3
Not all concerned.....4
(Don't know).....98
(Refused).....99

B8 Anaphylaxis is a reaction that can occur after vaccination. It is a severe, allergic reaction requiring immediate, medical treatment. Current estimates of anaphylaxis suggest that 1 to 10 people will experience an anaphylactic reaction for every 1 million doses of vaccine.

When considering whether to vaccinate your child would you say this risk of anaphylaxis is:

Acceptable.....1
Not acceptable.....2
(Don't Know).....98
(Refused).....99

B9 Fever is a common side effect after vaccination. Some young children with fever may have a febrile convulsion. Current estimates are that a febrile convulsion may occur once in every 12,000 children vaccinated.

When considering whether to vaccinate your child would you say this risk of febrile convulsion is:

Acceptable.....1
Not acceptable.....2
(Don't Know).....98
(Refused).....99

In case you are wondering: most common side effects of vaccines are minor. Serious reactions requiring immediate, medical treatment are very rare. If they do occur, doctors and nurses providing immunisation are trained in dealing with them.

Section C. PREVIOUS IMMUNISATION EXPERIENCE

C1 Have you ever refused a previous recommended childhood vaccination for your child or children?

YES_1 / NO _2 / NA_97 / DK_98 / REF _99 (Yes, go to C1a)

C1a. YES, Why?

Response Codes

Unsure whether the vaccine was necessary……..1
Worried about vaccine safety…….....2
Advised to delay by a health practitioner.....3
Child was ill…….....4
Other …….....96

C2 Apart from the reaction you reported, have you, your child, family member, or friend ever experienced a serious reaction after immunisation?

YES_1 / NO _2 / NA_97 / DK_98 / REF _99 (Yes, go to C2a)

C2a. YES, Who?

Child.....1
Family member.....2
Friend.....3
Friend's child.....4

Section D. COMMUNICATION/INFORMATION PRE-VACCINATION
I would like to ask you some questions about where your child was last immunised and information you may have received before your child's immunisation.

D1 Where did your child receive the immunisation?

Council immunisation clinic 1
General Practice 2
Community Health Centre.....3

D2 Who immunised your child?

GP.....1
Immunisation Nurse.....2
Both.....3

D3 Did you receive any information about potential vaccine side effects or reactions on the day your child was immunised from (*insert provider here*) who gave the vaccine?

YES_1 / NO _2 / DK_98 / REF _99 (NO, go to question D3)

YES, questions D3a, D3b, & D3c)

D3a. YES, who gave you information?
GP 1
Immunisation Nurse.....2
Other.....96
Not required.....0

D3b. What type of information did you receive?

Vaccine safety information sheet.....1
Vaccine safety folder.....2
Discussion.....3
Both info and discussion.....4
Not required.....0

D3c .Were you satisfied with the information you received?

YES_1 / NO _2 / DK_98 / REF _99 / NR_0(YES, go to question D4, NO, question 3d)

D3d. NO, WHY?

D4 Did you receive or seek additional information about the safety of childhood vaccines from other sources apart from the health care provider who gave the vaccine?

Yes (YES, go to question D4a)

No

D4 a. YES, Where or from whom did you receive or seek information?

GP.....1
Immunisation Nurse.....2
Vaccine manufacturer.....3
Family.....4
Friends.....5
Parent Helpline.....6
Internet.....7
Media (eg television, magazines).....8
Medical journals.....9

Other.....97

Section E. CHILD'S VACCINE REACTION
I am now going to ask you some questions about the vaccine reaction your child experienced following vaccination that you reported.

E1. How old was your child when he/she received the vaccination?

E2. Could you describe the type of reaction your child experienced?

E3. Were any of the following actions required for your child's vaccine reaction? (what did you do?)

1. A consultation with your GP to review your child.....YES_1 / NO _2 /
2. Called GP/immunisation clinic.....YES_1 / NO _2 /
3.Parent Helpline..... YES_1 / NO _2 /
4.Emergency department attendance..... YES_1 / NO _2 /
5.Hospital admission)..... YES_1 / NO _2 /
If yes how long ? – hours, days
6. Home treatment/observation..... YES_1 / NO _2 /

If YES to 1 -5 above

E3a. Did a healthcare provider suggest the reaction needed to be reported to the Department of Health?
YES_1 / NO _2 / DK_98 / REF _99/. NR_0

Section F. AEFI REPORTING
I will now ask you a few questions about your child's vaccine reaction that was recorded by the Immunisation Service . (*Youlinsert reporter type here*) reported your child's reaction to the Immunisation Service.

Reporter Types
(You (parent) / Your GP / the Immunisation nurse/ a hospital nurse / a hospital doctor / the Parent Helpline)

F1. I am interested in knowing why you initially contacted the (Immunisation Section or *insert other reporter type from above here)* about your child's reaction. Why did you contact the (*insert reporter type*)?

a .Parent worried about child's reaction.....1
b. Wanted more information/advice.....2
c. To report the reaction.....3
d. Media attention 4
e. Family/friend suggested reporting.....5
f. Other.....96

F2. For parents reporting to SAIS only:
Could you describe how you became aware of reporting your child's reaction to the Immunisation Service?
GP.....1
Nurse/Immunisation Nurse..... 2
Family/friends.....3
Immunisation pamphlet.....4
SA Health/SAIS website.....5
Parent Helpline.....6
Media (news,papers).....7
Blue Book.....8
Other.....96
Not required.....0

F3. Were you satisfied with the response you received when you contacted (*insert reporter type here*) about the reaction?

YES_1 / NO _2 / DK_98 / REF _99/. NR_0 (NO, question F3a)

F3a. Why were you not satisfied with the response?

Section G. AE IMPACT

The following questions are seeking information on how the vaccine reaction your child experienced may have affected your family.

G1. Did you need to miss attending work as a result of your child's vaccine reaction?

YES_1 / NO _2 / DK_98 / REF _99/. NR_0 (YES, question 1a)

G1a YES, How many days? .....

G2. Has the experience influenced your decision in relation to your child receiving further vaccinations?

YES_1 / NO _2 / DK_98 / NA_ 97 / REF _99 (YES, question 2a, NO, confirm below)

NO, will continue with recommended schedule.....1
NO, will continue with flu vaccination.....2
NO, will continue with schedule AND flu vaccination....3

2a. YES, How?

a Will continue with recommended schedule only.....1
b Will only accept additional vaccines if advised to by
GP or other medical provider.....2
c Hesitant to vaccinate for flu.....3
d Will not vaccinate for flu.....4
e hesitant to vaccinate.....5

G3. Has the experience influenced your decision in relation to your other child/ren receiving further vaccinations?
YES_1 / NO _2 / DK_98 / NA_ 97 / REF _99

(YES, question 3a, NO, confirm below)

NO, will continue with recommended schedule.....1
NO, will continue with flu vaccination.....2
NO, will continue with schedule AND flu vaccination....3

3a. YES, How?

a Will continue with recommended schedule only.....1
b Will only accept additional vaccines if advised to by
GP or other medical provider.....2
c Hesitant to vaccinate for flu.....3
d Will not vaccinate for flu.....4
e hesitant to vaccinate.....5

Section H. VACCINE SAFETY SURVEILLANCE PROCESS

The following question is seeking your opinions on monitoring vaccine safety.

H1. Are you aware that a system for monitoring and assessing vaccine safety exists in Australia?

YES_1 / NO _2 DK_98 / REF _99

H2. Who do you think is (or should if answered no above) involved in the process of monitoring vaccine safety in Australia?
For each option please tell me whether you think they are involved. Read options.

Health professionals.....1 YES_1 / NO _2 / DK_98 / REF _99
Vaccine companies.....2 YES_1 / NO _2 / DK_98 / REF _99
Government.....3 YES_1 / NO _2 / DK_98 / REF _99
Health researchers.....4 YES_1 / NO _2 / DK_98 / REF _99
Public reporting adverse events..5 YES_1 / NO _2 / DK_98 / REF _99

H3. Do you believe that parents reporting adverse events following immunisation to health professionals is an important part of the process of monitoring vaccine safety?

YES_1 / NO _2 / DK_98 / REF _99

H4. Do you believe vaccine companies should be involved in the process of monitoring vaccine safety after a vaccine is released for public use?
YES_1 / NO _2 / DK_98 / REF _99

Section J. DEMOGRAPHICS

I would like to ask some questions about you and your family. The answers to these questions help us to compare different family groups. The study is confidential and all questionnaires are analysed in an anonymous way. If I ask a question that you would prefer not to answer, please tell me and we can leave it.

J_1. Which of the following family types best describes your situation?

Married or in a de facto relationship.....1
Widowed.....2
Separated or divorced 3
Single.....4
Other.....5
Refused.....99

J_2. Are you?

Child's mother.....1
Child's father.....2
Caregiver/Guardian.....3

J_3. What is your age?

18 to 24 years.....1
25 to 34 years.....2
35 to 44 years.....3
45 to 54 years.....4
55 to 64 years.....5
Refused.....99

J_4. What is your postcode? (*write postcode*)

_____

J_5. What is the highest level of education you have completed?

Year 10 or below.....1
Year 11.....2
Year 12.....3
Certificate/Diploma at a TAFE college or similar.....4
University degree(Diploma, Bachelor, Honours).....5
Postgraduate degree (Grad Diploma/Certificate/Masters, PHD).....6
Refused.....99

J_6. The following question is about your total family income, before tax, last year in 2009. I will read out six income categories; please tell me which one your family would match. I can read out the categories as income per week or income per year. Which one do you prefer? (Read Chosen option)

	Per week	Per year
A	Less than $400	Less than $20,000
B	$400-$799	$20,000 - $40,000
C	$800-$1,150	$40,000 - $60,000
D	$1,150 - $1550	$60,000 - $80,000
E	$1550 - $1900	$80, 000 – 100,000
F	More than $1900	More than $100, 000
G	Refused	
H	Don't know /not sure	

J7. In what country were you born?

Australia
Other, PLEASE SPECIFY
Refused

J_8. What is the main language spoken in your home?

J_9. How many children are in your family?

1_ / 2_ / 3_ / 4_ / 5_ / 6

J_10. What are the ages and sex of each child in your family?

Finally, thank you for your help and time completing this survey.

Appendix 9 Ethical approval for Healthcare Provider study

Government of South Australia
SA Health

Women's & Children's Hospital

9th December 2010

Dr M Gold
Head, Allergy & Clinical Immunology
University Dept of Paediatrics
CYWHS

Research Secretariat
72 King William Road
North Adelaide SA 5006
Tel 08 8161 6521
Tel 08 8161 6390
Fax 08 8161 8177
www.cywhs.sa.gov.au

Dear Mike

Re: Vaccine safety monitoring study – a study of passive reporting as a mechanism of post marketing surveillance. REC2323/11/13

I refer to your letter dated 3rd December 2010 in which you responded to matters raised by the CYWHS Human Research Ethics Committee at its November 2010 meeting. I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

I note that you have provided signed Confidentiality Agreements and a verified copy of a police clearance for Ms Parrella. If in the future, the study involves other non CYWHS staff or students, a signed Confidentiality Agreement will be required and, if they visit any CYWHS site or access identifiable patient information, a National Police Certificate provided to the Ethics Committee and the Human Resources Department. The study may proceed on this proviso.

I remind you approval is given subject to:

- immediate notification of any serious or unexpected adverse events to subjects;
- immediate notification of any unforeseen events that might affect continued ethical acceptability of the project;
- submission of any proposed changes to the original protocol. Changes must be approved by the Committee before they are implemented;
- immediate advice, giving reasons, if the protocol is discontinued before its completion;
- submission of an annual report on the progress of the study, and a final report when it is completed. It is your responsibility to provide these reports – without reminder from the Ethics Committee.

Approval is given for three years only. If the study is more prolonged than this, an extension request should be submitted unless there are significant modifications, in which case a new submission may be required. Please note the approval number above indicates the month and year in which approval expires and it should be used in any future communication.

If University of Adelaide personnel are involved in this project, you, as chief investigator must submit a Human Research Approval notification form online at http://www.adelaide.edu.au/ethics/human/guidelines/ within 14 days of receiving this ethical clearance to ensure compliance with University requirements and appropriate indemnification.

Yours sincerely

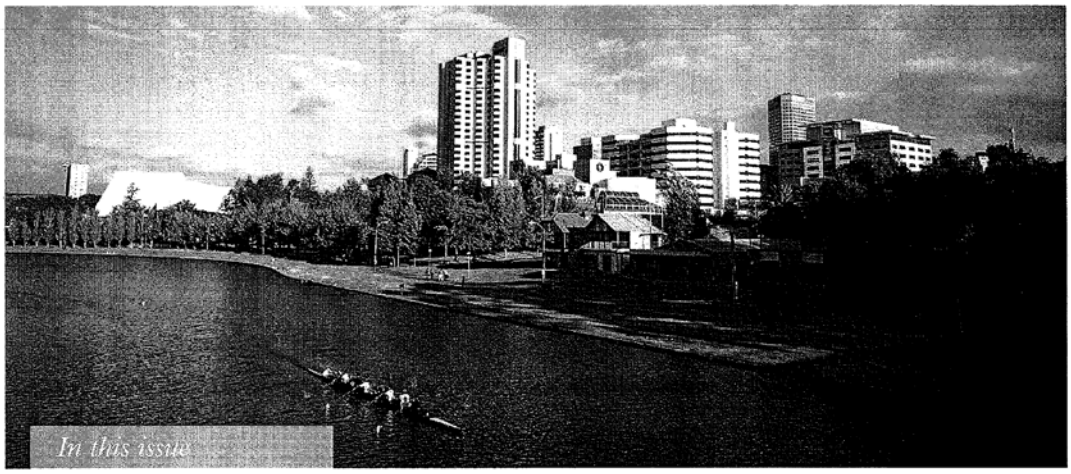
TAMARA ZUTLEVICS (DR)
CHAIR
CYWHS HUMAN RESEARCH ETHICS COMMITTEE

Appendix 10 RACGP advertisement

The Royal Australian College of General Practitioners

SA&NT faculty e-news

December 2010, Issue 22



© Tourism Australia

02 SA and NT GPs awarded the CPMEC Clinical Educator of the Year

03 6 reasons to be an RACGP member

05 RACGP SA Fellowship Preparation Program

06 RACGP SA Pre-exam Seminar

Welcome to the December issue of the RACGP SA&NT faculty e-news.

If you have any feedback on the content contained in this newsletter or would like to make a submission, the SA&NT faculty would love to hear from you.

Please feel free to email **sant.faculty@racgp.org.au**

Vaccine Safety Monitoring Study

The Discipline of Paediatrics, University of Adelaide is currently seeking GPs to participate in a research study on GPs' experiences of and opinions about vaccine safety surveillance. The primary method for monitoring vaccine safety in Australia relies on reports from healthcare professionals and the public. This study will examine GP views on vaccine safety surveillance.

Why is the research being done?

It is likely that at some stage in their careers, immunisation providers and other medical professionals will see an adverse event following immunisation (AEFI). The aims of this study are to describe and explain the knowledge, attitudes, practices and beliefs of medical professionals concerning the reporting of an AEFI and vaccine safety surveillance. It is hoped that this research will result in better understanding of the factors associated with reporting AEFIs and thereby help improve our vaccine safety surveillance system.

Who can participate in this research?

We are seeking GPs who regularly undertake consultations with children.

What would you be asked to do?

Your participation involves a face-to-face interview with the project researcher. Interviews will be held on site at your general practice at a time convenient for you and will take approximately 30–45 minutes. The interview will cover various issues relating to vaccine safety surveillance and will be recorded so that the conversation can be transcribed accurately. The researcher will ask you about your knowledge, views and experience of:

- reporting AEFIs
- postmarketing vaccine safety surveillance
- vaccine safety training.

For further information please contact Dr Michael Gold, **michael.gold@adelaide.edu.au,** Dr Helen Marshall, **helen.marshall@adelaide.edu.au** or Adriana Parrella, **adriana.parrella@adelaide.edu.au.**

For further information visit **www.racgp.org.au/sant** email sant.faculty@racgp.org.au or telephone 08 8267 8310

Appendix 11 Information Sheet, Healthcare Provider Study

Discipline of Paediatrics
School of Paediatrics and Reproductive Health
University of Adelaide, Adelaide, SA, 5005

Chief Investigator: Dr Michael Gold
Email: michael.gold@adelaide.edu.au

Project Researcher: Ms Adriana Parrella
Tel 8313 1412 Fax 8313 1406
Email: adriana.parrella@adelaide.edu.au

STUDY INFORMATION SHEET

"Vaccine Safety Monitoring Study - A study of passive reporting as a mechanism of post marketing surveillance"

Michael Gold, Helen Marshall, Annette Braunack-Mayer, Peter Baghurst, Adriana Parrella

The primary method for monitoring vaccine safety in Australia relies on reports from healthcare professionals and the public. This study will examine hospital healthcare provider views on vaccine safety surveillance.

Why is the research being done?
It is likely that, at some stage in their career, immunisation providers and other medical professionals will see an adverse event following immunisation (AEFI). The aims of this study are to describe and explain the knowledge, attitudes, practices and beliefs of medical professionals concerning the reporting of an AEFI and vaccine safety surveillance. It is hoped that this research will result in an understanding of the factors associated with healthcare provider reporting of AEFI and thereby help improve the vaccine safety surveillance system.

Who can participate in this research?
We are seeking medical professionals working in the Departments of Paediatric Emergency and General Medicine.

What would you be asked to do?
Your participation involves a face-to-face interview with the project researcher. Interviews will be held on site at the Women's and Children's Hospital, at a time convenient for you and will take approximately 30-45 minutes. The interview will cover various issues relating to vaccine safety surveillance and will be recorded so that the conversation can be transcribed accurately. The researcher will ask you about your knowledge, views and experience of:

- Reporting of AEFIs
- Post-marketing vaccine safety surveillance
- Vaccine safety training

What are the risks and benefits of participating?
There are no known or potential risks to participating in this study and we cannot promise you any benefit from participating in this research. Your participation is voluntary and you may withdraw your consent to participate at any time during the study.

How will your privacy be protected?
Any information collected remains confidential, that is:

- You will not be identified in any data collected
- Your interview data will only be accessed by the research team.
- Data will be stored on password-protected computer disks, and locked securely in the Discipline of Paediatrics for a minimum of 5 years.

How will the information collected be used?
Findings from this research study may be reported in medical journals and in a thesis by the project researcher. It may also be communicated to health professionals and researchers during conferences. You will not be identified in any publications/presentations arising from the project and you may request a copy of a summary of results.

Additional information
This study has been approved Dr Raftos (Paediatric Emergency). If you have any questions or would like more information on the research project please contact Dr Michael Gold or Adriana Parrella.

We thank you for considering participation in this research project.

Dr Michael Gold

The Research Team

Dr Michael Gold	Discipline of Paediatrics, School of Paediatrics & Reproductive Health University of Adelaide Head, Allergy and Immunology Women's & Children's Hospital Ph: 8161 7266
Prof. Annette Braunack-Mayer	Head, School of Population Health & Clinical Practice University of Adelaide Ph: 8303 3569
Dr Helen Marshall	Head, Paediatric Trials Unit School of Paediatrics and Reproductive Health Women's and Children's Hospital Ph: 8161 8115
A/Prof Peter Baghurst	Head, Public Health Research Unit Women's and Children's Hospital Children, Youth & Women's Health Service Ph: 8161 6935
Ms Adriana Parrella	Masters Medical Sciences Candidate, Discipline of Paediatrics & Public Health School of Paediatrics and Reproductive Health University of Adelaide Ph: 8313 1412

This study has been approved by: the Children, Youth & Women's Health Service Research Ethics Committee, Dr Wheaton, Head, Paediatric Division, Dr Raftos, Head, Paediatric Emergency and Dr Pearson, Head, General Medicine.

Should you have queries about the approval process or concerns about the manner in which the research is conducted, please contact the Secretary of the Committee, Ms Brenda Penny, Research Secretariat, ph 8161 6521.

Appendix 12 Consent form, Healthcare Provider study

ED Consultant Consent form example

CHILDREN, YOUTH & WOMEN'S HEALTH SERVICE (CYWHS)
HUMAN RESEARCH ETHICS COMMITTEE (HREC)

CONSENT FORM

STUDY TITLE

Vaccine Safety Monitoring Study - A study of passive reporting as a mechanism of post marketing surveillance.

I _____hereby consent to my involvement in the research project entitled:
Vaccine Safety Monitoring Study - A study of passive reporting as a mechanism of post marketing surveillance.

_____

1. I have received a copy of the study Information Sheet. The nature and purpose of the research project is described on the attached Information I understand it and agree to participate

2. I understand that I may not directly benefit by taking part in this study.

3. I acknowledge the possible risks, as outlined in the Information Sheet

4. I understand that I can withdraw from the study at any stage and that this will not affect any aspect of my relationship with this healthcare service.

5. I understand that there will be no payment to me for taking part in this study.

6. I have had the opportunity to discuss taking part in this research project with a family member, friend or colleague.

7. I am aware that I should retain a copy of the Consent Form, when completed, and the Information Sheet.

Please turn over

8. I consent to taking part in a 30-45minute face to face interview at a time convenient to me. I agree to the researcher contacting me by phone or email to negotiate a convenient time.

9. I consent to having the interview audio taped

10. The privacy and confidentiality of any information I provide will be safeguarded as explained in the Participant Information Sheet.

Full name of participant .....

Signed: .....

Dated:.....

Appendix 13 Interview Topic Guide, Healthcare Provider Study

Interview Schedule

Introductions
Purposes of the research.

Your experience of an AEFI
Tell me about an AEFI you have seen during the course of your work here or elsewhere.
Ask participant to
Describe the event, context.
What were you thinking when you observed the child
What happened?/How did it turn out?
Do you discuss AEFIs with your colleagues?

- **Reporting AEFIs**

With regards to the event you described earlier, did you report the AEFI?
Why/Why not reported?
How did you report it? Was it an easy/difficult process? Could you explain?
If you talked to an authority about the event what was the response from the person?

If you have never reported an AEFI, what do you think are the main factors that would lead to a doctor reporting an AEFI?
What would be your preferred format for reporting an AEFI? (ie phone call/ online reporting)
What do you think happens after an AEFI report is made?

- Is there a policy in your workplace for reporting AEFIs?

Thinking about the monitoring of vaccine safety
Could you describe your understanding of how vaccines are monitored for safety after they are released to the public?
How do you access communication regarding current vaccine safety issues?
Is there sufficient information available to you from surveillance authorities or other sources? Explain.
In your opinion, who should be responsible for monitoring the ongoing safety of vaccines?

What are your impressions of how vaccines are monitored for safety in Australia?

What strategies in your opinion should be employed for the monitoring of new vaccines? Should there be a difference in how new vaccines are monitored compared to existing vaccines?
Is there sufficient information on the safety of new vaccines?

From your experience, do you have any suggestions on how vaccine safety surveillance could be improved?

Your thoughts on vaccine safety training for healthcare providers
Tell me about any training you have had in vaccine safety either during your career or as a student.
Was the training and content adequate?
How do you update knowledge in vaccine safety?
From your experience, do you think doctors in general have sufficient training and knowledge in current vaccine safety issues?
What would be an ideal way to update or provide training?

Talking to parents about vaccine safety
How often do parents raise concerns about vaccine safety during your consultations?
What type of concerns do they have?
How do you respond to parents with concerns?

Interview Conclusion
The purpose of our interview today was to gain an understanding of AEFI reporting from a medical professional's perspective.
Is there anything you wish to talk about that we haven't covered or you wish to raise or comment on?

Appendix 14 Journal Publications

Parrella, A., Gold, M., Marshall, H., Braunack-Mayer, A. & Baghurst, P. (2013).
Parental perspectives of vaccine safety and experience of adverse events following immunisation
Vaccine, v. 31 (16), pp. 2067-2074

Parrella, A., Gold, M., Braunack-Mayer, A., Baghurst, P. & Marshall, H. (2014). Consumer reporting of adverse events following immunization (AEFI) Identifying predictors of reporting an AEFI.
Human Vaccines & Immunotherapeutics, v. 10 (3), pp. 747–754

Parrella, A., Gold, M., Marshall, H., Braunack-Mayer, A., Watson, M. & Baghurst, P. (2012). Parental views on vaccine safety and future vaccinations of children who experienced an adverse event following routine or seasonal influenza vaccination in 2010.
Human Vaccines & Immunotherapeutics, v. 8 (5), pp. 662-667

BMC Health Services Research

RESEARCH ARTICLE Open Access

Healthcare providers' knowledge, experience and challenges of reporting adverse events following immunisation: a qualitative study

Adriana Parrella[1,2*], Annette Braunack-Mayer[3], Michael Gold[1], Helen Marshall[1] and Peter Baghurst[1]

Abstract

Background: Healthcare provider spontaneous reporting of suspected adverse events following immunisation (AEFI) is central to monitoring post-licensure vaccine safety, but little is known about how healthcare professionals recognise and report to surveillance systems. The aim of this study was explore the knowledge, experience and attitudes of medical and nursing professionals towards detecting and reporting AEFI.

Methods: We conducted a qualitative study, using **s**emi-structured, face to face interviews with 13 Paediatric Emergency Department consultants from a tertiary paediatric hospital, 10 General Practitioners, 2 local council immunisation and 4 General Practice nurses, recruited using purposive sampling in Adelaide, South Australia, between December 2010 and September 2011. We identified emergent themes related to previous experience of an AEFI in practice, awareness and experience of AEFI reporting, factors that would facilitate or impede reporting and previous training in vaccine safety. Thematic analysis was used to analyse the data.

Results: AEFI reporting was infrequent across all groups, despite most participants having reviewed an AEFI. We found confusion about how to report an AEFI and variability, according to the provider group, as to the type of events that would constitute a reportable AEFI. Participants' interpretation of a "serious" or "unexpected" AEFI varied across the three groups. Common barriers to reporting included time constraints and unsatisfactory reporting processes. Nurses were more likely to have received formal training in vaccine safety and reporting than medical practitioners.

Conclusions: This study provides an overview of experience and beliefs of three healthcare professional groups in relation to identifying and reporting AEFI. The qualitative assessment reveals differences in experience and awareness of AEFI reporting across the three professional groups. Most participants appreciated the importance of their role in AEFI surveillance and monitoring the ongoing safety of vaccines. Future initiatives to improve education, such as increased training to health care providers, particularly, medical professionals, are required and should be included in both undergraduate curricula and ongoing, professional development.

Keywords: Adverse event following immunisation (AEFI), Surveillance, Healthcare provider, Reporting, Qualitative

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Full list of author information is available at the end of the article

Background

In Australia, the spontaneous reporting of adverse events following immunisation (AEFI) is the primary mechanism used for post-marketing passive surveillance (PMS) of licensed vaccines. Passive AEFI surveillance is common in many countries, worldwide [1-4]. The process relies on immunisation providers, health professionals, and consumers voluntarily submitting ad-hoc reports to jurisdictional public health and/or federal regulatory authorities [5]. Vaccine manufactures are mandated to report to the federal authority, the Therapeutic Goods Administration (TGA), and in four of the eight Australian states/territories, but not South Australia, health professionals are mandated by jurisdictional legislation to report to the local public health authority. At the federal level up until 2013, the Advisory Committee for Safety of Medicines (ACSOM), a subcommittee of the TGA was responsible for the ongoing evaluation of all drug and vaccine safety. As of 2013, in response to recommendations for an improved system of governance for vaccine safety monitoring [6], a new statutory Advisory Committee on the Safety of Vaccines (ACSOV) has been established to evaluate vaccine safety. Any medical events occurring after vaccination, that are regarded as "serious" and/or "unexpected" should be reported [7,8]. An established causal association with vaccination is not a pre-requisite for reporting [9].

Effective PMS is critical for a number of reasons. First, for new vaccines, pre-licensure clinical trials are not powered to detect rare adverse events that occur with a frequency of less than 1 in 1,000, or with delayed onset, and they are usually tested in homogeneous, healthy study populations [3,10]. Thus, PMS aims to identify potential safety signals which may require further investigation not identified in pre-licensure trials and that may become apparent outside the controlled conditions of clinical trials. Secondly, for established vaccines, PMS aims to monitor known adverse reactions and if the observed rate exceeds the expected rate, further investigation is required. Finally, PMS should detect program errors, such as incorrect vaccine administration or manufacture [11,12]. Hence, all licensed vaccines require specific pharmacovigilance plans that incorporate post-licensure passive surveillance and are "timely, efficient, sufficiently large and in place for the life of the vaccine" [11]. An example of the importance of voluntary reporting of suspected AEFI was demonstrated by the withdrawal of the Rotashield vaccine in the United States in 1999. Ten months post-licensure and following 1.5 million doses administered, 15 reported cases of intussusception, higher than expected to occur, signalled the need for suspension of its use and further evaluation of the vaccine [13].

Under-reporting is a known limitation of passive vaccine and adverse drug reaction (ADR) surveillance systems [12,14]. In Australia this is demonstrated by the marked variation of AEFI reporting rates across jurisdictions for the same vaccines [15,16]. The importance of and need for timely healthcare provider reporting of AEFI as they occur was highlighted by a recent Australian experience of a vaccine safety signal. On the 23rd April 2010, a seasonal trivalent influenza vaccine (STIV) for children aged less than 5 years was suspended nationally for three months due to an increased incidence of fever and febrile convulsions, [17] associated with the vaccine brand, Fluvax (CSL). In an analysis of AEFI reports submitted to the South Australian Department of Health in the first six months in 2010, the majority (71%) of influenza AEFI reports submitted by healthcare providers were received *after* the STIV program was suspended [18]. Subsequent reviews of AEFI surveillance in Australia following the STIV suspension have suggested that under-reporting and delayed reporting of febrile convulsions, contributed to delays in signal detection [6,19].

Healthcare professional AEFI reporting is an under-researched area, with only four studies conducted elsewhere, published to date [20-22]. All four studies employed quantitative methods to either measure awareness of surveillance, reasons for reporting or to compare actual AEFI reports by health professionals. The first examined Canadian family physicians' awareness of vaccine safety monitoring systems and reporting frequency for vaccine associated adverse events [20]. Less than half of the study respondents were aware of a monitoring system for AEFI, only one third knew of reporting criteria and only one in four had received vaccine adverse event education during medical training. The primary reason for not reporting was that an AEFI was never observed, the respondents did not know reporting was expected, the event did not seem serious enough or respondents were not aware of reporting procedures. Ranganathan et al. (2003) examined AEFI reports of Meningococcal serogroup C Conjugate (Men C) vaccine submitted to the Yellow Card Scheme (United Kingdom) by hospital doctors, General Practitioners (GPs) and nurses [22]. This study found nurses reported AEFI more frequently compared with GPs and hospital doctors and that completeness of the reports varied across the professional group. The third study of health professional AEFI reporting conducted in the United States included physicians, pharmacists, and nurses [21] and examined the frequency of reporting to the Vaccine Adverse Event Reporting System (VAERS), beliefs and awareness of AEFI reporting, barriers to reporting and strategies to increase reporting rates. Of all respondents, 71% had never reported an AEFI, with 17% indicating they were not aware of how to report. The study demonstrated significant differences in having ever reported an AEFI by

health professional type. Barriers to reporting included unclear definitions of a reportable AEFI, time pressures in completing a report, and confusion in whose responsibility it was to report. Reporting was associated with being alerted to look for specific events, discounting other explanations for the adverse event; observing the same AEFI repeatedly and whether the events occurred in vulnerable patient groups such as pregnant women, infants or patients aged ≥65 years. The fourth study is the most recent conducted to date and included family physicians, physician assistants, nurse practitioners, practice nurses and nurses working in paediatrics, family medicine and internal medicine [23]. The survey assessed demographics and professional characteristics and knowledge and attitudes toward identifying and reporting an AEFI to the Vaccine Adverse Event Reporting System (VAERS) in the United States. Although nearly three quarters of study participants were familiar with VAERS, only 14% were "very" or "extremely" familiar with the paper reporting procedure and approximately one third were not familiar when it was required to report an AEFI. Approximately 40% of all study participants had identified at least one AEFI, with only 18% indicating they had reported to VAERS. Respondents indicated they would report serious AEFI regardless of whether they were known (73%) or unknown (62%) to be associated with immunisation. Those who indicated that they were not familiar with submitting a paper report to VAERS were more likely not to report than those who were familiar with the process. Similarly, respondents who were not at all familiar with reporting criteria to VAERS tended not to report compared with those who were familiar with the requirements.

Studies of adverse drug reaction (ADR) reporting by health professionals have identified several factors that are common to under-reporting of AEFI. Ignorance of reportable events, lack of awareness of a reporting system, insecurity regarding causation (not possible to ascertain whether the drug caused the reaction) and lack of time are common reasons associated with lack of reporting [14,24-28]. Other factors not demonstrated in previous AEFI studies that have been associated with under-reporting of ADR include fear of litigation; indifference; lack of financial incentives to report and a belief that only safe drugs are released into the market [24,25]. Some parallels exist in adverse medical incident reporting studies. These studies reveal parallel differences in reporting behaviour between medical specialties where nurses are more likely to report to internal incident reporting systems than doctors and 'the fear of blame' as a common barrier to reporting by doctors [29-31].

Consumer perceptions and experience of health professional ADR reporting have demonstrated concern that health professionals' lack of clarity in recognising adverse medicine events prevents reporting of potential adverse events [32,33]. Two recommendations arising from a meeting of the Consumers Health Forum of Australia (CHF) in June 2011 were to improve and encourage adverse event reporting processes through training and education for health professionals [34]. These recommendations are echoed in a national review of Australian AEFI surveillance following the 2010 STIV safety signal to increase both consumer and health professional awareness of AEFI reporting and to improve communication and notification of AEFI between jurisdictional and federal health authorities [6].

It is likely that differences in healthcare provider AEFI knowledge and practice of reporting results in inconsistent adverse event data collection and, ultimately, inaccurate measurement of the incidence of vaccine adverse events, by delaying or missing important vaccine safety concerns [35]. Since spontaneous reporting is central to passive vaccine PMS and given that health professionals provide the majority of AEFI reports to surveillance systems [36], it is important to understand not only the factors such as awareness of and frequency of reporting, but also how health professionals identify/conceptualise a reportable AEFI. This paper presents results of a qualitative study that aimed to determine how healthcare providers identify and report AEFI within the South Australian context.

Methods

Design

Following a review of key findings from existing literature on AEFI and ADR reporting as described above and information obtained from a study of parent AEFI reporters we had previously conducted [37], we chose to adopt in-depth qualitative interviews for the study design as it was most suited to our research questions: What are the experiences, awareness and knowledge of healthcare providers in AEFI reporting and how do healthcare providers conceptualise a reportable AEFI? These questions and the associated study design are consistent with a social constructionist paradigm in qualitative research, enabling the interviewer to make meaning of each participant's "world", their individual perspectives and meanings in a context that is shaped by their organisational environment and broader social structures [38].

We chose to conduct individual, face to face interviews as appropriate to examine each participant's specific experience and understandings of AEFI and because it was most suited to participants' work schedules. The interviews were conducted with the General Practioners (GPs) and Paediatric Emergency Department (PED) consultants, between December 2010 and February 2011. Based on preliminary analysis of the interview data, it

was recognised that nurses also played an important role in AEFI reporting, and a further six interviews were conducted with two local council immunisation and four general practice nurses in September 2011.

Recruitment

We recruited twenty-nine healthcare professionals from an Emergency Department of a tertiary, paediatric hospital, GP clinics, and local council immunisation clinics in Adelaide, capital city of South Australia (population 1.6 million). Characteristics of participants are presented in Table 1. Purposive sampling was used to identify participants for the study [39]. The participants recruited in each category (see Table 1) represented a range of health professionals who were in a position to detect, manage and/or report an AEFI. The PED consultants were recruited via the Emergency Department with initial information about the study communicated to participants via the head of Emergency. All consultants except one agreed to participate. We used three strategies to recruit the GPs including contacting potential participants via professional (university research academics and clinical) contacts of the authors, advertising via an electronic distribution mail list of the local branch of the Royal Australian College of General Practitioners and finally via electronic communication within an academic organisation involved in training general practitioners. The study nurses were recruited via contacts of the authors, the general practice clinics involved in the study, and via the local Department of Health Immunisation Section.

Topic Guide

The semi-structured, open-ended interviews were conducted using a topic guide (see Table 2). The original interview schedule was developed from a review of key findings of literature surrounding AEFI and ADR reporting as described earlier. Each interview sought to explore participants' knowledge and experience of detecting, managing and reporting an AEFI; factors that would facilitate or impede AEFI reporting; understanding of AEFI surveillance and previous training in vaccine safety. All interviews were conducted at participants' workplace, ranging from 25 to 65 minutes.

Ethical considerations

Participation was voluntary and signed, informed consent was obtained before conducting the interviews. The study was approved by the University of Adelaide and Children Youth and Women's Health Service (CYWHS) Human Research Ethics Committees. This study adhered to the qualitative research review guidelines (RATS) [40].

Analysis

Each interview was audio-taped and data transcribed verbatim by AP. Thematic analysis was used to structure analysis of the transcripts [41] with NVivo, version 9 (QSR International, UK). Initially, open coding of interview data was undertaken. These codes were generated inductively from participants' descriptions of their experiences in responding to and reporting an AEFI, and awareness of vaccine safety surveillance. Following initial coding of transcripts, preliminary themes that captured information relevant to the research questions were generated. This process involved identifying patterns in the data: recurring ideas, perspectives and descriptions that depicted each participant's context and perspective. The final analysis for this study focussed on key themes, narratives, and professional histories emerging from the interviews. Data concordance was verified by AP and ABM, a trained qualitative researcher with extensive experience in medical and public health qualitative research. Key themes were discussed with the research team that included two clinicians with expertise in vaccine safety and surveillance (HM and MG) at regular team meetings. We achieved topical saturation as similar themes emerged from various participants from each professional group after preliminary analysis of initial interviews. Quotes that best illustrate important representation of participants' views and experiences identified through our iterative process of review and discussion are presented in the following section.

Results

Previous experience of an AEFI and reporting

Most participants (27/29) reported seeing or being involved in the care of children or adults with a suspected AEFI, in their current or previous workplace. The cases included children presenting with suspected hypotonic hypo-responsive events, anaphylaxis, febrile convulsion, non-febrile convulsions, extensive limb swelling, high fevers and skin rashes (reported as allergic events). Although participants described experience of at least one AEFI throughout their career, most stated they were

Table 1 Study participants

Professional group	Female	Male	Age range (years)	Mean number of years worked in professional group
Nurse	6	0	31-53	19
Paediatric Emergency Department specialist	6	7	35-57	15
General Practitioner	8	2	40-57	21

Table 2 Interview topic guide

Theme	Guiding question
Experience of an AEFI	1. Could you tell me about an AEFI you have seen during the course of your work?
	2. How often have you seen an AEFI in this workplace or during your career?
	3. How did you respond to the AEFI?
	4. How did the event turn out?
Reporting an AEFI	1. Have you ever reported an AEFI? Why?
	2. How have you reported?
	3. Was it an easy/difficult process? Could you explain?
	4. If you talked to an authority about the event what was the response from the person?
	5. If you needed to report an AEFI today how would you do it?
	6. What do you think are the main factors that would lead you to report an AEFI?
	7. Why would you report an AEFI?
	8. What would you not report as an AEFI?
	9. What would be your preferred format for reporting? Why?
Workplace	1. Can you tell me about whether AEFI are discussed with your colleagues?
	2. Could you describe any policy/protocol for reporting an AEFI in your workplace?
Surveillance	1. Could you describe your understanding of how vaccines are monitored for safety after they are released to the public?
	2. Who do you think should be responsible for monitoring vaccine safety in Australia?
	3. How do you access communication regarding vaccine safety issues?
	4. Is there sufficient information available to you from surveillance authorities or other sources? Explain.
	5. In your opinion, who should be responsible for monitoring the ongoing safety of vaccines?
	6. What do you think happens after an AEFI report is made?
	7. What is your impression of how safety is monitored?
Training	1. Could you tell me about any training you have had in vaccine safety either during your career or as a student?
	2. How do you update your knowledge in vaccine safety?
	3. What would be an ideal way to update or provide training?
	4. Do you think doctors and nurses have sufficient training and knowledge in current vaccine safety issues? Why?

"rare" or "not that common", and occurred "years" prior to the interview. The most recent events recalled were febrile convulsions following STIV vaccination in 2010 and a "severe local swelling" in the week prior to the study interview.

> *"I haven't had a lot of adverse reactions at all. They're quite rare actually. If you think of the number of kids we vaccinate. I've had lots of local reactions but I don't recall off the top of my head any significant."* GP 9

> *"We'd still be seeing the reactions rather than but no, not very common at all. Even less since we've used the acellular vaccine, even less."* GP 7

Of all participants, 19/29, (7 GPs, 5 nurses and 5 PED consultants), indicated they had reported an AEFI to a surveillance system at some point in their career, either in Australia or overseas. Only two participants stated they had reported more than once, despite the fact that most had worked for many years in the health system (a mean of 18 years for all three groups). When asked to recall when they had reported, a common response was in the distant past, with some as far back as "fifteen or twenty years ago."

> *"That one with the measles I would have reported. I think there was a couple of others too but it's going back a long way."* GP 7

Awareness of reporting

All nurses were familiar with paper and telephone reporting procedures to the local Department of Health and also described their workplace reporting processes, such as having the report forms on hand and/or an existing protocol for reporting adverse events (Table 3). Six of the thirteen PED consultants (46%) stated they were not aware of a system for reporting or how to report an AEFI.

Table 3 Participants' awareness of AEFI reporting protocol or policy in their work setting

Nurses	General practitioners	ED consultants
If we see an adverse event, then we do report. We have the forms for reporting. (General Practice nurse)	I think I would say that you know the majority that would be 99%, is done by our nurse and would probably only get reported from the nurse	I'd have to double-check. I'd have to ask a colleague
I would say there's one in the policy manual. (General Practice nurse)	No I don't know that there is one here actually.	We can just click on forms, adverse events reporting form and just print it out, so that's what we do.
The forms are in our filing cabinet. But I know you can get it from SAICU and I know it's on their website. We're actually in the process of doing a procedure, protocol. (General Practice nurse)	I would say there wouldn't be anything completely formal that we've ever discussed at a meeting or anything. I don't think there's ever been a formal policy. No.	*Not answered*
Not actually in writing but because I'm the only one here generally, anything that's out of the normal goes past me anyway. We always keep a copy of them (the adverse event reporting form) at the clinics. (Council immunisation nurse)	Not that I'm aware of. There may be, but not sure.	I don't really know because I've never had to do it because obviously it's quite rare.
I do the reporting and advise the doctors that I've done that as well. If we do any written documentation it's always scanned into the notes too. (General Practice nurse)	No actually we don't as far as I know have a policy. Probably we should, but no we don't.	I would have to look at information on our intranet that has information about reporting adverse reactions to vaccines and remind myself how to do it.
It is in our standard operation procedure that we do have that, if an adverse event occurred, it just says fill in a form. (Council immunisation nurse).	Well our practice nurse looks after all these things and she would report.	I remember looking up a number probably from the Immunisation Handbook.
	No not specifically. There hasn't been a designated discussion about what we do about these things when they occur.	I don't think so. I'm not familiar with a documented protocol as such.
	There's those blue forms.	I'd have to ask one of the other consultants what the procedure was, because I don't currently know.
	Not formal, but we know to report to ADRAC.	We've got it on our web on our intranet there's links to it. The numbers there or you make the notification or you just fill it in and send it off.
	I'd have to see what the protocol was, but we haven't had one for so long	Reporting would not be protocolised.
		We've got the blue forms. We fill in the blue forms and send them off.
		No, there is no protocol

"I would probably have to ask my colleagues how to do it." ED 4

"I'd have to ask one of the other consultants what the procedure was, because I don't currently know." ED 9

Two GPs were not aware of how to make a report, even though one stated having reported previously. The second GP had previously diagnosed an AEFI which would have been reported, had she known of a reporting system.

"I found it difficult to try and find out where I was meant to report and then due to competing demands didn't seek further information." GP 5

For those who indicated awareness, reporting was thought to occur generally either via the national adverse drug reporting system or the local Department of Health. Few participants indicated awareness of both national and local reporting systems. We found participants were generally confused about the various reporting options and unaware that reports could be notified via phone, postal, fax, electronic or online submission.

"It would be helpful if the practice nurses could report on my behalf." GP 10

"It would be nice to have a number, a telephone number with who to go to. That's the sort of thing we probably need with adverse events to vaccines." GP 6

When describing awareness of workplace policies, participants were also prompted to describe whether AEFIs were discussed during the course of their work. If an AEFI was discussed in the various workplace settings, it

would usually occur informally with colleagues if a patient presented with symptoms that were unusual or serious. For example, in the hospital setting, around the time of the influenza safety signal in 2010, the ED consultants recalled informal discussions with colleagues of febrile convulsion cases presenting to the ED. The nurses would discuss cases that were "out of the norm".

"We do discuss it between us quite a lot if you get something quite a bit different. You know such and such happened have you had that happen with yours or are you aware of that being anything? So we do usually discuss it amongst ourselves." GP 6

"We tend to talk about things that happen. If it was something serious I think generally we would discuss those things." GP 7

Recognition of a reportable AEFI

Participants were asked to describe the types of events they would consider necessary to report. All stated that a reportable AEFI was an event characterised as "serious" and/or "unexpected". Reactions were generally considered serious if they were life-threatening (such as anaphylaxis); clinically significant or severe (for example, convulsions); and/or relevant to the patient's future vaccinations, because of the potential impact on future vaccination decisions.

"I've never seen an anaphylaxis. I've never seen a hypotonic reaction. I've never seen anything I would classify as serious. Ever. I've never seen an AEFI that I've had to report." GP 3

"Most of the cases that present actually aren't significant events. So, that would be the usual fevers following vaccinations or localised reactions. Few actually meeting the criteria for being significant. I've not seen anyone with an anaphylaxis." ED 9

Two underlying interpretations were evident when participants described an "unexpected" AEFI. In the first instance, "unexpected" referred to an event that was rare, but with a known (but low) probability of occurring, such as anaphylaxis. These were regarded as unexpected because they were more severe and less common than the "normal" vaccine reactions.

"Beyond the reasonable in terms of you know what you would expect. It's obviously more severe." Nurse 3

When compared by professional group, all GPs and nurses would report this type of unexpected AEFI, (severe or rare, but previously recognised), whereas only half of the PED consultants explicitly stated or implied this. Discussion regarding febrile convulsions illustrated a difference in interpretation of "unexpected" across the groups. Most PED consultants stated that they had managed children who had experienced febrile convulsions in relation to influenza vaccination in 2010; however, only three could recall reporting this as an AEFI. When discussing the 2010 safety signal and opinions of why febrile convulsions were not reported, several reasoned that they are a known AEFI, that the children had experienced relatively minor convulsions, and that only prolonged convulsions that were "clinically significant" should be reported.

"I guess you know we saw a number of children not long after the vaccine was released with febrile, apparent febrile reactions to the vaccine who didn't appear to be particularly otherwise unwell. I guess febrile reactions to vaccines are relatively common, that we weren't particularly perturbed about it at all until there were reports of children becoming quite unwell and having prolonged convulsions and there is significant morbidity associated with those, particularly interstate. I'm not sure whether there were terribly many in Adelaide." ED5

The PED consultants tended to describe as reportable only those events that were very severe or life-threatening, often referred to as "clinically significant" or "dangerous."

"I think it has to be a very significant event… where it's well above the normal thing and potentially quite dangerous." ED 6

The second meaning attributed to "unexpected," was a reaction that was not known to occur following vaccination. This type of AEFI would be reported because there was no established scientific evidence available that connected it to a vaccination.

"If a child came back the next day or a week later and had an illness or an event that I couldn't in my mind relate necessarily to the vaccine then yes I would." GP3

In addition to serious and unexpected reactions, some participants considered all adverse events occurring following newly released vaccines should be reported. Three participants stated all reactions, regardless of severity, should be reported.

"Well I guess theoretically any reaction to a vaccine should be notified, even if it's a minor reaction. The flu

vaccine was a good case in that although we saw the children as having relatively minor febrile reactions to the vaccine there was obviously children who were having more severe end of the spectrum reactions associated with fever, so it's a good illustration that probably any reaction to a vaccine should probably be notified." ED 1

"I think any adverse event no matter how little or large needs to be reported." Nurse 2

Barriers to reporting

When discussing vaccine safety surveillance, most participants stated the critical role of healthcare providers in reporting AEFI but also recognised the limitation of passive surveillance of relying on healthcare providers to report.

"If you don't have reports you don't know how it's going out there in the arena, do you?" Nurse 6

"Well I think everyone involved in administering vaccines which includes GPs and nurses and anybody seeing people. So, it's really, all of us have to play a role." GP 4

"It seems to be more clinical adverse reactions are heavily dependent on the clinician reporting them." ED 10

"There's a lot of assumptions made. We're assuming someone's going to tell us and then we're assuming that we're going to notify someone else when we find out." GP 9

Although reporting by health professionals and the public was understood as key to monitoring AEFI, two participants did not believe they shared responsibility for AEFI surveillance.

"Not me. I don't know. There's probably some immunisation body.

The only way you're going to know that there's some problem with a vaccine is if people are going to report significant events post –vaccine. And then someone else can sort it out." ED3

"I think it should be a government department because it's a public health issue." GP5

The amount of information required in completing a report, time constraints, competing workplace priorities in the workplace and dissatisfaction with reporting methods were identified as barriers to reporting by the GPs and PED consultants. By contrast, the nurses did not describe any of these barriers.

"Busy clinicians really don't have time to sit down and fill out several pages of report form." ED 1

"The reporting system is too difficult. The only way I want to report anything is automatically through my software." GP4

Preferred format for reporting

Participants' preferences for a preferred format for reporting an AEFI varied across the three professional groups, and covered the current options for paper, phone, fax and electronic reporting. The nurses preferred either the phone or paper reporting, the GPs, phone or web-based reporting and the PED consultants varied in their opinions, stating paper/fax, phone and electronic formats. The phone was often stated as a convenient method for communicating and receiving immediate feedback/response with an immunisation professional. Paper reporting was believed useful to have a record or "trail" of communication with the local Department of Health and for the purpose of having patients' events recorded with their medical history.

"I prefer phone because I can ask questions for myself, as for if there was any correlation. So I'm reporting the incident but also following-up the information for myself or for the patient." Nurse 3

When discussing ideal electronic formats, GPs and PED consultants suggested creating systems that were linked to their workplace systems/practice management software and allowed for automatic submission.

"With electronic, particularly if there is a system built into your database using emergency as an example, if there is a reporting form built into the system so that it's prepopulated with demographic data and all you need to do is click some boxes, the form would be sent in automatically." ED 5

Training

All nurses had received some formal training in vaccine safety and AEFI reporting, such as Division of General Practice, Department of Health workshops, or post-graduate university training for immunisation providers. Most of the GPs and PED consultants could not recall specific training either pre- or post-graduation. All GPs and most PED consultants believed that, in general, doctors' pre-service education in vaccine safety and adverse event reporting was inadequate.

"I can't remember having any specific training on immunisations or reporting and adverse reactions. It's just assumed that we have obtained that knowledge somewhere rather than actually having a specific study or certification in vaccine." ED 8

"I would have to say I don't think I had any training as a student at all. Or at least can't recall it. I can't remember hearing anything about vaccinations in medical school apart from sick people with COPD need vaccinations but nothing about the vaccines or safety." GP 5

All participants supported strategies for updating knowledge via the continuing medical education programs of their relevant professional accreditation organisations.

Discussion

This is the first qualitative study, to our knowledge, that explores healthcare provider AEFI reporting awareness, practices and attitudes. We found reporting was infrequent across the three groups interviewed and conflicting views between groups as to what events would constitute an AEFI. Potential reasons for this could be that an AEFI occurs infrequently; that an AEFI is not recognised as such; and/or that an AEFI is recognised, but not reported. Our results show events which were either completely unexpected (that are not known to occur following vaccination), or which might represent an increase in expected reactions were less likely to be reported.

This study has shown that the requirement for all "serious" events to be reported to authorities, regardless of whether they were causally related to the vaccination, was interpreted differently amongst participants and by professional group. All participants would report the most severe events, often termed "life-threatening," or "dangerous." However, we found from the PED consultant interviews that, on the whole, they would only report events that were perceived as "life threatening." Compared with the nurses and GPs, they were less likely to report other events that were not as severe and those that are a known AEFI. The under-reporting of febrile convulsions following STIV in April 2010, could possibly be an illustrative example. Based on these interviews, we could reason that the PED consultants did not report febrile convulsions because this is a known complication of immunisation associated with fever. Taken together with the belief that most of the children they treated had experienced minor, (or not clinically significant) convulsions illustrates their differing interpretation of "serious" compared with GPs and nurses. Possibly, working in an environment in which one regularly sees serious and life-threatening presentations, compared with other settings, such as an immunisation clinic or family physician's workplace, increases a hospital emergency doctor's threshold for the definition of "severe" or "serious" and, therefore, what would be reported. Viewed in this light, under-reporting can be explained partly by the varied interpretation of what constitutes an AEFI.

The context of the workplace setting in this study is important to consider in relation to understanding factors that might influence a health professional's decision to report an AEFI. We did not seek information from each work setting involved about whether in fact there was an established policy or protocol for reporting. However, from the interviews we conducted, it was apparent that reporting was an established norm for immunisation nurses in local council clinics, as a council nurse's core work is providing immunisations to the public. Having report forms at hand and documented protocols for AEFI reporting facilitated reporting in such settings. We suggest there are three possible explanations for the variations in awareness of participants from the general practice and hospital settings (Table 3). First, it may be that there was no current policy in place. Second, if a policy existed, it had not been introduced or established effectively within the workplace. For example, in the hospital setting, the ED consultants did have access to the local Department of Health reporting form via the internal intranet; however, few indicated awareness of it during interviews. This would suggest a need to ensure staff are informed and updated about accessing the reporting link. Given that the study occurred less than 12 months after the safety signal associated with the seasonal influenza vaccine and subsequent relay of public health alerts to hospitals and primary healthcare settings regarding the occurrence of febrile convulsions and need to report, it was surprising that there were such low levels of awareness. A third explanation for low levels of awareness amongst the GPs and ED consultants could be that reporting was not seen as a prime function of medical staff and might be delegated to nursing or administrative staff. Apart from one GP who indicated that the nurse at his practice would be responsible for reporting as part of her role in immunising patients, we found no evidence of delegated reporting amongst the GPs. In the ED setting, delegating the reporting to a registrar who was undertaking an ED rotation was described by some consultants and hence could explain their unfamiliarity with the actual processes of reporting, regardless of whether it was to local or national surveillance authorities. In this context one could speculate that reporting was not seen as a primary function of the clinician, but rather an administrative function to be performed by non-medical staff or, as in the ED setting, junior medical staff.

Despite the limitations of passive surveillance, it is not likely to be replaced by alternate methods of surveillance that do not rely on healthcare professionals' awareness or readiness to report, such as data linkage [42-44]. Passive surveillance should monitor vaccine safety and detect safety signals in real time or near-real time. Alternate methods of surveillance such as data linkage or sentinel surveillance are usually used to detect known events and to test hypotheses for associations between a vaccine and an AEFI [45] but are limited by timeliness of reporting. Thus, there is an ongoing need for robust passive AEFI reporting systems. From this study it is clear that, even if an AEFI is recognised, there are significant barriers to reporting by health care providers. These barriers are consistent with factors identified in previous studies of AEFI and ADR reporting [20,21,24] and include a lack of awareness or confusion about reporting systems, a lack of time to report and differing perceptions of a reportable AEFI. Unlike other studies, we did not find evidence about fear of litigation, or that vaccine adverse events are not reported because of inherent trust that licensed vaccines are all safe [24].

Few participants in this study were aware of both local and national reporting processes. Future research should explore whether a single pathway for AEFI reporting may be preferred by healthcare providers, rather than the existing system which provides a choice between reporting to the local Department of Health within each Australian jurisdiction or the national body (TGA). We also found differing preferences for the varied methods of reporting. In addition to these barriers, under-reporting may in part be attributed to the administration of less reactogenic vaccines in more recent years that has resulted in lower occurrence of some reactions. This would result in less awareness of reporting, as practitioners are less likely to be familiar with a system if they do not need to use it. However, this would not explain the differences in awareness across the three professional groups, as nurses were more familiar with both reporting processes and specific workplace protocols for reporting.

We found the nurses were more likely than the doctors to have received formal training in vaccine safety surveillance, which generally occurred as professional development training. This finding is consistent with previous published studies that reported low levels of vaccine safety education during medical training in Europe and Canada [20,46] and an unpublished, cross-sectional survey of 452 GPs, GP nurses, midwives, paediatric and community nurses, conducted in Sydney, Australia [47]. Our study confirms a need to provide adequate education across healthcare providers' training, both pre- and in-service, which has been recognised internationally [46,48]. Adverse event reporting should be incorporated in continuing medical education programs.

The strength of this study lies in its qualitative approach. This format allowed participants to provide detailed accounts of their experiences and understanding of AEFI and reporting system. We were also able to sample participants from different work settings and professions. However, there were some limitations that may affect the generalisability of our findings beyond this study. Firstly, our participants all came from the one jurisdiction, and their responses may have been shaped by the organisational context for reporting of AEFI in that jurisdiction. Second, we acknowledge that participants in this study self-selected to participate and may provide an element of responder bias, since more motivated individuals or those with an interest in immunisation may have participated. However, we expected that responder bias would have been associated with greater familiarity with AEFIs and reporting systems than was evidenced in our study. Third, most participants had completed undergraduate training decades previously and this may have influenced their recall of adverse event training.

Our findings support the recommendations of the two reviews into AEFI surveillance in Australia, which were initiated because of the occurrence and delayed detection of febrile convulsions post STIV in 2010. Both reviews highlighted deficiencies in healthcare provider reporting [6,19] and recommend a need to improve AEFI detection and reporting by introducing strategies aimed at increasing awareness of national reporting and strengthening communication within the surveillance system. Future research that would inform strategies to improve AEFI reporting should aim to include the perspectives of workplace managers and surveillance authorities as key informants.

Conclusion

Although the majority of participants had observed an AEFI in clinical practice and understood the importance of their role in AEFI reporting for post-marketing safety surveillance, we found reporting was infrequent. Reporting was related to the perceived interpretation of a reportable AEFI. The current guideline of reporting "serious" and "unexpected" events was interpreted differently in the three work settings and this would suggest there needs to be clearer definition and guidelines about reportable adverse events. Barriers to reporting included lack of time and knowledge of reporting processes. To test the magnitude of these factors, further research should be conducted among a larger representative group of healthcare professionals across Australia.

The participants' recall of training in vaccine safety suggests that there is a need to increase education and training in vaccine and drug adverse events and current reporting methods, at both undergraduate and postgraduate

levels, particularly for medical professionals. Specific strategies for updating knowledge should be implemented via the professional relevant accreditation bodies and continuing medical education programs.

The surveillance system and its methods for reporting should be easy to access, widely promoted and "user friendly" to both health professionals and consumers with formats for reporting designed so that the system is accessed effectively in different work settings. The limitation of any passive surveillance system is the submission of reports and the barriers identified in this study should be addressed as the Australian system is strengthened.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
AP with the supervision of MG, ABM and HM developed the study design, performed the data collection, data analysis and wrote a draft manuscript. ABM assisted in data analysis. The drafts of this article were revised critically by all authors. All authors have contributed to the draft and approved the final version of the manuscript.

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