

Adverse events following immunisation (AEFI): Optimising passive surveillance to improve immunisation safety in Victoria

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Abstract

Vaccines are a cornerstone of public health saving millions of lives each year, however, adverse events following immunisation (AEFI) are a reality. Comprehensive post-licensure vaccine safety surveillance is therefore essential to maintain confidence in immunisation, inform policy and ensure the ongoing safety of immunisation programs.

Vaccine pharmacovigilance in Australia has been criticised and found inadequate due to its inability to inform on vaccine safety events in a timely manner. In 2010 this meant failure to prevent serious neurological sequelae arising from increased febrile reactions with one particular brand of influenza vaccine. Subsequent expert reviews of Australian AEFI surveillance proposed the Victorian state-level enhanced passive surveillance system “SAEFVIC” as a potential model system, with suggestion to expand to jurisdictions that did not have robust AEFI surveillance. However, despite this recommendation, no evaluation of SAEFVIC’s ability to provide effective vaccine pharmacovigilance had been undertaken.

My doctoral research evaluates “SAEFVIC”, the Victorian AEFI surveillance system’s ability to detect and investigate emergent vaccine safety issues with the findings presented in a range of publications and discrete reviews. Within this thesis I have developed real-time investigation of vaccine safety issues, which have informed policy decisions on immunisation program delivery and ensured community confidence. Description of the system epidemiology provides a foundation for research integrity. Individual studies have identified opportunities for improvement and guided amendments to data collection to better inform on at-risk populations.

I explored and applied a simple, feasible and replicable measure of disproportionality for signal detection enabling implementation of routine signal detection. The establishment of contemporary reporting and visualisation has contributed to national expansion of SAEFVIC as an integrated surveillance platform, markedly increasing national capability to provide “comprehensive and effective post-licensure AEFI

surveillance critical to maintain confidence in immunisation and inform evidence-based policy for vaccine safety”.

My research has provided the evidence-base to optimise the SAEFVIC passive AEFI surveillance system and—through translation of the findings into policy and practice—helped consolidate Victoria as a leader in Australian AEFI surveillance, a major southern hemisphere partner in global AEFI surveillance and ultimately made immunisations safer.

The timeliness of my doctoral thesis has become prophetically pertinent in the midst of the 2020 global Coronavirus SARS-CoV-2 crisis, with calls for development and release of novel vaccines at “pandemic speed”, highlighting the need for robust and timely vaccine safety surveillance.

Declaration

This is to certify that:

- I. The thesis comprises only my original work towards the PhD, except where indicated in the Preface
- II. Due acknowledgment has been made in the text to all other material used.
- III. The thesis is fewer than 100,000 words in length, exclusive of figures, tables, maps, bibliographies and appendices.

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Hazel Clothier

1 May 2020

Preface

Within this thesis, I present nine peer-reviewed published first author papers (with multiple co-authors) within thesis chapters. Ten first author conference presentations (oral or poster) are listed on page vii with abstracts, presentations or posters provided in Appendix 2. Additionally, five peer-reviewed publications and six conference presentations that I co-authored during—and relevant to—my PhD are listed on page ix.

Each publication included in this thesis were initiated and written by me. I conducted the literature search, analyses and writing for each of the papers. Co-authors of the papers provided assistance with the analytical design, interpretation of the results and editing of manuscript drafts. Jock Lawrie provided specific support for transformation of data into Microsoft PowerBI that enabled me to perform statistical analyses of proportional reporting ratio across multiple vaccine-adverse event pairs. As such, I have provided authorisation forms from each co-author of published manuscripts, as well as a declaration of collaborative work from my principal supervisor (MR). All work included in this thesis was carried out after my enrolment as a higher degree research student.

I acknowledge the Australian Government for awarding me an Australian Research Trainee Scholarship for the duration of the studies.

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Publications & presentations

First author publications arising from this thesis:

1. **Clothier HJ et al.** Surveillance of adverse events following immunisation in Victoria (SAEFVIC), Australia, 2018. *Communicable Diseases Intelligence*, 2020; 44(2):1-27
2. **Clothier HJ et al.** Early signal detection of adverse events following influenza vaccination using proportional reporting ratio, Victoria, Australia. *PloS ONE* 2019; 4(11) e0224702
3. **Clothier HJ et al.** Human papillomavirus vaccine in boys: background rates of potential adverse events. *Medical Journal of Australia* 2013; 198(10):554–8
4. **Clothier HJ et al.** Bacillus Calmette-Guerin (BCG) vaccine adverse events in Victoria, Australia: analysis of reports to an enhanced passive surveillance system. *Drug Safety*, 2015; 38:79-86
5. **Clothier HJ et al.** Allergic-related adverse events following seasonal influenza containing vaccines, 2015. *Euro Surveillance*, 2017; 22(20):pii=30535
6. **Clothier HJ et al.** Adverse events following vaccination of older people may be under-reported. *Medical Journal of Australia* 2017; 207(7):301-302
7. **Clothier HJ et al.** Evaluation of “SAEFVIC”, a pharmacovigilance surveillance scheme for the spontaneous reporting of adverse events following immunisation in Victoria, Australia. *Drug Safety* 2017; 40(6):483-495
8. **Clothier HJ et al.** Consumer reporting of adverse events following immunization. *Human Vaccines and Immunotherapeutics*, 2014; 10:3726-30
9. **Clothier HJ et al.** SAEFVIC: Surveillance of adverse events following immunisation (AEFI) in Victoria, 2012. *Victorian Infectious Diseases Bulletin*. 2014;17(1): 2–8

First author conference/symposium presentations

Oral presentations

1. **Clothier HJ et al.** Volume counts: investigating a spike in serious adverse neurological events following immunisation. Accepted *Public Health Association Australia Immunisation Conference, Perth, June 2020*
2. **Clothier HJ et al.** Improving vaccine safety surveillance using business intelligence software: Victoria, Australia. *New Zealand Immunisation Conference, Auckland, September 2019*
3. **Clothier HJ et al.** SAEFVIC: Impact of implementing enhanced passive surveillance for adverse events following immunisation. *Public Health Association Australia Immunisation Conference, Adelaide, June 2018*
4. **Clothier HJ et al.** Allergic-related adverse events following seasonal influenza containing vaccines. *Public Health Association Australia Immunisation Conference, Brisbane, June 2016*
5. **Clothier HJ et al.** Consumer reporting of adverse events following immunisation. *Public Health Association Australia Immunisation Conference, Darwin, June 2014*
6. **Clothier et al.** Partial tip, unknown iceberg: adverse events following immunisation with BCG vaccine. *Australian Society of Infectious Diseases Conference, Canberra, May 2013*
7. **Clothier HJ et al.** Human papillomavirus vaccine in boys: background rates of potential adverse events. *Australian Society of Infectious Diseases Conference, Canberra, May 2013*

Invited expert panel representative

Vaccine Safety Symposium, National Centre for Immunisation Research and Surveillance, Sydney, 2014

Poster presentations

1. **Clothier HJ et al.** Examining the relationship between AEFI reporting and vaccine coverage. *Public Health Association Australia Immunisation Conference, Adelaide, June 2018*

2. **Clothier et al.** Partial tip, unknown iceberg: adverse events following immunisation with BCG vaccine. *Australian Society of Infectious Diseases Conference, Canberra, May 2013*
3. **Clothier HJ et al.** Human papillomavirus vaccine in boys: background rates of potential adverse events. *Australian Society of Infectious Diseases Conference, Canberra, May 2013*

Co-authored publications and presentations

Peer-reviewed research publications

1. Baxter CM, **Clothier HJ**, Perrett KP. Potential immediate hypersensitivity reactions following immunization in preschool aged children in Victoria, Australia. *Human vaccines & Immunotherapeutics*, 2018; Apr 6:1-5.
2. Littlejohn ES, **Clothier HJ**, Perrett KP, Danchin M. Surveillance of adverse events following the introduction of 13-valent pneumococcal conjugate vaccine in infants, and comparison with adverse events following 7-valent pneumococcal conjugate vaccine, in Victoria, Australia. *Human vaccines & Immunotherapeutics*, 2015; 11:1828-35.
3. Crawford NW, **Clothier HJ**, Hodgson K, Selvaraj G, Easton ML, BATTERY JP. Active surveillance for adverse events following immunisation. *Expert Rev Vaccines*, 2014 Feb; 13(2):265-76
4. Martin TJ, Crawford NW, **Clothier HJ**, Fahey M, BATTERY JP. Acute disseminated encephalomyelitis and routine childhood immunisations. *Victorian Infectious Diseases Bulletin*, 2014; 17(2): 1–4
5. Dodd et al. (**Member of the Global H1N1 GBS Consortium collaboration group**) International collaboration to assess the risk of Guillain Barré Syndrome following Influenza A (H1N1) 2009 monovalent vaccines. *Vaccine*, 2013; 31(40):4448-58

Oral & poster conference presentations

1. Lawrie J, **Clothier HJ**, BATTERY JP. Streamlining automated vaccine safety signal detection in Victoria, Australia. *New Zealand Immunisation conference, Auckland, September 2019*

2. Lewis G, **Clothier HJ**, McMinn A, Crawford NW. Vaccination errors reported to SAEFVIC, Victoria, 2008–2013. *Poster: Public Health Association Australia Immunisation Conference, June 2014*
3. Martin TJ, Crawford NW, **Clothier HJ**, Fahey M, Buttery JP. Acute disseminated encephalomyelitis and routine childhood immunisations. *Poster: Public Health Association Australia Immunisation conference, June 2014*
4. Danchin M, **Clothier HJ**, Perrett KP, Crawford NW, Buttery JP. Diarrhoea and all AEFI reported to SAEFVIC post introduction of rotavirus vaccines in Victoria, 2007–2016. *Presentation & Poster: Public Health Association Australia Immunisation conference, June 2016*
5. Perrett KP, Addison M, Harris A, **Clothier HJ**. Immediate Hypersensitivity Adverse Events Following Immunisation in Preschool Aged Children in Victoria. *Presentation & Poster: Public Health Association Australia Immunisation conference, June 2016*
6. Selvaraj G, **Clothier HJ**, Buttery JP, Crawford NW. Reporting patterns for severe local reactions (SLRs) following immunisation, 2007-2015, Victoria. *Presentation & Poster: Public Health Association Australia Immunisation conference, June 2016*

Abbreviations

ABS	Australian Bureau of Statistics
ATSI	Aboriginal and Torres Strait Islander
ADR	Adverse drug reaction
AEFI	Adverse event following immunisation
ACCA	Advisory Committee on Causality Assessment
ACSOV	Advisory Committee on the Safety of Vaccines
ACT	Australian Capital Territory
ACIR	Australian Childhood Immunisation Register
AIR	Australian Immunisation Register
ASVR	Australian School Vaccination Register
ASPREN	Australian Sentinel Practice Research Network
ASGS	Australian Statistical Geography Standard
BCG	<i>Bacillus Calmette-Guerin</i>
CAEFISS	Canadian Adverse Events Following Immunization Surveillance System
CDC	Centers for Disease Control and Prevention
CARM	Centre for Adverse Reactions Monitoring
CVDL	Centre for Victorian Data Linkage
CNAEFIS	Chinese National AEFI Information System
CVU	Clinical vaccinology update
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CCP	Critical Control Point

DAEN	Database of Adverse Event Notifications
DoH	Department of Health
DtaP	diphtheria, tetanus, acellular pertussis
DTP	diphtheria, tetanus, pertussis
EBGM	empirical Bayes geometric mean
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GP	General practitioner
GACVS	Global Advisory Committee on Vaccine Safety
GAVI	Global Alliance for Vaccines and Immunization
GRiP	Global Research in Paediatrics
GVAP	Global Vaccine Action Plan
GVSI	Global Vaccine Safety Initiative
GVP	Good Pharmacovigilance Practices
GBS	Guillain Barré syndrome
HCP	Healthcare provider
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HREC	Human Research Ethics Committee
HHE	hypotonic-hyporesponsive episode
ImPS	Immunisation Provider System
IRR	Incidence risk ratio
ILI	Influenza-like-illness

ICD	International Classification of Disease
ISoP	International standard of practice
LMIC	low to middle income countries
MMR	measles-mumps-rubella
MESH	Medical Subject Headings
MARC	Medicines Adverse Reactions Committee
MHRA	Medicines and Healthcare Products Regulatory Agency
MCRI	Murdoch Children's Research Institute
NIP	National Immunisation Program
NRA	National Regulatory Authority
NSW	New South Wales
NZ	New Zealand
NT	Northern Territory
OMOP	Observational Medical Outcomes Partnership
PAEDS	Paediatric Active Enhanced Disease Surveillance
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsortTium
PRAC	Pharmacovigilance Risk Assessment Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRR	Proportional reporting ratio
PHAC	Public Health Agency of Canada
4vHPV	Quadrivalent human papillomavirus vaccine
QLD	Queensland
ROR	Reporting odds ratio
RR	Reporting risk

RCH	Royal Children’s Hospital
SANE	Serious adverse neurological event
SPRT	sequential probability ratio test
SAEFI	Serious adverse event following immunisation
SMS	Short-message-service
SDA	Signal detection algorithm
SA	South Australia
SWOT	Strengths-weaknesses-opportunities-threats
SNAT	Surveillance Network Assessment Tool
SAEFVIC	Surveillance of adverse events in the community
Tas	Tasmania
TGA	Therapeutic Goods Administration
TOWS	Threats-opportunities-weaknesses-strengths
TIV	Trivalent Influenza vaccine
US	United States
UMC	Uppsala Monitoring Centre
VAERS	Vaccine Adverse Events Reporting System
VENICE	Vaccine European New Integrated Collaboration Effort
VVWG	Vaccine Vigilance Working Group
VIC	Victoria
VAED	Victorian admitted episodes dataset
VEMD	Victorian emergency minimum dataset
WA	Western Australia
WHO	World Health Organization

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Chapter 1: Introduction

In February 2009 I joined the SAEFVIC team as the Epidemiologist and Surveillance Manager, working part-time (0.4EFT). SAEFVIC is a central reporting enhanced passive surveillance system integrated with clinical services in the state of Victoria, Australia. It provides expert immunisation safety advice to reporters and health-care workers, as well as for children and adults who have experienced an adverse event following immunisation (AEFI)(1).

SAEFVIC had commenced two years earlier in the May of 2007, with the stated objectives to 1) improve reporting of AEFI 2) detect, validate and inform on potential vaccine safety signals and 3) to help maintain confidence in immunisation services(1). The system had originated as a voluntary paper-based reporting service and was now seeing increasing uptake by general practice and immunisation services across Victoria.

As an incoming epidemiologist it was soon apparent that there was little documentation of the surveillance system structure, efficiency and effectiveness. Within the first 12-months of my joining SAEFVIC the system was twice challenged. First in 2009, when Australia initiated rapid deployment of a new vaccine for circulating pandemic influenza strain H1N1pdm2009, for which there was prior precedent from a 1976 pandemic vaccine of potential serious AEFI with paralysing Guillain Barré Syndrome (GBS)(2). While subsequent studies identified minimal increased risk of GBS with the 2009 vaccine(3-5), the performance characteristics of Australia's AEFI surveillance systems were brought into question(6). This event was shortly followed in 2010 by an increase in fever and febrile seizures associated with the Australian-manufactured Fluvax® brand of seasonal influenza vaccine that resulted in severe brain damage in at least one previously healthy infant(7, 8). The speed of recognising the problem and calling for cessation of vaccine administration to the vulnerable infant group was severely criticised(6, 9). As a result, formal investigations of events were undertaken to review national surveillance processes and ability to raise timely alerts. Central to the findings of two expert reviews, led by Stokes and Horvath respectively, was the lack of a comprehensive national AEFI surveillance

system(6, 9). Instead, they described fragmented and divergent jurisdictional systems with inadequate capacity to inform vaccine pharmacovigilance(6). Victoria's SAEFVIC service was cited as a robust system with potential to be modelled by those jurisdictions lacking appropriate AEFI surveillance(9).

The concept for this PhD emerged from the reviews' premise that SAEFVIC was suggested as a model system for Australia; albeit in the absence of any comprehensive assessment of the system's effectiveness in achieving its purpose. It was therefore imperative that SAEFVIC be evaluated according to its purported objectives and strengthened to ensure safe immunisation in Victoria and prior to any potential expansion as a national system for vaccine safety surveillance in Australia.

1.2 Rationale

At commencement of this PhD in 2013, SAEFVIC had been in operation for five years. Vaccine pharmacovigilance in Australia had recently been criticised and found inadequate, with SAEFVIC suggested as a potential model system in the review by Stokes(9): a finding reiterated a year later in the Horvath review(6).

However, despite this recommendation, no evaluation of SAEFVIC's ability to provide effective pharmacovigilance surveillance had been undertaken.

Therefore we wanted to know how SAEFVIC was performing and what opportunities existed to optimise the surveillance system for vaccine pharmacovigilance in Victoria, especially before considering any expansion as a nationally available surveillance system.

This doctoral research work is original in that it provides the first comprehensive evaluation of an AEFI surveillance system in Australia and synthesises systems and methods that have not been previously applied in this context. The intention of this work is to provide robust and effective vaccine safety surveillance, provide information for action and thus maximise the safety of immunisation.

1.3 Relevance

Vaccines are a cornerstone of public health saving millions of lives each year(10, 11), however, adverse events following immunisation (AEFI) are a reality. Comprehensive post-licensure **vaccine safety surveillance is therefore essential** to maintain confidence in immunisation, inform policy and to deliver an effective and safe immunisation program(12).

However, Australia had been **criticised for its inability to inform on vaccine safety** events in a timely manner(9). In 2010 this meant many distressing febrile convulsions in young children and failure to prevent serious neurological sequelae in an otherwise healthy infant, arising from increased febrile reactions with the locally-manufactured Fluvax® brand of influenza vaccine(7, 8).

This obvious need for improvement to systems in Australia required a response to the expert reviews and evidence of learning from the challenges experienced. Moreover, as Australia is historically an “early adopter” of vaccines **our vaccine safety knowledge has potential to lead and inform both nationally and internationally(13).**

This doctoral research provides detailed description of the processes and epidemiology of the Victorian vaccine safety surveillance system “SAEFVIC”(14, 15). **My evaluation of “SAEFVIC”—an Australian first** for evaluating a passive AEFI surveillance system—determines the system’s ability to detect and investigate emergent vaccine safety issues. Additionally this research explores the application of a simple and feasible measure of disproportionality for signal detection. The findings of these research studies provide the evidence-base to optimise the system and—following translation into practice—elevate the **Victorian surveillance system to be a leader in Australian AEFI surveillance.**

The impact of my doctoral work has become particularly relevant with the advent of the global Coronavirus SARS-CoV-2 crisis bringing calls for development and release of vaccines at “pandemic speed” and thus highlighting **the need for robust and timely vaccine safety surveillance(16, 17).**

1.4 My doctoral work

I commenced the PhD part-time in 2013 in conjunction with continued employment as the epidemiologist and surveillance manager for SAEFVIC. This enabled me to direct research activities to meet industry-driven areas of interest and to translate findings from investigations as they were undertaken into practical implementation. This saw SAEFVIC strengthen over the duration of the PhD such that the final chapter is able to demonstrate improvements and efficiencies gained as a direct result of this doctoral research.

I have worked in public health for decades but not with the discipline it takes to construct a PhD thesis. This has challenged me to think strategically, identify the gap of knowledge and refine my research questions from an applied field-based response perspective to meet academic requirements. Application of standard constructs to descriptive epidemiology (for example Strobe statements) has elevated my descriptive epidemiology. *Chapter 7: Signal detection* in particular brought a new skill-set through application of statistical algorithms to the dataset: work which has been well received within the vaccine pharmacovigilance communities of both Australia and New Zealand. I have gained fluency in use of Microsoft PowerBI as an informatic analytical platform using cloud-based sharing mechanisms. Communicating the findings of my research through a variety of platforms has brought confidence to my participation in scientific debate.

1.5 Objective and aims

The objective of this research is to optimise the SAEFVIC passive AEFI surveillance system with the overarching aim being to improve the capacity of passive AEFI surveillance in Australia to detect, investigate and validate vaccine safety signals in a timely manner for current and new vaccines.

This objective is broken into more specific aims below. These aims also correspond to the publications that have arisen from this PhD.

1.5.1 Aims

- To **evaluate** the current SAEFVIC surveillance system ability to meet its stated objectives
- To **demonstrate** how SAEFVIC data can be used to inform vaccine pharmacovigilance
- To **explore and apply** concepts to develop signal detection capability for SAEFVIC
 - **Determine** if background rates of potential AEFI can be estimated using Victorian hospital administration datasets
 - **Apply** a signal detection method to SAEFVIC data and **evaluate** it as a reactogenicity signal detection method for fever and allergy AEFI with Influenza vaccines
- To **optimise** SAEFVIC to detect, investigate and validate vaccine safety signals and support expansion of SAEFVIC to other jurisdictions and thus strengthen vaccine pharmacovigilance in Australia.

1.6 Research questions

The overarching research question was “What are the opportunities to optimise the SAEFVIC passive AEFI surveillance system?”. In order to address this question and achieve the aims as stated above, the following specific research questions were developed. (*Question 2 arose in the course of investigating Question 1)

Question 1: Does the AEFI surveillance system, SAEFVIC, meet its stated objectives?

Question 2*: What does consumer reporting of AEFI contribute to SAEFVIC in Victoria?

Question 3: Is SAEFVIC useful for informing vaccine pharmacovigilance?

Question 4: Can Victorian hospital administration datasets be used to estimate background rates? (and so improve signal detection)

Question 5: Can a signal detection algorithm provide timely signal detection?

Question 6: How have the findings of this PhD been incorporated to optimise SAEFVIC?

All of these questions are relevant to the population of Victoria, with external implications discussed at the conclusion of the PhD.

1.7 Thesis statement

Vaccines are a cornerstone of public health, saving millions of lives each year. However, as with any pharmaceutical, vaccines can give rise to adverse reactions following immunisation (AEFI). Comprehensive and effective post-licensure surveillance of AEFI is therefore critical to maintain confidence in immunisation and inform evidence-based policy for vaccine safety.

The Victorian state-level AEFI surveillance system, SAEFVIC, comprises comprehensive, centralized data with clinical validation of AEFI. This PhD provides a critical review and evaluation of SAEFVIC to meet its objectives to detect, validate and inform on vaccine safety issues and provides the evidence-base to optimise data utilisation. Integration with signal detection algorithms has aided identification and investigation of vaccine safety signals.

Translation and implementation of study findings has seen SAEFVIC improve vaccine pharmacovigilance, facilitated signal detection and validation investigations, inform on vaccine safety practices and become an established leader in Australian AEFI surveillance. Expansion of the system nationally is assisting with national data consistency and jurisdictional comparability. This PhD has shaped SAEFVIC to provide robust and effective vaccine safety surveillance in Victoria and Australia, ultimately making immunisations safer.

1.8 Thesis overview

Chapter 1: Introduction - is a summary of the rationale, relevance, objective and aims of my thesis

Chapter 2: Literature review - provides a comprehensive literature review describing adverse events following immunisation (AEFI) and passive AEFI surveillance globally

and in Australia. The review outlines the benefits of evaluating surveillance systems in general and AEFI surveillance systems in particular.

Chapter 3: Methods – considers the overall study design, elements of bias and confounding and provides a detailed description of SAEFVIC data collection and collation; data sources used through this thesis and; a summary of analytical and statistical methods used.

Chapter 4: SAEFVIC early years - provides a foundational epidemiological overview of SAEFVIC surveillance data at the commencement of this PhD, presented as a publication titled;

“SAEFVIC: Surveillance of adverse events following immunisation (AEFI) in Victoria, 2012”.

Chapter 5: SAEFVIC evaluation - presents a literature review on evaluation of surveillance systems and two published papers. The first paper, titled;

“Evaluation of “SAEFVIC”, a pharmacovigilance surveillance scheme for the spontaneous reporting of adverse events following immunisation in Victoria, Australia ”

provides the main body of work and clearly identifies gaps in the surveillance system’s ability to meet its objectives. The second paper titled;

“Consumer reporting of adverse events following immunization”

arose as an extension of the evaluation, responding to industry-driven interest in this specific element of surveillance.

Chapter 6: Informing pharmacovigilance - provides three published papers that clearly establish that SAEFVIC is useful for informing vaccine pharmacovigilance and public health practice and policy, titled;

“*Bacillus Calmette-Guerin* (BCG) vaccine adverse events in Victoria, Australia: analysis of reports to an enhanced passive surveillance system”;

“Allergic-related adverse events following seasonal influenza containing vaccines, 2015 “ and;

“Adverse events following vaccination of older people may be under-reported“.

Co-authored papers that also support this research question are listed above with first-authored conference presentation abstracts and posters presented in Appendix 2.

Chapter 7: Signal detection - includes a literature review on AEFI signal detection as background to two studies undertaken to explore aspects and issues encountered with signal detection. Presented as published papers: the first study is titled;

“Human papillomavirus vaccine in boys: background rates of potential adverse events”.

The second study titled;

“Proportional reporting ratio enhances influenza vaccine pharmacovigilance, Victoria, Australia”

provides proof of principle that using a statistical algorithm can enhance utility for AEFI signal detection.

Chapter 8: SAEFVIC maturation - presents a descriptive epidemiological overview of SAEFVIC at the end of this PhD in a publication titled;

“SAEFVIC: Surveillance of adverse events following immunisation, 2018, Victoria, Australia”.

The paper demonstrates how the integration of study findings have matured SAEFVIC, increased capability to inform and direct on vaccine safety issues and illustrates how routine use of PRR (studied in *Chapter 7: Signal detection*) informs on a signal event.

Chapter 9: Optimising SAEFVIC - provides an overall discussion of the work in the thesis; strengths and limitations of my work; how the findings of my thesis have contributed to the field, as well as future directions to continue the strengthening of vaccine pharmacovigilance in Australia.

Chapter 2: Literature review

2.1 Chapter introduction

This Chapter provides background on the importance of vaccines, adverse events following immunisation (AEFI) and describes the foundation of AEFI surveillance. Passive AEFI surveillance systems are detailed in both the global and Australian context. The chapter culminates with a description of SAEFVIC, the Victorian passive AEFI surveillance system.

Further detail on SAEFVIC surveillance and data outputs at the time of commencement of this PhD are provided in *Chapter 4: SAEFVIC early years*, with a publication summarising SAEFVIC in 2012. Clothier *et al.* SAEFVIC: Surveillance of adverse events following immunisation (AEFI) in Victoria, 2012. *Victorian Infectious Diseases Bulletin*. 2014 Mar;17(1):2-9.

Additional literature reviews are provided in *Chapter 5: SAEFVIC evaluation* on evaluation of surveillance systems and in *Chapter 7: Signal detection* regarding signal detection as part of pharmacovigilance.

2.2 Importance & success of vaccines

Vaccines and the benefits of immunisation are considered one of the most successful and cost-effective health interventions known, saving the lives millions of individuals—mainly children—every year and drastically reducing the burden of morbidity and disability from viral and bacterial illnesses(10, 11). Global vaccine campaigns have seen the eradication of smallpox, almost worldwide disappearance of polio and targets set for elimination of measles, including in Australia(10, 18).

The World Health Organization (WHO) currently lists 26 disease as having a vaccine available, with a further 24 vaccines in the pipeline(19). Advances in novel preventative and therapeutic vaccines are bringing future hope for an end to HIV(20), malaria(21), tuberculosis, some cancers(22) and even the development of substance

abuse vaccines is underway(23, 24). Increasing sophistication, including innovations such as nanovaccinology, add to favourable trends for user friendly, less painful and invasive inoculation techniques(25).

While immunisation saves the lives of approximately 3 million children per year, 2 million more lives could be saved even with existing vaccines(26). The Global Alliance for Vaccines and Immunization (GAVI) through the Global Vaccine Action Plan provide frameworks for overcoming the major barriers of financing, through facilitating vaccine delivery platforms, and bringing more equitable access to life-saving vaccines in all communities(10, 27).

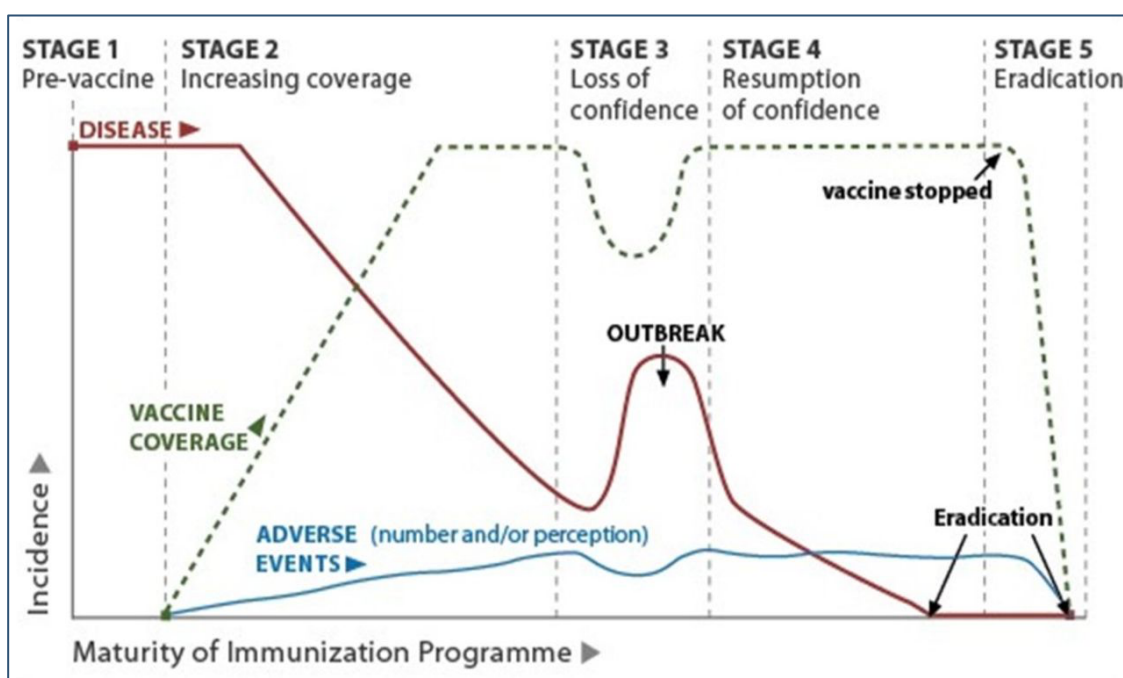
2.2 Challenge for vaccination

However, beyond these financial and logistical aspects, there is an equally important barrier in the growing perception of vaccines as no longer needed as the success of immunisation programs reduces incidence and fear of vaccine-preventable diseases(26). Moreover, as the fear of disease diminishes concerns may transfer to the risk of vaccine side effects. Vaccines, as with any drug, are not free of side-effects and recipients may also experience adverse events as a normal reaction to the intended controlled stimulus to the immune system of immunisation.

The public awareness of vaccine side effects is particularly so as vaccines are administered primarily to healthy individuals thus shifting the fulcrum of risk-benefit adjudication as public concern about possible AEFI and expectations for vaccine safety increase (28-31). This leads to the classic evolution cycle of immunisation programs as illustrated by Chen and Orenstein (Figure 1)(32).

The impact from this phenomenon of vaccine refusal has already come to fruition as seen with the decline in measles-mumps-rubella vaccine uptake in the UK being associated with a resurgence of measles cases(33). The World Health Organization (WHO) recognised “vaccine hesitancy—the reluctance or refusal to vaccinate despite the availability of vaccines—to be one of the top ten threats to global health in 2019”, with the prospect of reversing the progress made in tackling vaccine-preventable diseases(34).

Figure 1: Evolution of immunisation program(32)



With the benefits of vaccination being well recognised, many immunise without question, however, there remains a need for informed consent, accompanied by transparent and effective communication of risks(35). Therefore effective surveillance and monitoring for adverse events following immunisation (AEFI) to provide ongoing risk assessment is a cornerstone for ensuring accurate information within such informed consent(31).

2.3 Adverse events following immunisation (AEFI)

An adverse events following immunisation (AEFI) is defined as:

“any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine”(36).

An AEFI may therefore include vaccine-associated adverse events, AEFI due to programmatic issues or coincidental events, as well as temporal associations that may be unrelated to vaccine administration (Box 1)(37). It is an encompassing definition that accommodates all suspected associations, reflected in the observations of an individual reporter, without bias to interpretation.

Box 1: Adverse event following immunisation reaction categories and examples(37)

Vaccine product-related reaction

- An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product
- **Example:** Extensive limb swelling following DTP vaccination

Vaccine quality defect-related reaction

- An AEFI that is caused or precipitated by a vaccine that is due to one of more quality defects of the vaccine product including its administration device as provided by the manufacturer
- **Example:** Failure to fully inactivate a lot of polio vaccine leads to cases of paralytic polio

Immunisation error-related reaction

- An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable
- **Example:** Transmission of infection by contamination of a multi-dose vial

Immunisation anxiety-related reaction

- An AEFI arising from anxiety about the immunisation
- **Example:** Vasovagal syncope episode in an adolescent during/following vaccination

Coincident event

- An AEFI that is caused by something other than the vaccine product, immunisation error or immunisation anxiety but a temporal association with immunisation exists
- **Example:** A fever occurs at the time of the vaccination, but is in fact caused by malaria

*DTP = diphtheria tetanus, pertussis containing vaccine

2.3.1 Vaccine cause-specific reactions

The first two categories described in Box 1 above are vaccine-cause specific reactions attributable to either;

- i) the inherent properties of the vaccine (including adjuvants and stabilisers), or
- ii) a defect in the quality of the vaccine.

An individual may react to a vaccine even if it has been manufactured and handled correctly. Such reactions may arise from an immune response to a component of the

vaccine leading to anything from mild inflammation at the injection site to life-threatening anaphylaxis. These types of vaccine-cause specific AEFI require clinical management of the vaccine recipient.

Vaccine-defect related reactions arise from deviations in the manufacturing process that impact an individual's response to the specific vaccine batch/es affected. A famous and devastating example of vaccine-defect occurred in the early years of oral polio manufacturing when polio virus was inadequately inactivated leading to 12,000 vaccines containing live virus resulting in 40,000 cases of polio disease of which 200 cases were permanently paralysed and 10 cases died(38). Management of vaccine-defect reactions requires improvement and adherence to manufacturing guidelines and quality control processes. As scrutiny by National Regulatory Authorities (NRA's) and use of good manufacturing guidelines has strengthened, the potential for quality defects to occur has declined and is now rare(39).

2.3.1.1 Vaccine reactions by frequency and severity

The frequency and severity of AEFI can be categorised as;

- a. Common or minor reactions
- b. Rare or serious reactions

Vaccines are intended to induce an immune response in the recipient to the administered vaccine antigens and thus confer immunity to future disease exposure-events. Therefore responses such as injection site reaction, fever and systemic symptoms related to immunogenic reactivity to either vaccine antigen—or to vaccine components such as adjuvants or stabilizers—are expected (Table 1). These reactions are usually mild and subside without requiring intervention and are therefore tolerated within the risk-benefit of immunisation, even when occurring in more than 10% of recipients.

The occurrence of local (pain, redness, swelling) or systemic reactions (fever, malaise, headache) vary by the type of vaccine antigen and may mimic mild versions of the relevant vaccine-preventable disease. For example, a local injection-site papule is expected 1-2 weeks following BCG immunisation that progresses to mild ulceration

before healing with a typical mild scar, although this may be more pronounced among populations with tendency to form keloid (thickened) scars(40). Fever is a common systemic reactions for most antigens. When arising following live-attenuated vaccines, such as measles, the symptoms are mild compared to wild-type disease, however may be significant in severely immunocompromised individuals. Changes in vaccine development that reduce antigen exposure or reactive formulation components have led to reductions in common reactogenic AEFI, for example local reactions occurring in >10% with whole-cell diphtheria-tetanus-pertussis (DTP) are reduced to 1-10% with use of acellular formulation (DtaP)(39).

Table 1: Frequency of occurrence of reported AEFI(39)

Frequency category	Frequency in rate	Frequency in %
Very common	$\geq 1/10$	$\geq 10\%$
Common (frequent)	$\geq 1/100$ and $< 1/10$	$\geq 1\%$ and $< 10\%$
Uncommon (infrequent)	$\geq 1/1000$ and $< 1/100$	$\geq 0.1\%$ and $< 1\%$
Rare	$\geq 1/10,000$ and $< 1/1000$	$\geq 0.01\%$ and $< 0.1\%$
Very rare	$< 1/10,000$	$< 0.01\%$

Rarely, severe and/or serious AEFI may occur. The terms serious and severe are not interchangeable. Severity is a measure of intensity and may be used to describe a specific medical event such as fever or an injection site reaction being classified as mild, moderate or severe. A serious AEFI, however, is one that results in an outcome of medical significance such as death, life-threatening, requires hospitalisation (or prolongs hospitalisation), results in (or requires intervention to prevent) significant disability/incapacity or is a congenital anomaly/birth defect(41). Anaphylaxis for example is always a serious event as it is potentially fatal, although with appropriate intervention is manageable. Some serious reactions are documented as AEFI associated with particular vaccines although the rare frequency of occurrence make it difficult to conduct the studies required to attribute causality to the vaccine(42).

While vaccines are rarely contraindicated, consideration of individual circumstances that may increase the risk for serious reactions, such as immunocompromised state or documented history of anaphylaxis to a vaccine, is required. Options may include giving immunisation in a timeframe before immunocompromising therapy commences or providing immunisation under appropriate medical supervision with facilities to manage short-term serious reactions should they arise, for example, vaccination of a child who has previously experienced a hypotonic-hyporesponsive-episode (HHE) as an AEFI(43).

2.3.2 Immunisation error-related reactions

Immunisation error-related reactions are distinguished from vaccine-defects as they refer to processes that occur after the vaccine has left the manufacturing site such as: storage/transportation conditions, prescribing and administration of the vaccine. Note that the error itself may be recorded as an AEFI for its potential to cause harm, that is, whether or not it results in a related reaction outcome (Table 2).

Table 2: Immunisation error-related reactions(39)

Immunisation error		Related reaction
Error in vaccine handling	Exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluents where applicable)	Systemic or local reactions due to changes in the physical nature of the vaccine, such as agglutination of aluminium-based excipients in freeze-sensitive vaccines
	Use of a product after the expiry date	Failure to protect as a result of loss of potency or non-viability of an attenuated product
Error in vaccine prescribing or non-	Failure to adhere to a contraindication	Anaphylaxis, disseminated infection with live attenuated vaccine

adherence to recommendations for use	Failure to adhere to vaccine indications or prescription (dose or schedule)	Systemic and/or local reactions, neurological, muscular, vascular or bony injury due to incorrect injection site equipment or technique
Error in administration	Use of an incorrect diluent or injection of a product other than the intended diluent	Failure to vaccinate due to incorrect diluent, reaction due to inherent properties of whatever was administered other than the intended diluent
	Incorrect sterile technique or inappropriate procedure with a multi-dose vial	Infection at/beyond the site of injection
	Incorrect mode of administration (e.g oral vaccine administered intra-muscular)	Failure to protect, reaction due to introduction of immunisation product to non-intended site.

Immunisation error-related reactions are preventable and so timely identification and mitigation strategies are essential. Events may occur for individual vaccinees or in clusters. For example a geographic cluster may be noted as being associated with common faulty transportation or storage arising in a cold-chain breach (either as increased temperature or freezing of vaccine) or be attributable to a particular provider making vaccine-handling, administration or prescribing errors. Clusters may also occur in relation to a particular immunisation event or even vial; for example, where vaccine preparation error such as using an incorrect diluent has occurred, or contamination of a multi-dose vial.

Education of health care professionals and development of robust vaccine formulations and sophistication of transportation and storage systems to routinely monitor parameters will help to mitigate risk of immunisation errors of administration and handling(44, 45). On the other hand the continuing expansion and complexities of immunisation programs may lead to increasing risk for immunisation errors in prescribing and/or failures in adherence to recommendations(46). Influenza vaccines

are now age-group specific due to specific consideration to avoid reactogenicity and febrile seizures in young infants alongside high dose formulations developed specifically for improved efficacy with the senescent immune systems of the elderly(41). Incorrect prescribing or inadvertent mis-selection of formulation could lead to increased risk of fever and febrile seizure in infants or vaccine failure in the elderly. Rotavirus vaccines provide another example of potential serious outcomes from vaccine prescribing error. Studies investigating the potential increased risk of intussusception with rotavirus vaccines determined that the risk increased with age, resulting in strict age-limited protocols for administration of the multi-dose schedule(41).

While immunisation-errors are usually self-limiting events they are of particular concern because they are preventable in the first instance and also because they are destructive to the risk-benefit of immunisation programs. Programs continually develop to mitigate immunisation-errors, such as use of pre-mixed single-use syringes, thus removing the potential for diluent errors, however these often come with compromises such as increased vaccine-lability and need to maintain cold chain(45).

2.3.3 Immunisation-anxiety reactions

Immunisation may give rise to stress reactions in anticipation of—or as a result of—the injection event, unrelated to the content of the vaccine. Common anxiety reactions include light headedness, dizziness and hyperventilation or in younger children, breath-holding. Fainting is a relatively common anxiety response that is mostly benign, however in some individuals can result in a convulsion. Management of immunisation-anxiety reactions are generally pre-emptive such as thoughtful preparation away from line of sight and placing the recipient in a lying down position(47). Individual anxiety is expected, however clusters and mass hysteria events have also been documented and may require investigation to distinguish from vaccine-defect reactions(48, 49).

2.3.4 Coincident events

Coincident events may also be recorded as AEFI. Such events are most commonly seen in early life, as this is the time when vaccination and infections and illnesses are

equally common. Previous research has identified that fever reported as an AEFI is more likely due to a concurrent infectious processes rather than immunisation itself(50).

Coincident/temporal associations may also be observed with rare serious events. For example, the incidence of sudden infant death syndrome peaks around 2-3 months of age, which is coincident with the primary infant vaccine schedule. Therefore it is likely that SIDS will occur in children who have been recently immunised. In Australia the coincidence of SIDS occurring within 48 hours of vaccination is estimated to be 3.5 cases per year(51).

Possibly the most famous and damaging attribution of coincidence to causality is that of the measles-mumps-rubella (MMR) vaccine and autism controversy(52, 53). The temporal association arises as emergence and diagnosis of developmental regressive behaviour of autism occurs at approximately two years of age, which is 4-6 months after routine schedule for MMR vaccination(54). The association was purported as causal in a study published by Wakefield *et al.* in the Lancet in 1998, but which was later refuted as fraudulent and fully retracted in 2010(53). However, intense public concern persists regarding the temporal association of measles-mumps rubella vaccination and autism despite numerous studies over more than a decade demonstrating the safety of these vaccines(52, 55, 56).

It is therefore important for well designed studies to demonstrate such events as having coincident and not a causative association with immunisation(51, 57).

Events of expected coincident conditions that have potential to occur as adverse events can be measured to establish “background rates” of such conditions. The background rate of the condition can be utilised to analyse observed versus expected temporal events(58, 59). Such background rates of disease have been used to support vaccine safety assessment of mass vaccination with pandemic H1N1 influenza vaccines, addressing hypothesised increase risk of Guillain Barré syndrome(5, 60).

2.4 Vaccine pharmacovigilance

“Vaccine Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding, prevention, and communication of adverse events following immunization, or of any other vaccine—or immunization—related issues”(61).

Vaccine development phases require comprehensive studies to detect and quantify potential adverse events and ensure the safety of vaccines released to the market. However, pre-licensure studies may be underpowered to detect rare events, may not include all population variabilities (especially high risk groups such as pregnant women, those with co-morbidities or discrete ethnic or Indigenous populations) and do not account for ongoing vaccine production issues or seasonal formulation variations. Therefore, continuous scrutiny of adverse events following immunisation post-licensure is an integral part of routine pharmacovigilance of any national immunisation program in order to maintain program credibility and to guide policy and practice(62, 63).

Post-licensure pharmacovigilance facilitates assessment of long-term effectiveness and potential safety concerns that were not detected or statistically associated with vaccination in phase 3 trials(64). Development of vaccines for rotavirus provides one such example. The first vaccine, Rotasheid[®], was withdrawn from use following determination of an association with intussusception(65). Two new rotavirus vaccines were subsequently licensed following large pre-licensure trials that did not find an increased risk of intussusception. However, through post-licensure monitoring, a small increased risk of intussusception was detected for both vaccines, for which alterations to the age-limits for vaccination scheduling were made to minimise the risk(66, 67).

Vaccine administration and postulated AEFI may occur in temporal associations and with plausible biological causal relation. An example arose with quadrivalent vaccines against human papillomavirus (4vHPV) for the prevention of cervical cancer being in temporal association with ovarian insufficiency (absent menarche or early menopause)(68). As 4vHPV administration is targeted to adolescent girls there was a perceived biological plausibility as both vaccine and ovarian insufficiency relate to

elements of reproductive health. In response to mounting negative media pressure Japan withdrew the vaccine: the program subsequently collapsed, resulting in a dynamic risk of cervical cancer based on year of birth and vaccine program delivery(69-71). Australia, however, continued and in 2013 expanded the program to include boys. There is now evidence that there has been a substantial decline in vaccine-targeted cervical disease among vaccine-eligible women(72).

This example highlights the need for adequate vaccine safety surveillance systems to support robust detection and investigation of the causal relation of alleged AEFI ,to allay fears and ensure the potential of vaccination programs can be realised(73, 74). Current evidence indicates no increased risk of ovarian insufficiency following 4vHPV(75).

Periodic vaccine safety controversies are likely to continue as more national immunisation programs mature. With near elimination of target vaccine-preventable diseases resulting in relative greater prominence of adverse events following immunisations—both as true reactions and temporally coincidental events—it is paramount that vaccine safety capabilities be continuously improved to potentially mitigate the impact of future vaccine safety concerns(76). Models have shown that education on risk-benefit of vaccine safety and infection risk is a key to maintaining vaccination levels that are sufficient for herd immunity(77).

For this reason, robust vaccine pharmacovigilance mechanisms to monitor and evaluate vaccines post-licensure are critical for maintaining the public's confidence in and acceptance of vaccines, as well as to assure that the vaccines are providing the level of protection and safety anticipated when they were licensed(64, 66). The World Health Organization identifies the establishment and strengthening of AEFI reporting systems as a priority towards attaining equitable access to safe immunisation(10, 63). This is documented through the *Global Vaccine Safety Blueprint* (2011) mission “to optimize the safety of vaccines through effective use of pharmacovigilance principles and methods”(36). The Blueprint, currently being redrafted for the next decade, provides eight aspirational objectives for vaccine pharmacovigilance programs, implemented through the Global Vaccine Safety Initiative(78). The first four objectives

relate directly to the components of vaccine pharmacovigilance and the latter four to supporting elements required for effective system functioning (Box 2)(36).

Box 2: Global Vaccine Safety Blueprint: Eight strategic objectives

1. AEFI detection
2. Investigation of safety signals
3. Vaccine safety communication
4. Tools and methods
5. Regulatory framework
6. Technical support and trainings
7. Global analysis and response
8. Public-private information exchange

2.5 AEFI Surveillance

Surveillance is

“the ongoing, systematic collection, analysis, and interpretation of health data, essential to the planning, implementation and evaluation of public health practice, closely integrated with the dissemination of these data to those who need to know”(79)

Public health surveillance “provides the scientific and factual database essential to informed decision making and appropriate public health action: the key objective of surveillance is to provide information to guide interventions”(80).

AEFI surveillance systems “aim to detect (or provide a means to investigate) unexpected events, or changes in rates of expected events, rare, late-onset, or population-specific adverse events time-associated with vaccination, regardless of causality”(36, 62). Surveillance information is used to detect when a vaccine safety

issue ('signal') may be present and prompt action, which assists in maintaining confidence in immunisation programs(63, 81). Surveillance data in isolation, regardless of sequential temporal association, are not sufficient to establish a causal relationship between vaccines and AEFIs(82). Structured causality assessments are required to assess possible causal links and ultimately guide the clinical component of evidence-based decision-making(28, 83).

Surveillance is defined as “the ongoing systematic collection and analysis of data and the provision of information that leads to action”(80). The characteristics of an ideal AEFI safety surveillance will permit timely detection of vaccine-associated events, facilitate rapid and reliable investigation of potential AEFI vaccine associations, inform appropriate action and be flexible and sustainable (Box 3)(84).

Box 3: Characteristics of an ideal surveillance system

- Rapidly identify and address events potentially associated with programmatic errors.
- Quickly detect and estimate rates of events possibly associated with vaccines
- Provide timely evaluation of relevant vaccine safety concerns.
- Facilitate investigations to provide relevant information for benefit-risk assessment.
- Be sustainable and affordable: requiring minimal change in resources and procedures.
- Be simple and flexible to adapt to the evaluation of new safety concerns.

Surveillance systems should therefore be designed and implemented to provide focused, reliable and timely evidence that is gathered efficiently and presented effectively. However this does not require surveillance to necessarily have complete coverage of the population and there may be instances when monitoring or non-continuous data collection is appropriate. As priorities, information requirements and

available resources differ, a number of different strategies have been developed(80). Outlined below are commonly used types of surveillance systems.

2.5.1 Episodic surveillance

Episodic surveillance or specific studies may be incorporated into, or complimentary to, standard surveillance systems as a means to expand immunisation safety activities. Epidemiological studies (for example, cohort or case series studies) provide a means to focus on safety concerns for a particular vaccine, cohort or period of transition.

Sentinel surveillance systems can provide opportunities to intensify case ascertainment in key population areas, either geographically or in clinical severity. Australia has two national sentinel surveillance systems that have periodically been expanded to include AEFI: the Australian Sentinel Practice Research Network (ASPREN) and the Paediatric Active Enhanced Disease Surveillance (PAEDS)(85, 86).

ASPREN monitors a specific set of clinical presentations to a network of approximately 100 general practitioners participating Australia wide(85). Conditions under surveillance include Influenza-like-illness (ILI), gastroenteritis, varicella and shingles with presentation incidence reportable against total consultations. In more recent times manual reporting has been superseded by automated data extractions. These data extractions could be configured to report on return visits within a specified timeframe following vaccination as an indicator of potential AEFI.

PAEDS is an active hospital-based sentinel surveillance system that targets serious conditions presenting to selected hospitals across Australia (two within Victoria)(86). Several of the conditions under surveillance can occur as AEFI, for example intussusception. As an established sentinel network, PAEDS can be rapidly expanded to include additional items of interest, provided the condition is sufficiently serious to warrant hospital admission, such as including febrile seizures following the 2010 febrile-seizure association with influenza vaccine(87). As an active system, PAEDS is expected to detect all cases admitted to the hospital, however the denominator is not specific to vaccinees and so rates cannot be calculated.

2.5.2 Active surveillance

Active surveillance aims to identify all AEFI events in a defined population within a defined time period and has the potential to address many of the inadequacies of stand-alone passive surveillance mechanisms. Utilising methods to maximise case ascertainment in the chosen population negates the underreporting deficit that occurs with passive reporting and allows for more precise estimates to be made of the incidence of AEFIs(88).

However, active surveillance is generally resource intensive and consequently costly. It is therefore generally used to target new vaccines, pre-specified AEFI, vaccines in sub-populations of interest, or to test a hypothesis that may in turn have been informed by potential signals generated from passive surveillance(88, 89). Newer approaches, using mobile phone short-message-service (SMS) technology, semi-automated response systems or data mining of already existing data sources, may provide economical opportunities for expanded or continuous active surveillance systems(90-93).

AusVaxSafety is an Australian nationwide active surveillance system operating across more than 300 sentinel sites. Information regarding potential AEFI are collected as responses solicited through automated SMS or email sent in the days following vaccination(94). It was established in 2014 to monitor AEFI with influenza vaccines in children in response to the 2010 febrile-seizure event. AusVaxSafety has since provided safety information following introduction of new vaccines, such as Zoster vaccine in adults aged 70–79 years, and for programme changes such as pertussis booster vaccines in children aged 12 months to 6 years. From 2019 AusVaxSafety will implement active vaccine safety surveillance of all vaccines on the NIP Schedule(94). While significantly adding to the nations ability to monitor and provide vaccine safety information(95), there are limitations of the sentinel participation and restriction to time constraint of soliciting responses within the first few days of vaccination(94). Time distant AEFI will not be captured and populations who are less engaged with online or smartphone technologies may be under-represented(90, 95, 96).

2.5.3 Passive Surveillance

The most frequently utilised systems for AEFI surveillance are passive surveillance systems, which rely upon spontaneous reporting of AEFI. These are relatively simple and low-resource systems for identifying AEFI that can potentially be further investigated using cohort or case series designs(36).

Limitations of passive AEFI surveillance are well documented(28, 97-99) and are summarised below in Table 3(100). Timeliness is often poor and overall sensitivity (ability to detect all AEFI) and specificity (ability to distinguish true AEFI from coincident events) are low(28, 101). Poor case ascertainment is a recognised issue with estimates showing up to 95% under-reporting, even in systems specifically targeting the reporting of serious AEFI(102, 103). Under-reporting may be further exacerbated where reporting of AEFI is not a legislated notifiable condition as is the case in some jurisdictions of Australia(100).

Table 3: Typical advantages and disadvantages of voluntary reporting in passive surveillance systems(100)

Advantages	Disadvantages
• Relatively simple to establish • Population-based • Cost efficient • Timely • Detects rare, serious events • Generates hypotheses about new events • Detects changes in frequency of known events	• Under-reporting inevitable • Potential for reporting bias • Inconsistent data quality & completeness • Does not confer causation • Cannot determine AEFI incidence due to lack of denominators

An important methodological limitation of passive AEFI surveillance systems is that they do not collect the data necessary for formal epidemiological investigations. This is

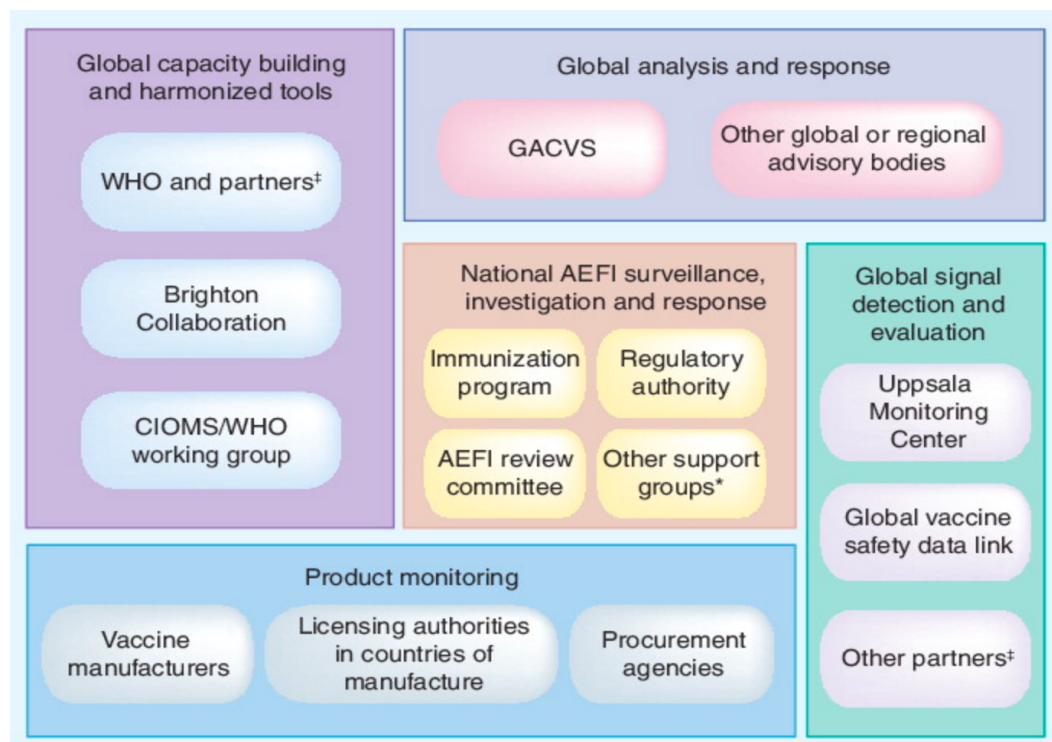
because the reporting collates data only for the number of persons who may have experienced an AEFI, precluding calculation of rates which require comparator denominator data of the total number of people vaccinated.

If relevant data are available, reporting risk estimates may be calculated using AEFI reports for the numerator and doses of vaccines administered, vaccine doses distributed or vaccine coverage data for the denominator as an imperfect definition of the exposed population. Findings may be compared to background rates of conditions occurring in the unvaccinated population(58, 104). However, due to the inherent under-reporting in the passive surveillance numerator, such reporting risks will remain an underestimate of actual AEFI risks. This is discussed further in *Chapter 3: Methods*.

2.6 Global support for AEFI surveillance

In order to support and coordinate systems globally, the WHO in collaboration with other partners, coordinate various global initiatives that aim to strengthen and support countries on vaccine safety issues, including national AEFI surveillance, investigation and response. The components of the WHO Global Vaccine Safety Support Network are schematically presented in Figure 2(105).

Figure 2: Components of a Global vaccine safety support network



2.6.1 Global capacity building

The WHO partners and vaccine experts developed a set of global strategies laid out in the *Global Vaccine Safety Blueprint* in order to leverage international commitment and to set out a framework for coordinated action to support vaccine safety monitoring globally and enable AEFI to be investigated wherever they occur(106). The *Global Vaccine Safety Blueprint* (2011) mission is “to optimize the safety of vaccines through effective use of pharmacovigilance principles and methods”.

The Global Vaccine Safety Initiative (GVSII) was established to implement the Blueprint, with the Global Vaccine Action Plan (GVAP) framework approved as a framework by the World Health Assembly in May 2012(10, 107).

2.6.1.1 Global coverage of AEFI surveillance

One objective of the Global Vaccine Action Plan is to improve health by extending the benefits of immunisation to all people(10). Coupled with this objective is the need to address inequities in global immunisation safety by enhancing AEFI surveillance and this has led to considerable improvements to global coverage of AEFI surveillance.

The WHO reports on global trends in AEFI reporting using AEFI reporting ratios (annual AEFI reports per 100,000 surviving infants) as the indicator with a milestone measure of minimal reporting ratio of 10 considered as a proxy measure for a functional AEFI reporting system(10, 108). The number of countries reporting any AEFI has increased from just 17% in 2000 (32 of 191 countries) to 64% in 2015 (124 of 195 countries)(76, 108). However the number of countries meeting the minimum AEFI reporting ratio indicator remains low, increasing from 8% in 2000 to 42% by 2015(39, 108). This leaves almost half of the global population living in countries without functional vaccine safety monitoring systems(106).

2.6.1.2 Guidelines for AEFI surveillance

Globally the processes for vaccine pharmacovigilance vary(29, 98, 109-113). Variation arise not only through sophistication but also as systems necessarily need to be adaptive to peculiarities of individual healthcare structures(28, 111, 114).

Guidance on structures and minimum requirements for establishment of AEFI surveillance systems are provided through the *Global Manual on Surveillance of Adverse Events Following Immunization*, published in 2014(39). These guidelines are particularly relevant for low and middle income countries aiming to establish systems: the requirements are generally exceeded by highly resourced countries that have had surveillance systems in place for many years.

The minimum requirements to record a case report include an identifiable patient, reporter, suspect vaccine, and adverse event. However to adequately monitor trends, and perform functions in regard to detection and investigation of signals, additional information on patient demographics, comorbidities, concomitant vaccines, as well as the clinical description of the adverse event, are required(29). Consideration for strengthening any surveillance system should therefore involve assuring the quality of reports rather than just increasing the number of reports.

Collaborative bodies have been established to improve consistency so that safety data across trials and surveillance systems can be compared: the Brighton Collaboration provides standardised AEFI case definitions(115, 116) and the Council for International Organizations of Medical Sciences (CIOMS) advises on medical terminology coding systems(117, 118).

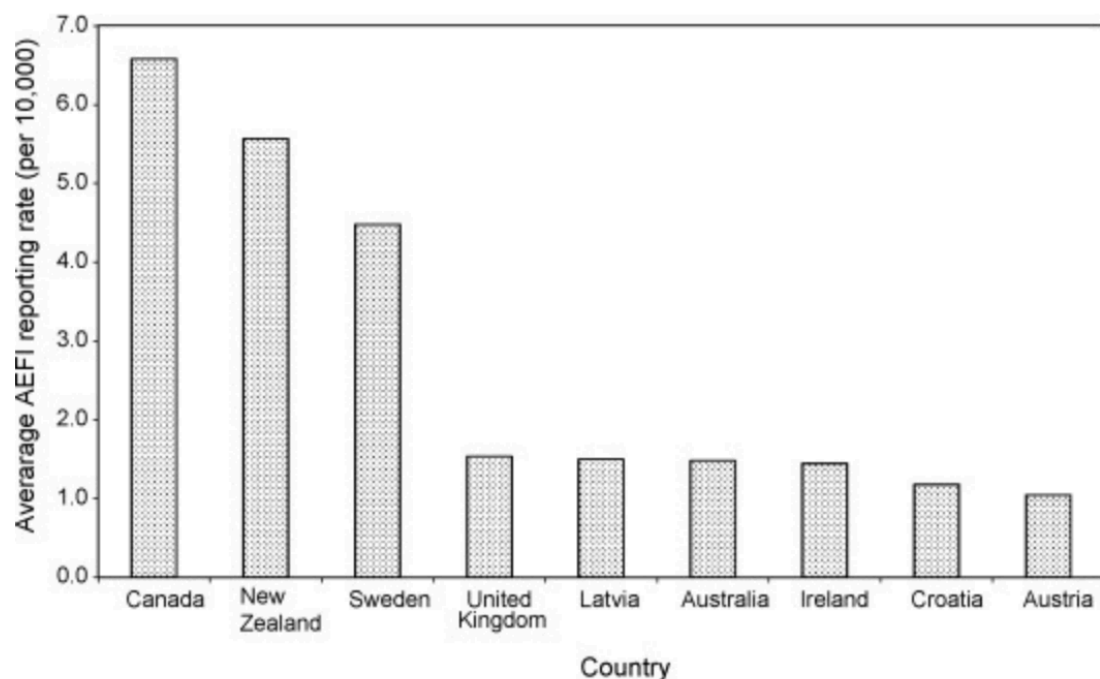
2.6.2 Global analysis and Response

The Global Advisory Committee on Vaccine Safety (GACVS) is an independent expert clinical and scientific advisory body that advises the World Health Organization on vaccine safety issues of potential global importance. The role of the GACVS is both “to analyse and to interpret reports of the adverse effects of vaccines that impact on global vaccination programs and strategies, and to foster the development of improved surveillance systems to detect any adverse effects of vaccines, particularly in low-and middle-income countries”(105). This global pharmacovigilance landscape is a complex network of systems feeding adverse event information towards the central WHO repository managed by the Uppsala Monitoring Centre (UMC).

2.6.2.1 Uppsala Monitoring Centre (UMC)

The Uppsala Monitoring Centre (UMC) is the field name for the WHO Collaborating Centre for International Drug Monitoring and hosts a worldwide database of individual case safety reports, called VigiBase(119). The database receives reports concerning all health-related products with adverse events following immunisation representing about 8.5% of all reports held in VigiBase. Although there are currently 136 member countries to the WHO, the majority of case reports involving vaccines are contributed by the USA and individual European countries(119). In 2005 (and prior to establishment of SAEFVIC) Australia ranked 6th in average annual AEFI reporting rate per 10,000 population (aged under 5 years) according to VigiBase (Figure 3)(120).

Figure 3: Average yearly AEFI reporting rate*, by country, VigiBase (Letourneau *et al.* 2008)

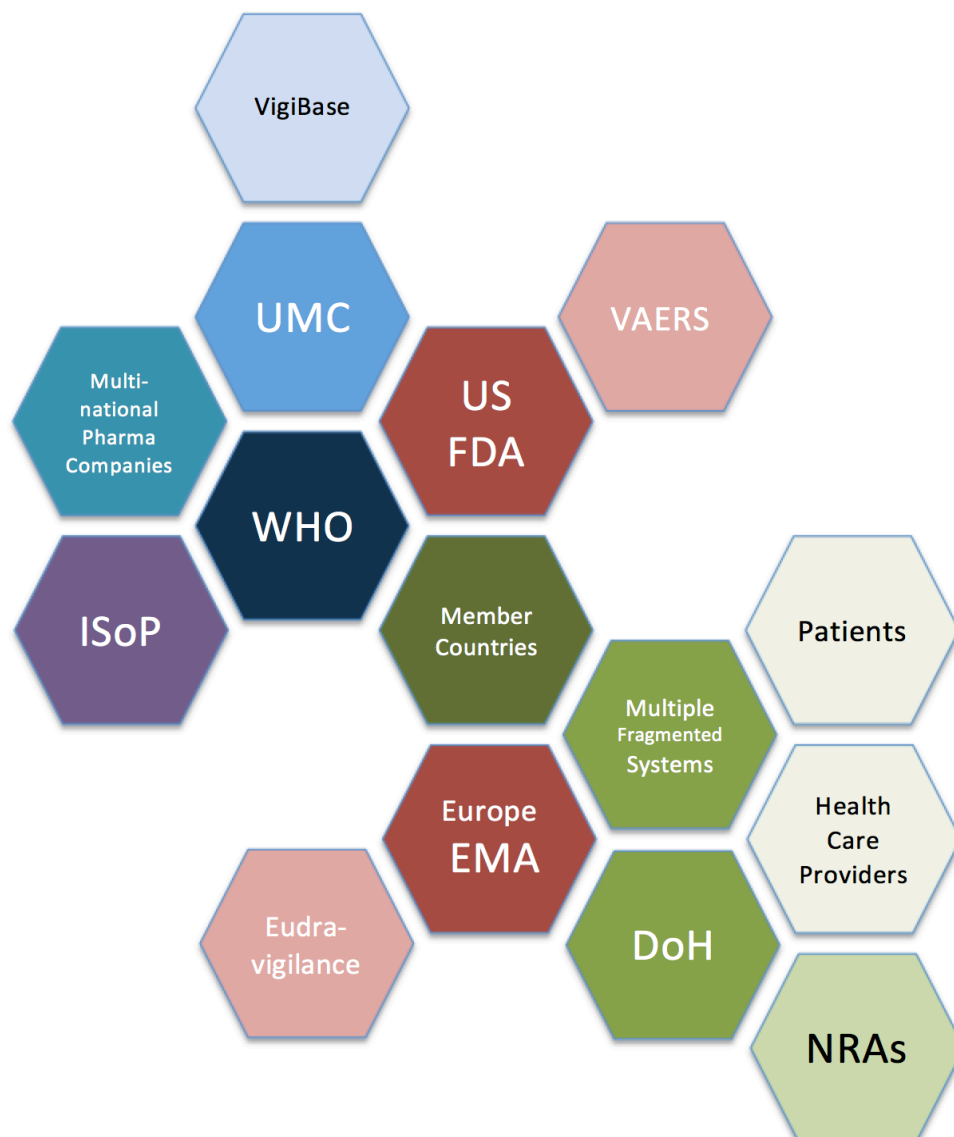


* for population less than 5 years of age, 1 January 1996–30 May 2005.

Through VigiBase, the UMC provides useful information in monitoring the safety of vaccines by bringing together data from a network of pharmacovigilance centres and vaccine manufacturers from worldwide sources thus providing a larger volume of data to facilitate signal detection and investigation analyses(119).

The schematic below (Figure 4) demonstrates the complexity of the current pharmacovigilance landscape and highlights the dominant contribution from the US Vaccine Adverse Events Reporting System (VAERS) and European Eudravigilance reporting systems. SAEFVIC sits within the “multi-fragmented systems” connected to Australia as a component of “Member Countries”(121). As Australia is a recognised leader in formulating immunisation policy and provides sizeable representation of the southern hemisphere it would be impressive if improvements to adverse event reporting could bring Australia to feature as predominantly as its US and European counterparts as an informant to global pharmacovigilance.

Figure 4: Schematic representation of the global pharmacovigilance landscape (adapted from Schuere *et al.* 2017)(121)



2.7 National AEFI surveillance systems

Industrialised countries, and particularly those that produce vaccines, have had National Regulatory Authorities and structures for AEFI surveillance in place for many decades as an integral part of drug and vaccine safety.

In some countries, AEFI reporting occurs via the same channels as those used for adverse drug reactions to medicines (e.g. UK,(122) New Zealand(123)), whereas others use vaccine-specific reporting forms and/or surveillance systems that are unique to vaccines and differ from the medicine safety monitoring systems within their own countries (e.g. the USA,(124) Canada,(125) the Netherlands(126)).

While efficiencies of scale may suggest it appropriate for vaccine AEFI surveillance to be captured within a broader pharmaceutical adverse event surveillance system, there are important differences. Vaccines are administered to entire cohorts of the population as opposed to pharmaceuticals that are mainly used in specific, smaller numbers of individuals exclusively for therapeutic purposes. This increased volume and scale of administration increases the implications for adverse events. AEFI may also be perceived as more important to the health of the population and have a community responsibility because vaccines are administered for the benefit of both the individual and for the community, not just the individual as is the case for pharmaceuticals(31). Furthermore, as vaccines are administered voluntarily to predominantly healthy individuals, the tolerance for adverse events and acceptance of risk is reduced(30, 31).

While these differences do not preclude a combined system, the efficiency for AEFI detection, reporting and communication must be appropriately sensitive, timely and responsive to community concerns.

Historically Australia used a combined system but since 2011 moved to a separate vaccine-specific reporting and analysis platform(127). Summary descriptions of AEFI surveillance systems in industrialised countries similar to Australia are provided below, with further information on evaluations of these systems, where available, discussed in Chapter 5: Evaluation of AEFI surveillance systems.

2.7.1 USA

In the USA, the passive surveillance system Vaccine Adverse Events Reporting System (VAERS) was implemented in 1990 by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) to provide a unified national focus for collection of all AEFI reports of clinical importance(124, 128, 129). Around 30,000 events are reported annually, from both healthcare professionals (38%), vaccine manufacturers (30%) and the public (14%), to this system(129). Collated de-identified data are publicly available at <https://vaers.hhs.gov/data.html> and updated approximately 4–6 weeks after receipt.

VAERS has provided some of the first safety data after the introduction of a number of vaccines and/or identified potential new vaccine safety issues from small clusters or with unusual clinical features (130-138). Due to the size and longevity of the database, VAERS serves as a useful source of cases for further investigation of AEFI signals and/or rare events(97, 138-142). New tools are being developed and applied to automate screening for signals using statistical algorithms and pattern recognition in extremely large databases(143-145).

2.7.2 Canada

The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) has been in existence since 1987(146). It is a voluntary vaccine-specific reporting system in which AEFI reports collected by provincial and/or territorial public health authorities are submitted to the national Canadian AEFI database, overseen by the Vaccine Safety Section in the Centre for Immunization and Respiratory Infectious Diseases of the Public Health Agency of Canada (PHAC)(146-148). While reporting nationally is voluntary, several Canadian provinces and territories have laws requiring that healthcare professionals report AEFI. CAEFISS receives approximately 3,000 reports per annum—although it is noted that technical difficulties have prevented some jurisdictions from reporting—with predominantly (90%) from health providers(149). Vaccine safety concerns are managed through the Vaccine Vigilance Working Group (VVGW) with a specific expert panel known as the Advisory Committee

on Causality Assessment (ACCA) convened to review serious AEFI. Information and quarterly reports are provided at www.canada.ca/en/public-health/services/immunization/canadian-adverse-events-following-immunization-surveillance-system-caefiss.html

2.7.3 Europe

In the majority of European countries, AEFI surveillance is carried out under the auspices of the European Medicines Agency (EMA). The EMA is the medical regulatory agency of the European Union and also coordinates the Pharmacovigilance Risk Assessment Committee (PRAC), which is responsible for assessing and monitoring the safety of human pharmaceuticals, including vaccines. While the development of vaccine safety systems has been heterogeneous, vaccine safety surveillance across all countries relies on passive reporting of suspected AEFI(150). AEFI reporting uses the same route and forms as used for adverse drug reactions (ADRs) in all except four countries (Switzerland, Finland, Norway and Netherlands (children)), thereby missing some important detail specific to vaccine administration(150). Collated data on suspected adverse reactions from the various country systems are held in the EudraVigilance database.

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was established in 2007. The network aims to strengthen the monitoring of the benefit-risk balance of all pharmaceuticals through development of best practice guidelines (*Good Pharmacovigilance Practices* (GVP))(151, 152). This coordinated collaboration has assisted to amend deficiencies identified in earlier studies from 2000, where a survey of EU Member States (plus Norway and Switzerland) identified several inconsistencies. Particular issues highlighted included: “lack of full-time staff and funding, lack of definitions, lack of denominators and, as a consequence, lack of proper analyses, and inappropriate or non-existent feedback”(150).

Established in 2005, the European Centre for Disease Prevention and Control was designed with the aim to strengthen Europe’s defences against infectious diseases. The European CDPC supports links between the stakeholders and aims to provide stable and transparent information on adverse reactions following immunisation, with

the final goal of increasing compliance to safe and effective vaccination programs(112).

However, interesting divergences in reporting remain. One example is in the UK, where the Medicines and Healthcare Products Regulatory Agency (MHRA) is responsible for monitoring medicines, including vaccines. Submissions of suspected adverse event reactions are via the Yellow Card Scheme (www.yellowcard.gov.uk), a voluntary reporting system that has been open to medical practitioners and dentists since 1964; extending to other health practitioners in the 1990s and further extending to patients and their families in 2005. The yellow card scheme has a peculiar limitation of requirement to report only serious AEFI once a vaccine has been on the market for more than two years(153).

A call for unification of efforts has arisen in Europe because although relevant surveillance systems were identified across 26 countries, there was variability in reporting procedures and analysis performances(150). Recognition of these differences led to prioritisation to identify minimum requirements for a “qualified AEFI surveillance system” in order to reach a shared gold standard(154).

2.7.4 New Zealand

In New Zealand, the safety monitoring of medicines (including vaccines) is conducted through Medsafe. Suspected adverse reactions to vaccines are reported to the Centre for Adverse Reactions Monitoring (CARM) of the New Zealand Pharmacovigilance Centre, which informs the Medicines Adverse Reactions Committee (MARC) of any potential vaccine safety issues(155). Healthcare professionals and consumers in New Zealand are encouraged to report any suspected AEFI in a passive AEFI surveillance system(156). A commentary review in 2002 suggested opportunities for system enhancement through data linkage, active surveillance and the potential for separating surveillance of vaccine adverse events from other pharmaceuticals(157). However, the system remains a single data repository(158). Information on reported vaccine adverse event data are publically available since 2012 through the *Suspected Medicine Adverse Reaction Search* online tool(158).

CARM received 1,275 adverse event reports relating to vaccines in 2017(159). New Zealand has one of the highest AEFI reporting rates per capita, however, the small population means New Zealand is less likely to provide early detection of new rare AEFI(160, 161).

2.8 Australia

The Therapeutic Goods Administration (TGA) is the national regulatory authority in Australia responsible for regulating medicines and vaccines and for monitoring their safety once on the market(162). The principles and objectives for the Australian AEFI surveillance system were developed, in part, based on the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS)(163). This post-marketing passive reporting surveillance system, in existence for many years, has evolved from one initially including only doctors, to encompassing more enhanced approaches with numerous reporter types (e.g. general public and state and territory health departments)(164). As individual states and territories have primary responsibility under Australia's constitution for public health issues, including vaccine delivery and safety issues(165), variant structures have been developed by the individual jurisdictions to collect, collate and report on AEFI to the national level(166).

In 2005, a National Vaccine Safety Workshop reviewed vaccine safety surveillance in Australia, with an ambition to work towards developing a national vaccine safety strategy(166). While the process of centralised notification to the TGA provided strengths in review, analysis and regular publication of summary data, it was recognised that the significant differences in surveillance systems among the jurisdictions was a weakness. Conflicting priorities were also identified between the need for timely reporting at the national level versus concluding the investigation and completing the report for the individual at the local level. These variances in jurisdictional reporting lead to complexity in the analysis and interpretation of AEFI surveillance data nationally(166, 167).

This review and critique of the systems strengths and limitations led to recommendations for improving AEFI surveillance being made(166), which were later

reiterated by Horvath in his review of surveillance in 2010(167). However, the “Review of the management of adverse events associated with Panvax® and Fluvax®: outcomes of recommendations” which details a system review conducted in 2012 (but not published until December of 2017) makes reference to progress made, but also indicated that the recommendations had not been specifically addressed and further work was needed(127).

Summarised reports of AEFI in Australia are published annually in *Communicable Disease Intelligence*(168) and—since August 2012—an online searchable database containing records of all adverse event reports for medicines and vaccines has been made available on the TGA website, called the Database of Adverse Event Notifications (DAEN)(169). The DAEN can be found at www.tga.gov.au/database-adverse-event-notifications-daen Information on the limitations of data available via the DAEN is provided, stressing the importance of referring to analyses of the reporting rates and trends, such as those regularly published for vaccines in the journal *Communicable Diseases Intelligence*(170).

2.8.1 Jurisdictional variation

As described above, passive AEFI surveillance in Australia originated as individual state and territory based systems that were encouraged, but not obliged, to share data nationally(100).

Surveillance practices differ considerably across the states, as do the level of resources available for surveillance and clinical management of AEFI(166).

AEFIs are recommended as notifiable conditions in all jurisdictions of Australia; however, the specific legislative requirements for AEFI reporting vary between jurisdictions (Table 4)(171).

In May 2000 the Therapeutic Goods Administration (TGA)(38) undertook responsibility to collate and review AEFI surveillance data, however the jurisdictional diversity borne from the early days remains evident with marked regional differences in surveillance methodologies and reporting rates(6).

Table 4: AEFI notification requirements by jurisdiction, Australia

Jurisdiction (State or Territory)	Notifiable (authorising legislation)
Australian Capital Territory	Yes (<i>Public Health Act 1997</i>)
New South Wales	Yes (<i>Public Health Act 2010</i>)
Northern Territory	Yes (<i>Notifiable Diseases Act 2016</i>)
Queensland	Yes (<i>Public Health Act 2005</i>)
Western Australia	Yes (<i>Health Regulations 1995</i>)
South Australia	Not under legislation; but recommended
Tasmania	Not under legislation; but recommended
Victoria	Not under legislation; but recommended

The table in Box 4 presents AEFI reporting rates in 2013 (at commencement of this PhD) and shows the two territories, Northern Territory and Australian Capital Territory had the highest AEFI reporting rates(172).

Box 4: 2013 National report showing diversity in jurisdictional reporting rates(172)

Table 3: Adverse events following immunisation records, ADRS database, 1 January to 31 December 2013, by state or territory

State or territory	AEFI records		Annual reporting rate per 100,000 population*		
	n	%	Overall	'Serious' outcome [†]	Aged <7 years
Australian Capital Territory	153	5	40.8 (34.6–47.8)	0.8	8.5
New South Wales	641	20	8.8 (8.1–9.5)	0.3	2.5
Northern Territory	66	2	28.1 (21.7–35.7)	2.6	12.3
Queensland	692	22	15.2 (14.0–16.3)	0.8	6.9
South Australia	201	6	12.1 (10.5–13.9)	0.8	5.9
Tasmania	41	1	8.0 (5.7–10.9)	0.4	2.9
Victoria	1005	32	17.9 (16.8–18.9)	0.7	10.2
Western Australia	317	10	13.0 (11.6–14.5)	0.9	7.2
Other [§]	45	2	na	na	na
Total	3,161	100	13.9 (13.4–14.4)	0.7	6.3

* Average annual rates per 100,000 population calculated using mid-2013 population estimates (Australian Bureau of Statistics).

† See previous reports^{2,3} for criteria used to assign causality ratings.

‡ AEFI records defined as 'serious' (i.e. recovery with sequelae, hospitalisation, life-threatening or death).

§ Records where the jurisdiction in which the AEFI occurred was not reported or was unclear. AEFI records in this category were notified mainly by pharmaceutical companies (n=38), general practitioners (n=5), members of the public (n=1) and nurses (n=1).

2.8.2 Limitations

In recent years the Australian system has come under intense scrutiny. In 2009, introduction of pandemic monovalent H1N1 2009 influenza vaccine was reliant on AEFI surveillance to determine the risk of vaccine-associated Guillain Barré syndrome (GBS). GBS was considered a vaccine risk as increased incidence had been observed in association with a pandemic-response H1N1 strain vaccine in 1976 (173, 174). This was followed in the next year (2010), by an unexpected and alarming increased risk of fever and febrile seizures following immunisation with an Australian-manufactured brand of seasonal trivalent influenza vaccine (Fluvax® CSL Biotherapies, Australia) (175-177). In response, the Chief Health Officer of Australia suspended the use of influenza vaccines in children under 5 years of age (178). However, considerable criticism was raised that systems had been inadequate to detect the safety signal in a more timely manner and prevent further cases prior to the suspension(9). In response to these events, two expert reviews were commissioned; the West Australian Stokes Ministerial Review reviewed the public health response and the TGA commissioned Horvath Review was tasked “to provide recommendations for the improvement of AEFI surveillance in Australia”(6, 9, 167).

The Australian AEFI surveillance system—according to the Stokes/ Horvath reviews—were found to be sub-optimal. Stokes’ review “revealed an adverse event reporting system that is not robust or timely” and described the combination of state-based and national reporting as “confusing”(9). Horvath recognised that while “monitoring of AEFI in Australia is in keeping with international systems of passive adverse events surveillance” “improvements could be made”(167). Recommendations were presented across seven specific areas (Box 5), all of which were accepted by the Government with a two-year timeframe agreed for implementation, with a 2012 review of the recommendation outcomes indicating progress being made(6, 167).

Box 5: Recommended areas for vaccine safety improvement, Horvath, 2011(6)

Recommended areas for vaccine safety improvement

1. The governance of the vaccine safety system
2. Defining surveillance objectives and establishing protocols and procedures for managing adverse events following immunisation.
3. Improving the national system for timely reporting of adverse events following immunisation.
4. Raising community and health professional awareness of vaccine safety monitoring to ensure more complete reporting of adverse events following immunisation.
5. Nationally agreed protocols for national immunisation program action and communication.
6. Transparency and the functions of the TGA to ensure better access to vaccine safety information for consumers and health professionals.
7. Vaccine usage and safety monitoring data

2.8.3 Victoria

AEFI surveillance in Victoria, prior to 2007, relied on spontaneous reports from health professionals submitted direct to the TGA. Although Victoria was the second most populous state in Australia, with an estimated population of 5.96 million, and a birth cohort of 75,000 per annum it ranked next to last of all jurisdictions nationally for AEFI reporting with 2.6 per 100,000 population in 2003(1, 14).

In 2007 the Department of Health funded the establishment of a state-level enhanced passive surveillance system called *Surveillance of Adverse Events Following Vaccination in the Community* (SAEFVIC) in order to address the observed deficit in AEFI reporting in Victoria compared to other states and to improve AEFI services in Victoria(14).

The Stokes report, published in 2010, specifically noted this Victorian state-based AEFI surveillance system, SAEFVIC, as a possible model for use by states that did not have a robust AEFI surveillance(9).

2.8.3.1 SAEFVIC enhanced passive AEFI surveillance system

SAEFVIC is a Department of Health funded and independently operated service comprised of a central reporting enhanced passive surveillance system integrated with clinical services. It provides expert immunisation safety advice to reporters and health-care workers, as well as for children and adults who have experienced AEFI(1). At its inception in 2007 the stated objectives for SAEFVIC were to 1) improve reporting of AEFI 2) detect, validate and inform on potential vaccine safety signals and 3) to help maintain confidence in immunisation services(1).

A full description of the SAEFVIC vaccine pharmacovigilance surveillance system (as at 2013 and commencement of this PhD) is provided in Appendix 1: Clothier *et al.* Surveillance of adverse events following immunisation in Victoria: The model of SAEFVIC(1). Detailed methods for data collection, collation and analysis are described in *Chapter 3: Methods*.

The overarching goal of this PhD was to optimise SAEFVIC: therefore the body of works presented in the subsequent chapters document SAEFVIC in various iterations of its maturation. At commencement of this PhD in 2013, SAEFVIC was in its fifth year of operation and held 5,382 reports with 7,554 reactions listed in the dataset (as a person may describe multiple AEFI from a single immunisation event). A summary of SAEFVIC surveillance data and activities at this timepoint is presented in *Chapter 4: SAEFVIC early years*, as a publication titled “SAEFVIC: Surveillance of adverse events following immunisation (AEFI) in Victoria, 2012”(179).

As at the end of 2019, 11 years since inception and at the end of this PhD, SAEFVIC held 16,168 reports with 24,153 reactions. These data are summarised in *Chapter 8: SAEFVIC maturation*, in the publication titled “SAEFVIC: Surveillance of adverse events following immunisation (AEFI) in Victoria, 2018”.

SAEFVIC has since evolved to a semi-national surveillance system with additional expansion of the clinical assessment component, called AEFI-CAN(180). Discussion of the incorporation and impact of this PhD in this maturation of SAEFVIC and opportunities for future exploration are presented in the final *Chapter 9: Optimising SAEFVIC*.

Chapter 3: Research methods

3.1 Study design

This doctoral thesis comprises a body of work leading to practical implementation of concepts and creation of transformational change within the SAEFVIC enhanced passive surveillance of adverse event following immunisation (AEFI) system.

SAEFVIC, as a post-licensure AEFI surveillance system, is considered a phase IV observational, non-interventional study conducted in a naturalistic setting in line with current practice(181). Through receiving and collating reports of adverse events following immunisation, SAEFVIC aims to detect, validate and inform on potential vaccine safety signals and thus maintain confidence in immunisation services(1).

SAEFVIC, as a collection of AEFI reports, may be considered as a retrospective cohort in that persons reported all experienced a common event (vaccination) and, at the time of reporting, both the exposure and the outcome (AEFI) were known(182). However, partiality arises as information on the non-exposed (unvaccinated) arm of the cohort is absent.

The foundation of these studies is to provide information, through interpretation of aggregated data, towards examining the utility and capability of the SAEFVIC passive surveillance system to identify and validate signals within the cohort.

3.1.1 Observational studies

Observational studies are those where the researchers observe the effect of a risk factor or intervention—in this case the reactogenic effect of immunisation—without any intervention to the exposure(182). Studies can be conducted prospectively, with participants recruited after the exposure has occurred and followed to determine the outcome, or retrospectively after both intervention and outcome have already occurred. Observational studies such as cohort, cross-sectional, case-control, ecological and case series, generate hypotheses of associations and are not confirmatory of causation(82, 183).

Advantages of observational studies include being of relatively low complexity and therefore cost-efficient, with ethical constraints minimised to predominantly data privacy issues given that no interventions—in the context of vaccine or medication safety studies—are undertaken(183, 184). However, observational studies are vulnerable to systematic errors of bias and confounding(183). This is discussed further in section 3.5 below)

3.1.2 Data sources

This PhD is primarily focused on data held by SAEFVIC for the purpose of surveillance of adverse events following immunisation in the state of Victoria. In addition a variety of data sources were accessed to address specific research questions and to enable calculation of proportions and risks; namely population distribution data (Australian Bureau of Statistics (ABS)), hospital admission and emergency department attendance data (Victorian admitted episodes dataset (VAED) and Victorian emergency minimum dataset (VEMD)), administered immunisation data (Australian Immunisation Register (AIR) and its precursor the Australian Childhood Immunisation Register (ACIR)) and vaccine doses distributed data from the Department of Health and Human Services, Victoria: each of which are described in further detail in below (Section 3.4: Supporting data sources).

3.2 SAEFVIC

Surveillance of adverse events following vaccination in the community (SAEFVIC) is an enhanced passive surveillance system linked with clinical support services. The system commenced in May 2007 and is operated through a partnership of the Murdoch Children's Research Institute, The Royal Children's Hospital and Monash Health, with funding provided by the Department of Health and Human Services, Victoria. As a jurisdictional service its primary function is to provide vaccine safety vigilance information on adverse events occurring within the state of Victoria. However, there is a broader agenda for SAEFVIC as an entity to further vaccine pharmacovigilance in a capacity supporting research activities. Therefore the term SAEFVIC is referred interchangeably as both a database and as an entity. The model of SAEFVIC is described in Appendix 1 (published prior to this PhD)(1), with specific elements

relevant to research activities within this thesis expanded upon in the following sections.

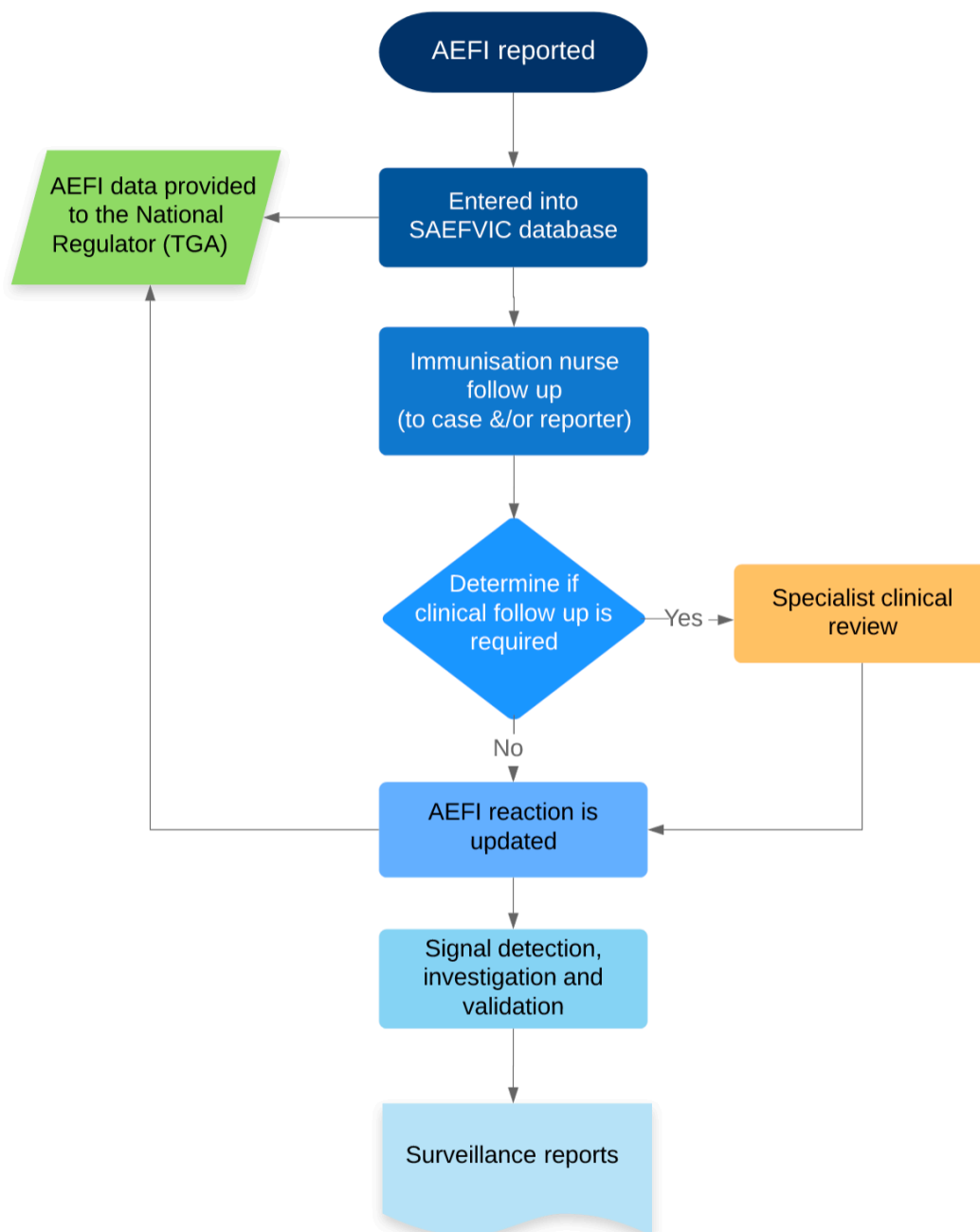
3.2.1 Surveillance process

Reporting of AEFI to SAEFVIC has been described previously and forms part of the descriptive studies within this thesis. As an overview, any person who perceives an AEFI has occurred may submit a report to SAEFVIC, however education for reporting to—and receiving feedback from—SAEFVIC targets immunisation and healthcare providers. Flexible reporting platforms are offered: the original paper-based form being submitted by post or fax being augmented with online reporting from 2010. All reported vaccinees for whom consent is provided for follow-up, are contacted by an immunisation nurse to elicit relevant clinical information and maximise data field compliance. Consent is almost universal with less than 2% denied in the 12-year history of consent: a majority of absent consent originate from active surveillance reporting. Reports progress from submission to being in-progress while under review, before being deemed complete, or referred for clinical review. Data quality is managed through an authorisation step, where a senior immunisation nurse reviews all reports for consistency to clinical case definitions and completed documentation. A schematic flow chart of these processes is presented in Figure 5 below.

Victorian AEFI are reported to the national regulator, the Therapeutic Goods Administration (TGA) on receipt of the initial report, with any clinical review amendments provided subsequently. Significant serious AEFI are reported directly to the Department of Health, Canberra; the Department of Health and Human Services Victoria and de-identified to the pharmaceutical manufacturing company of the implicated vaccines. Aggregated reports are presented quarterly to the Department of Health and Human Services, Victoria and on request to providers. SAEFVIC processes and data interpretations have been regularly presented at conferences (*Chapter 1: Introduction* lists those arising from—or co-authored and relevant to—this PhD and first authored conference abstracts, presentations and posters are provided in Appendix 2).

3.2.1.1 Flow of SAEFVIC surveillance process

Figure 5: Schematic flow diagram of SAEFVIC surveillance process



3.2.2 SAEFVIC data

This PhD employed all data available within the SAEFVIC dataset. The SAEFVIC cohort can be defined as all people who have been vaccinated and experienced an AEFI that was reported in Victoria during the period defined for each study.

The SAEFVIC AEFI reporting form collects information on demographic characteristics of the vaccine recipient, details of vaccine(s) received and description of AEFIs experienced. The current (2019) AEFI reporting forms (printed and online), clinical follow up and clinic visit record form are provided in Appendix 3.

Categories created to collapse data fields according to relevant groups or subgroups and to facilitate analyses are described in the individual studies presented in this thesis. Commonly calculated data fields and categories created include;

1. Age at vaccination: calculated by subtracting vaccination date from date of birth
2. Time to report: calculated as the period between vaccination date and reported date with subtraction of time to onset of symptoms, if known.
3. Age group: defined using age at vaccination. Studies used different age groups depending on whether conforming to the National Immunisation Program (NIP), AIR/ACIR denominator or other conventions.

For analyses of surveillance efficiency and for signal detection data are routinely extracted for analysis using date reported, not date of vaccination, as date reported considers the reporting processes and also the reality of data availability for investigations. On occasions an individual may only report an AEFI in a historical context arising due to concern for onward vaccination: meaning there may be considerable time-gap between the time of vaccination and reporting. These historical reports are excluded from some analyses (as stated in individual methods sections), however the period defining “historic” is subjective. Occasionally, reports are entered into SAEFVIC for persons yet to receive an immunisation as a means to document the pre-immunisation clinical consultation. These reports are designated as “non-events” in the dataset: as numbers are small inclusion is generally insignificant, however methods statements clarify if they are excluded from analyses.

Data completeness is discussed in *Chapter 5: SAEFVIC Evaluation*, as a component of the evaluation outputs and as a STROBE statement in the descriptive epidemiology summary presented in *Chapter 8: SAEFVIC maturation*(185). Completeness was

strongly influenced by introduction of online reporting in 2010, which mandated minimum dataset fields: the uptake of online reporting was progressive through the duration of the PhD (see publications in Chapter 5 and 8)(15, 185).

Transformational impact of this PhD on data is evident with changes incorporated over the 7-year study period, in particular introduction of vaccinee demographic indicators of pregnancy and Indigenous status, surveillance data source (active or passive) and onward vaccination information resulting from clinical review. These are discussed further in *Chapter 9: Optimising SAEFVIC*. Milestone timepoints including inter-relation with these doctoral studies are described below in Section 3.2.3 below.

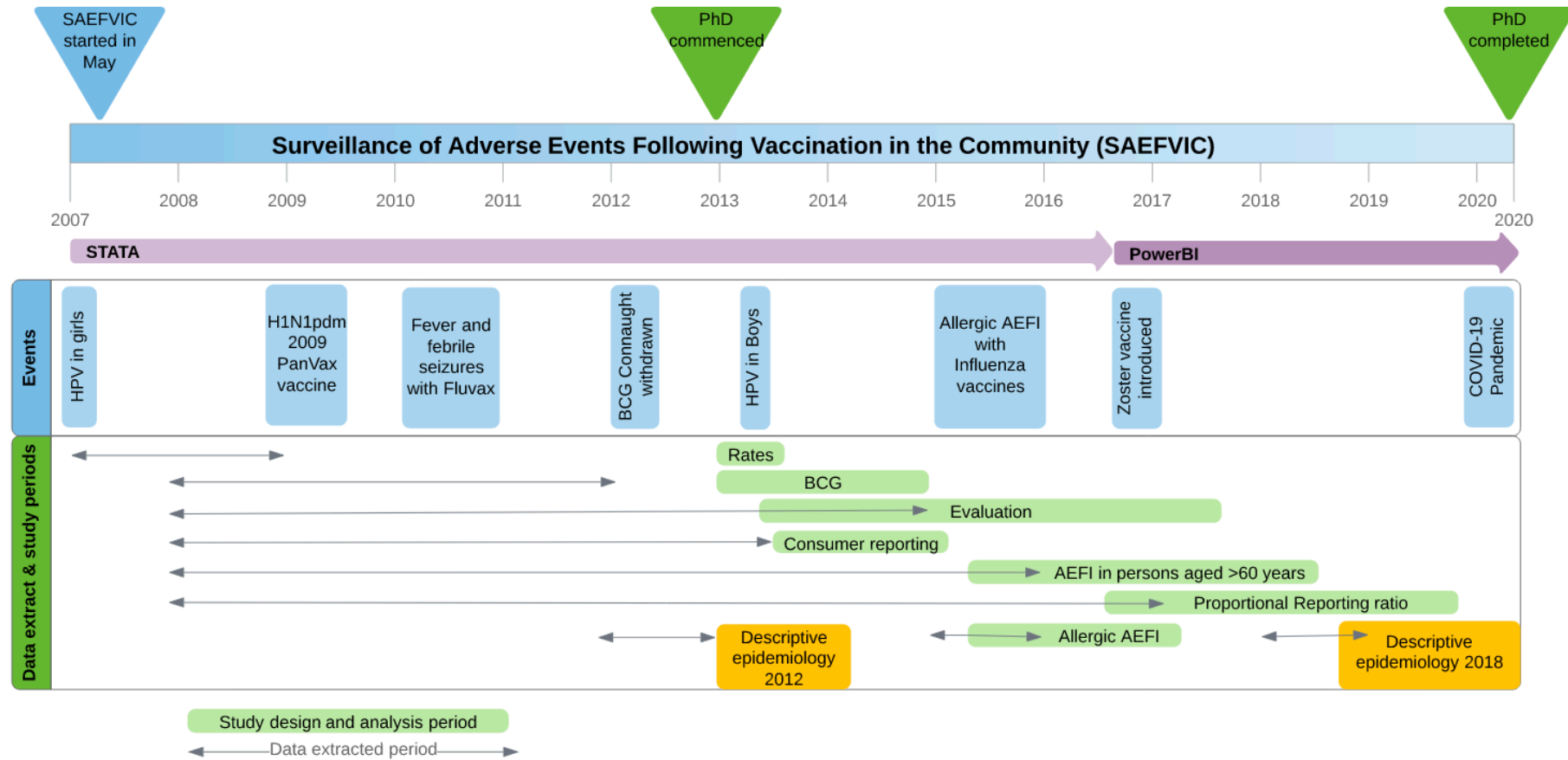
3.2.2.1 Granular detail of AEFI data

An AEFI report is a case report relating to outcome from one immunisation encounter, with each report assigned a unique identifier. However, multiple vaccines may be coadministered at that encounter and the case may experience multiple reactions. The AEFI report may be submitted by the case or guardian as a first person report, or by a secondary party such as the immunisation provider or a health care practitioner. Data are recorded with this granular level of detail to facilitate a broad range of analyses across a variety of perspectives: informing on the process of data collection (i.e delineating health care provider or consumer reported) as well as AEFI by case demographic, vaccines administered or reaction outcomes. Base records are held as a single line by case and reaction, with multiple line duplication for each vaccine administered. This complexity requires vigilance in what parameter is being counted—case, vaccine or reaction—and management of duplications of individual case report by identifier.

3.2.3 Milestone timepoints

During the course of this doctoral work specific milestone points are recognised as either being influential on surveillance trends or as transformations arising through this thesis. In addition—and not documented here—are the national immunisation programme changes(detailed in the Australian Immunisation Handbook and in National annual surveillance reports)(186, 187) (Figure 6).

Figure 6: SAEFVIC surveillance timeline, noting key timepoints and milestones



3.2.4 Ethical approval

The Murdoch Children's Research Institute is the data custodian of the SAEFVIC database, auspiced under the Human Research Ethics Committee of the Royal Children's Hospital, Victoria (RCH-HREC). Permission to access data for the purpose for which it was collected—that is, as a public health surveillance system for vaccine safety monitoring—was granted by the RCH-HREC under provisions of a registered database DA017-2013-04 (2013—2016) and from August 2016 onwards under the Research Ethics and Governance of the Royal Children's Hospital, Victoria approval No. 37194. For the purposes of this PhD the ethical approval was registered with the University of Melbourne Ethics Committee No.1340750. Where specific studies fell outside the purposes of the registered database, additional low and negligible risk ethical approval was sought and is recorded in the respective publications.

3.3 Population under investigation

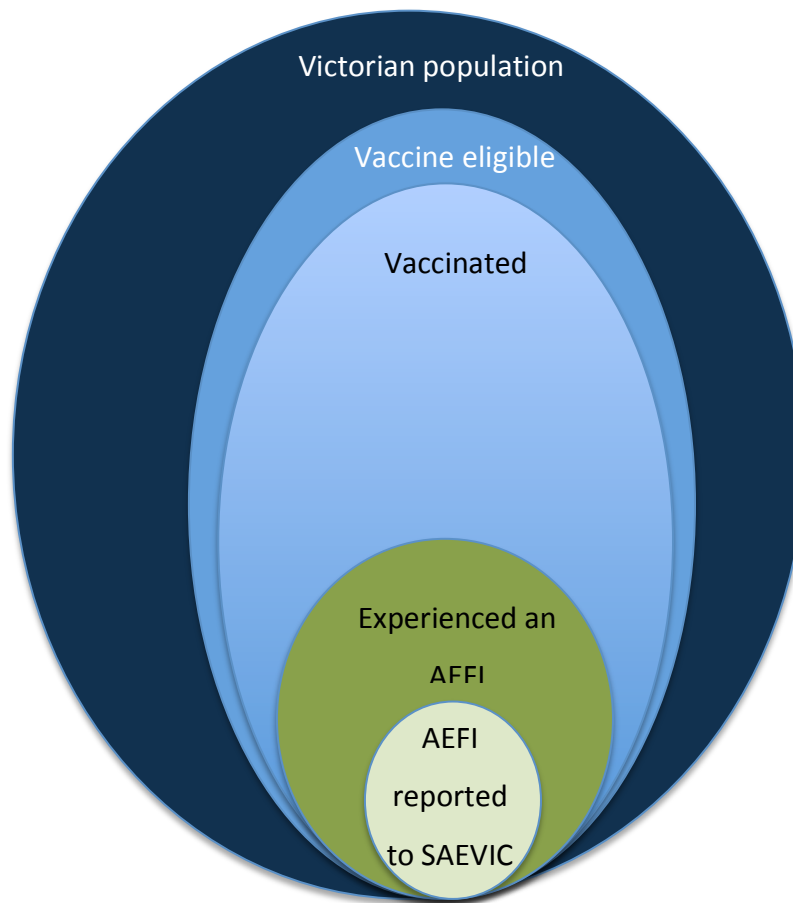
SAEFVIC receives reports of adverse events following immunisation that have occurred in Victoria: the immunisation may have been administered in Victoria or anywhere worldwide. The various populations as relevant to vaccine pharmacovigilance are schematically presented in Figure 7. Further details of these populations and the representative datasets used within this PhD to estimate them are described in sections 3.3.1 (numerator) and 3.3.2 (denominator).

Victorian population is estimated through census data collected by the Australian Bureau of Statistics (ABS). SAEFVIC records all AEFI that are reported in Victoria and therefore the population under investigation is the entirety of Victorian residents and any persons who maybe temporarily located within Victoria at the time of experiencing an AEFI. As the latter group is small and has no corresponding denominator they are considered synonymous to the residential population.

Vaccine eligible population is detailed in the national immunisation policy (NIP) as those persons or at-risk cohorts recommended to receive vaccines. However, the NIP changes over time and there are variations in vaccine funding and recommendations for at-risk cohorts that may be difficult to quantify. The ABS may support estimates of

populations by age group or Indigenous status (although Indigenous status may be declared differently for statistical purposes compared with access to health services) but lacks information on health risk indicators such as pregnancy, co-morbidity or travel.

Figure 7: Schematic of population categories relevant to vaccine pharmacovigilance



Vaccinated population data may be recorded in national or jurisdictional immunisation registers (see discussion in section 3.4.1 below)

Experienced an AEFI will be evidenced depending on the individuals perception of firstly having an adverse event and secondly it being associated with vaccination. Mild events prompting no health contact are unquantifiable. Serious AEFI may be recorded in hospital administration datasets (VAED, VEMD) although positive predictive value of ICD-10 coding is imperfect(188, 189).

Reported AEFI will be according to the traditional “notification pyramid”, influenced by the hierarchy of health contact according to seriousness or severity of the reaction directing consumer concern and health seeking behaviour(190). Individuals may seek to resolve concerns independently through internet resources or access health care through increasing levels of contact such as; health phone support services; visiting general practitioner and; attendance at hospitals as an emergency department visit or admission, which consequently influences reporting propensities and data accessibility.

3.3.1 Numerator

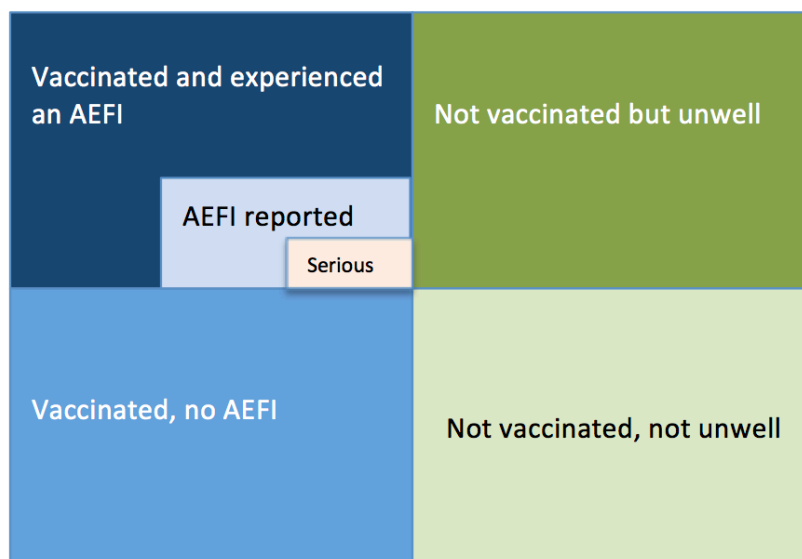
For this PhD the numerator is adverse events following immunisation (AEFI) and various subsets thereof, for example by; vaccines administered, reaction type, seriousness of the reaction and/or demographics of the vaccinee.

Descriptive epidemiology may consider the numerator in two ways; as AEFI reports received by SAEFVIC, for which the population is the entirety of the database and is therefore known or; as a sample of persons who experience an AEFI and report to SAEFVIC, for which inferential statistics should be applied as the entire population who have experienced an AEFI is not known.

Under-reporting is a known limitation of passive surveillance systems (as described above). The level of case ascertainment is undefined and can be influenced by reporting behaviour stimuli such as education, clinical alerts or media(190). It would also be anticipated that propensity to report would increase over time as knowledge of SAEFVIC increased; although not necessarily evenly across all numerator subsets or cohorts.

Calculations may consider elements from a 2x2 contingency table (Figure 8)

Figure 8: Contingency table for vaccination and AEFI



Analyses of AEFI reports are inconsistently presented in the literature, with AEFI reporting rates a commonly used terminology. A true incidence rate requires the measure of AEFI (or AEFI reporting) frequency within a defined population by specific unit of time such as person-years. However, the common convention of stating AEFI reporting rate by size of the population initially at risk (for example per 100,000 population, not accounting for those having already received vaccination) is more accurately a proportion. Additionally AEFI reporting may be stated in the absence of expressed unit of time, referring only to the case count in the numerator and size of population in the denominator.

Calculations should therefore reflect AEFI reporting as either a;

- i) proportion of a population
- ii) incidence proportion within a population, for a specified time period
- lii) rate within a population, by specific unit of time

Where determining subgroups within AEFI reporting require a subjective or categorical sampling measure—for example AEFI deemed to meet the definition of serious or a case definition for a specific reaction—calculations may be considered as a sample estimate from within the AEFI reported population as a different researcher may have a different interpretation of the definition.

3.3.2 Denominator

The true exposed denominator for calculating incidence of AEFI is the vaccinated population, for which the lack of data thereof is frequently reiterated throughout this PhD, as it is in the broader literature. Proxy measures are equally fraught due to the population-specific targeting of vaccinations, multiple-dose schedules and variations in program funding influencing both vaccine distribution and recording of immunisation encounters.

Inclusion of population not eligible for vaccination within the denominator will falsely diminish AEFI incidence estimation, likewise failure to account for multi-dose schedule will erroneously increase incidence risk estimates.

This PhD adopts three widely applied conventions for denominator approximation

1. vaccines administered
2. general population
3. vaccine doses distributed

Additional consideration is given to background rates of conditions that may present as an AEFI reaction in section 3.3.2.4.

3.3.2.1 Vaccines administered

Vaccine administered is the definition of an exposed population denominator for calculating the risk of an AEFI occurring per vaccination encounter, which could be further defined by subpopulation demographics. Ideally every immunisation encounter would be recorded in a register. However, accurate immunisation lifetime registers remain rare(191). In Australia, vaccines may be administered in a variety of settings (local council, general practice, school, industry), each with their own record-keeping systems, which are not compulsorily linked to a single collated repository. Where immunisations are recorded into a central register it is usual to record vaccine brand, dose and vaccine recipient age but generally lack further demographic information or provider details. Furthermore, vaccines funded through national or jurisdictional programs may attract incentives that influence both administration and recording behaviours(192, 193). The 2019 introduction of the My Health Record may offer opportunities for improved capture of vaccination encounters, depending on

consumer uptake and if privacy concerns can be ameliorated sufficiently for data to be accessed for surveillance purposes(194).

3.3.2.2 General population

As vaccines are commonly and widely distributed in the general population, counts for some age-groups can provide a proxy measure of the vaccinated population. This is a reasonable estimation in the infant cohort where immunisation coverage with the national immunisation program directed 3-dose schedule at 2,4 and 6 months in Victoria has now breached the 94% target threshold(195). However, it is less reflective for other age groups where vaccination can be spread over a wide-range of years (influenza vaccines), or is targeted to a high-risk attribute not recorded in general population data such as a co-morbidity, pregnancy or travel.

It is paramount that methods statements make clear the underlying population denominator proximity to the expected vaccinated denominator. An example of the caution required when considering proxy population denominator is that of Rotavirus vaccines. In Victoria the schedule changed in July 2017 from RotaTeq® 3-dose schedule (2, 4 and 6 months of age) to Rotarix® 2-dose (2 and 4 months)(186). Convention is to calculate AEFI per population (risk according to complete vaccine schedule), in which case RotaTeq® will present with higher overall risk by nature of having the third dose. Multiplying the population denominator according to the dose exposure would be more accurate, enabling a comparison of risk per vaccination event.

Immunisation coverage should not be assumed as generalisable across the entire population strata. For example there are inconsistencies in vaccine uptake and vaccine hesitancy associated with beliefs and ethnicity, which can also give rise to geographic and socio-economic distributive patterns in the data(196). Limited description of this effect is presented in a poster in Appendix 2.

3.3.2.3 Doses distributed

Vaccine doses distributed provide an exaggerated estimate of vaccine doses administered. An unknown quantity of doses distributed will not be administered, for example, through natural wastage or incomplete usage of a multi-dose vial. However it may be an acceptable assumption that distribution patterns are relatively constant for

a given setting with known program parameters, such as the Department of Health distributions to Victoria.

Vaccine doses distributed have been used traditionally for retrospective vaccine reactogenicity comparisons and remain a useful support for analyses distinguishing immuniser provider type (for example, public and private hospitals, pharmacy or council settings)(197, 198).

3.3.2.4 Background rates of reactions

While incidence of AEFI by vaccine or population may be the main focus of surveillance, there is also interest in ascertaining the attributable risk of a reaction to immunisation. This requires knowledge of the background incidence of the reaction (symptom, condition, disease) of interest. There are prescribed lists of conditions notifiable under legislation, predominantly of infectious nature, with anaphylaxis included from November 2018(199), which can provide a background rate if records persist prior to introduction of a vaccine, or enhanced follow-up provides case vaccination status. Serious conditions that warrant medical attention may be recorded in hospital administration datasets for emergency department visitations or hospital admissions. For example, Guillain Barré syndrome is considered to have good capture within hospital datasets due to the severity of the paralysing condition and need for neurological assessment(173). However, despite use of case definitions and standardised international classification of disease coding, positive predictive value of records may be suboptimal. This was demonstrated in a recent audit of anaphylaxis recorded within a Victorian hospital admissions dataset, which showed a low positive predictive value for ICD-10 coding to identify anaphylaxis due to immunisation(188).

Many AEFI would not require medical attention beyond seeking reassurance and would be managed domestically, such as fever, redness at the site of injection or lethargy. Attempts to ascertain background rates have used prescription data (for allergic rash) or health information seeking either through medical advice (nurse on-call) or social media(200, 201). As electronic data-capture from routinely collected electronic health care data sources expand, new opportunities emerge for AEFI monitoring(93), either associated with immunisation (as re-attendance) or as

disaggregated assumptions of association (fever events during the influenza vaccination period) for which appropriate ethics may enable ascertainment of vaccination status. This latter method was used during the 2010 Fluvax® event with febrile convulsions (ICD-10 code R56.0) presenting to hospital ED, followed up for vaccination status as a means of active case finding during the 2010 Fluvax® event(202).

3.4 Supporting data sources

3.4.1 Australian Immunisation Registers

The landscape of national immunisation registers expanded during the course of this PhD to incorporate separate childhood and vaccine specific school-aged registers into a single national Australian Immunisation Register (AIR).

Varied jurisdiction-based registers and extraction programs from primary care practice software systems provide localised data in addition to interaction to inform the national registers(203). Additionally in Victoria (and South Australia) the local government held Immunisation Provider System (ImPS) uploads electronic records directly to the national register/s(203).

Linkage of these registers with healthcare outcome data, including vaccine safety data, have been demonstrated as feasible but are yet to be entrenched into routine practice(204, 205).

This PhD utilised data from original Australian Childhood Immunisation Register (ACIR) and latterly the AIR: descriptions of which are provided below. No data were accessed from the National Human Papillomavirus (HPV) Vaccination Program Register prior to its absorption within the AIR, therefore description is in context of its contribution to the all-of-life register since 2017.

3.4.1.1 Australian Childrens Immunisation Register (ACIR)

The Australian Immunisation Register (ACIR) served as the national immunisation register from 1996 until replacement by the AIR in 2016. ACIR recorded details of vaccinations given to children under seven years of age who resided in Australia and

were enrolled in Medicare on an opt-out basis and, if not eligible for Medicare, for whom a doctor or immunisation provider submitted an immunisation record(192, 203). ACIR records were accessible until a child reached 14 years of age.

Although lauded as “the world’s first attempt in developing a near-complete population-based immunisation register”(206), with an estimated 99% of Australia’s children enrolled in Medicare by their first birthday and the system being an opt-out, there were several limitations. Under-reporting, common with the original paper-based notifications improved with advances to online reporting and, in particular, where commercial developers of general practice software incorporated capacity for electronic exchange of information to registries. The range of vaccinations recorded was incomplete, limited primarily to the targeted NIP vaccines. Various incentives to both parents and providers for completing a child’s immunisation, administering immunisations, submitting reports of immunisation encounters have positively influenced immunisation coverage and data ascertainment into the register.

3.4.1.2 Australian Immunisation Register (AIR)

The Australian Immunisation Register (AIR) is a national register that aims to record all vaccines given to all people in Australia(207). It evolved as a progressive expansion of the ACIR: in January 2016 capture of immunisation information was raised from children aged under 7 years to young adults up to 20 years; then further broadened in the September of 2016 to include all-of-life vaccines administered. From the 2017 school year, the HPV Register was brought under the umbrella of AIR as the Australian School Vaccination Register (ASVR) recording all adolescent vaccinations given through school based programs, with full absorption completed by late 2018 upon which the HPV/ASV register closed(208).

The AIR receives data on all immunisations given through general practice (GP) and community clinics, which include all vaccines funded under the NIP, as well as any privately funded vaccines given through general practice such as travel vaccines. Individuals registered with Medicare are automatically included in AIR (regardless of any vaccination record), whereas persons without Medicare (for example refugees)

will be recorded retrospectively only upon submission of an initial immunisation report. Vaccinations administered outside of the GP or community setting, including those administered overseas, may be voluntarily submitted for inclusion to an individual's immunisation record, providing minimum documentation requirements are met(207).

A review of national reporting to AIR described how accuracy had improved with 86% of records deemed as accurate, largely influenced by the uptake of electronic automation of data extraction from GP practice software favouring over paper submissions. Victoria had a lower error of 3% compared to the national average of 13% attributed to the strict no jab-no play/pay policy incentivising reporting to the register(209). Scope of the review was however limited to childhood vaccines specified in the NIP and not indicative of accuracy for non-NIP vaccines(209, 210). Notably almost 70% of influenza vaccine encounters for at-risk children in a NSW 2016 study were not reported to AIR, which is a significant gap for a priority vaccination program(211).

AIR, and the preceding ACIR, records minimum vaccinee demographics of age and gender but does not inform on comorbidities or risk factors that attract funded or recommended vaccinations, or on immunisation provider.

AIR, as an all-of-life register with records of all enrolled in Medicare, regardless of an immunisation event, provides a close estimate of the vaccine eligible population as well as immunised population (a+c). As audits of data completeness become available the utility of AIR as a denominator will become clearer(210).

3.4.1.3 Data access

A range of standardised de-identified aggregate and unit-level reports are available from AIR for access by registered health care providers through an online portal(212). SAEFVIC is a registered state-wide provider. The report AIR002A providing number (or percentage) of individuals who have received valid vaccinations was used, with selection of all Victorian postcodes (3000–3999); age calculated at vaccination date and; vaccine brand.

As part of the My Health Record integration, individuals can choose to not share details of their immunisation record in reports generated from AIR for vaccination providers or approved secondary research purposes(194, 207). This control extends for guardians of children under aged 14, after which it becomes the individuals choice whether to share their immunisation history or not. In time, studies will need to consider consumer acceptance to share their immunisation history and the impact of withholding, particularly any inequities across subgroups(194).

3.4.2 Australian Bureau of Statistics

The Australian Bureau of Statistics (ABS) is the independent statistical agency of the Government of Australia providing key statistics on a range of population, economic, social and environmental issues(213). Data are collected via a national census conducted every five years. Population demography data are progressively released including population and population growth projections with a range of state-level information available including age (year), sex, country of birth and Indigenous status. Geographical areas are classified according to the Australian Statistical Geography Standard (ASGS) with correspondence tables assigning postcode to statistical areas. The 17th and most recent Australian census was held on 9 August 2016 with results available on the ABS website from 27 June 2017.

On commencement, this PhD used census data and projected estimates from the 2011 census, with studies from late 2017 onward using the 2016 census. The specific datasets used are referenced in the relevant study methods.

3.4.2.1 Data access

Data were freely accessible from the ABS website(213).

3.4.3 Vaccine doses distributed

The Department of Health contracts distribution of government funded vaccines according to pre-order allocations and provider requests. Providers are recommended to order one month supply on a monthly basis with up to one month supply in reserve while awaiting delivery(214). No data were available on returns or wastage.

3.4.3.1 Data access

Dose distribution data were provided to SAFEVIC upon request to the Immunisation Department, Victoria. Data were received as excel spreadsheets with data aggregated to brand, packaging multiples, recipient provider type and month of distribution. In 2019 discussion commenced regarding continuous remote data access using the cloud environment.

3.4.4 Hospital administration datasets

Victorian hospital administration datasets, VAED (admissions) and VEMD (emergency department presentations) were accessed to estimate background rates of selected conditions that may present as adverse event following immunisation with Gardasil® (*Chapter 7: Signal detection*). This equates to (b) “not vaccinated, reaction” in the 2x2 contingency scenario.

Hospital administration VEMD data were also explored in the co-authored investigation monitoring emergency presentations of fever during the seasonal influenza vaccination period as a proxy indicator of potential vaccine safety signal(202).

3.4.4.1 VAED

VAED collates administrative and clinical data detailing separations (as an admitted episode end-point) from all Victorian public and private hospitals, including rehabilitation centres, extended care facilities and day procedure centres. Records are accessible from 2000 onwards.

3.4.4.2 VEMD

VEMD collates administrative and clinical data detailing presentations at Victorian public hospitals with designated emergency departments (ED). Various access points to data are captured: initial assessment at triage; ICD-10 codes assigned on discharge, noting need to avoid duplication should the person be “discharged” from the ED to become an admission.

For this PhD data linkage of VAED and VEMD was manually processed by the data custodians using Medicare number as the unique identifier with linkage output

provided de-identified for final analysis. Since 2016 the Department is progressing a comprehensive data linkage program through The Centre for Victorian Data Linkage (CVDL)(205). <https://www2.health.vic.gov.au/about/reporting-planning-data/the-centre-for-victorian-data-linkage>

3.4.4.3 Data access

At the time of data access for study of background rates (*Chapter 7: Signal detection*)(215), ethical approval was granted through the Victorian Department of Health as data custodians in accordance with protocols for data linkage at the time. Data linkage was conducted within the Department using a potentially re-identifiable unique identifier, such that fully de-identified data could be provided for the study.

As at July 2019 hospital administrative data are more readily available with provisions for a number of accessible and restricted fields for each dataset, providing there is evidence of correlation to specific business purposes, via the HOSdata website, available at: www.bettersafercare.vic.gov.au/our-work/performance-and-safety-reporting/HOSdata(216).

3.5 Bias and confounding

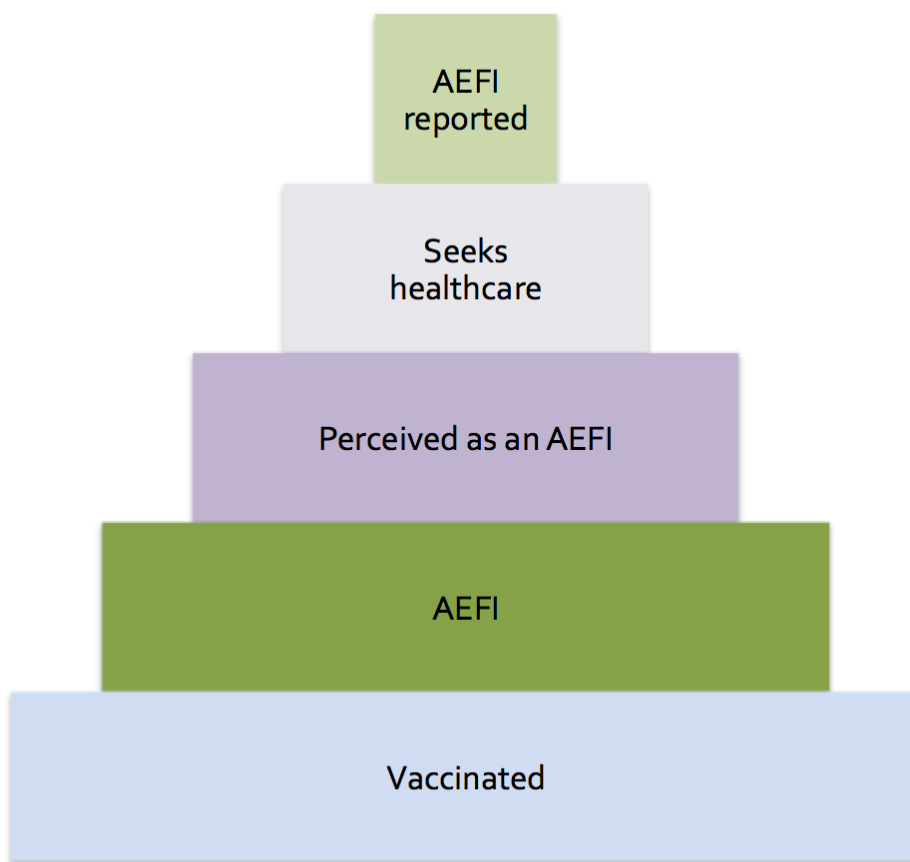
Bias and confounding can threaten quality of epidemiological studies, however, their presence does not necessarily imply that findings should be disregarded(217). Rather, assessing the potential impact of bias on inferences drawn and study conclusions is warranted, taking account of methods used, the study sample and the nature of the population from which it is drawn(217).

Bias may be defined as “any systematic error in the design, conduct, or analysis of an epidemiological study that results in a mistaken estimate of the association between exposure and risk of disease”(218). Many individual biases have been described(219), however they are broadly classified as selection and information bias(220). Selection biases are “distortions that result from procedures used to select subjects and from factors that influence study participation” and information bias arises as ‘bias in estimating an effect can be caused by measurement errors in the needed information’.

(218, 220). For this reason information bias may also be called measurement bias, whereby measurement can be impacted by choice of tool, assessor attitude or patient participation(217, 220).

In the AEFI surveillance setting, bias may occur in each of the notification layers dependant on equitable access to, or propensity to use, healthcare services(190) (Figure 9).

Figure 9: Notification pyramid for AEFI surveillance



Under-reporting is a widely known constraint of passive surveillance especially in submission of AEFI reports(102, 190). While reporting is passive, periodic motivation may impact on perception and recognition of AEFI and therefore case ascertainment, with variable representative consistency(221). Perception and capture of AEFI that occur distant in time from immunisation raise a particular element of recall bias leading to under-ascertainment(222). Missclassification bias in the description of the presenting AEFI reactions may arise with both description and method of recording,

for example ascribing signs and symptoms to clinical case definitions or use of ontological terminologies(183). Opportunities for minimising or regulating missclassification bias are discussed in *Chapter 9: Optimising SAEFVIC*, as one of the future opportunities in passive AEFI surveillance.

Confounding is a “distortion of the estimated effect of an exposure on an outcome, caused by the presence of an extraneous factor associated both with the exposure and the outcome”(223, 224).

Confounding is implicit in AEFI surveillance because vaccines are administered to different sub-populations, ranging from the general healthy population (e.g. infant vaccines) to targeted at-risk groups defined by ethnicity (e.g hepatitis A vaccines), health risks (e.g Indigenous and older persons) or risk behaviours (e.g hepatitis B and travel vaccines) for vaccine preventable disease exposure(183).

Confounding by indication may occur when a vaccine is indicated for a specific group that is in turn associated with one or more risk factor, including a particular co-morbidity, type of reaction, outcome severity, or propensity for reporting, either directly as a consumer or through their health care seeking behavior(225). One example is Zoster vaccine targeted to older persons for the prevention of shingles and who are, by the nature of their age, more likely to have comorbidities and experience depleted immunity with ageing and therefore more likely to report an AEFI compared to other sub-populations. Another example arises with febrile reactive vaccines given to young children, who in turn have a higher risk for febrile seizures and therefore having a confounded propensity to report fever-related AEFI. There are also delineators by funding policy, for example, specific vaccine brands are funded for—and therefore associated with—different risk profiles within the population, such as occurs in some school-based programs or in seasonal influenza vaccination programs whereby particular brands of influenza vaccine may be funded for healthcare workers or vaccine formulations specific for age groups, for example junior influenza vaccines for young children.

It is therefore reiterated throughout this thesis that the findings, being based on observational studies and highly information biased spontaneous/passive reporting,

generate hypotheses of causation through observation of associations and are not investigatory of causation(42, 226). Rather, they serve to detect aberrations in data as “signal” events, which can then be referred for the next step—beyond this remit of this thesis—for determination of causal association with vaccine, for which guidelines exist(42), although the discipline continues to evolve(226-228).

Consideration of bias is contained within individual investigations, including representativeness geographically; by vaccinee demographics; AEFI reaction type and severity and; reporter type. In two studies the primary focus is to describe and proffer remediation to address bias: evidencing under-reporting of AEFI in older persons (*Chapter 6: Informing pharmacovigilance*) and the influence of consumer reporting on AEFI surveillance (*Chapter 5: SAEFVIC evaluation*)(229, 230).

Indication confounding is specifically accounted for in the investigation of proportional reporting ratio (PRR) for signal detection through age-specific stratification to adjust for association of fever/febrile seizure and age (*Chapter 7: Signal detection*)(231).

Acknowledging these elements of bias and confounding gives reason not to generalise findings beyond the population of analysis and in particular supports the rationale for the study investigating background rates of neurological conditions in boys, rather than assuming the historic AEFI pattern in girls would be applicable (*Chapter 7: Signal detection*)(215).

Limitations thematic through these doctoral studies—including those of bias and confounding—are discussed in *Chapter 9: Optimising SAEFVIC*, alongside potential opportunities for future developments towards mitigation(232).

Despite these known limitations, post-licensure surveillance provides the extended sample size and long follow-up period, beyond the capacity of pre-licensure clinical trials, necessary to inform pharmacovigilance(184, 233). This improves potential for detection and investigation of rare AEFI, those arising a lengthy period after immunisation or in cohorts excluded from—or under-represented—in clinical trials(233). The latter is pertinent to vaccine safety where immunisations are recommended to pregnant, Indigenous or co-morbid populations, or situations where

vaccines are inadvertently used contradictory to prescribing guidelines(183). Further, the longevity of the SAEFVIC dataset provides opportunities for longitudinal studies of AEFI recurrence through reports of individuals experiencing AEFI with subsequent vaccination administered either in the general practice setting or through supervised vaccination within the SAEFVIC clinical support environment(234, 235).

3.6 Analytical techniques

A variety of approaches were employed to address research questions within this thesis. Analytical techniques are described in further detail within their respective chapters

3.6.1 Analytic tools

Statistical analyses were conducted using two tools: STATA statistical packages (StataCorp. *Stata Statistical Software*: College Station, TX: StataCorp LLC) and Microsoft Power Business Intelligence (PowerBI) software(236).

3.6.1.1 STATA

STATA was the standard statistical tool in use at commencement of the PhD. SAEFVIC data were imported from Excel or comma separated value (.csv) files as date-stamped extracts. Due to the multiplicity incorporated in a single AEFI report arising from concomitant vaccine administration and multiple symptoms describable, three base tables were required:

1. vaccinee case reported
2. vaccines administered
3. reactions described

Analyses were performed on the base tables individually and combinations. Some permutations, for example, reactions described in association with concomitantly administered vaccines were particularly convoluted to employ.

Manipulated data and statistical computations were exported to Microsoft Excel for graphical interpretation and visualisation.

3.6.1.2 Microsoft PowerBI

PowerBI was adopted as the preferred analytical tool in 2018 providing an informatic overlay to SAEFVIC data held in the source Microsoft SQL Server database hosted at MCRI. PowerBI permits establishing tabulated and graphic visualisation of data, including statistical parameters that can be continually refreshed to the underlying data. This was particularly beneficial for large-complex computations of PRR for multiple vaccine-reaction pairs over multiple time-points.

An example of standard reporting template in PowerBI, demonstrating data splicing options and incorporation of graphics is provided in Box 6. Further examples of data visualisation are presented in *Chapter 8: SAEFVIC maturation* and *Chapter 9: Optimising SAEFVIC* and in the conference presentation in Appendix 2.

3.5 Literature reviews

A number of literature reviews are presented among the Chapters of this PhD. Each used a combination of search strategies including MESH-terms, reference list reviews and citation queries to ensure broad capture of published and grey literature.

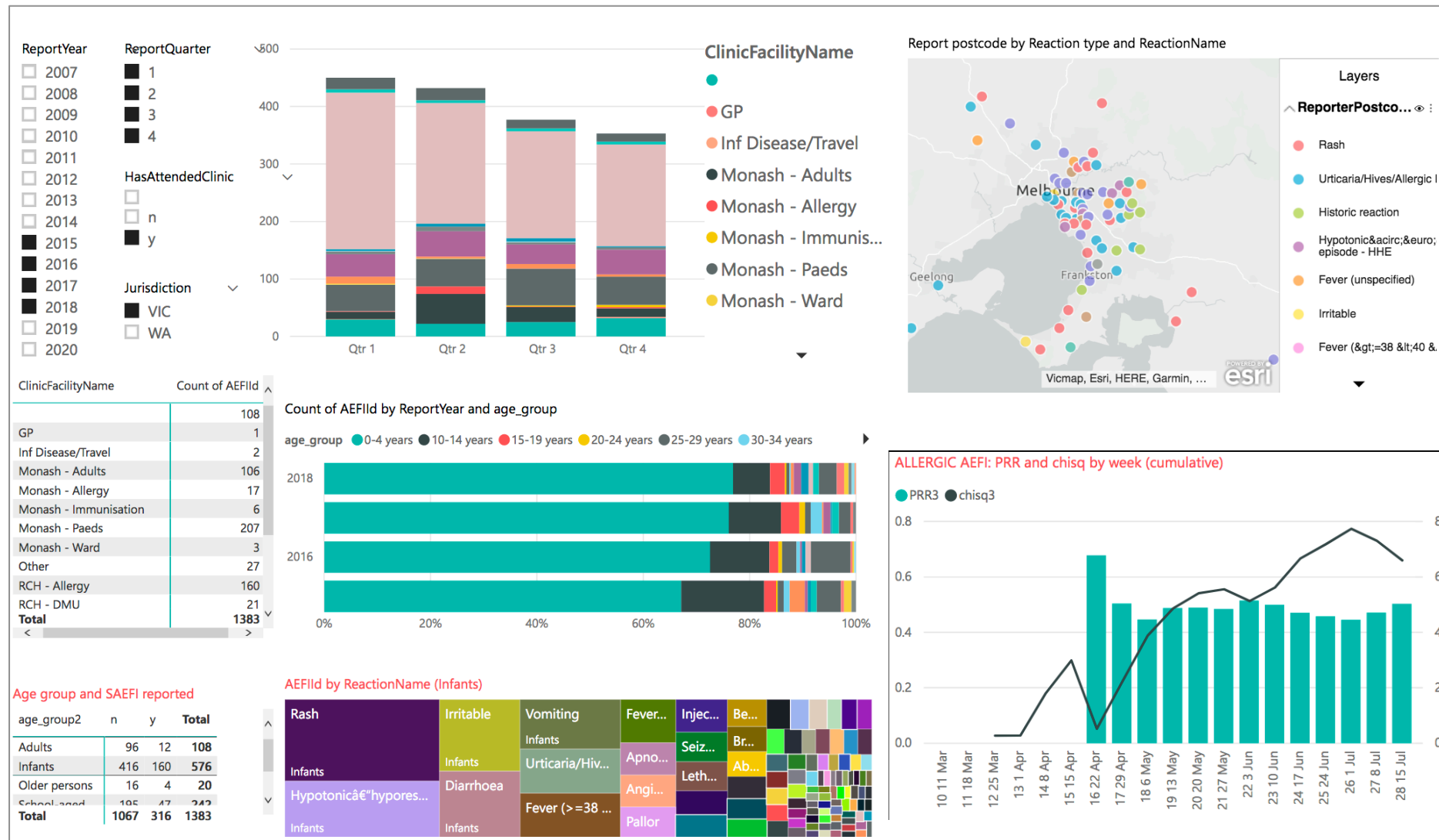
References were managed using EndNote version 8 (Clarivate Analytics <https://endnote.com/>). A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guided literature review was conducted as a component of the literature review for *Chapter 5: SAEFVIC Evaluation*, with details and schematic provided below.

3.5.1 Systematic search strategy

To seek examples of surveillance system evaluations a systematic literature search strategy was conducted using the PRISMA requirements in Medline, Scopus, Web of Science and Google Scholar. Citations were collated and reviewed using Covidence(237).

Four domains were included in the search, using truncations of key words (Table 5) with the aim of identifying “Evaluation of adverse event following immunisation surveillance system” or “evaluation of post-licensure vaccine safety monitoring” or combinations thereof.

Box 6: Example of PowerBI data visualisation tools



A general domain of “vaccine pharmacovigilance” was included to ensure exhaustive capture of articles. Searches were conducted on title/abstract and included all date ranges available in the search databases and was updated to August 2019.

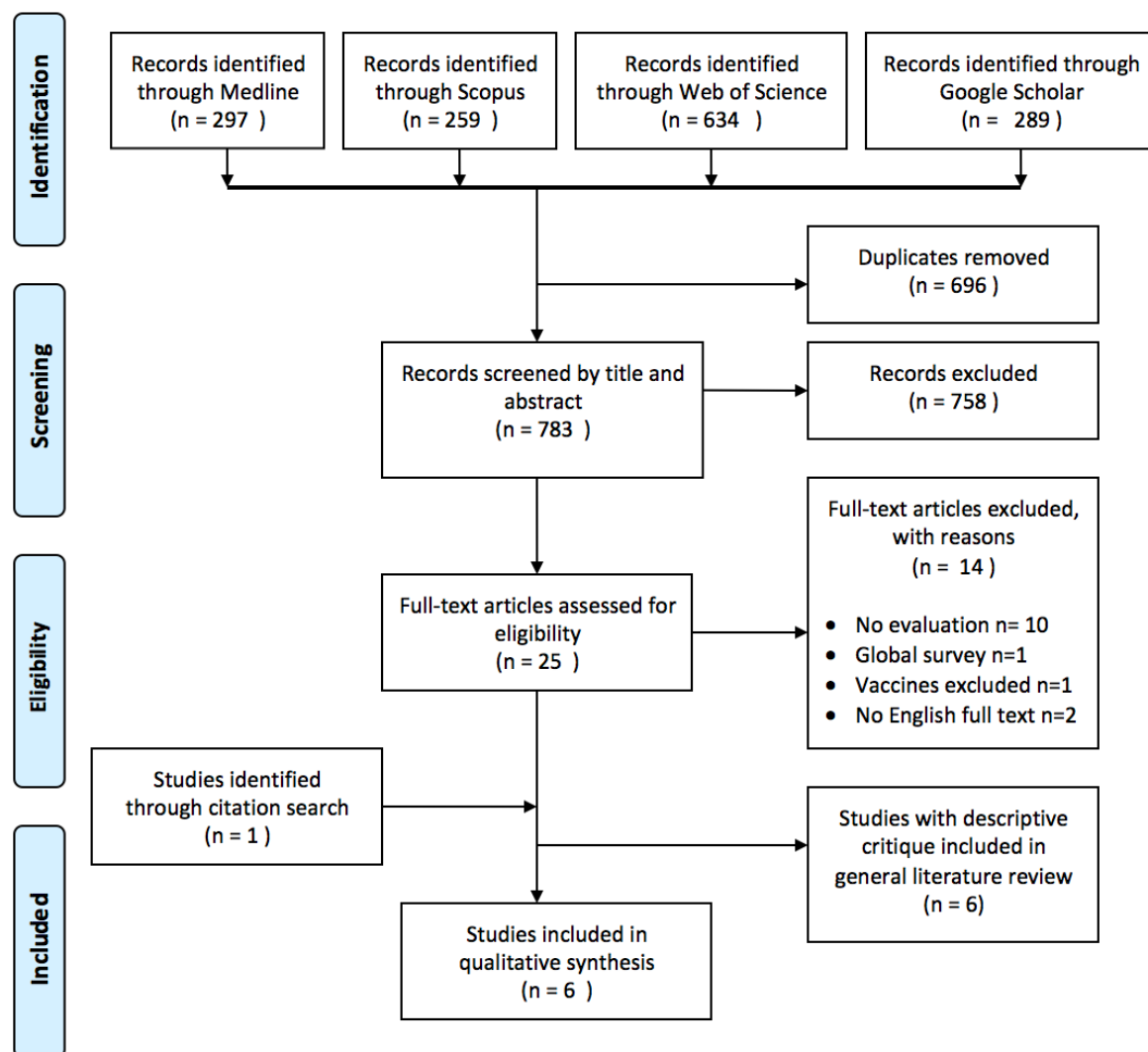
Table 5: Search domains, alternative terms and truncations and domain sequences applied

Domains [alternatives and/or truncations]	Sequences
Evaluation [evaluat*, review]	Evaluation adverse event surveillance immunisation
Adverse events [event*, safety]	
surveillance [monitor*]	Evaluation lincensure surveillance immunisation
Immunisation [Immuni*, Vaccin*]	
Post-licensure [licens*]	Surveillance adverse events immunisation #
	Vaccine pharmacovigilance

additional sequence used in Google Scholar to increase the return of articles which was otherwise only 14 records. When used in the other databases this sequence returned >2000 articles so was omitted.

The search was conducted without restrictions. There were no non-English articles requiring abstract review without a translation. Screening was initially conducted on the titles and abstracts to remove publications that were not relevant to the review or that focused on a vaccine, AEFI, specific purpose, or evaluated AEFI data outcomes rather than evaluation of the system (n=758). Full text review was conducted for 25 articles, of which 15 were excluded (Figure 10). Two of these excluded articles may have used a structured evaluation however, there was no English translation of the full article available. This search strategy resulted in 11 articles for inclusion in the qualitative review. A search through the citations of these 11 articles revealed 1 further articles for inclusion.

Figure 10: Prisma flow chart of literature search outcomes



Of the 12 articles that gave some description of an AEFI surveillance system evaluation, one was the SAEFVIC evaluation(15). Six articles provided some insights or critique of the surveillance system, either without a structured evaluation process or focusing only on the healthcare workers who submitted AEFI reports. These were maintained for their contribution to the general literature review; US VAERS (2004, 2015), Canada (2014), China (2015) Juventud, Cuba (2016), India (2018)(129, 142, 238-241).

Six articles described application of structured evaluation criteria to a national AEFI surveillance system; US, VAERS (1999), Brazil (2011), Australia, SAEFVIC (2017), Harare & Guruve districts in Zimbabwe (2018) and Abidjan (2018)(15, 101, 242-245). Only those for the US,VAERS and Brazil were published prior to the SAEFVIC evaluation.

Chapter 4: SAEFVIC early years

4.1 Chapter introduction

The overarching aim of this PhD was to optimise SAEFVIC, the Victorian passive AEFI surveillance system prior to an intention to expand it as a national system. An overview of SAEFVIC was provided in the context of Australian passive AEFI surveillance in *Chapter 2: Literature review* with the methods encompassed in the surveillance system outlined in *Chapter 3: Methods*.

At commencement of this PhD in 2013, SAEFVIC had completed five years of operation. While the model of SAEFVIC had been previously described in 2010(1) (written prior to commencement of this PhD and provided in Appendix 1), no comprehensive analysis of data had been presented.

This Chapter provides a foundational descriptive epidemiological review of SAEFVIC surveillance and data outputs at the time of commencement of this doctoral research, presented as a publication summarising SAEFVIC in 2012(179). This publication, documenting the early years of SAEFVIC, is written from the perspective of the data custodians for informing the stakeholder audience of both trends in adverse event reporting and quantification of workload.

Highlighted within the publication are elements addressed in subsequent chapters; particularly the lack of a denominator hampering data analyses (*Chapter 5: SAEFVIC evaluation*) and absence of mechanisms to detect adverse event signals (*Chapter 7: Signal detection*).

Combined with the publication on the model of SAEFVIC, published prior to the PhD (Appendix 1), this publication provides the background for the remaining Chapters that answer the research questions aimed to evaluate and optimise SAEFVIC surveillance.

4.2 Research aim

To provide a descriptive epidemiological overview of SAEFVIC surveillance and data at the time of commencing this PhD.

4.2.1 Publication: SAEFVIC in 2012

Clothier *et al.* SAEFVIC: Surveillance of adverse events following immunisation (AEFI) in Victoria, 2012. *Victorian Infectious Diseases Bulletin*, 2014; 17(1):2-9

SAEFVIC: Surveillance of adverse events following immunisation (AEFI) in Victoria, 2012

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SAEFVIC is an enhanced passive surveillance system for adverse events following immunisation (AEFI) combined with clinical services in Victoria. AEFI reports received in 2012 were accessed and epidemiology of AEFI reporting described with a focus on the National Immunisation Program (NIP) vaccines and age groups. Improvements and advances in SAEFVIC services throughout 2012 are also described.

A total of 828 AEFI reports were received describing 1406 reactions. Seventy per cent (575/828) of reports were for children aged less than seven. AEFI reporting rate by vaccine ranged from 37 to 177 per 100,000 doses administered. While 20 per cent of reports met the definition of serious AEFI, a majority of AEFI reported (38 per cent) were minor/expected reactions of injection site reactions or fever. AEFI monitoring detected an increase in AEFI reported following 4-valent HPV vaccine (Gardasil®), which on further investigation was confirmed to not be clinically significant.

Reports received via the online facility, which commenced in 2010, continued to increase, reaching 27 per cent of all reports received in 2012. Nurses comprised approximately 55 per cent of reporters. SAEFVIC implemented two new education services in 2012: a one-day conference and an educational 'roadshow'. Clinical services were expanded to include Telehealth.

SAEFVIC provides Victoria with a comprehensive and robust surveillance reporting system, which continues to expand and develop according to stakeholder requirements.

Introduction

An adverse event following immunisation (AEFI) is "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"¹. Surveillance of AEFI is therefore an integral part of any immunisation program and aims to record significant or rare AEFI, regardless of causality². These AEFI include any unexpected events, or changes in rates of expected events, time-associated with vaccination. AEFI reported include vaccine adverse events, AEFI due to programmatic issues or coincidental events. The

surveillance information is used to detect vaccine safety 'signals', prompt action and maintain confidence in immunisation programs^{3,4}. Community expectations for safety are high⁵.

Surveillance of Adverse Events Following Vaccination In the Community (SAEFVIC) is a public health partnership initiative of the Victorian Immunisation Program funded by the Department of Health, Victoria. It comprises a central reporting enhanced passive surveillance system integrated with clinical services⁶. This specialist service was established in 2007 to help immunisation providers report and follow-up children and adults who have had an AEFI.

Spontaneous reporting of AEFI by healthcare providers (passive

surveillance), provides a simple, cost-effective and broad-reaching system, however passive systems have low sensitivity and cannot alone prove causality. Therefore SAEFVIC enhances surveillance via integration with clinical services whereby AEFI can be further investigated and described as part of a cohort or case series. In addition, SAEFVIC is the Victorian coordinating site for Paediatric Active Enhanced Disease Surveillance (PAEDS)⁷. PAEDS⁷ actively monitors for adverse events of interest such as intussusception post oral rotavirus vaccines and for febrile seizures⁸.

SAEFVIC reports quarterly to the Immunisation Advisory Committee (IAC) of the Victorian Department of Health. This report collates and

summarises SAEFVIC surveillance activity in 2012, with a focus on children aged less than seven years and adults in the context of the National Immunisation Program (NIP) in Victoria⁹ and the continuing development of educational and clinical services provided by SAEFVIC.

Methods

AEFI reports received by SAEFVIC in 2012 were extracted by report date. Reports of AEFI for vaccines administered more than ten years prior (2002 or earlier) were excluded. Approval was granted by the Royal Children's Hospital Human Research Ethics Committee for this registered database (DA017-2013-04).

Australian Childhood Immunisation Register (ACIR)¹⁰ is a national register that records vaccinations given to children under seven years¹⁰. Vaccine doses administered data for 2012 were extracted by vaccine brand and age group as at March 2013. For children aged less than seven years, AEFI reporting rates were calculated per 100,000 doses administered. Denominator data for the primary and pre-school NIP cohorts were approximated using 0<9mths and 9mth-<5years according to the ACIR cohort data ranges available.

Annual AEFI reporting rates per 100,000 population were calculated using the corresponding mid-year estimated resident population, described by the Australian Bureau of Statistics (ABS)¹¹. Comparison of reports and reporting rates to other states and territories were made using published data available for 2011(3).

AEFI reactions were categorised according to SAEFVIC standard case

definitions or reported verbatim⁶. An AEFI was determined as serious if the report indicated a reaction that: resulted in death; was life threatening⁶; required in-patient hospitalization or prolongation of an existing hospitalization; resulted in persistent or significant disability/incapacity; caused a congenital anomaly/birth defect¹² or; was deemed medically important by SAEFVIC clinicians [JPB & NWC]

Seasonal enhanced surveillance was conducted to monitor trivalent influenza AEFI; reports were received via passive surveillance or, for specific AEFI of febrile seizure, via Paediatric Active Enhanced Disease Surveillance (PAEDS) which reviews information on all febrile seizures attending sentinel hospitals across Australia (of which the Royal Children's Hospital is one site) and collates data on those that occur temporally associated with immunisation.

Data analyses and control chart were performed using Stata 13 (Statacorp, Texas) and Excel 10 (Microsoft, Redmond, WA). Statistical comparisons of proportions were calculated using two-sample test

of proportions and comparison of rate ratio using incidence rate ratio. P-values of <0.05 were considered statistically significant.

Results

AEFI reports

In 2012, SAEFVIC received 828 AEFI reports (14.7 per 100,000 population), 18 per cent less than the rate of 18.0 per 100,000 population (n=994) in 2011 (unpublished data).

A majority of reports (82 per cent, n=677) received were for children. Reporting rates were similar for male and female younger children (P=0.08) but significantly higher for females across all age groups (P=0.02) (Table 1).

Vaccines

A total of 1712 vaccines had been administered to the 828 persons reporting an AEFI, a median of two per vaccinee. The childhood primary vaccination series administered at two, four and six months of age (Infanrix-Hexa[®], Prevenar 13[®] and Rotateq[®]) were the most frequently reported (Table 2).

Table 1: AEFI reports and rate per 100,000 population, by age group and sex, SAEFVIC, 2012

Age group (years)	AEFI reports (per 100,000 population)			Male:female rate ratio (95% CI)	P-value
	Male	Female	Total		
<7*	315 (123.1)	258 (106.3)	575 (115.3)	1.16 (0.98, 1.37)	0.080
<1*	161	137	298		
1-3.5	61	51	113		
3.6-6	93	70	163		
7-<19	25 (6.0)	77 (19.6)	102 (12.6)	0.31 (0.19, 0.49)	<0.001
19-<60	19 (1.2)	75 (4.6)	94 (2.9)	0.26 (0.15, 0.44)	<0.001
60+	16 (3.1)	41 (6.9)	57 (5.1)	0.45 (0.24, 0.82)	0.005
TOTAL	375 (13.5)	451 (15.9)	828 (14.7)	0.85 (0.74, 0.98)	0.02

* Sex not known for two reports

* <http://www.apsu.org.au/surveillance-systems/paeds/>

** <http://www.humanservices.gov.au/customer/services/medicare/australian-childhood-immunisation-register>

‡ A life-threatening event* is an event/a reaction in which the vaccinee was at risk of death at the time of the event/reaction; it does not refer to an event/reaction that hypothetically might have caused death if it were more severe (e.g. anaphylaxis).

Table 2: AEFI reports by NIP schedule and vaccine, Victoria, 2012

National Immunisation Schedule (NIP) vaccines			
Age group	Vaccine brand	Number of reports (%)	Estimated rate per 100,000 doses administered
0,2,4,6 months	H-B-Vax II® Paediatric formulation*	1 (0.1)	106
	Infanrix hexa®	258 (31.1)	118
	Prevenar 13®	247 (29.8)	116
	RotaTeq®	247 (29.8)	117
12,18 months, 4yrs	Priorix®	187 (22.6)	125
	Hiberix®	48 (5.8)	65
	NeisVac-C®	56 (6.8)	74
	Varilrix®	27 (3.3)	37
	Infanrix-IPV®	143 (17.3)	177
	Prevenar 13®**	22 (2.7)	44
12–13 yrs (girls)	Gardasil®	60 (7.2)	n/a
15–16yrs	Boostrix®	18 (2.2)	n/a
50–59 yrs	Boostrix®	10 (1.2)	n/a
65+ yrs	Pneumovax 23®	29 (3.5)	n/a

* H-B-Vax II = Hepatitis B vaccine

** supplementary catch up for children aged 12–35 months during Oct 2011–Sept 2012

AEFI reactions

The 828 AEFI reports described 1406 reactions (a vaccine recipient may describe multiple AEFI reactions) of which 240 were included in the 164 reports meeting the definition of serious adverse event (SAEFI).

The distribution and frequency of reactions listed in AEFI reports for 2012 are shown in Table 3. Frequently reported AEFI were similar in both children and adults, however the proportions varied. Minor/common/expected injection site reaction was the most frequently reported reaction (12 per cent, n=163) overall as well as for both children (10 per cent, 97/931) and adults (14 per cent, 66/475). Reactions reported more commonly in children were diarrhoea, rash, fever, irritability and persistent crying. Common reactions in adults included severe injection site reactions, pain in limbs, influenza like illness and nausea.

Specific vaccine monitoring

Influenza vaccines

An inactivated trivalent influenza vaccine (TIV) was administered in 13 per cent (104/828) of the AEFI reports—either singularly or in combination with other vaccines—compared with 17 per cent (172/994) in 2011 and 33 per cent (308/942) of reports in 2010. The most frequently

reported TIV was Fluvax®, followed by Fluarix® (Figure 1), which was a change from previous years but proportional to the 2012 doses distributed (data not shown).

All four reports of AEFI with Fluvax® administered to children less than seven years were in the contra-indicated under five years age group. Three experienced AEFI: fever (> 400 Celsius) with vomiting (n=2) and febrile seizure (n=1).

4-valent HPV vaccine (4vHPV)

Increased monitoring of reports received following 4vHPV (Gardasil®) was undertaken in 2012 prior to the introduction of 4vHPV for boys. A potential signal of an increase in AEFI was observed in late 2012 (Figure 2). On investigation this was attributed to increased reporting of general headache, with more than two-thirds accompanied by dizziness or feeling faint. Clinical review deemed the increased reporting of mild symptoms was not significant and was possibly related to increased awareness ahead of the extension of 4vHPV school vaccination to boys scheduled in 2013.

Figure 1: Proportional contribution of individual influenza vaccines to TIV AEFI reports received, by year, Victoria, 2008–2012

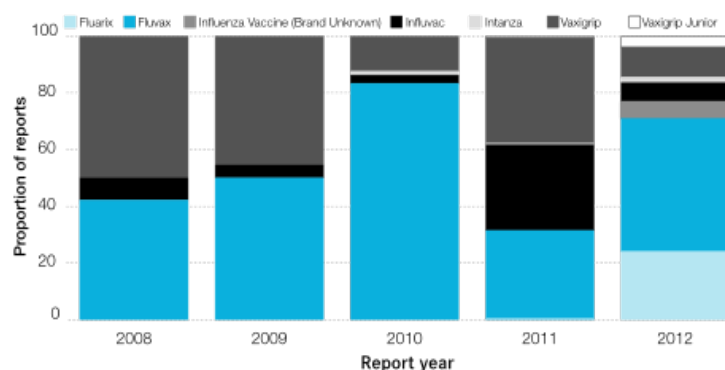


Table 3: AEFI reactions reported (where n>=10 & selected conditions) by age group, SAEFVIC, 2012

Age group (yrs)	Children <7 years		School aged and adults		Comparison of proportions p-value
	No. of reports	Proportion	No. of reports	Proportion	
Reaction					
Injection site reaction - minor/common/expected	97	0.104	66	0.139	0.054
Rash	83	0.089	21	0.044	0.002
Vomiting	59	0.063	14	0.030	0.007
Fever (not measured)	50	0.054	21	0.044	0.442
Fever (>=38 to <40 °C)	56	0.060	13	0.027	0.007
Drug error (program error)	49	0.053	10	0.021	0.005
Injection site reaction - severe	44	0.047	14	0.030	0.113
Irritable	56	0.060	0	0.000	<0.001
Diarrhoea	51	0.055	4	0.008	<0.001
Pain in limb	14	0.015	38	0.080	<0.001
Lethargy	24	0.026	21	0.044	0.063
Erythema	21	0.023	22	0.046	0.014
Urticaria/Hives/Allergic rash	27	0.029	5	0.011	0.028
Vasovagal episode (syncope, faint)	18	0.019	14	0.030	0.228
Hypotonic hyporesponsive episode*	31	0.033	0	0.000	<0.001
Headache	3	0.003	25	0.053	<0.001
Angioedema	13	0.014	10	0.021	0.322
Respiratory symptoms	12	0.013	10	0.021	0.243
Lymphadenopathy	12	0.013	9	0.019	0.376
Nausea	3	0.003	18	0.038	<0.001
Abdominal pain	14	0.015	6	0.013	0.719
Paresthesia	0	0.000	21	0.044	<0.001
Seizure-febrile*	20	0.022	0	0.000	0.001
Crying (persistent)*	17	0.018	0	0.000	0.003
Influenza-like-illness	1	0.001	16	0.034	<0.001
Exacerbation of eczema or asthma	12	0.013	2	0.004	0.121
Abscess	12	0.013	1	0.002	0.046
Allergic reaction (generalised)	6	0.006	6	0.013	0.233
Dizziness	0	0.000	12	0.025	<0.001
Nodule at injection site	10	0.011	1	0.002	0.082
Pallor	9	0.010	2	0.004	0.272
Pruritis	3	0.003	8	0.017	0.006
Seizure-afebrile	10	0.011	1	0.002	0.082
Fever >40°C	10	0.011	0	0.000	0.023
.....					
Apnoea	7	0.008	0	0.000	0.058
Anaphylaxis	3	0.003	3	0.006	0.400
Intussusception	7	0.008	0	0.000	0.058
.....					
Total	931		475		

* definition is restricted to children

In 2012, 20 per cent (164/828) of reports met the definition of a serious adverse event (SAEFI). A majority of SAEFI (87 per cent) were in children under seven years. Similar proportions of children and adults with SAEFI reported hospital admission (40 and 48 per cent respectively) and all cases over 40 years of age (n=6) were admitted, although the reason for their admissions were not confirmed as being a result of the SAEFI alone.

One death was reported within a two-week period following an immunisation, however on clinical case review no causative evidence of association to immunisation was identified.

Figure 2: Control chart for 4-valent HPV vaccine AEFI, SAEFVIC, 2012

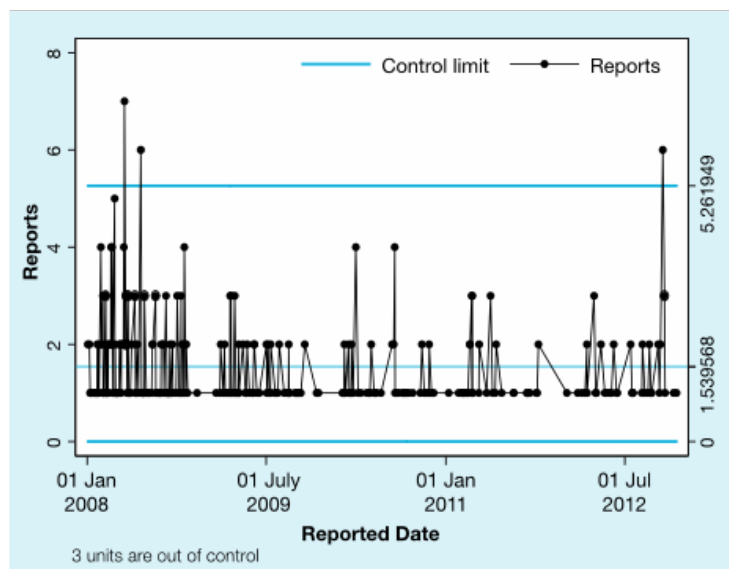
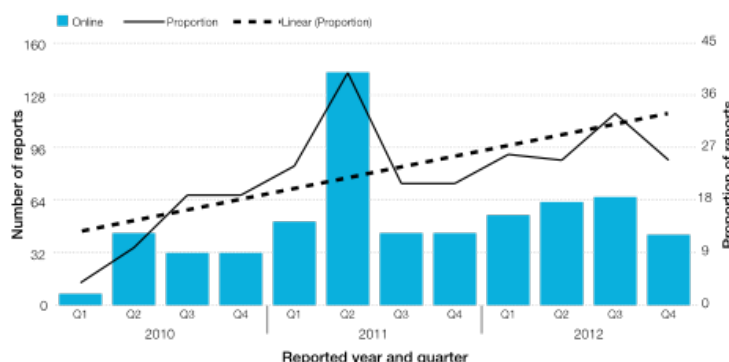


Table 5: Number of SAEFVIC clinic attendees by age group and clinic facility, 2012

Age group	Royal Children's Hospital (RCH)	Monash Medical Centre (MMC)	Royal Melbourne Hospital (RMH)	Telehealth*	Total (%)
Children (<18 years) n=673	221	28	0	10	259 (38%)
Adults 19yrs+ n=155	0	7	4	0	11 (7%)
Total	221	35	4	10	270 (33%)

* Telehealth commenced August 2012

Figure 3: Number, proportion and linear trend of reports submitted online, Victoria, 2010–2012



Clinical review

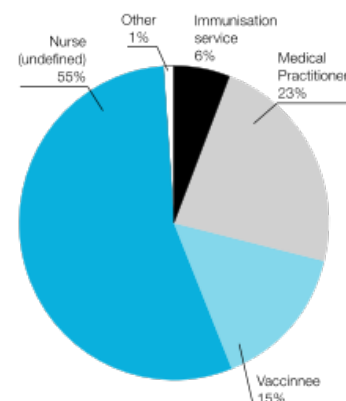
An immunisation nurse reviews each AEFI report submitted to SAEFVIC. Where appropriate, a specialist clinic appointment with an immunisation physician is offered and supervised vaccination either in clinic, as a day patient or overnight admission can be provided. In 2012 a total of 270 patients were seen in SAEFVIC clinics, with a majority (82 per cent) attending the Royal Children's Hospital (Table 4).

Reporting modality

Online reporting commenced in 2010. In 2012, 27 per cent (227/828) of reports were received by this modality. An increasing trend of online reporting, both in overall numbers and as a proportion of reports received, was observed (Figure 3).

Nurses were the most frequent reporters of AEFI (55 per cent), followed by doctors (includes hospital physicians and general practitioners). Reports originating from consumers (vaccinees or their parent/guardian) comprised 15 per cent of reports received in 2012 (Figure 4).

Figure 4: Proportion of AEFI reports received by reporter type, SAEFVIC, 2012





Discussion

The magnitude of AEFI reporting to SAEFVIC, Victoria was less in 2012 compared to the previous year, a trend also observed in the Western Australian Vaccine Safety Surveillance (WAVSS) and in national AEFI data for the first six-months of 2012 in children aged less than seven^{13, 14}. This observation was most likely due to elevated reporting in 2011 arising from heightened awareness and concern for AEFI following the increased incidence of febrile seizures post TIV that occurred in 2010¹⁵.

A majority of AEFI reports (82 per cent) were received for children aged less than seven years. This is expected, as children are also the main vaccine recipients with immunisation coverage estimates for Victoria in 2012 were 90.5 per cent at 12 months of age and 92.4 per cent at 60 months of age¹⁶.

Services for adults are also important for maintaining consumer confidence, especially as new vaccines—such as Zostavax® for shingles prevention—become more widely available for adults. Adults had a much lower uptake of clinical review services at only seven per cent compared to more than a third of children reported with an AEFI.

In August 2012, Telehealth was added as a consultation option. Telehealth is a web-based video-consultation service available with Medicare rebate payable according to specific eligibility criteria¹⁷. It is anticipated that Telehealth will broaden uptake of clinical services as well as improve accessibility for cases in regional areas.

The higher AEFI reporting rate in school-aged females was expected considering 4vHPV vaccine was funded for females 12–13 years as part of the NIP schedule in 2012. This program will be expanded to school-aged boys in mid-2013 and so sex-

equalisation in reporting is anticipated in this age group in future analyses. An initial increase in AEFI reporting may also be anticipated due to heightened awareness in the early stages of vaccination in a new population (Weber effect)¹⁸. Likewise it cannot be assumed that AEFI reporting patterns will be the same between boys or girls as analyses of background rates of potential AEFI in this age population indicate differences may be expected¹⁹.

The oft discussed absence of a complete whole-of-life immunisation register significantly hampers the ability to present AEFI as rates and permit comparisons between vaccines or recipient cohorts²⁰. Further, interpreting AEFI reporting rates by vaccine brand or antigen is complicated by co-administration of vaccines at each NIP schedule point; hence any AEFI with primary series vaccines will be attributed to each of Infanrix hexa®, Prevenar 13® and RotaTeq®. Similarly comparisons of reporting rates between jurisdictions may be reflective of the different surveillance systems in place²¹.

Several recommended vaccines, including some NIP scheduled vaccinations such as influenza, meningococcal C and varicella vaccines (including NeisVac-C® and Varilrix®), were not funded in 2012 for recording on the ACIR, so doses administered data may be under-reported. Such under-reporting of denominator data would result in elevated AEFI reporting rates, however as our study demonstrated rates lower than for other ACIR funded vaccines, this would imply either that AEFI rates are truly lower for these vaccines, or more likely that there is good voluntary reporting compliance to ACIR of vaccines administered.

SAEFVIC data have been demonstrated as useful for validation of vaccine safety signals^{6, 22}. In

2012, control chart analyses were implemented as a means of monitoring for possible safety signals. Control charts are widely used in health settings as a simple visual means of indicating deviations in stable systems^{23, 24}. The chart shows the standard deviation of the number of AEFI reports received as time-series and provides control limits as an indication of process stability. A potential signal event was observed in AEFI reports following 4vHPV immunisation in late 2012, which on review was deemed not clinically significant, but indicated the potential utility of the control chart analyses. The two earlier signals evident in the 4vHPV control chart were known events occurring within 12-months of the 4vHPV program commencement in 2007 and attributed to an early Weber effect and an episode of mass psychogenic hysteria at a secondary school²². Further prospective studies are needed to determine the sensitivity of control charts for early signal detection and usefulness as a monitoring tool.

Four reports were received for Fluvax® administered to children aged less than five years. Fluvax® has been contraindicated in this age group following an increased rate of febrile seizures in 2010²⁵. These cases were reported to the Department of Health and providers notified of the serious drug administration error.

Stability of data is an important factor in signal detection and changes to data collection methods impact on ability to interpret surveillance findings. For example, specific active surveillance programs for trivalent influenza vaccines were in place during 2012 that would increase solicited reporting to SAEFVIC, particularly for the preferred brands for use in children aged less than five years such as Fluarix®. Therefore it was not appropriate to compare AEFI reporting rates between vaccine



brands and infer a comparison of the safety profiles.

An inherent limitation of passive surveillance systems is under-reporting, with estimates as high as 95% reported²⁶. Systems to facilitate ease of reporting are therefore important. SAEFVIC commenced online reporting in 2010, aiming to provide a convenient reporting modality, available 24/7. The upward trend of online reporting continued in 2012, reaching almost one-third of all reports received.

While a majority of reports received were from healthcare providers, self-reporting by vaccinees or their parent (consumer) was not uncommon. The contribution of consumer reporting to pharmakovigilance is the focus of several recent publications within Australia and internationally²⁷⁻²⁹. Further evaluation is required to ascertain if consumer reports merely increase common, expected reactions; the impact on signal detection and to investigate resource requirements should consumer reporting be purposely solicited.

Nurses submit more than half of all AEFI reports received by SAEFVIC. In recognition of this, SAEFVIC implemented two education initiatives in 2012; a roaming educational 'roadshow' and a one-day conference style Clinical Vaccinology Update (CVU)*. The roadshow provides an immunisation update for nurses across metropolitan and regional hospitals targeting paediatric wards, special care nursery and neonatal intensive care units and midwifery wards. The CVU is an opportunity for immunisation providers and interested health care professionals to meet and discuss new vaccines, vaccine preventable disease epidemiology and vaccine safety. The CVU will be run twice yearly, alternating between the

Royal Children's Hospital and Monash Medical Centre. Keeping stakeholders well-informed and building networks between immunisation facilities and SAEFVIC is crucial in maximising AEFI reporting and in providing effective and efficient vaccine safety service.

Conclusion

Adverse event following immunisation reporting in Victoria in 2012 was lower than for 2011 and no clinically significant signal detections were confirmed. SAEFVIC provides Victoria with a comprehensive and robust surveillance reporting system, which continues to expand and develop according to stakeholder requirements.

How to contact SAEFVIC

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Tel: 1300 882 924 (option 1)

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Chapter 5: Evaluation

5.1 Chapter introduction

This Chapter comprises the PhD study to evaluate SAEFVIC with the goal to determine if the objectives of the surveillance system had been met, presented as a publication titled *“Evaluation of “SAEFVIC”, a pharmacovigilance surveillance scheme for the spontaneous reporting of adverse events following immunisation in Victoria, Australia”*. However, firstly this Chapter provides a comprehensive introduction outlining why evaluation of public health surveillance systems is important, discusses the various guidelines available and is accompanied by a review of the literature on evaluations of AEFI surveillance systems (the PRISMA guided search strategy for this review is presented in *Chapter 3: Research methods*)

At the time of commencing the SAEFVIC evaluation in 2014, there were few publications of AEFI surveillance system evaluations. While there were several reviewing a surveillance systems performance in regard to one objective or monitoring of a specific vaccine or AEFI reaction, there were few that evaluated the system holistically for its surveillance system performance attributes (section 5.6).

The SAEFVIC evaluation used traditional public health surveillance evaluation guidelines commonly utilised within the public health arena at the time. However, subsequent to commencement of the evaluation alternative or expanded models offer interesting considerations for future structured analyses of surveillance system functionality and effectiveness. These are included in the Chapter literature review for completeness. Likewise, since publishing the SAEFVIC evaluation, other system evaluations have been forthcoming and are also included in the discourse of the literature review in this Chapter (section 5.7).

During the evaluation, a secondary research question arose. On establishment, SAEFVIC targeted reports from health care providers, however the evaluation identified that an increasing number of reports were coming direct from consumers.

We were unsure what contribution consumer reporting had on AEFI reporting trends and whether it was something we should encourage (or deter). This led to the research question “*What does consumer reporting of AEFI contribute to SAEFVIC?*”

The findings from this body of work identified knowledge gaps, leading to additional explorations to strengthen SAEFVIC, in particular the investigation of capacity for signal detection (presented in *Chapter 7: Signal detection*) as well as providing the foundation for onward studies beyond this PhD as outlined in the final *Chapter 9: Optimising SAEFVIC*.

By late 2019 the SAEFVIC evaluation had been cited 5 times and consumer reporting research cited 19 times. In addition to the publications presented in this Chapter are several conference presentations, poster presentations and co-authored papers, which are presented/listed in Appendix 2.

5.2 Research questions

According to the World Bank Toolkit for surveillance evaluation, the foremost question to address is: “what are the goals and objectives of the surveillance system and is it meeting them?”(251).

5.2.1 Question 1: Does the AEFI surveillance system, SAEFVIC, meet its stated objectives?

Publication: Clothier HJ *et al.* Evaluation of “SAEFVIC”, a pharmacovigilance surveillance scheme for the spontaneous reporting of adverse events following immunisation in Victoria, Australia. *Drug Safety*. 2017 Jun;40(6):483-495

5.2.2 Question 2: What does consumer reporting of AEFI contribute to SAEFVIC?

Publication: Clothier HJ *et al.* Consumer reporting of adverse events following immunization. *Human Vaccines and Immunotherapeutics*, 2014; 10:3726-30

5.3 Evaluation of surveillance systems

Surveillance is defined as;

“the ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination [of this information] to those who need to know” and act upon that information(79).

Surveillance is a core function of public health that—as defined above—is essential to the planning, implementation and evaluation of public health practice. Systems comprise a collection of processes and components that include data collection, data quality monitoring, data management, data analysis and result interpretation, resulting in disseminatable information. Such information can be used to guide public health decisions, whether it be planning, prevention, management, promotion or resource allocation and ultimately aims to improve the quality of decisions and effectiveness of actions.

In terms of pharmacovigilance surveillance data, analysis is typically performed to monitor changes in trends and to detect the presence (or absence) of signals that may require investigation, intervention or other actions. Gaps, inadequacies or bias in the processes or components of surveillance may lead to misinformation, mis-direction of resources, or at worse a failure to detect a signal that leads to preventable outcomes going unchecked(12).

There is no agreed-upon metric for evaluating the quality of adverse event reporting systems(246). Performance indicators or measures for evaluation would be easier to determine if there were a standard surveillance system on which comparisons could be made. However, there is no one-size-fits-all surveillance system as health structures and systems differ globally and even within countries. This is exemplified by the review of European surveillance systems and the call for unification(150). Likewise the multi-jurisdictional health structures of Australia provide diverse AEFI surveillance systems with varying depth of reporting(167). Therefore, although perspectives and evaluations of pharmacovigilance systems globally offer insights to improve passive

AEFI surveillance(29, 101, 112, 113), it is necessary for individual systems to ascertain if they are performing as intended and maintaining public health relevance given changing health care practices, immunisation program targets, population epidemiology and information needs.

Moreover, given the many components of a surveillance system, it is understandable that studies tend to focus on evaluating or improving specific components of the surveillance process, rather than evaluating overall system functioning(247). However, it is not appropriate to extrapolate the findings from evaluations focusing on performance relating to one vaccine or adverse event as indicative of overall performance, as there may be reporting biases that cause findings to not be broadly generalizable. Biases can arise for example through; variations in risk perception, media attention, or Weber effect for new vaccines affecting motivation to report, and/or age-limitations through targeting of the vaccine program or adverse event outcomes(221, 248-250). The essential questions for evaluating surveillance systems, according to the World Bank toolkit for surveillance system evaluation, are presented in Box 7(251). Drewe *et al.* recommend consideration of economic attributes also be included(252).

Box 7: Surveillance system evaluation: the essential questions

- What are the goals and objectives of the surveillance system and is it meeting them?
- What is the public health importance of the diseases or health events under surveillance?
- How does the system operate?
- What resources are required?
- What are the system's attributes?
- Is the system communicating with data sources?
- Is there communication and feedback between the different administrative levels?
- Does the system provide useful information?
- Is it leading to public health action?
- Are the findings provided to—and used by—policymakers?

Guidelines for the establishment of adverse event following immunisation (AEFI) surveillance systems, published by WHO in 2014(39), will aid toward providing some consistency and comparators across systems, particularly for low and middle income countries embarking on their first systems and for whom the Guidelines are aimed at. However, SAEFVIC was established in 2007—and likewise comparative systems such as VAERS (US) and CAEFISS (CANADA) were established several decades ago—long before any system standardisation or conformity was available(1, 124, 146).

5.3.1 Benefits of evaluation

The World Health Organization defines evaluation as;

“a systematic way of learning from experience and using lessons learned to improve current activities and promote better planning by careful selection of alternatives for future action”(261)

Surveillance in simplistic terms provides information for action, with the ultimate goal to improve health outcomes using evidence-based decision-making(253). However, the scientific basis of surveillance relies on the quality of the initial data in determining relevance and accuracy through all stages of observation, data collection, analyses, data dissemination and informative reporting(12).

Evaluation focuses on how well the system operates to meet its objectives while making effective use of its resources. Monitoring provides an ongoing assessment of surveillance processes and measures of system performance, such as the completeness and timeliness of data collection and reporting. When combined, the processes of evaluation and monitoring assist to identify opportunities to improve surveillance system performance, provide indicators to aid data interpretation and ultimately improve capability of the system to meet its objectives and achieve its desired outcomes(254).

As outlined in Chapter 2 section 2.6.1.1, the WHO considers an indicator of 10 AEFI reported per 100,000 surviving infants per annum as a proxy measure for evidence of a functional AEFI reporting system(108). However, this is merely a milestone of a system

being present, not evidence of effective functionality. The system is deemed fit for purpose if “complete, valid and representative data are available in a reasonable timeframe and that can be used effectively for the purpose intended”(106).

Requirement for rigour in surveillance systems remains topical: a review by Groseclose *et al.* in 2017 providing an excellent overview of the breadth of surveillance systems in the public health arena and consideration for evaluation as both the demands on public health and available technologies continue to advance(247).

While the concept of evaluations being undertaken on a routine basis is appealing, it is more likely that particular situations would encourage initiation or “trigger” an evaluation (Table 6)(255). Different triggers might influence the decision on which attributes to evaluate or processes to follow(255). Care should be taken however if an evaluation is pursued whereby system attributes are assessed independent of one another, rather than as a holistic event-chain, as key insights into system processes and outcomes may be missed. Where surveillance aims to provide “information for action”, evaluation leads to modified surveillance processes and thus supporting the generation of relevant and accurate information for public health decision-making and policy formulation(247).

5.3.2 Evaluation triggers

Table 6: Triggers for conducting an evaluation, ECDPC Handbook (abbreviated)(255).

Trigger	Evaluation aspects
Initial evaluation	Ensure adequate performance of a new system
Compare systems	Compare strengths and weaknesses between systems
Regular periodic evaluation	Systematic evaluation to ensure system still fit for purpose
Requirements	Requirement to conduct fundamental review of system performance
Cost of surveillance	Inform economic changes and prioritise surveillance components
Data quality monitoring	Identify issues for further investigation and/or address

	aspects of data quality
New technology or other system innovations	Review implementation of technical innovations for effectiveness
Change in demography	Investigate representativeness of the system
New surveillance standards	Determine acceptance, usefulness and relevance of new standards in terms of public health
Change in case definitions	Revised case definitions may impact on sensitivity and specificity of surveillance
Evaluating syndromic surveillance or switching to syndromic surveillance	Switching to syndromic surveillance may be less costly than indicator-based surveillance but integration, performance and usefulness may change.
Mass gathering	Assess ability to perform in a mass gathering event both during and after a mass gathering.
Occurrence of a major/new public health event	Assess ability to perform in a major public health event (e.g pandemic or natural disaster): focus on early warning and response function of surveillance and/or efficiency for a newly introduced condition.
Preparedness	Assess ability to perform and maintain function with an unexpected event. Verify preparedness for a predefined event and evaluate how effectively the system can meet its objectives in altered circumstances
Change in public health policy	Ability of the system to measure the impact of changes in public health policy on the target population
Introduction of control measures	Is the system able to measure the impact of the intervention and provide accurate information for the purposes of program monitoring?

5.4 Evaluation guidelines

A variety of guidelines or frameworks exist for evaluating surveillance systems across health and veterinary disciplines(256, 257). However, while providing adaptations for specific settings or outcome measures and additional layers of practical guidance as field-tools, they are largely based on a set of core foundations: being the attributes

that influence the relevance, effectiveness, and impact of the surveillance system(247, 256). There is increasing awareness for the need to consider economic attributes(252), both in terms of cost-efficiency of the system but also in terms of the broader cost-benefit economic value of effective pharmacovigilance reducing outcomes associated with vaccine-safety issues and subsequent improvements in morbidity, mortality and quality of life(258). However this is an extensive body of work and beyond the scope of this PhD.

An overview of sentinel guidelines for evaluation of public health systems is presented below culminating with a tabulated summary of surveillance system attributes. Specific examples of structured surveillance system evaluations using these guidelines, or variations thereof, are presented in section 5.6.

5.4.1 Centers for Disease Control (CDC)

The CDCs “*Guidelines for Evaluating Public Health Surveillance Systems*”, originally published in 1988(14), were updated in 2001 to accommodate advances in health data technologies(259).

The CDC guidelines focus on assessment of eleven system attributes; simplicity, flexibility, data quality, acceptability, usefulness, sensitivity, specificity, predictive value positive, representativeness, timeliness, and stability. The content provides detailed explanation of each attribute as a concept with suggestions for measurable criteria, which are further outlined in a field guideline template published in 2013(260).

Several frameworks have been created for evaluating surveillance systems for specific outcomes such as communicable disease surveillance(261) or surveillance for early detection of outbreaks(262). The CDC Guidelines have provided the foundation for evaluation of Australian national surveillance systems such as the National Notifiable Diseases Surveillance System and the Australian Sentinel Practice Research Network (ASPREN)(85, 263).

5.4.2 European Centre for Disease Prevention and Control (ECDPC).

The ECDPC evaluation guide “*Data quality monitoring and surveillance system evaluation – A handbook of methods and applications*” published in 2014 (after the

SAEFVIC evaluation had been conceptualised). The guide was developed after a review in 2010 identified inconsistencies regarding practices for monitoring data quality in European Union member states(255). The Handbook provides a technical document with step-wise guidance and indicators for evaluation of public health surveillance systems. It aims to build upon the attribute-based approach of earlier guidelines (including those of the CDC) and includes consideration of how components of surveillance systems interact; the triggers for evaluation and; provides a “decision tree approach” matrixing applicability of methods and focal attributes for varying evaluation scenarios. The handbook scopes beyond traditional guidelines to address interpreting evaluation results and potential interventions.

5.4.3 CDC Environmental Public Health Surveillance evaluation framework

Recognising the complexity and multidisciplinary nature of environmental public health surveillance led to development of a systematic framework and set of criteria to guide development and evaluation of environmental public health indicators(257). Evaluation models across three categories: environmental regulatory, public health surveillance, and environmental health programs were considered(257).

The framework extends beyond the primary focus being on system attributes by incorporating the evaluation elements across three assessment phases: Phase I scientific feasibility and relevance; Phase II analytical soundness, technical capacity and feasibility and Phase III interpretation and utility. The premise being that establishing the program goals and priorities (Phase I) considers the “public health importance, stakeholder concern, technical capacity and practicality, data and information quality, meaningfulness for public health action, and policy development”(243). However the scientific basis also needs to be practical and feasible (Phase II), requiring assessment of data properties such as quality, accuracy, as well as understanding the feasibility of system processes over time. Phase III considers the adage of surveillance being information for action and therefore measures the program utility to be used to design and measure intervention and prevention strategies and follow them over time. To design a system that is meaningful for determining appropriate public health actions requires ability to be anticipatory, available, appropriate, cost-effective, temporally and spatially scaled, easily quantifiable, and timely(257).

While developed for the field of environmental public health the concept has relevance for pharmacovigilance and may provide broader consideration of the evolutionary phases of surveillance systems as they mature and diversify with integration across health data networks.

5.4.4 OASIS

Oasis was developed in 2011 as a standardised assessment tool of epidemiological surveillance systems originally aimed at animal health(264). The Oasis framework is derived from modification of 3 tools: i) Surveillance Network Assessment Tool (SNAT) developed in the Caribbean for animal health surveillance, (ii) the Critical Control Point (CCP) assessment method developed for food safety and (iii) the guidelines for evaluation of surveillance systems developed by the CDC and WHO(264).

Oasis provides an attribute-based evaluation across 78 assessment criteria divided into ten sections, representing the functional parts of a surveillance system. Results are presented quantitatively in pie, histogram and radar charts providing simple visual interpretation and ability to compare across systems(256, 264). The method has been used in France (infectious equine disease surveillance)(265) and Africa (cross border infectious disease surveillance)(266).

An interesting development of Oasis for multi-sectoral collaborations has recently been published in 2019(267). The matrix design is intended to provide a semiquantitative tool to facilitate analysis of the organisational structure as well as functionality of integration and collaborations occurring across multi-sectoral components of the surveillance system. While predominantly aimed at One-Health, the concept may have relevance for the future of vaccine pharmacovigilance as surveillance expands across multiple health data sources and data-linkage strategies(93).

5.4.5 Surveillance system attributes for evaluation

Guidelines described above and systematic reviews of evaluation tools ascribe evaluation criteria across a range of surveillance system attributes(251, 257, 259).

Table 7 below provides a collation of system attributes as an adaptation and expansion of a similar table presented in Groseclose's review of recent advances in public health

surveillance systems(254). Although Groseclose's review was published in 2017, the attributes listed remain largely unchanged from the CDC guidelines of 16 years earlier (2001) as used for the SAEFVIC evaluation; the three notable exceptions being cost-effectiveness, system security and standards used (as marked by *)(257).

Table 7: Surveillance system attributes (adapted from Groseclose *et al.*)

Attribute	Definition	Measurement considerations	Influential factors
Acceptability	Willingness of persons and organisations to participate in the surveillance system.	• Participation rate of data providers • Completeness of case report data • Timeliness or frequency of data reporting • Responsiveness to requests for information	Influenced by time and effort required to complete and submit reports or by perceptions of the benefits derived from participation in the surveillance system
Cost-effectiveness*	Relationship between the expected outcomes and the costs of surveillance to achieve these outcomes.	• Direct system operational costs • Indirect future costs or savings through impact on public health strategies	Can be viewed from participant, institutional or stakeholder perspective
Data quality	Completeness and validity of data in the surveillance system.	• Case ascertainment (completeness) • Proportion of unknown, invalid, or missing values for reported data elements • Proportion of data entries that correctly reflect the true value of the data collected (validity).	Validity may be estimated by the proportion of errors in surveillance system data compared to analogous data from one of the system's data sources.
Flexibility	Ability of the surveillance system or its processes to adapt with little additional time or resources to changing	• Observing system response to ○ new requirements ○ changes in processes ○ environment	Examples include new health-related events, case definition changes, modification of policies affecting the patient population eligible to receive

	epidemiologies, information needs, technologies, or clinical practices.	• Best evaluated retrospectively	care from participating reporting sources, or introduction of new information technologies.
Predictive value positive (PVP)	Proportion of cases reported to the system that actually have the health condition under surveillance.	• Determine if reports represent true or confirmed cases of the health event under surveillance.	Low PVP may be addressed by case definition revision, request of additional data, or staff training to increase reporting accuracy
Representativeness	Ability of the system to accurately describe the occurrence of a health condition under surveillance over time and its distribution in the population by place and person.	• Compare reported cases to all actual cases/events. • Described in terms of ○ geographic coverage ○ demographic distribution ○ clinical manifestation	Information on all cases/events is seldom available
Security*	Processes and methodologies to keep surveillance data and information confidential, available, and accurate.	• Security policies in place • Security practices reviewed • Security levels & procedures are defined and enforced • Data use and release policy available • Access to system software application is controlled	Evidence of security breaches may trigger evaluation
Sensitivity	Sensitivity of a surveillance system to (α) case detection (proportion of individuals who	• Sensitivity measure of ○ case detection ○ outbreak detection	Simulated or authentic data may be used Case definition depends on (α) the

	have the condition of interest), (b) outbreak, and (c) case definition (ability of the case definition criteria to accurately represent the health condition of interest and classify the cases to which it is applied).	○ case definitions	health condition under surveillance; (b) knowledge of the epidemiology of the condition; (c) ability to describe the condition based on clinical signs and symptoms, laboratory criteria, or epidemiological criteria; and (d) availability of relevant data elements in the surveillance system's data sources
Simplicity	Structure and ease of operation of the system across the surveillance process cycle from data collection to use. Systems should be as simple as possible while still meeting their objectives.	• Characterised in terms of ○ availability, amount, and type of data ○ number and type of organisations providing and using the data monitored ○ number and type of data interchanges and transformations within the system; ○ data provider and system operator training requirements ○ type of information technologies used by the system.	
Stability	Ability to collect, manage, and provide data without failure	• Number or duration of unscheduled outages	

	(reliability) and to be operational when needed (availability).	• Comparison of the desired and actual amount of time or resources required for the system to collect, manage, analyze, interpret, and release data from the system • Presence or absence of continuity of operational procedures to maintain system performance.	
Standards used*	Use of data exchange, messaging, or other information technology standards by a surveillance system that enhances the ability of the system and its software applications to communicate, exchange data, and use the information that has been exchanged.	• The system uses data standards (e.g., ICD, MedDRA, or SNOMED) ** as valid values for appropriate data variables • Ability to translate its variable values to data standard concepts • The system uses standard data interchange protocols to exchange data with other information systems.	
Timeliness	Time between any two steps in the surveillance process. Steps in the surveillance process will vary by system.	• Measure time elapse between operations ○ event to reporting ○ reporting to data completeness ○ request for information to delivery or interpretation ○ feedback to stakeholders	The relative importance of timeliness of surveillance process intervals varies by surveillance objective and health event under surveillance.

Usefulness	Ability to meet the expectations for use and impact on public health initiatives ability to be used by EPH practitioners to design and measure intervention and prevention strategies and track the success of these programs over time can convey a meaningful and simplified message that is easily understood by policy makers and relevant stakeholders	Measures for evidenced based policies include applicability to community interests, concerns, and overall goals
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* Not included in the CDC Evaluation guidelines

**ICD = International Classification of Disease(268) / MedDRA = Medical Dictionary for Regulatory Activities(269) / SNOMED clinical terminology(270)

5.4.6 SWOT analysis

An alternative to health evaluation guidelines are the SWOT (strengths-weaknesses-opportunities-threats) analysis and TOWS (threats-opportunities-weaknesses-strengths) matrix tools originally developed for the business sector. Similar to health evaluations, SWOT and TOWS facilitate a structured approach to guide organisations and/or direct programs and policies(271).

The SWOT analysis examines the opportunities and threats in both internal and external environments to create a list of strengths, weaknesses, opportunities and threats. It includes recognition of the important distinction between the internal factors, over which the organisation has more control, than the latter external factors(271, 272). The TOWS matrix is used as a continuation from the SWOT analysis to generate strategies for program management that use the identified “strengths to either take advantage of opportunities or avoid threats, that exploit opportunities to overcome weaknesses, or that rectify weaknesses to circumvent threats”(273).

These tools can provide an opportunistic approach for public health planning, particularly meeting challenges posed as immunisation programs expand into multidiscipline and collaborative initiatives with resultant complex organisational and stakeholder relationships. Examples of use in the immunisation setting include developing vaccine shortage policies in the US(272) and evaluation of a Canadian provincial AEFI surveillance system(273), which is described in section 5.6 below.

5.5 Evaluation of passive AEFI surveillance systems

Development of surveillance programs is dynamic and iterative process, therefore the evaluation process should be equally progressive throughout the surveillance system lifecycle from development to maturation(257). Lifecycle stages would require description upon system establishment, monitoring of functionality during operation and comprehensive evaluation of the system attributes to consolidate maturity. However, evaluations typically respond to a specific question or programmatic challenge, rather than as progressive monitoring of system performance(254).

Component evaluation themes are described below, concluding with consideration of global and collaborative system evaluations.

The limited array of structured holistic evaluations of passive AEFI systems, similar to the SAEFVIC evaluation undertaken as part of this PhD, are detailed in section 5.6.

5.5.1 System description

The evaluation cycle should begin with a description of AEFI surveillance systems at the time of establishment, its goals and indicators. With current global advocacy for establishment of surveillance systems as an essential requirement of immunisation programs(10), the early description of system design, performance objectives, stakeholder setting, public health dynamic and epidemiological demography should be encouraged.

More commonly, however, surveillance system descriptions are conducted retrospectively after a number of years of system operation and therefore combine the system description alongside some measure of the system performance. An excellent example is the review undertaken in Albania: AEFI surveillance was initiated in 2001 addressing prior ad hoc reporting, with a comprehensive review conducted almost 15 years later in 2016 detailing the mapping of stakeholders, stepwise progress in establishing the surveillance framework for AEFI detection and response alongside clarification of the various roles and responsibilities(274). The review concluded that, while having achieved the first goal of the Global Vaccine Safety (GVS) Blueprint by establishing a minimal capacity for vaccine safety control, there was need to improve capacity to evaluate safety of vaccines, to investigative options for active surveillance and incorporate digital technologies to improve availability of the AEFI data for regulators and other data users(274).

Another comprehensive description of an AEFI surveillance system is that of the Chinese National AEFI Information System (CNAEFIS)(239). China is a highly populous (1.4 billion in 2020) rapidly-developing country and sees an average of over 500 million vaccine doses administered annually through an extensive nationally funded vaccine program. The volume of the program, in addition to approximately 80% of vaccines

being manufactured domestically, demands a credible AEFI surveillance system to detect and respond to emerging vaccine safety signals and address community and media concerns(239).

CNAEFIS, established in 2005 and brought under the central control of the China CDC in 2010, was reviewed in 2013. The review described the legislative framework, reporting standards and use of surveillance data. Reporting had increased approximately 30% per year (reaching 300,000 reports) and the system was credited as being a vital resource for decision-making by China's vaccine National Regulatory Authority and related stakeholders. “Strengthening capabilities of passive surveillance, developing active surveillance methodologies and including data mining methods for signal detection and analytical methods for causality assessment” were identified as priorities for future capacity-building(239).

In Australia, a basic outline of data collection, analysis and reporting at the national level are provided within the methods section of annual reports on AEFI surveillance(81, 164, 170, 172, 187, 275-284). The Victorian SAEFVIC surveillance model was described in the third year of operation, detailing the structures, processes and data management, with summary of impact over the three years after inception(1).

The US VAERS system has moved beyond the static publishing of system structures in scientific journals to a comprehensive updatable description publicly available on its website (<https://www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html>). It provides the system objectives, scope of reports sought, reporting requirements and responsibilities, explains limitations to the system and data interpretation and has links to reports as well as other vaccine safety monitoring activities such as the Vaccine Safety Data Link Project and the Clinical Immunization Safety Assessment (CISA) Network(285).

5.5.2 System functionality

As a surveillance system develops it is appropriate to ascertain if it meets individual performance criteria, is responsive to programmatic challenges and to investigate any discordance in signal detections (that is, the surveillance system fails to inform on, or

falsely indicates a signal. A plethora of articles detail individual aspects of such passive AEFI surveillance functionality, for example: examination of AEFI with a specific vaccine; a particular clinical reaction or syndrome; an individual signal event or; impact on one aspect of policy-setting(247). As previously discussed, care should be taken before assuming findings from a constrained setting are externally applicable to the broader functionality of the overall surveillance system. Of equal importance, particularly in the absence of a comprehensive evaluation, is ensuring interpretation appropriately considers the quality of the underlying data, especially case ascertainment and demographic representativeness.

5.5.2.1 Under-reporting as a system limitation

Incomplete case ascertainment and under-reporting are known constraints with passive AEFI surveillance(286), however this should not be an excuse to avoid quantification of local-reporting patterns, including biases within reporting trends such as the observed female predominance in AEFI reporting(287). Furthermore, programs typically assess surveillance data quality as the proportion of data variables with missing or unknown data, with attempts to validate the accuracy of the values reported less frequent(247). Both misclassification and underreporting result in underestimation of AEFI among the targeted population and limit the usefulness of these data for monitoring progress towards addressing vaccine safety issues and/or disparities in immunisation program delivery.

There is mounting evidence on the importance of immunisation in target population sub-groups, such as during pregnancy, and therefore increased questioning of the ability of AEFI surveillance to adequately capture data on these population subgroups(288). Successful implementation of vaccination programs into the antenatal population, such as for prevention of influenza and pertussis, requires robust adverse event surveillance and should be a key consideration for maternal immunisation programs(289).

A systematic review by Cassidy *et al.* in 2015 concluded there were no published reports outside of the USA of ongoing AEFI surveillance systems that specifically targeted pregnant women or neonates(290). However a global survey identified there

may be AEFI surveillance systems capturing events in these populations but not reported in the literature(291). This emphasises the importance to describe and document surveillance systems, their attributes and performance characteristics and particularly their ability to capture data and inform on population subgroups. This has been highlighted more recently in Australia with identification of potential under-reporting of AEFI in vaccine-target groups such as older Australians(229) and in a 2019 study identifying gaps in informing immunisation policy and practice for Australian Indigenous people(292).

5.5.3 System maturation

The requirement for evaluation of surveillance systems continues as platforms mature and expand.

India, the largest low-middle income country, which also has significant vaccine manufacturing industry, provides an informative account of the sustained program capacity-building efforts and attainment of quality management certification undertaken by the National Regulatory Authority(NRA) to assure vaccine safety(293). The AEFI surveillance system, articulated in-country through the 2015 *Operational Guidelines*, is detailed with exacting reporting timeframes, links to an online reporting portal (www.idsurv.org) and an outline of the multi-disciplinary committees that provide the technical support for investigation and causality assessment at state and national level, with additional “zonal consultants” assessing serious reported AEFI(293). The vigorous steps to strengthen AEFI surveillance resulted in the India-NRA assessment by WHO in 2016 recognising vaccine pharmacovigilance as its most mature function(294).

Across the globe, developed surveillance systems are expanding, such as by; incorporating data linkage with other health data sets (for example the US Vaccine safety datalink project(295, 296) and proposed in Australia with the expanded immunisation register(297)); exploring advanced statistical methodologies and algorithms for improved signal detection and; integrating new technologies into routine surveillance systems such as the use of informatics for improved interpretation and dissemination of surveillance data(254, 298).

Evaluation is essential to ensure vaccine safety surveillance keeps pace with the advances being made. There is both increasing range and volume of vaccines currently in use and a strong vaccine development pipeline associated with broadening complexity in formulations as well as technologies for vaccines delivery(238)

5.5.4 Global collaborations

Concept for evaluation should not be limited to individual surveillance systems but also consider collaborations within continents and globally.

A review of AEFI surveillance systems across European Union member states (and neighbouring Norway) identified disparities in both structure and responsible authority for AEFI surveillance, leading to inconsistency in data collection, clinical support, AEFI definitions and even the list of reportable events varying between countries(150). In response, the Vaccine European New Integrated Collaboration Effort (VENICE) project was created with the aim to intensify collaboration and increase standardisation in the reporting and analysis of AEFI(112, 150). A survey five years later found continued heterogeneity in regulations, reporting procedures and analysis performance but with emerging commitment to strengthen unification(154).

Global reporting of AEFI to the WHO adverse event database was also found deficient, with a quantitative analysis determining that 82% of all vaccine-related reports were received from only three countries, being US, Canada and UK and several member states not forwarding any AEFI reports at all(120). Timeliness of reporting was equally variable and overall poor with an average of 2.4 years elapsing between onset and report date: such deficiencies in the timeliness and representativeness of global reporting could hinder or prevent generation of safety signal events. GACVS, the global body established to advocate and provide support for establishment of vaccine safety programs – including surveillance, reviewed its *impact, reach and challenges* 15 years on (2016)(299). GACVS roles is stated as “to analyze and to interpret reports of the adverse effects of vaccines that impact on global vaccination programs and strategies, and to foster the development of improved surveillance systems to detect any adverse effects of vaccines”(300). As WHO cites effective and open communication of vaccine

safety information between regulatory authorities as the greatest challenge and responsibility of pharmacovigilance centres, GACVS serves as an important facilitator to bridge gaps in vaccine safety capacity globally(299). This is particularly important as almost all (93%) vaccine safety professionals across 26 low to middle income countries responding to the 2012 WHO Blueprint landscape survey said international collaboration was desirable and almost half (45%) indicated their countries, at least in part, relied on vaccine safety information from other countries(106).

International collaborations and consistencies in surveillance would be leveraged if the calls for unified minimum requirements for reporting as part of a functioning pharmacovigilance system, originally posed by WHO in 2010, were actualised(301). If development of a universal standardised system could not feasibly consolidate regional individualities, the sharing of best practices, including a common reporting form should be considered to support efforts to strengthen vaccine pharmacovigilance activities on a global scale(29, 121).

Looking to the future, and particularly as new vaccines are introduced, there is an argument to alter the pace of the vaccine development lifecycle based on perception of vaccine safety risk. That is, there is increasing acceptance of risk in early stages of highly beneficial vaccines, provided that there is rigour in post-marketing surveillance and investigations can be rapidly initiated(302). However, many of these rapidly deployed newly introduced vaccines—for example, conjugate meningococcal A and Ebola vaccines—are likely to be first used in low to middle income countries(LMIC), where the population have a high incidence of the target diseases(303, 304). Yet conversely, as previously discussed, the capacity for program evaluation and safety monitoring post-licensure in LMICs is relatively weak(84), accompanied by limited experience in implementing epidemiological vaccine safety studies(106, 111). Therefore explicit description of established surveillance systems, with detailed critique of performance criteria and identification of gaps in systems or exclusion of population subgroups, are essential as shared learning opportunities supporting establishment of systems in less-resourced environs(109).

5.6 Structured AEFI surveillance system evaluations

Although specific structured guidelines for evaluating public health surveillance systems have existed and been advocated for for decades, they have been infrequently applied holistically to passive AEFI surveillance systems. With increasing advocacy, even demand, for establishing AEFI surveillance systems—and alongside maturation of existing systems—continuation of publication of structured evaluation findings is anticipated. For example the comprehensive description of China's surveillance system, CNAEFIS published in 2015, indicates it is conducting an evaluation using CDC guidelines, albeit the findings are not yet published as of 2019(239).

Using a PRISMA directed search strategy (described in Chapter 3: Methods), six articles were identified that described application of structured evaluation criteria to a passive AEFI surveillance system (and were published in English); US VAERS(242), Brazil(101), Victoria (SAEFVIC), Australia (15), and Hurare & Guruve districts in Zimbabwe(243, 244) (245): of which only VAERS (1999) and Brazil (2011) were published prior to the SAEFVIC evaluation. These are summarised below, with the business organisation model (SWOT & TOWS) overviewing the broader vaccine safety program in Manitoba, Canada (2014) included for completion(273).

5.6.1 United States (VAERS)

The US VAERS system was evaluated in 1999, eight years into operation, using the CDC guidelines (1988 version)(305). The comprehensive description of the system highlighted deficiencies common to passive AEFI surveillance systems, notably underreporting and complexities in data interpretation with multiple vaccines and multiple AEFI reportable from an individual event and the lack of an exposed population denominator(242). Even in these early years sensitivity for serious AEFI was deemed 'reasonable', however only 1% sensitivity to mild reactions such as rash after MMR vaccine(99) Timeliness of reporting had improved with 42% of AEFI reports received within one month of onset , rising to 98% within one year(242). Although structured evaluation was not repeated, further periodic in-depth reviews were conducted in 2004 and 2015. The description in 2004 reiterated the breadth of use of

VAERS data but also highlighted common misconceptions in interpretation of VAERS data. The authors cautioned against the perception that all adverse reactions were reported and emphasised that VAERS data represented purely temporal associations: additional investigation and assessment of causality being required before considering whether specific medical events occurred more frequently among vaccinated individuals compared to the general population(142). The review clarified that as “data cannot be used to calculate the incidence of adverse reactions after vaccination”, “statistics should not be interpreted or presented as relative risks of specific vaccine adverse events” but used only as a hypothesis generation tool identifying areas to be further evaluated(142). The 2015 review focused on VAERS data analysis, including limitations and ease of misconceptions especially in the absence of ability to calculate incidence rates and was particularly informative for healthcare providers in understanding their role and interpretation of VAERS data(129).

5.6.2 Brazil

The passive AEFI surveillance system in Brazil commenced in 1998. An evaluation on performance indicators from 2002 to 2005, with specific focus on the infant schedule, was conducted using the CDC guidelines and published in 2011(101). The system structure was described, emphasising simplicity of reporting and information flow; however, complexities in data analysis and case confirmation requiring well-trained personnel were noted as constraints. The evaluation concluded the system had low sensitivity, consistent with known limitations of passive surveillance, however, was informative and useful for guiding vaccine safety policy. Recommendations included developing methodologies for sentinel surveillance in hospitals or major cities and electronic immunisation records for improving system sensitivity(101).

In a similar situation to Australia, Brazil noted the large territorial area and regional differences, with 26 states and single federal district, brought specific challenges to the operationalisation of surveillance(101). However, a further exploratory study recognised that jurisdictional variance can also be beneficial, with analysis at the local level on occasion able to provide information not perceived within collated national data(306).

5.6.3 Harare & Guruve districts, Zimbabwe

Zimbabwe has included the requirement for AEFI surveillance systems in its immunisation policy since 2000. However, reviews of national data indicated low-levels of district AEFI reporting, triggering a series of evaluations using the CDC guidelines as a framework to direct attribute-based assessment, predominantly from the health care worker perspective(243, 244). Those for Harare City and Guruve district were published as descriptive cross sectional studies in 2016 and 2018 respectively(243, 244). Additional similar structured evaluations were mentioned in referencing for Kwekwe district, Zaka district and Matebeleland North Province; however these were either in non-english language and/or locally available reports only.

The evaluation of Harare City AEFI surveillance found only 21 of 28 AEFI identified in 2015 were reported via the AEFI surveillance system. Despite low overall reporting, the evaluation concluded the system was considered useful, was simple, flexible, timely and stable but costly, especially for the small number of reports received. The positive predictive value was reported as high, in that 25 reports were investigated as being causal to vaccination but sensitivity was undetermined. Immunisers alluded to the AEFI surveillance system being useful through data being used at the local level with half of survey respondents reporting having undertaken actions such as intensifying health education campaigns, making follow-ups or stopping student nurses from administering vaccines in order to reduce immunisation errors. While healthcare workers were deemed as highly knowledgeable, reasons for under-reporting included work overload, lack of feedback and fear of victimisation by superiors(243). Guilt for having caused harm was another barrier identified in similar, cited but unpublished, district evaluations.

In Guruve, knowledge of the surveillance system was considered as good among the majority of health workers and the required resources for surveillance were available, yet no AEFI had been reported in the preceding year(244). Health workers' fear of personal consequences, being blamed for causing adverse events and being investigated were cited as the main reasons for failure to report AEFIs and therefore poor system performance(244). Such fear and concerns about blame and being

responsible for the event as barriers to reporting are not uncommon among developing countries' health care workers, having also been identified in South African, Kenyan studies(111), and Cote d'Ivoire(245).

5.6.4 Manitoba, Canada

The Canadian precinct of Manitoba established a vaccine best practice project following the 2010 influenza pandemic with the three aims: to optimize the vaccine safety system; to maintain professional and public confidence in the safety of vaccines, and; to address growing anti-immunization concerns. One component of the project was to commission an evaluation of the AEFI surveillance response to address gaps between practice and the broader vaccine safety priorities and objectives of the National Immunisation Strategy(273). The evaluation was structured using SWOT and TOWS principles(271, 273).

The organisational focussed evaluation identified opportunities to strengthen professional development of health care providers through access to free online immunisation training and creation of an immunisation newsletter providing education and vaccine safety updates. System functionality was improved by transition to simplified electronic reporting and streamlining processes through synthesis with existing immunisation systems such as vaccine inventory and client immunisation databases. Exploration of technical aspects included procedures for causality assessment, determining background rates and signal detection methodologies(273).

5.7 Evaluation of SAEFVIC

The evaluation of SAEFVIC in 2015 responded to five triggers(255):

1. **Initial establishment of a surveillance system:** although the system had been described(1), no evaluation had been undertaken since commencement 7 years prior in 2007.
2. **Regular periodic evaluation:** timely to ensure the system was fit for purpose
3. **Continuous demand that surveillance be adequate for changes in public health practice:** SAEFVIC commenced operation coincident with the

introduction of a new vaccine (Gardasil®) and national vaccination policy for targeting school-aged children. The system subsequently served to support evaluation of vaccine interventions, both before and after the introduction of new vaccines(198) or changes in vaccine strain or formulation (seasonal or valent)(198, 307, 308).

4. **Data quality monitoring:** important to identify issues for further investigation and/or address aspects of data quality, particularly as new analysis tools were being initiated.
5. **Structural changes:** it had been proposed for SAEFVIC to be expanded as a national system(127).

The evaluation was structured using the CDC *Updated Guidelines for Evaluating Public Health Surveillance Systems*(259). These guidelines were chosen as they were the most commonly used guidelines in the communicable diseases arena(309): Oasis being fledgling at the time with paucity of findings outside of zoonoses, and the ECDP guidelines had yet to be published. The CDC guidelines had been used to evaluate Australian health surveillance systems previously and were also the guidance for the evaluation of the US VAERS in 1999 and the Brazil AEFI surveillance system in 2011(85, 101, 242, 263). The guideline criteria are data focused facilitating a desktop review with limited qualitative perspective from stakeholders. The CDC guidelines omit economic and cost-benefit criteria.

The evaluation of SAEFVIC aimed to determine if the goals and objectives of the surveillance system were met and is presented in the publication below, followed by the secondary research question arising from the evaluation to consider the influence of consumer reporting of AEFI. The impact of the research findings and future implications are described in *Chapter 9: Optimising SAEFVIC*.

Evaluation of ‘SAEFVIC’, A Pharmacovigilance Surveillance Scheme for the Spontaneous Reporting of Adverse Events Following Immunisation in Victoria, Australia

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Abstract

Introduction Australia is traditionally an early adopter of vaccines, therefore comprehensive and effective post-licensure vaccine pharmacovigilance is critical to maintain confidence in immunisation, both nationally and internationally. With adverse event following immunisation (AEFI) surveillance the responsibility of Australian jurisdictions, Victoria operates an enhanced passive AEFI surveillance system integrated with clinical services, called ‘SAEFVIC’ (Surveillance of Adverse Events Following Vaccination In the Community).

Objective The aim of this study was to evaluate Victoria’s current AEFI surveillance system ‘SAEFVIC’ and inform

ongoing quality improvement of vaccine pharmacovigilance in Victoria and Australia.

Methods We conducted a retrospective structured desktop evaluation of AEFI reporting received by SAEFVIC from 2007 to 2014, to evaluate the system according to its stated objectives, i.e. to improve AEFI reporting; provide AEFI signal detection; and to maintain consumer confidence in vaccination.

Results AEFI reporting has tripled since SAEFVIC commenced (incidence risk ratio [IRR] 3.04, 95% confidence interval [CI] 2.35–3.93), raising Victoria to be the lead jurisdiction by AEFI reporting volume and to rank third by population reporting rate nationally. The largest increase was observed in children. Data were utilised to investigate potential signal events and inform vaccine policy. Signal detection required clinical suspicion by surveillance nurses, or prior vaccine-specific concerns. Subsequent vaccination post-AEFI was documented for 56.2% (95% CI 54.1–58.4) of reports, and the proportion of children due or overdue for vaccination was 2.3% higher for those reporting AEFI compared with the general population.

Conclusion SAEFVIC has improved AEFI surveillance, facilitates signal investigation and validation, and supports consumer confidence in immunisation. Expansion of the system nationally has the potential to improve capacity and capability of vaccine pharmacovigilance, particularly through data consistency and jurisdictional comparability in Australia.

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Key Points

The spontaneous adverse event following immunisation (AEFI) surveillance system 'SAEFVIC' has strengthened vaccine pharmacovigilance in Victoria, Australia.

Integration of clinical support services for vaccine safety is associated with increased AEFI reporting.

A majority of patients experiencing AEFI successfully continued with further vaccinations.

1 Introduction

Australia, as a traditionally early adopter of vaccines, requires comprehensive and effective post-licensure vaccine pharmacovigilance to maintain confidence in immunisation, both nationally and internationally [1, 2]. Furthermore, as vaccine programmes mature, and the incidence of vaccine-preventable diseases declines, there is often a resultant increase in public concern about adverse events following immunisation (AEFI) [3–5].

AEFI surveillance systems aim to detect or provide a means to investigate unexpected events and changes in rates of expected events, as well as rare, late-onset, or population-specific adverse events time-associated with vaccination, regardless of causality [1, 6]. Surveillance information is used to detect vaccine safety 'signals' and prompt action, which will help to maintain confidence in immunisation programmes [2, 7] and to ultimately provide safety data to support evidence-based decision making [3, 8].

Globally, the processes for vaccine pharmacovigilance vary, as demonstrated by the number of reviews of AEFI surveillance [4, 9–14], as systems need to adapt to individual healthcare structures [3, 12, 15]. Passive spontaneous reporting AEFI surveillance systems are most frequently used as they are relatively simple and low-resource systems [6]. However, limitations are well-documented; timeliness is often poor and overall sensitivity (ability to detect all AEFIs) low, with some estimates showing up to 95% underreporting [3, 16–19]. While passive surveillance is imperfect, the alternative of active surveillance, which aims to identify all AEFI events in a defined population in a defined period, can be costly and resource-intensive, and is therefore generally used to target new vaccines, prespecified AEFIs, vaccines in subpopulations of interest, or to test an hypothesis [20].

1.1 Passive Adverse Event Following Immunisation (AEFI) Surveillance in Australia

In Australia, AEFI surveillance currently comprises a variety of jurisdictional-based reporting systems, with marked regional differences in surveillance methodologies and reporting rates [21], and a central data repository managed through the Office of Product Review of the Therapeutic and Goods Administration (TGA) [22]. This system has come under intense scrutiny in recent years. In 2009, the influenza pandemic and introduction of monovalent H1N1 2009 influenza vaccine saw a reliance on AEFI surveillance to determine the risk of vaccine-associated Guillain-Barre syndrome (GBS), as had been observed with a previous H1N1 Influenza pandemic vaccine in 1976 [23, 24]. This was followed in 2010 by an unexpected increased risk of fever and febrile seizures following immunisation with one brand of trivalent influenza vaccine (TIV) (Fluvax[®] and Fluvax Junior[®], CSL Biotherapies, Australia) [25–27]. Although the Chief Health Officer of Australia suspended the use of TIV in children under 5 years of age 6 weeks after the commencement of the seasonal TIV programme [28], there was considerable criticism that systems were not adequate to detect the safety signal in a more timely manner and prevent further cases before the suspension occurred [29]. One such case led to severe permanent sequelae in a previously healthy 1-year-old, and a resultant eight-figure settlement between the family, manufacturer and state government [30, 31]. In response to these events, two expert reviews were commissioned: the West Australian Stokes Ministerial Review investigated the public health response, and the TGA-commissioned Horvath Review was tasked to provide recommendations for the improvement of AEFI surveillance in Australia [21, 29].

The Australian system for vaccine pharmacovigilance, as presented in the Stokes/Horvath reviews, was found to be suboptimal. The Stokes review "revealed an adverse event reporting system that is not robust or timely" and described the current dual state-based and national reporting as "confusing" [29]. Horvath recognised that while "monitoring of AEFI in Australia is in keeping with international systems of passive adverse events surveillance", improvements could be made [21]. The Victorian state-based AEFI surveillance system, called 'SAEFVIC' (Surveillance of Adverse Events Following Vaccination In the Community), was noted as a possible model for use by states without robust AEFI surveillance [29].

1.2 SAEFVIC (Surveillance of Adverse Events Following Vaccination In the Community)

Victoria, the second most populous state in Australia, has an estimated population of 5.96 million, and a birth cohort of 75,000 per annum [32]. In 2007, a vaccine pharmacovigilance system called SAEFVIC, comprising enhanced passive surveillance integrated with clinical services, was established in order to improve AEFI surveillance and address a perceived weakness in AEFI reporting in Victoria compared with other states [33, 34]. At inception, the stated objectives for SAEFVIC were to (1) improve reporting of AEFIs; (2) detect, validate and inform on potential vaccine safety signals; and (3) help maintain confidence in immunisation services [34]. No evaluation of the surveillance system and its ability to meet its stated objectives has yet been undertaken.

1.3 Objective

The aim of this study was to provide a desktop evaluation of SAEFVIC, in Victoria, Australia, over its first 7 years of operation, to determine if the system objectives were met, and to inform ongoing quality improvement of vaccine pharmacovigilance for Victoria and Australia.

2 Methods

The *Updated Guidelines for Evaluation of Public Health Surveillance Systems* [35] were used to develop a framework to determine whether SAEFVIC addressed its stated objectives. Individual questions to respond to the stated SAEFVIC objectives were established, with each question developed on the basis that it could be answered within this desktop evaluation (Table 1). Note that the counting of reports and categorizing of AEFIs does not include an assessment of causality.

2.1 Data Sources

2.1.1 Australian Jurisdiction AEFI Reporting Rates

Published annual summary reports of AEFIs in Australia, by state and territory, were available from 2002 to 2014 [7, 31, 33, 36–43].

2.1.2 SAEFVIC AEFI Data

SAEFVIC system AEFI reports detailing patient demographics, immunisation provider, vaccines administered and description of the reaction experienced are submitted to SAEFVIC by phone or via an online web-based portal

(<http://www.saeftvic.org.au>). Immunisation nurses follow-up all reports to facilitate clinical management, and consultation with a medical immunisation specialist is offered to those who have experienced a serious AEFI or have concerns. AEFI symptoms are classified according to standardised clinical case definitions [8]. These AEFI reporting processes have been previously described in detail [34].

AEFI reports submitted from 2007 to 31 December 2014 were extracted by date reported. Reports submitted direct to the TGA prior to SAEFVIC commencement in May 2007 had been retrospectively entered into the database to make these data a complete record for 2007. Reports for persons investigated prior to vaccine administration (e.g. for pre-existing allergy, comorbidity or vaccine hesitation), or reporting an historical adverse event, were excluded. Age at vaccination was calculated from the date of birth (DOB) and the date of vaccination.

2.1.3 Vaccine Doses Administered: Australian Childhood Immunisation Register

Vaccines-administered data for children up to 7 years of age during the study period were requested in December 2015 and were provided as aggregate totals by brand name, antigen and recipient age (in months) at the time of vaccination.

2.1.4 Population Data: Australian Bureau of Statistics (ABS)

Population census data were accessed from online open-access tables of mid-year estimated residential population (ERP) for Victoria from 2007 to 2014, by sex and age (in years) and remoteness area [44].

2.2 Definitions

Serious AEFIs were defined as those requiring hospital admission, resulting in death, being an acute life-threatening episode,¹ resulting in significant or permanent disability, or congenital anomaly. In addition, AEFIs considered to be medically important by SAEFVIC clinicians were included [45]. Immunisation age-groups were defined as an approximation of the 2014 Australian National Immunisation Program (NIP) schedule, i.e. infant (0–11 months), child (1 to <7 years), school-aged (7–18 years) and adult (19+ years) [46]. Remoteness area

¹ Life-threatening event is an event/reaction in which the client was at risk of death at the time of the event/reaction; it does not refer to an event/reaction that hypothetically might have caused death if it were more severe.

Table 1 Evaluation framework questions, data sources and analysis methods

Research questions	Data utilised	Analysis
OBJECTIVE 1: Improve AEFI surveillance in Victoria		
Has Victoria's AEFI reporting rate and rank, compared with other jurisdictions, improved?	Published Australian Annual reports of AEFI surveillance	Comparison of overall rank of reported annual AEFI rate per 100,000 population by jurisdiction
Has AEFI reporting in Victoria increased?	SAEFVIC data	Frequency of AEFI reports by year reported and subgroups by age cohort and serious AEFI
Reporting volume		
Is the quality of reporting acceptable?	SAEFVIC data	Review of data fields collected and review of key fields (Vaccinee demographics, vaccine information and clinical detail) in dataset to identify missing data
Data completeness		Days to report calculated as days from vaccination date to reported date (minus days from vaccination to AEFI symptom onset) for both all reports and serious reports
Timeliness		Reports per 100,000 population
Is SAEFVIC surveillance representative?	SAEFVIC data	
Immunisation age cohort	Australian Bureau of Statistics census mid-year ERP by individual year of age and sex	
Sex		Number of reports and percentage of male reports within all AEFI reports and by age cohort
Geographic	SAEFVIC vaccinee residential postcode, proportionally correlated to remoteness area category using Australian Bureau of Statistic correspondence tables	Reports per 100,000 population
OBJECTIVE 2: Detect and validate signals		
Is there evidence that SAEFVIC has detected, validated or informed on vaccine safety signals?	SAEFVIC internal and external reporting (including reporting to the Department of Health and Human Services), publications and personal communication with the Service Director (JB)	Review for any evidence of standard protocol; analyses conducted; commentary within routine reporting; specific signal report or publication
OBJECTIVE 3: Maintain confidence in immunisation		
Do persons reporting AEFI continue to receive vaccination?	SAEFVIC data	Frequency and proportion with documented further vaccination and comparison of proportion for serious AEFI vs. other AEFI
Are children reporting AEFIs more or less likely to complete vaccination as those not reporting AEFIs?	SAEFVIC data (children 0 to <7 years) Australian Childhood Immunisation Register: (1) matched record for SAEFVIC-reported AEFI cases by medicare number; and (2) state level data	Comparison of the proportion of cases considered as 'due or overdue for vaccination' among SAEFVIC AEFI-reported vaccinees and statewide data for children <7 years
<i>AEFI</i> adverse event following immunisation, <i>SAEFVIC</i> Surveillance of Adverse Events Following Vaccination In the Community, <i>ERP</i> estimated residential population		

was determined using the vaccinee's residential postcode corresponding to the Australian Bureau of Statistics (ABS) remote area classification [47]. Due or overdue for vaccination was defined consistent with the Australian Childhood Immunisation Register (ACIR) rules for determination of immunisation status, meaning that "a child has received the scheduled vaccinations according to age for hepatitis B (hepB); diphtheria, tetanus and whooping cough (DTPa); *Haemophilus influenzae* type b (Hib); polio (IPV); pneumococcal and measles, mumps and rubella (MMR)" [48].

2.3 Analyses

Descriptive analyses and statistical calculations were conducted in Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and Stata 13 (StataCorp LP, College Station, TX, USA).

The average annual population-based AEFI reporting risks were calculated using the ABS mid-year ERP [32], and calculated as age-specific (number of AEFI reports/ (ERP) $\times$ 100,000). Reporting risks per 100,000 vaccine doses administered were estimated for children aged

<7 years who received vaccines funded through the NIP) and were recorded in the ACIR [46].

We estimated differences in proportions and used the Chi-square test for trend to assess changes over time. The 0.05 level of significance was used for all analyses.

AEFI reports submitted to SAEFVIC for children aged <7 years were submitted to the ACIR for matching by Medicare number (an individual healthcare identifier), with return of those matched being listed as due or overdue for vaccination at 5 years of age. The ACIR holds records until the vaccine recipient reaches 15 years of age, therefore record matching was restricted to AEFI reports from 2010 onward.

3 Results

3.1 Improve AEFI Reporting

3.1.1 Reporting Volume

A total of 7184 AEFI reports were received by SAEFVIC from 2007 to 2014 for vaccinees aged from birth to 91 years. A majority (88%) were from healthcare providers, but the proportion received directly from vaccinees (or their guardian) increased to 20% by 2014. A total of 13,695 vaccines were associated with these reports, with a median of two vaccines administered per AEFI case reported. Three-quarters (74%) of vaccinees were coadministered.

Nationally, the AEFI reporting risk for Victoria improved from a low of rank 7 (out of 8 jurisdictions) in the pre-SAEFVIC years 2003–2005 to rank 3 among the eight national jurisdictions and top state, as judged by reports per 100,000 population (Fig. 1). The number of AEFI reports received in Victoria tripled in the 7 years from SAEFVIC inception, predominantly in the first 12 months, rising from 354 reports in 2007 to 1293 reports in 2014, and being more than double the number received by any other jurisdiction [43]. Correspondingly the reporting risk, which had averaged at 3.6 per 100,000 population across the 4 years pre-SAEFVIC, increased from 6.7 per 100,000 to 22.1 per 100,000 population in 2014 (incidence risk ratio [IRR] 3.04, 95% confidence interval [CI] 2.35–3.93) (Table 2).

3.1.2 Data Completeness

Data fields recorded in the SAEFVIC dataset were well-completed for vaccinee demographic details (patient identifier, DOB, sex and area of residence), being either a required field for report submission or with >99% completion (DOB unknown for 27 vaccinees [0.4%], sex

unknown for 13 vaccinees [0.2%]). Vaccine name was a required field and the date of vaccination was unknown in only 104 (1.4%) reports. Vaccine dose was missing for 245 (3.4%) reports, while vaccine batch information was incomplete for 7600 (55.5%) of the 13,695 vaccinees reported. A summary of the AEFI reaction is required for all reports, and while additional clinical details were complete for approximately two-thirds of reports, time of onset was unknown for 1365 (19.0%), and information on the outcome or resolution of AEFI was unknown for 1967 (27.4%). The proportion of unknown data fields was similar across all reporting years (data not shown). Consent to contact the patient for follow-up was not recorded for 1446 (20.1%) reports, with the proportion of omitted consents falling in each consecutive year of reporting, from 43% in 2007 to 14% in 2014. Post-AEFI, SAEFVIC clinic attendance information was not recorded for 51 reports (0.7%).

Data fields notably absent from the SAEFVIC report format were vaccinee indigenous status, if the vaccinee was pregnant at the time of vaccination (and weeks' gestation), site of vaccine administration, and site of reported injection site reaction.

3.1.3 Timeliness

The median time from vaccination to AEFI symptom onset was 0 days (range 0–364 days), with 50% of reports received within 6 days of symptom onset (range 0 days to 13 years). Reporting of serious AEFIs was slower, with a median of 11 days to report following symptom onset. No trend in timeliness of reporting was identified.

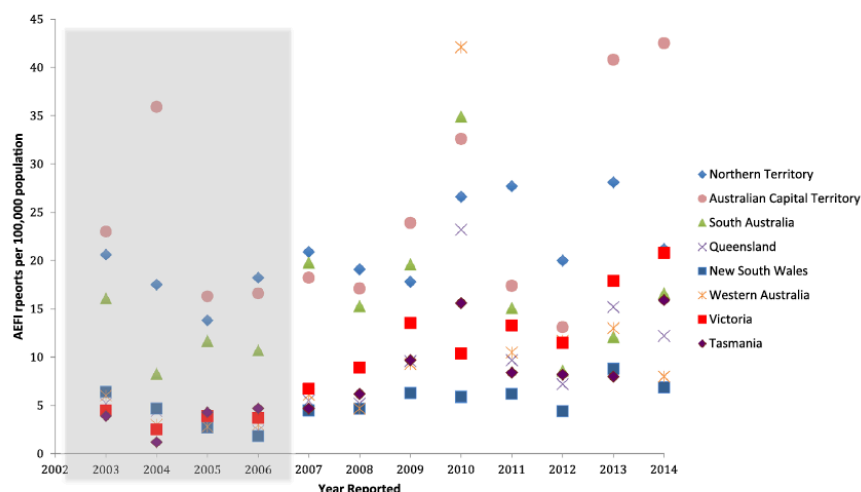
3.1.4 Representativeness

Age and sex The majority of AEFI reports received were for children (33.4%) and infants (29.7%), which reflects the Australian NIP. The increase in AEFI reports from 2007 to 2014 varied by age group, with a marked increase observed for children and infants and minor increases for adults. AEFI reports for the school-aged children did not increase until 2013, coincident with the expansion of the human papillomavirus vaccine programme from females only to both males and females (Table 2; Fig. 2).

Overall, AEFI reporting was higher for females ($p < 0.001$), but the sex ratio varied by age group, being predominantly males among infants and children, and predominantly females in the school-aged and adult age groups (Table 2).

Geographic AEFI reporting risk per 100,000 population by geographic remoteness area category was lowest for outer regional (12.3) and highest for inner regional (20.5), with a similar reporting risk for major cities and remote areas (14.9 and 14.2, respectively).

Fig. 1 National AEFI reports per 100,000 population by Australian jurisdiction and year of report (*shaded area* is pre-SAEFVIC), 2003–2014 (2010 may include active surveillance data as surveillance systems responded to the unexpected increased reactivity of Fluvax Bio CSL® trivalent influenza vaccine 2010 formulation). AEFI adverse event following immunisation, SAEFVIC Surveillance of Adverse Events Following Vaccination In the Community



3.1.5 Serious AEFIs

Approximately one-fifth of reports met the definition of a serious AEFI, with a higher proportion observed in infants and no difference in the ratio of males to females reporting serious AEFIs. The overall trend in the proportion of serious AEFI reports increased by <1% over the 7-year study period (Chi-square trend 0.7%, $p < 0.001$) (Table 2).

3.2 Detect and Validate Signals

Review of SAEFVIC internal and external reports identified evidence of processes supporting signal detection comprising (1) clinical suspicion as individual AEFI reports are received and reviewed by immunisation nurses; (2) quarterly analyses of number of all reports; number and proportion of reports relating to influenza vaccines, serious AEFIs and children <7 years of age; AEFI reporting per 100,000 doses administered for children aged <7 years; and descriptive summaries of serious AEFI cases; (3) comparison of quarterly data with the previous quarter and with the same reporting period 1 year prior to investigate potential seasonal variations; and (4) annual summary to provide crude trends. No statistical signal detection or data mining methodologies were routinely conducted. Exploration of signal detection methods such as control charts, geographic distribution by postcode and proportional reporting ratio methods was evident from inclusions in internal reports since 2012 (unpublished data, reports to Department of Health Immunisation Advisory Committee) [34]. Twelve reports of signal validation investigations were identified, all of which were initiated in response to clinical suspicion of increased reporting raised by SAEFVIC nurses, specific queries posed to SAEFVIC, or

monitoring of a new vaccine or vaccine delivered to a new subpopulation. Investigation methods varied according to the signal characteristics, but generally involved clinical review of the cases alongside descriptive epidemiology and/or additional epidemiological studies, including comparison of reporting rates and self-controlled case series (Buttery J, Director, SAEFVIC, personal communication) [49, 50]. A number of publications used SAEFVIC data to facilitate studies and investigations to detail specific AEFIs and guide immunisation policy [51–55].

3.3 Maintain Confidence in Immunisation

Clinical consultation with an immunisation specialist was accessed by almost one-third (28.9%) of vaccinees with a reported AEFI, rising to over half of those reporting a serious AEFI, and with the highest proportion of attendees being infants (Table 3). Over half (56.2%, 95% CI 54.1–58.4) of clinical consultation attendees received further immunisations on site, regardless of whether the AEFI experienced met the definition of serious or not ($p = 0.903$) (Table 3). For the remaining 44%, not all would have required further vaccination, and others may have elected to receive immunisation using their usual provider within the community.

ACIR records were accessible for 71% (1944/2724) of the children <7 years of age who were reported to have an AEFI from 2010 to 2014, and with sufficient data to be eligible for ACIR record matching (82%, 2724/3340), of whom 9.3% (180/1944; 95% CI 8.0–10.6%) were documented as due or overdue for their routine immunisations subsequent to their AEFI report. This was 2.3% higher than the state proportion of 7.0% being due/overdue (as at 31 December 2014) ($p < 0.0001$) [56].

Table 2 AEFI reports by year, age cohort, sex, serious AEFI category and clinical consultation attendance, SAEFVIC, 2007–2014

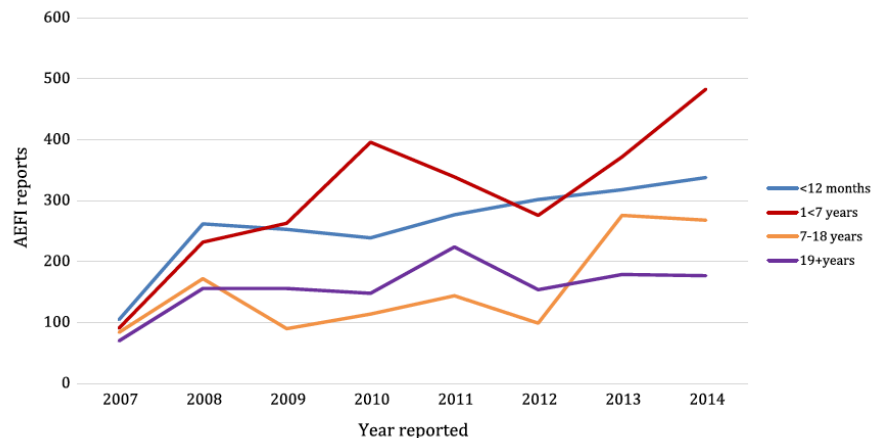
AEFI reports	Vaccine schedule ^a	Year reported						Total (%)	Male/female (% male) [Unk = 14]	Serious N (%) [95% CI]
		2007	2008	2009	2010	2011	2012	2013	2014	
All		354	832	789	908	1004	843	1161	1293	7184 (18.7) [17.7–19.7]
Infants <12 months	HepB DTPa Polio Hib PCV	105	262	253	239	277	302	318	338	2094 (63.1)* [28.9–33.8]
Children 1 to <7 years	Rotavirus MMRV Men C PCV13	91	232	263	396	339	276	372	483	2452 (34.1)
School age, 7–18 years	4vHPV, HepB, DTP	84	172	90	114	144	99	276	268	1247 (17.4)
Adult, 19 + years	DT Pneumovax 23	70	156	156	148	224	154	179	177	1264 (17.6)
Unknown		4	10	27	11	20	12	16	27	127 (1.8)
Reports per 100,000 population		6.7	15.7	14.6	16.6	18.1	14.9	20.3	22.1	
Serious [n (%)]		62 (17.5)	130 (15.6)	158 (20.1)	139 (15.3)	174 (17.3)	166 (19.7)	254 (21.9)	261 (20.2)	1344 (18.7)
Attended clinical consultation [n (%)]		118 (33.3)	292 (35.1)	336 (42.5)	238 (26.0)	262 (25.8)	267 (31.2)	249 (21.4)	297 (23.0)	2059 (28.7)

AEFI adverse event following immunisation, SAEFVIC Surveillance of Adverse Events Following Vaccination In the Community, CI confidence interval, DTPa diphtheria tetanus, pertussis (acellular), HepB hepatitis B, Hib Haemophilus influenzae b, PCV pneumococcal conjugate vaccine, MMRV measles, mumps rubella, varicella

* Significant at the $p < 0.05$ level

^a National Immunisation Program recommended schedule, 2014, by antigen

Fig. 2 AEFI reports by age group and year of report, SAEFVIC, 2007–2014. *AEFI* adverse event following immunisation, *SAEFVIC* Surveillance of Adverse Events Following Vaccination In the Community



4 Discussion

The state of Victoria implemented an enhanced passive surveillance system for AEFI with the aim of improving reporting; detecting, validating and informing on potential vaccine safety signals; and to help maintain confidence in immunisation services. This evaluation shows that, over the 7 years since the inception of SAEFVIC, AEFI reporting has increased in the number of reports and in comparison with other Australian jurisdictions, and is broadly representative for vaccine-recipient age groups and geography. There is a strong record of SAEFVIC supporting signal validation and facilitating investigation of signal or potential signal events, although all were initiated from clinical suspicion by SAEFVIC clinical staff or external queries. Using the available measures of clinic attendance, revaccination, and completion of the vaccination schedule as indicators of confidence in immunisation, persons with AEFIs reported to SAEFVIC were more likely to be due or overdue for vaccination than the general population; however, the gap of 2% was encouragingly small.

4.1 Improve AEFI Reporting

Improving AEFI reporting requires both increased case ascertainment and quality of reporting. AEFI reporting rose from second to last to top state-ranked position following SAEFVIC implementation. The two higher reporting jurisdictions are territories with small populations and federal funding. However, as each jurisdiction in Australia has different AEFI surveillance systems, direct comparisons of AEFI surveillance systems are difficult.

Despite this increase in reporting, and consistent with the known limitations of passive (spontaneous) reporting systems, we do not know how complete case ascertainment

is. Activities to further increase reporting volume require careful consideration of the potential to value add to the data proportional to the increase in resource requirements. An upward trend in consumer reporting has been previously shown as a beneficial contribution to AEFI surveillance and could be further encouraged through increasing parent awareness of AEFI surveillance and access to reporting options [57]. Likewise, the system will need to continue to adopt modern reporting modalities for ease of reporting [58]. However, any improvement to quantity in reporting needs to also consider quality. Data on vaccinee demographics were well-reported; however, remedy of the omission to collect data on indigenous status or gestational weeks at the time of vaccination was necessary and has subsequently been implemented in order to provide vaccine pharmacovigilance for these priority health populations.

AEFI reporting trends reflected the NIP-targeted age and sex cohorts, and therefore interpretation of changes in trends must be considered alongside changes in vaccination programmes. Increased reporting may also be a reflection of increasing vaccines administered and/or improved vaccine coverage as a variety of Government incentives have been implemented in recent years [59]. Calculation of AEFI reports per 100,000 vaccine encounters would provide more accurate and meaningful interpretation of data; however, the current immunisation register, being limited to records for children aged <7 years, and only for a prescribed range of vaccine antigens, restricts this [60–62]. As of late 2016, the ACIR was expanded to record immunisations from birth to death, addressing this priority gap for pharmacovigilance [63].

SAEFVIC is a physically metropolitan located service, however representativeness of AEFI surveillance was broadly consistent across both metropolitan and regional areas of the state of Victoria. More uniform case ascertainment may be achievable if AEFIs were added to

Table 3 Clinical consultation attendance and revaccination, by age group and AEFI category, Victoria, 2007–2014

Age group	Serious AEFI				Other				Total				Compare SAEFI vs. other			
	Clinic data available	Attend clinic review	Further vaccination documented		Clinic data available	Attend clinic review	Further vaccination documented		Clinic data available	Attend clinic review	Further vaccination documented		Attend clinical consultation (95%CI)	Further vaccination documented (95%CI)		
<12 months	653	461 (70.6)	317 (68.8)		1436	687 (47.8)	461 (67.1)		2089	1148 (55.0)	778 (67.8)		+22.8%* (18.4, 27.1)	+1.7% (–3.8, 7.1)		
1 to <7 years	362	147 (40.6)	56 (38.1)		2076	322 (15.5)	151 (46.9)		2438	469 (19.2)	207 (44.1)		+25.1%* (19.8, 30.4)	–8.8% (–18.4, 0.8)		
7–18 years	141	56 (39.7)	16 (28.6)		1091	224 (20.5)	118 (52.7)		1232	280 (22.7)	134 (47.9)		+19.2%* (10.8, 27.6)	–24.1%* (–37.6, –10.6)		
19+ years	155	35 (22.6)	3 (8.6)		1093	90 (8.2)	16 (17.8)		1248	125 (10.0)	19 (15.2)		+12.4%* (5.8, 19.0)	–9.2% (–21.4, 3.0)		
Unknown	27	11 (40.7)	6 (54.4)		99	26 (26.3)	14 (53.8)		126	37 (29.4)	20 (54.1)		+14.5% (–6.0, 34.9)	0.7% (–34.4, 35.8)		
Total	1338	710 (53.1)	398 (54.5)		5795	1349 (23.3)	760 (56.3)		7133	2059 (28.9)	1158 (56.2)		+29.8%* (26.9, 32.7)	–2.8% (–4.8, 4.3)		

Data are expressed as *n* (%)

SAEFI serious adverse event following immunisation

* Significant at the *p* < 0.001 level

notifiable conditions, although the two jurisdictions with the highest reporting rates (Northern Territory and Australian Capital Territory) do not have legislation for AEFI reporting, whereas Western Australia (rank 5) does [64].

Maximising ascertainment of serious, and often rare, adverse events remains a key objective of AEFI surveillance. Reporting of serious AEFIs to SAEFVIC increased minimally and to a lesser extent than non-serious AEFIs. It is not known if this was due to pre-existing, high case ascertainment or if it identifies a gap in surveillance. Exploration of data linkage of emergency department presentation and hospital admission data with AEFI reports would aid confirmation of serious AEFI case ascertainment.

Time to report an AEFI varied widely and in some cases was many years after the event. However, acceptable timeliness of AEFI reporting is difficult to define as individual or healthcare provider motivation for reporting is more likely to be prior to future vaccination than to support surveillance activities [65]. The Weber effect of increased adverse event reporting for new therapies has been observed with vaccine pharmacovigilance, and reports also increase following media alerts [49, 66]. The counterintuitive finding that reporting of serious AEFIs was slower than for non-serious AEFIs may perhaps be explained by the need to seek medical help in the first instance, with reporting completed on conclusion of medical care. This finding supports the need for alternative approaches that identify cases on first presentation, for healthcare independent of pharmacovigilance reporting practices.

The SAEFVIC database provides a rich source of data for additional studies, including data linkage potential. This evaluation of SAEFVIC attributes and detail of data will support compliance with *The Reporting of studies Conducted using Observational Routinely collected health Data (RECORD)* statement [67].

4.2 Signal Detection and Validation

The absence of any de novo signal detections generated from SAEFVIC data was unsurprising as it would require a signal strong enough to be distinguished from background levels. Similar conclusions were reached by Postila and Kilpi in their study of AEFIs in the Finnish population [9]. In contrast, the large dataset and enhanced clinical information were beneficial for responsive rapid review for signal investigation, validation and informing vaccination policy [50–54]. SAEFVIC system objectives should be revised to appropriately reflect the utility of passive surveillance. However, as the potential for signal detection should not be ignored, investigation of data visualization and signal detection methods, as well as ascertainment of

the predictive value for signal detection alongside applicability within the resource structure of Victorian and Australian systems, is also warranted [21, 29].

Interpretation of passive AEFI surveillance is hampered in Australia by poor measures of exposed population denominators and availability of background rates in the absence of immunisation exposure for comparisons [3, 19, 62, 68]. This inability to calculate AEFI incidence rates from surveillance data was considered to directly contribute to the delay in response to early suspicions of the febrile seizure signal that occurred in 2010 [29]. Even with expansion to an all-of-life immunisation register (which occurred in Australia in September 2016), timeliness of data may remain an impediment to real-time signal detection. Therefore, identifying and validating alternative data sources that can provide proxy for an exposed vaccinated population, such as doses-distributed data or other health administration data, particularly for adults, should be explored [69].

4.3 Maintain Confidence in Immunisation

Surveys have indicated up to 14% of parents whose child experienced an AEFI would be hesitant to accept future immunisation [70]. While measuring community confidence in a public health activity using surveillance data alone is limited, this study showed that although experiencing a serious AEFI could be a deterrent to further vaccination, among those who attended clinical review the absolute percentage of people not presenting for further vaccination did not substantially differ between those experiencing a serious AEFI and those who did not. The ultimate endpoint for an immunisation programme is timely and complete immunisation. We used the national endpoint of completion at 63 months of age, given that reporting and attending SAEFVIC clinics may cause delays in completing on schedule. The fact that children who had an AEFI reported were marginally more likely to be overdue for vaccines than the statewide <7-year population was not unexpected and was an encouragingly small (2.3%) difference. It is also possible that some patients would still receive their overdue vaccine and further close the gap; however, as data were extracted a minimum of 14 months after the initial AEFI experience, there was ample time for any further vaccination to have been completed and recorded.

This is a limited evaluation of consumer confidence using the proxy of revaccination as an indication of vaccinee client satisfaction. Likewise, it does not include perceptions on immunisation provider confidence to recommend vaccination or provide clinical management of those experiencing an AEFI, or in risk categories for AEFI. However, the SAEFVIC clinical services will contribute to

increase awareness of clinical support and causality assessment, which, along with general awareness of vaccine pharmacovigilance, may play a role in vaccine safety confidence [20, 71, 72].

5 The Future

As an early adopter of vaccines, Australia provides post-licensure vaccine pharmacovigilance for the international community, as well as for its own national immunisation programme; however, a review in 2010 deemed the fragmented and multifaceted jurisdictional-driven systems as inefficient and cumbersome [29]. Improvements have since been made, with SAEFVIC data fields expanded in 2016 to include vaccinee indigenous status, if the vaccinee was pregnant at time of vaccination (and weeks' gestation), site of vaccine administration and site of reported injection site reaction. Other improvements have included increased frequency of jurisdictional reporting to, and availability of, nationally collated data, and a clinical advisory collaboration (AEFI-CAN) [73]. Western Australia has been a key partner for SAEFVIC in developing both passive and active AEFI systems, and integration of these evolving methodologies will be important moving forward. However, a unified national AEFI surveillance system remains elusive. Victoria's SAEFVIC model, already successfully disseminated to Western Australia since 2011 [64, 74], and with incorporation of improvements identified through this evaluation, is an ideal candidate for a unified AEFI surveillance system operated at the jurisdictional level for individual patient and immunisation provider support, with rapid provision of data to the TGA.

6 Conclusions

Comprehensive and effective post-licensure AEFI surveillance is critical to maintain confidence in immunisation and inform evidence-based policy. The Victorian state-level system, SAEFVIC, is a leader in Australian AEFI surveillance comprising comprehensive, centralized data with clinical validation of AEFIs. SAEFVIC has improved vaccine pharmacovigilance, facilitated signal validation investigations and informed on vaccine safety practice. Optimisation of data utilization remains a priority, in particular appropriate methodologies to aid signal detection. Expansion of the system nationally would provide data consistency, jurisdictional comparability, and markedly increase capacity and capability of AEFI surveillance in Australia.

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Compliance with Ethical Standards

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Conflict of interest Hazel Clothier, Nigel Crawford and Jim Buttery receive salary for their respective employee roles with SAEFVIC. Jim Buttery also serves on data safety monitoring committees for the vaccine manufacturer Seqirus Pty Ltd, for which his employer, Monash Health, receives compensation. Melissa Russell and Heath Kelly have no conflicts of interest that are directly relevant to the content of this study.

Ethical approval The Human Research Ethics Committee, Royal Childrens Hospital, granted approval for this study (DA017-2013-04).

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Consumer reporting of adverse events following immunization

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Abbreviations: AEFI, Adverse event following immunization; HCP, Health care provider

Surveillance of adverse events following immunisation (AEFI) is an essential component of vaccine safety monitoring. The most commonly utilized passive surveillance systems rely predominantly on reporting by health care providers (HCP). We reviewed adverse event reports received in Victoria, Australia since surveillance commencement in July 2007, to June 2013 (6 years) to ascertain the contribution of consumer (vaccinee or their parent/guardian) reporting to vaccine safety monitoring and to inform future surveillance system development directions. Categorical data included were: reporter type; serious and non-serious AEFI category; and, vaccinee age group. Chi-square test and 2-sample test of proportions were used to compare categories; trend changes were assessed using linear regression. Consumer reporting increased over the 6 years, reaching 21% of reports received in 2013 ($P < 0.001$), most commonly for children aged less than 7 years. Consumer reports were 5% more likely to describe serious AEFI than HCP ($P = 0.018$) and 10% more likely to result in specialist clinic attendance ($P < 0.001$). Although online reporting increased to 32% of all report since its introduction in 2010, 85% of consumers continued to report by phone. Consumer reporting of AEFI is a valuable component of vaccine safety surveillance in addition to HCP reporting. Changes are required to AEFI reporting systems to implement efficient consumer AEFI reporting, but may be justified for their potential impact on signal detection sensitivity.

Introduction

An adverse event following immunisation (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.”¹ AEFI surveillance forms part of post-licensure vaccine safety monitoring worldwide and is a critical component of every immunisation program.² Surveillance systems aim to record rare AEFI, unexpected events, or changes in rates of expected events. By maximizing reporting and use of report data, the ability to rapidly detect and investigate potential vaccine safety ‘signals’ is enhanced.^{2–4}

Passive surveillance systems, which rely upon spontaneous reporting of AEFI, are most frequently utilised for AEFI surveillance.¹ They have demonstrated advantages of being useful, simple and timely systems to identify AEFI reports that can then be further investigated and/or described as part of a cohort or case series, however, overall sensitivity is low.^{5,6} Under-reporting is a known issue with estimates showing up to 95% under-reporting occurring even in systems specifically targeting serious AEFI reports.⁷ Reporting is predominantly by health care providers

(HCP), a group which is more likely to report already known AEFI than unexpected events.⁸

In response to these limitations, there is growing advocacy to encourage self-reporting by vaccinees or their parents (consumers) to maximize data collection.^{8–11} This was highlighted in Australia following the suspension of the 2010 seasonal influenza program for children following an increase in febrile seizures.¹² However, evaluations of the relative contribution and utility of consumer reporting to pharmacovigilance are rare.¹¹

In Victoria, Australia, reporting of AEFI is voluntary, however HCP are requested to report to the state-based AEFI surveillance system, SAEFVIC, an enhanced passive surveillance system established in 2007. It aims to enhance reporting by combining passive surveillance of AEFI with clinical services for reporting HCP and individuals experiencing AEFI.¹³ To attend a clinical follow-up appointment a referral from a medical practitioner is required. Detection and validation of vaccine safety signals, either as occurrences of serious AEFI or increased frequency in minor/common expected AEFI, is a core objective. AEFI reports are collated and summary information forwarded by the next working day to the national regulatory agency, the Therapeutic Goods

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Administration (TGA), which collates AEFI reports from all Australian jurisdictions.

SAEFVIC targets reporting from HCP, but accepts consumer reports if they arise. A key question to determine whether to target consumer reporting as well is: Are consumers less likely than HCP to report “significant” (serious or targeted) AEFI? There are currently no published data comparing the proportion of consumer and HCP reports considered to be serious AEFI, although there is increasing evidence of consumer awareness of AEFI.^{14,15} This is important for informing if the additional demand on resources to receive, collate and respond to an increased number of AEFI reports via consumers is justified, and whether it is beneficial to surveillance system objectives and the immunisation program.

Reports to SAEFVIC can be made by telephone, facsimile, mail and, since 2010, online (www.saeftvic.org.au/). The online reporting interface was developed specifically for HCP reporters; but can also be utilized for consumer reporting.

Reviewing the potential for consumer reports to contribute to vaccine safety surveillance objectives will help inform future directions of AEFI surveillance locally and internationally.

Results

A total of 5455 reports were included. Reporter type was known for 99% ($n = 5394$) of reports, of which 515 (10%) were from consumers and 4879 (90%) from providers (of which 0.2% originated from pharmaceutical companies).

The proportion of direct consumer reports increased from an average of 6% of all reports received from 2007–2011 to 15% in 2012 and 21% in the first 6 months of 2013 (linear trend $P < 0.001$) (Fig. 1).

Age groups

Consumer reports were more likely to describe AEFI in a child than providers ($P < 0.001$), but were less likely to describe adults ($P < 0.001$) (Table 1).

Serious AEFI

Overall 18% (969/5455) of SAEFVIC reports received in the first 6 years of operation (2007–2013) met the definition of ‘serious’. No trend over time was observed in the proportion of serious AEFI reported each year ($P = 0.26$).

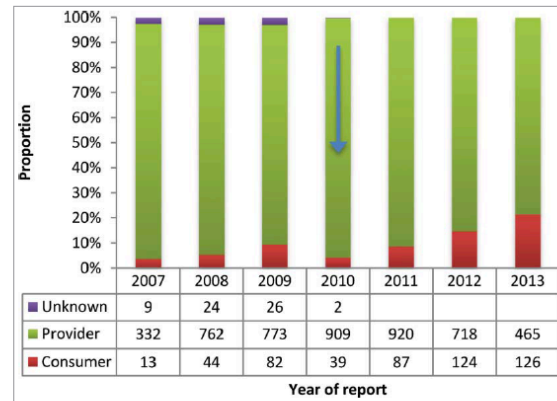


Figure 1. Proportion of AEFI reports received from consumers and providers, Victoria, 2007–2013*.

* Arrow indicates commencement of online reporting facility¹.

Consumers were more likely to report a serious AEFI than providers; 22% compared with 17% ($\chi^2 = 5.61$, $P = 0.02$).

Time taken to report

Consumers were marginally slower to report an AEFI than providers with 44% compared to 50% reports received within 7 days of symptom onset respectively ($P = 0.005$) but by 100 days both reporter types were equal at approximately 80% of reports submitted (Fig. 2)

Reporting modalities

Online reporting now comprises approximately one third of all reports received, with a relative decrease in fax and postal reporting (Fig. 3).

A marked decline in reporting by telephone was observed from 2007 to 2010 as alternative methods became more popular. However, a reverse of this trend was observed in 2012 and 2013 directly as a result of consumer reporting ($P < 0.001$) (Fig. 4).

Specialist vaccine safety clinic referral

Specialist vaccine safety clinic was attended by 30% (1629/5455) of persons for whom an AEFI was reported. A larger proportion of consumer reported AEFI 39% (203/515) required

Table 1. Number and proportion of AEFI reports received by age group and reporter type

Age at vaccination		Number of reports received (%)			Comparison of proportions P value
		Consumer	Provider	Total	
Child	<7	379 (74)	2912 (61)	3291	<0.001
School	7–<19	76 (15)	807 (17)	883	0.267
Adult	19–<60	38 (7)	717 (15)	755	<0.001
Elderly	60+	16 (3)	350 (7)	366	<0.001
Total		509 (10)	4786 (90)	5295	

*Age not available for 99 reports

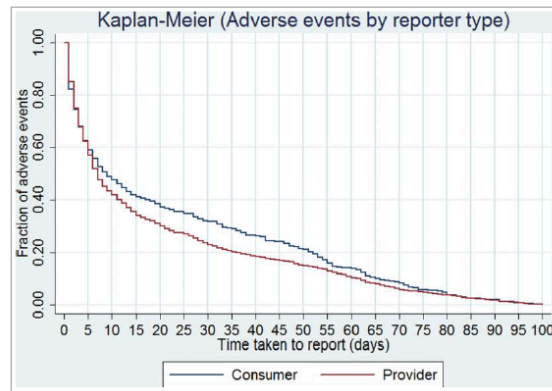


Figure 2. Kaplan-Meier comparison of consumer and provider time to report in days.

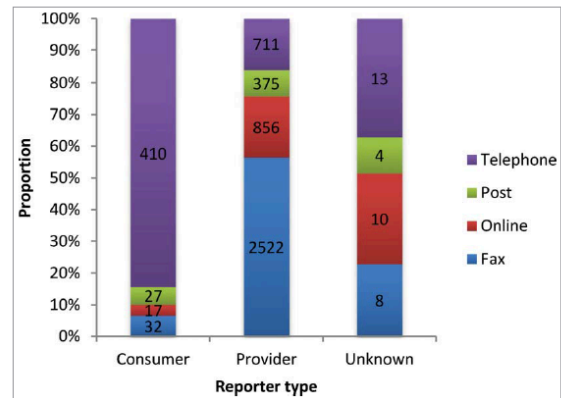


Figure 4. Proportion of AEFI reports received by reporter type and reporting modality.

specialist clinical referral compared with 29% (1406/4879) of HCP reported AEFI (χ^2 25.006, $P < 0.001$).

Discussion

AEFI surveillance in Victoria has, in its first 6 years of operation, focused on health care provider reporting, however, unsolicited consumer reports have steadily increased and now comprise one-fifth of all AEFI reported.

Consumer AEFI reporting to the Victorian SAEFVIC vaccine safety service was not intentionally solicited, however, the increase over the study period was likely influenced by a number of contributing factors making reporting more accessible. These factors included: 1) a highly publicized vaccine safety scare and suspension relating to influenza vaccination of children in 2010 in Australia,¹² which may have raised consumer awareness of AEFI in children generally; 2) the formation of a SAEFVIC website for online reporting (October 2010); 3) more prominent

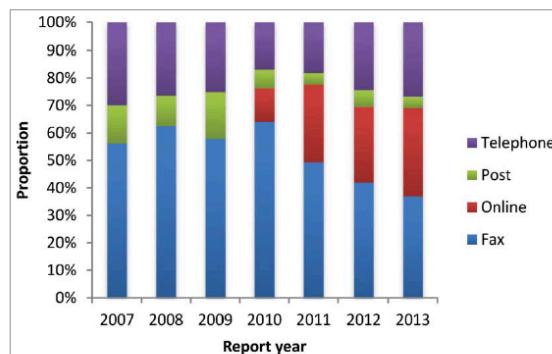


Figure 3. Proportion of AEFI reports received by reporting modality and year of report.

inclusion of SAEFVIC information on the Department of Health Immunisation website (December 2012), and; 4) the implementation of a SAEFVIC information sticker provided as a pilot to attendees of 2 tertiary hospital immunisation centers (March 2012) followed by general distribution together with national immunization program vaccine supplies to providers (September 2012). In 2013 the SAEFVIC Victorian vaccine safety service phone number was also included on an information sheet given to parents as part of the secondary school immunisation program.

Interestingly a 2011 survey conducted in South Australia found one-third of parents whose child had experienced an AEFI reported the symptoms to either an HCP or the department of health¹⁶ and their reporting was not associated with awareness of AEFI surveillance systems.¹⁵ With this finding, and our observation of increasing unsolicited consumer reporting, it would suggest consumer reporting is already entrenched in vaccine safety surveillance even in the absence of a direct decision to encourage consumer reporting and that AEFI surveillance systems need to be able to accommodate such reports and address issues arising.¹⁷

Consumer reporting was notably skewed toward reporting AEFI in younger children rather than in adults themselves. However, the presumption that consumers would be more likely to report a high proportion of minor or common AEFI was not upheld. Our retrospective review has described for the first time in vaccine pharmacovigilance, that consumers reported a higher proportion of serious AEFI than HCP (22% *versus* 17% ($p = 0.018$)). This is in contrast to review of medicines consumer reporting to the Netherlands, Denmark's and UK's adverse drug reaction (ADR) systems, which found HCPs were as or more likely to report serious ADRs.⁹⁻¹¹

Determining the contribution impact of consumer reporting upon the generation or earlier detection of safety signals is outside the scope of this study. Our study did not demonstrate any advantage in timeliness of reporting from consumers. Furthermore, international studies have suggested that it may be appropriate to analyze consumer and HCP AEFI reports separately, in addition to combined datasets, in order to maximize signal

detection.¹⁰ Avery *et al.* found that while combining patient and HCP reports generated more potential signals than HCP reports alone; some potential signals in the 'HCP-only' data set were lost when combined with patient reports.⁹

Significant differences in the profiles of consumers who report AEFI have been described (e.g. ethnicity and perception of and experience with immunisation and AEFI).¹⁸ In Australia the only noted demographic difference was that consumer-reporters were more likely to be Australian-born than non-reporters.¹⁵ Understanding reporting profiles of both HCP and consumers is important for assessing potential biases in data collection and further studies will be required to assess the impact of increasing consumer reporting on signal detection.

If consumer reporting is to be routinely solicited, appropriate reporting modalities and increases in the resources for responsive management will also be required. Prior to the increase in consumer reporting, the predominant reporting modalities in Victoria were by fax, with replacement by online reporting as it became available in 2010. As consumer reporting increased, the trend reversed, with 85% of consumers reporting by phone. Consumer ability to report to SAEFVIC by modes other than telephone is restricted by the current online registration process, which implies, but is not actually limited, to being a provider. New reporting modalities taking advantage of modern communication technologies such as SMS¹⁹ and/or a smart-phone applications may help with both accessibility and timeliness. These could be offered as an 'on-demand' reporting tool, integrated with other immunisation applications or provided pro-actively at the immunisation encounter. These strategies carry the potential to record a range of outcomes and integrate into active surveillance strategies.⁶

SAEFVIC services, unlike many passive surveillance systems, include the option for specialist review at its integrated clinical services for AEFI management and planning of subsequent vaccination. A significantly higher proportion of consumer reported vaccinees with AEFI attended for specialist clinical review compared to those reported by providers. Potential explanation for this may include serious AEFI being more likely to require an immunisation specialist consultation, as well as a possible preference by reporting consumers for a specialist opinion which may have prompted their decision to report. It is unknown if there was prior knowledge of the availability of these clinical services prior to reporting.

Methods

Data for AEFI reports received by SAEFVIC in the 6-year period July 2007–June 2013 were extracted (ethics approval - DA017-2013-04) and analyses conducted using Excel 2010 (Microsoft, Redmond, WA) and Stata 13 (Statacorp, Texas). Reports initially submitted to TGA and redirected to SAEFVIC were excluded from analyses as they primarily related to part of a specific investigation using non-standard surveillance reporting mechanism (e.g., Panvax H1N1TM vaccine in 2009) and reporter information was not provided.

Reporter type, as stated at the time of reporting by phone or entered on the AEFI report form, was defined as *Consumer* if submitted directly to SAEFVIC by a vaccinee, parent, guardian or family member; *Provider* if submitted by a health care professional, pharmaceutical company, or any representative of a health care provider institution or; *Unknown* where reporter type could not be ascertained. Reporter type is recorded as that of the first point of contact made (i.e. either consumer or provider), with information from any subsequent reports merged into the initial record, therefore determination of duplicate reporting was not possible. Submission modality was recorded manually prior to commencement of the online database in 2010, after which it became a mandatory data field completed at the time of report receipt with online submission automatically recorded and option of post, fax or telephone selected manually.

Four age categories were defined as: child (birth to less than 7 years of age); school aged (7 to 18 years); adult (19 to less than 60); and elderly (60 years and older). Age at the time of vaccination was calculated by subtracting date of birth from date of vaccination. Reports with data fields of 'date of birth' or 'date of vaccination' missing - and therefore age at vaccination unknown ($n = 160$) - were excluded from analyses related to age.

Descriptions of reported AEFI are recorded in the database verbatim and categorized according to standard case definitions where available.¹⁵ Reports were review by specialist immunisation nurses or clinician for verification of the AEFI and determination of medical importance.¹² Serious AEFI were those that resulted in death; were life-threatening; required in-patient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity, or; were a congenital anomaly/birth defect.¹⁶

Time taken to report was calculated as the difference in days between report submission and date of vaccination minus days to symptom onset where this information was available. Comparison of consumer and reporter time taken to report was demonstrated using Kaplan-Meier analysis and by proportion reported within 7 days.

Calculations to determine differences in proportions and proportional reporting ratios excluded reports with unknown variables (reporter type, reporting modality).

The Chi-square test (χ^2) was used to compare the proportions of consumer and provider reporting designated as serious AEFI and requiring clinical referral. Comparison of consumer and provider reporting by vaccine age group were calculated as 2-sample test of proportions.

Chi-square statistic for trend (regression) was used to test trend of proportions between consumer and provider reporting by telephone. Tests were considered statistically significant at $P < 0.05$.

Conclusion

This study identified that consumer reporting of AEFI is already an integral component of vaccine safety surveillance and needs to be accommodated in future development at both state

and national level. Accepting or advocating consumer reporting may potentially benefit signal detection as well as improve consumer confidence in immunisation by improving vaccine safety communication between immunisation services and the community. A characterization of resources required to implement an efficient consumer AEFI reporting system is needed along with ongoing investigation of any demographic reporting biases or impact on signal detection sensitivity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Chapter 6: Informing pharmacovigilance

6.1 Chapter introduction

A key element of the evaluation of SAEFVIC as a passive AEFI surveillance system (Chapter 4: SAEFVIC evaluation) was to identify if SAEFVIC met its objective to inform vaccine pharmacovigilance (as part of “*to detect, validate and inform on potential safety signals*”(1)). The evaluation identified that a number of early publications provided some evidence of SAEFVIC attaining this objective, but these were predominantly limited to clinical reviews of specific AEFI reactions(47, 234, 310).

Therefore the research question “Is SAEFVIC useful for informing vaccine pharmacovigilance” remained to be addressed. The investigations presented in this chapter were conducted in response to vaccine safety issues arising during the evaluation period. Each explores a different aspect of safety, namely i) vaccine-specific event, ii) clinical suspicion of an increase in allergy-related events and iii) ascertaining if surveillance could inform on an at-risk population. These studies provide confirmation of SAEFVICs utility to inform across a range of vaccine pharmacovigilance aspects.

The first publication informs on AEFI with a specific vaccine, bacillus *Calmette–Guérin* (BCG) for prevention of tuberculosis. Australia faced a forced rapid change between BCG vaccine base-strains following a flood at the original vaccine manufacturing plant resulting in world-wide vaccine shortage(311). This study provided the evidence-based justification to accept the risk-safety profile of the substitute vaccine and continue the TB vaccination program in Australia.

The second publication summarises the investigation and outcome findings of an AEFI signal event hypothesised in 2015. As the seasonal influenza immunisation program progressed there was a perceived increase in reporting of allergy-related adverse events. While ultimately determined to be of mild clinical significance, the ability for

SAEFVIC to inform vaccine pharmacovigilance was essential in providing reassurance, given the heightened concern following the serious febrile-seizure event in 2010(312). These study findings were presented and discussed at the *National Advisory Committee for the Safety of Vaccines* and were instrumental in informing the decision to continue with the seasonal influenza vaccine program in 2015(313).

The third publication arose from concern that AEFI surveillance may not adequately capture potential AEFI signals following introduction of the new Zostavax® vaccine in late 2016, which targeted 70–79 year olds. This study described AEFI reported for persons aged over 60 years and identified that there was potentially under-reporting in this age group. The impact of this finding was central to the policy decision to expand the active surveillance system, AusVaxSafety, to incorporate monitoring of Zostavax®.

The outcomes and impacts arising from the findings are discussed in more detail at 9.2.3 with limitations and future potential in study design described at 9.3.

In addition to the three first author publications presented in this Chapter, I also provided significant contribution for several other studies during the course of the PhD and co-authored 4 publications and 5 conference presentations (listed in the thesis preface)

6.2 Research question

6.2.1 Question 3: Is SAEFVIC useful for informing vaccine pharmacovigilance?

6.2.1.1 Investigating AEFI with a specific vaccine

Publication: Clothier *et al.* Bacillus Calmette-Guerin (BCG) vaccine adverse events in Victoria, Australia: analysis of reports to an enhanced passive surveillance system. *Drug Safety*, 2015; 38:79-86

6.2.1.2 Investigating a possible AEFI signal event

Publication: Clothier *et al.* Allergic-related adverse events following seasonal influenza containing vaccines, 2015. *Euro Surveill.* 2017;22(20):pii=30535

6.2.1.3 Investigating AEFI in a specific population

Publication: Clothier *et al.* Adverse events following vaccination of older people may be under-reported. *Medical Journal of Australia*. 2017;Vol(7):301-2.

6.3 Publication: BCG AEFI, Victoria, Australia

Drug Saf (2015) 38:79–86
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ORIGINAL RESEARCH ARTICLE

Bacillus Calmette-Guérin (BCG) Vaccine Adverse Events in Victoria, Australia: Analysis of Reports to an Enhanced Passive Surveillance System

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Melissa Russell · Mee Lee Easton · Julie-Ann Quinn ·
Jim P. Buttery

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Abstract

Background Bacillus Calmette–Guérin (BCG) vaccine is used worldwide, with high efficacy against childhood *Mycobacterium tuberculosis* (TB) meningitis and miliary TB. BCG vaccine is considered safe, with serious systematic adverse events following immunization (AEFI) of immunocompetent recipients being rare, although adverse event rates vary between differing BCG strains. In Victoria, Australia, AEFI are reported to SAEFVIC (Surveillance of Adverse Events Following Vaccination In the Community), an enhanced passive surveillance system operational since 2007.

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Objective To describe the epidemiology of reported BCG AEFI in Victoria, Australia, particularly following the 2012 recall of Connaught BCG vaccine, substitution with Denmark-SSI vaccine and subsequent programme delivery adjustments.

Methods Retrospective analysis of reported BCG AEFI in Victoria, Australia, for the 6-year period 2008–2013. Incidence rates were calculated using available doses-distributed, doses-administered and population data denominators with 95 % confidence intervals.

Results The predominant BCG AEFI reported were abscess and lymphadenopathy, with higher reports for males than for females ($p = 0.039$). The rates of AEFI per 10,000 doses distributed were similar for the Connaught and Denmark-SSI strains, at 11.6 and 15.4, respectively

Key Points

The Bacillus Calmette–Guérin (BCG) vaccine recall in 2012, global BCG vaccine supply shortages and subsequent unplanned BCG vaccine strain changes required effective adverse events following immunization (AEFI) surveillance to monitor the changes.

AEFI surveillance in Victoria, Australia, was inadequate for meaningful interpretation of results, but new practices described will maximize data completeness and facilitate future investigations.

The Australian experience and lessons learned serve as a timely reminder to BCG vaccination programmes worldwide to review AEFI surveillance systems.

surveillance capacity to support evaluation of the three events occurring in 2012: product recall, vaccine strain substitution and programme delivery adjustment.

2 Methods

De-identified data on adverse events following BCG immunization were extracted from the SAEFVIC database on 20 May 2014 for all reports received by SAEFVIC from 1 January 2008 up to and including persons vaccinated prior to 31 December 2013. Where the locally administered BCG strain was not identifiable, the date of vaccination was used to assume that the vaccinee had received either Connaught strain (vaccination up to and including August 2012) or Denmark-SSI strain (vaccination during September 2012–December 2013). Ethics approval was granted (reference DA017-2013-03).

Prior to data extraction, all reports received were accessed and attempts were made to ascertain any missing information (provider details, vaccinee demographics, batch number).

Reports were excluded if the vaccine was administered overseas and the vaccine strain was not known ($n = 3$); a normal BCG injection site response was considered as 'expected' ($n = 7$); and following a Mantoux tuberculin skin test ($n = 1$). Reports arising from drug administration errors not resulting in an AEFI ($n = 2$), or where BCG was administered concomitantly with other vaccines and the AEFI was either at the non-BCG vaccination site or was clinically assessed and determined to be not associated with BCG immunization, were described but excluded from numerical analyses.

Australian Bureau of Statistics population census data were used as the denominator for demographic analyses by age and sex [22]. Multi-dose vials-distributed data from 2008 to 2013 by month and BCG vaccine brand were provided by the Department of Health, Victoria. Rates of reported AEFI per 10,000 doses distributed were calculated, assuming 10 doses per vial for Connaught strain and 100 doses per 10-vial pack of Denmark-SSI vaccine distributed.

Doses-administered data were obtained from the two specialist BCG vaccination clinics that administered all publicly subsidized BCG vaccine from September 2012 to the end of 2013.

Surveillance capacity to inform on BCG AEFI was assessed for reporting timeliness and ability to interpret data, considering completeness of data fields and available denominators for rate calculation.

Descriptive and statistical analyses were conducted in Excel 2010 (Microsoft, Redmond, PA, USA) and STATA version 13 (StataCorp, College Station, TX, USA).

3 Results

SAEFVIC received 62 reports of persons experiencing an adverse event following BCG administration that met the study criteria: 52 following Connaught strain and 10 following Denmark-SSI strain vaccination. The reported number of BCG AEFI cases increased over the first 5 years of SAEFVIC operation but declined in 2013 (Fig. 1).

A majority ($n = 39$, 63 %) of AEFI reports were for males, with a male-to-female ratio of 1.7:1 ($p = 0.039$). Sixty vaccinees were aged less than 5 years (median age 5 months, range 22 days to 3 years 8 months). The remaining two vaccinees were aged 5 and 19 years.

The 62 AEFI case reports described 72 reactions, of which abscess was the most frequent (64 %), followed by lymphadenopathy (32 %) [Table 1; Fig. 2]. No deaths were reported. Three cases with abscess were hospitalized during the course of their treatment. None were reported as immunosuppressed.

Six AEFI reports were received where BCG was administered concomitantly with other vaccines and the reactions occurred at the non-BCG vaccination site or were attributed to the other vaccines: fever ($n = 2$), hypotonic–hypo-responsive episode ($n = 1$), injection site reaction—minor ($n = 3$), nodule at injection site ($n = 2$) and urticaria ($n = 1$).

Five reports pertained to drug administration errors [incorrect administration site ($n = 2$) and overdose ($n = 3$)], of which three involved an abscess at the site of administration. All five errors arose from vaccination administered in the community setting prior to September 2012.

3.1 Surveillance Attributes

The time to symptom onset was unstated for 20 reports (32 %); for the remainder, the time from vaccination to

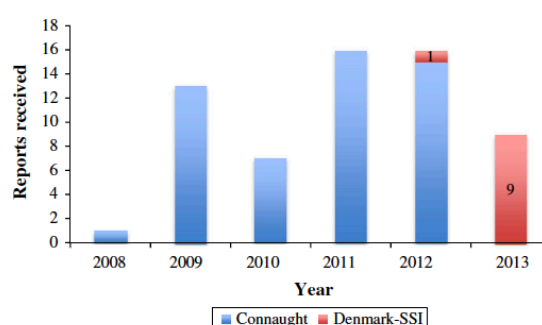


Fig. 1 Reported bacillus Calmette-Guérin (BCG) adverse events following immunization (AEFI) cases, by year and vaccine strain, Victoria, 2008–2013

Table 1 Adverse events following immunization (AEFI) reactions reported by bacillus Calmette-Guérin (BCG) vaccine strain, Victoria, 2008–2013

AEFI reaction	Total	AEFI reactions, by vaccine strain		
		Connaught	Denmark-SSI	<i>p</i> value for test of proportions
Abscess	46 (64 %)	34 (59 %) ^a	9 (82 %)	0.1455
Erythema nodosum	1	1		
Lymphadenopathy	23 (32 %)	21 (37 %)	2 (18 %)	0.2449
Nodule at injection site	1	1		
Urticaria/allergic rash	1	1		
Total	72	58 ^a	11	

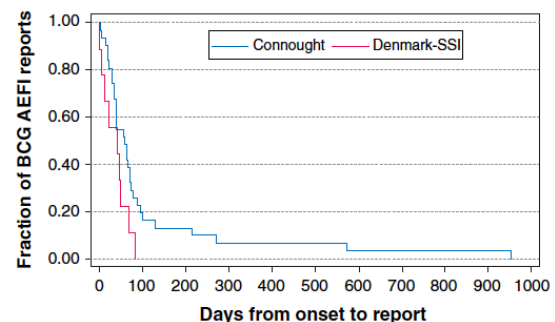
^a Excludes three abscesses attributed to vaccine administration errors

**Fig. 2** Axillary lymphadenopathy following bacillus Calmette-Guérin (BCG) vaccination

symptom onset ranged from 48 hours to 168 days (median 35 days, interquartile range 26–56 days). The time to report from the onset of symptoms ranged from 0 to 953 days (median 45 days, interquartile range 23–79 days), with more than 80 % of all reports—and 100 % of Denmark-SSI AEFI reports—being received within 100 days of symptom onset (Fig. 3).

Vaccine batch information was completed for approximately half of all reports (53 %), increasing from 0 % in 2008 to 100 % of reports with batch details accessible following the programme change in 2012.

Three of the four recalled batches had been distributed in Victoria between April 2011 and June 2012: C3787AA (3,090 doses), C3787AC (8,290 doses) and C3787AG (220 doses). Batch C3787AE was not distributed in Victoria.

**Fig. 3** Kaplan–Meier analyses of bacillus Calmette-Guérin (BCG) adverse events following immunization (AEFI) showing time from symptom onset to reporting, by vaccine strain, Victoria

Eight AEFI reports, related to two of the batches [C3787AA ($n = 2$) and C3787AC ($n = 6$)], were received. The reactions, all reported in 2012, were as follows: for C3787AA, lymphadenopathy ($n = 1$) and nodule at injection site ($n = 1$); and for C3787AC, abscess ($n = 5$) and lymphadenopathy with nodule at injection site ($n = 1$). Three additional reports of expected BCG site reactions were received directly as a result of notification of the batch withdrawal but were not included in the study analysis.

Further retrospective follow-up of cases and ascertainment of vaccine batch data were hampered by insufficient information being available: provider details being unavailable for almost one third (27 %) of cases.

3.2 Data Interpretation and Denominators

Overall, the incidence of reported BCG AEFI cases per 10,000 doses distributed varied by year (Table 2). The estimated rate of reported AEFI cases per 10,000 doses distributed was 11.6 for Connaught strain and 15.4 for Denmark-SSI strain (ratio 0.756, 95 % confidence interval 0.38–1.67; $p = 0.414$).

Calculation of more accurate rates for reported AEFI cases, using doses-administered denominator data for Connaught strain, was not possible in the absence of a consistent database or record of BCG vaccine administration prior to September 2012. Following the change of vaccine strain and service delivery in September 2012, the two accredited tertiary specialist clinics recorded 1,593 doses of Denmark-SSI administered (53 % to males) from 1 September 2012 to 31 December 2013. Ten AEFI reports (0.6 %) were received by 20 May 2014 (20 weeks post-vaccine period), giving an incidence rate of 62.8 reported AEFI cases per 10,000 doses administered. This confirmed usage of only 25 % of available Denmark-SSI doses occurred despite batching of BCG vaccinees in central clinics. The usage of available Connaught doses by the

minimum 99 documented providers receiving publicly funded vaccine supply is unknown.

4 Discussion

We retrospectively reviewed and summarized BCG AEFI reported to a passive surveillance system in Victoria, Australia, over the 6-year period 2008–2013, and we assessed the capacity of the surveillance system to inform on BCG AEFI in the context of a product incursion, strain substitution and programme delivery adjustment.

BCG AEFI reporting increased over the initial 5 years from 2 to 16 reports annually, before a marked drop in 2013, coinciding with programme delivery changes. While the increase in AEFI reporting was broadly in step with increasing BCG vaccine distribution, an observed increase in all vaccine AEFI reporting occurred over the same time period as awareness of reporting AEFI to SAEFVIC, which commenced in May 2007, improved [23]. Despite the increase, it remains likely that these reports represent an underestimation of AEFI because of the nature of passive reporting coupled with the ongoing lack of clarity over what constitutes an AEFI with BCG [10, 25]. The BCG recall was likely a contributing factor for the higher rate of reported AEFI cases per dose distributed—for both the newly introduced Denmark-SSI vaccine and retrospectively for recently administered Connaught vaccine—seen in 2012.

A majority of AEFI reports were for infants, consistent with the patient population expected for BCG administration in Australia [7]. More AEFI reports were received for males than for females, which was in contrast to both the population sex ratio at birth (male:female 1.05:1) and AEFI in young children reported in Victoria for all vaccines (male:female 1.2:1 [22, 26]) but is an anomaly that has been observed before in a BCG AEFI study in Oman [27].

Table 2 Bacillus Calmette-Guérin (BCG) vaccine doses distributed and reported adverse events following immunization (AEFI) cases per 10,000 doses distributed, by year, Victoria

Year	Estimated individual doses distributed (reported AEFI cases)		Incidence risk per 10,000 doses	95 % confidence interval
	Connaught	Denmark-SSI		
2008	8,800 (1)		1.1	(0.03–6.3)
2009	9,570 (13)		13.6	(7.2–23.2)
2010	10,340 (7)		6.8	(2.7–13.9)
2011	11,680 (16)		13.7	(7.8–22.2)
2012 ^a	4,340 (15)		34.6	(19.4–56.9)
		1,000 (1)	10.0	(0.3–55.6)
2013		5,500 (9)	16.3	(7.5–31.0)
Total	44,730 (52)		11.6	(8.7–15.2)
		6,500 (10)	15.4	(7.4–28.3)

^a Includes stimulated AEFI reporting following BCG vaccine batch recall

A marginal male preponderance was observed in the doses-administered data for 2012–2013 (for which accurate sex data were available), where 53 % of vaccinees were male. BCG vaccination is reserved for high-risk populations in Australia; if more males are being vaccinated, it would be interesting to determine the factors underlying this. Subjective hypotheses include the following: the threshold for reporting AEFI may be lower in males; male infants may be favoured for travel for parental homeland visits; more males are born in the populations with highest utilization of BCG vaccination [28]; or male vaccinees have a higher risk of AEFI.

AEFI reactions of abscess and lymphadenopathy reported in Victoria were consistent with the known common reactions experienced post-BCG immunization [16, 29, 30]. However, comparisons of AEFI proportions or rates were limited because of the different methodologies and cohorts used in published studies and the lack of consistent application of case definitions [9, 10]. A prospective Australian study of 1,246 BCG recipients conducted after the change to Connaught strain in 1996 recorded lymphadenitis in 1 % and abscess in 2.5 % of the 918 recipients who completed follow-up. However, the study population included adult defence force personnel and is not immediately applicable to the current Australian BCG vaccination recommendations, which focus on children [16].

It is possible that AEFI involving lymphadenopathy occurred after the data extraction for this study or had occurred but not yet been reported. However, this risk was minimized, as 20 weeks had elapsed between the end of the study period (31 December 2013) and data extraction (20 May 2014), a period four times greater than the median time to symptom onset and the period in which a majority of reactions are reported to occur [16].

BCG is administered intradermally, which is a more technically complex mode of administration than intramuscular vaccination and requires expert immunizer training. Technique errors are known factors for adverse reaction occurrence [10]. Therefore, it is possible that more of the reported abscess and local reactions were in fact due to poor administration technique than was documented [3 abscesses were attributed to incorrect administration: intramuscular ($n = 1$) and overdose ($n = 2$)]. Attempts to ascertain administration issues or to analyse AEFI by provider type were restricted by poor reporting of provider type or contact details for further follow-up.

The catalyst for this review of adverse effects following BCG vaccination in Victoria arose following the 2012 recall of Canadian Sanofi Pasteur vaccine, secondary to a possible breach in sterility. This study identified eight adverse reactions associated with two of the four recalled batches. However, batch number was poorly recorded, with

almost half of the reports having no batch information available, despite considerable efforts by the SAEFVIC clinical team to follow up individual patients. Some of the difficulty in obtaining batch details arises from vaccine being administered overseas. However, without this key information in situations where a recall is necessary, any comment on a change in adverse events relating to a particular batch is not possible.

The analysis would be strengthened if the number of reports received were presented as rates. Two denominator options are ordinarily available: (1) doses administered and (2) doses distributed. In Australia, BCG doses-administered data are not readily available, as BCG is not included in vaccinations compulsorily recorded in the national Australian Childrens Immunisation Register (ACIR), which records selected vaccinations given to children under 7 years of age [31]. Therefore, the rates are routinely calculated as AEFI per doses distributed, as a proxy. However, in the case of BCG, this would be particularly misleading, as distributed doses would not account for vaccine wastage arising from BCG vaccine being supplied in multi-dose vials. In Australia, Connaught vaccine was available in a 10-dose vial, so a single vial could account for between 1 and 10 vaccinations delivered. Denmark-SSI vaccine is available only in 100-dose packaging, comprising multiples of 10×1 mL vials, with each vial being 10–20 doses, depending on recipient age. If vials are not fully used for vaccine administration, this will lead to underestimation of AEFI rates. Therefore, the similar reported AEFI rates of 15.4 and 11.6 per 10,000 doses of Denmark-SSI and Connaught vaccine distributed, respectively, become difficult to interpret and may in fact be a fallacy of the multi-dose vial packaging variances. The documented wastage of 75 % following centralization of BCG in September 2012 may indeed be lower than the wastage of Connaught BCG, which was provided to multiple providers who may have been more likely to immunize individual patients 'on demand', rather than batching into clinics to maximize vial usage.

Following the programme delivery changes and restriction of BCG administration to specialized clinics, accurate data on doses administered were available. These data provided a Denmark-SSI reported AEFI rate of 62.8 per 10,000 doses administered, a figure four times that obtained using doses distributed. However, our finding of 0.5 % AEFI with Denmark-SSI doses administered remained lower than those reported in a 2007 Netherlands strain-specific study, where abscess was reported in 2.5 % and lymphadenitis in 0.1 % [30], but this may be reflective of under-reporting to our retrospective passive surveillance system, compared with their active cohort follow-up.

It is important to ascertain accurate BCG AEFI profiles to permit strain selection for TB control programmes and,

in particular, in advance of possible advocacy for broader usage of BCG immunization for potential 'non-specific' immunological advantages [32, 33] or in HIV patients, where Denmark-SSI strain has had higher reported AEFI rates than other strains [34].

5 Conclusion

BCG AEFI in Victoria, Australia, mainly consist of abscess and lymphadenopathy, with higher reports for males than for females. The capacity of surveillance to evaluate adverse events in the Australian BCG immunization programme was found wanting in 2012, just as it had been at the time of the previous strain change in 1996 [16]. Passive AEFI surveillance was inadequate for meaningful interpretation of results, with the capacity to inform on AEFI rates or to compare AEFI profiles between BCG vaccines derived from different strains being severely limited by the lack of adequate denominator data and poor timeliness of reporting. Estimations of AEFI rates varied depending on the calculation method used.

In Victoria, Australia, new practices implemented, with BCG vaccination being limited to specialist provider sites, will maximize data completeness, provide timely AEFI management and reporting, and facilitate future investigations. The other states in Australia have variable practices with regard to BCG administration and AEFI follow-up, so national co-ordination is required. This study highlights the potential benefit of expanding the Australian Childrens Immunisation Register to include all vaccinations, as well as encompassing all-of-life, as previously advocated, in order to provide adequate vaccine delivery and programme evaluation in Australia [35].

Robust and effective AEFI surveillance is of paramount importance as countries are faced with unplanned vaccine strain changes following the BCG recall in 2012 and subsequent global vaccine supply shortages. The Australian experience and lessons learned serve as a timely reminder to BCG vaccination programmes worldwide to review AEFI surveillance systems.

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6.4 Publication: Allergic AEFI in 2015, Victoria

SURVEILLANCE AND OUTBREAK REPORT

Allergic adverse events following 2015 seasonal influenza vaccine, Victoria, Australia

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Australia was alerted to a possible increase in allergy-related adverse events following immunisation (AEFI) with 2015 seasonal trivalent influenza vaccines (TIV) by the Victorian state vaccine safety service, SAEFVIC. We describe SAEFVIC's initial investigation and upon conclusion of the 2015 influenza vaccination programme, to define the signal event and implications for vaccine programmes. Allergy-related AEFI were defined as anaphylaxis, angioedema, urticaria or generalised allergic reaction. Investigations compared 2015 TIV AEFI reports to previous years as proportions and reporting risk (RR) per 100,000, stratified by influenza vaccine brand. The initial investigation showed an increased proportion of allergy-related AEFI compared with 2014 (25% vs 12%), predominantly in adults, with insufficient clinical severity to alter the programme risk-benefit. While overall TIV AEFI RR in 2015 was similar to previous years (RR: 1.07, 95% confidence interval (CI): 0.88–1.29), we identified a near-doubling RR for allergy-related AEFI in 2015 (RR: 1.78, 95% CI: 1.14–2.80) from 2011 to 2014 with no difference by vaccine brand or severity increase identified. This increase in generalised allergy-related AEFI, across all used vaccine brands, supports evidence of variable reactogenicity arising from influenza vaccine strain variations. This investigation underlines the importance of effective seasonal influenza vaccine pharmacovigilance.

Introduction

The Australian southern hemisphere seasonal influenza vaccination programme typically runs from March to September, with influenza vaccine funded through the National Immunisation Programme (NIP) for health-care workers, adults >65 years of age and individuals over 6 months of age with special risk conditions [1]. Adverse events following immunisation (AEFI) are

reported to the relevant jurisdictional surveillance system, which in the Australian state of Victoria is via voluntary reporting to the Victoria vaccine safety service, SAEFVIC. SAEFVIC was established in 2007 and comprises a passive surveillance system coupled with clinical services [2]. AEFI reports to SAEFVIC are received primarily as unsolicited reports from immunisation providers or healthcare workers, with direct reporting from vaccinees or their guardians accounting for approximately one fifth of reports [3]. Immunisation nurses review all reports and provide follow-up, including referral for specialist clinical consultation as required.

Influenza vaccines have been subject to additional safety surveillance monitoring in Australia since an episode of increased reactivity of one seasonal trivalent influenza vaccine (TIV) brand occurred in 2010, causing high fever and febrile seizures in children aged under 5 years [4,5].

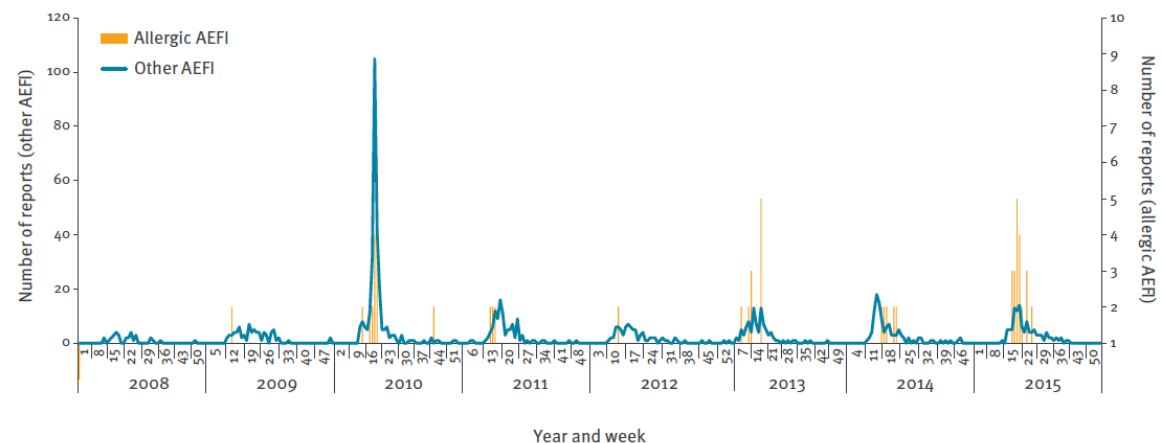
In week 2 of the 2015 TIV Influenza vaccine programme, SAEFVIC nurses receiving AEFI reports were alerted to a possible increase in allergy-related AEFI with TIV. This possible signal was reported to the national regulatory authority, the Therapeutic Goods Administration (TGA) [6]. This paper describes SAEFVIC's investigation initially and upon conclusion of the 2015 influenza vaccination season to define the signal event and provide guidance for future vaccine pharmacovigilance.

Methods

Reported AEFI with influenza vaccines were extracted by date reported. Data included demographic details as well as information on vaccine administered, reactions experienced and clinical consultations. Reports of drug administration errors not resulting in AEFI were excluded. Allergy-related AEFI were clinically defined as cases of confirmed anaphylaxis, angioedema,

FIGURE 1

Reports of trivalent influenza vaccine adverse events following immunisation by allergy-related category and week reported, Victoria, Australia, 2008–2015



AEFI: adverse events following immunisation.

The peak in 2010 corresponds to febrile-seizure signal event and increased reporting of febrile AEFI.

urticaria or generalised non-specific allergic reaction. Reports of anaphylaxis were confirmed according to Brighton Collaboration case definitions [7]. All other AEFI reported, including less defined symptom descriptions of itchiness, pruritus or rash with no further description, were categorised as 'Other'. Analyses were conducted using Excel (Microsoft Corporation, Redmond, WA, US) and STATA 13, StataCorp, Texas, US). Research Ethics and Governance of the Royal Childrens Hospital, Victoria granted approval for this study (DA017–2015–07).

Initial investigation

The initial investigation compared the proportion of allergy-related AEFI reported to SAEFVIC with any influenza containing vaccine between 1 January and 3 May 2015 with proportions to similarly categorised data received for the whole of 2014, as convenience comparison data. In addition the Australian regulatory authority, TGA, was notified and publicly accessible data from the national Database of Adverse Event Notifications (DAEN) [8] were accessed for any allergy-related AEFI with TIV with the aim to provide insight on the national distribution of the potential signal.

Monitoring of the proportion of allergy-related AEFI was conducted through the remainder of the influenza season (April–October), with comparison to 2014 using the chi-squared test and alongside individual clinical review of serious AEFI, including anaphylaxis, as a determinant of clinical severity.

Signal investigation

On conclusion of the southern hemisphere seasonal TIV programme on 31 October 2015, additional analysis of all SAEFVIC TIV AEFI reports for the previous eight seasons (since system commencement), 2008–2015, was conducted to define the signal event.

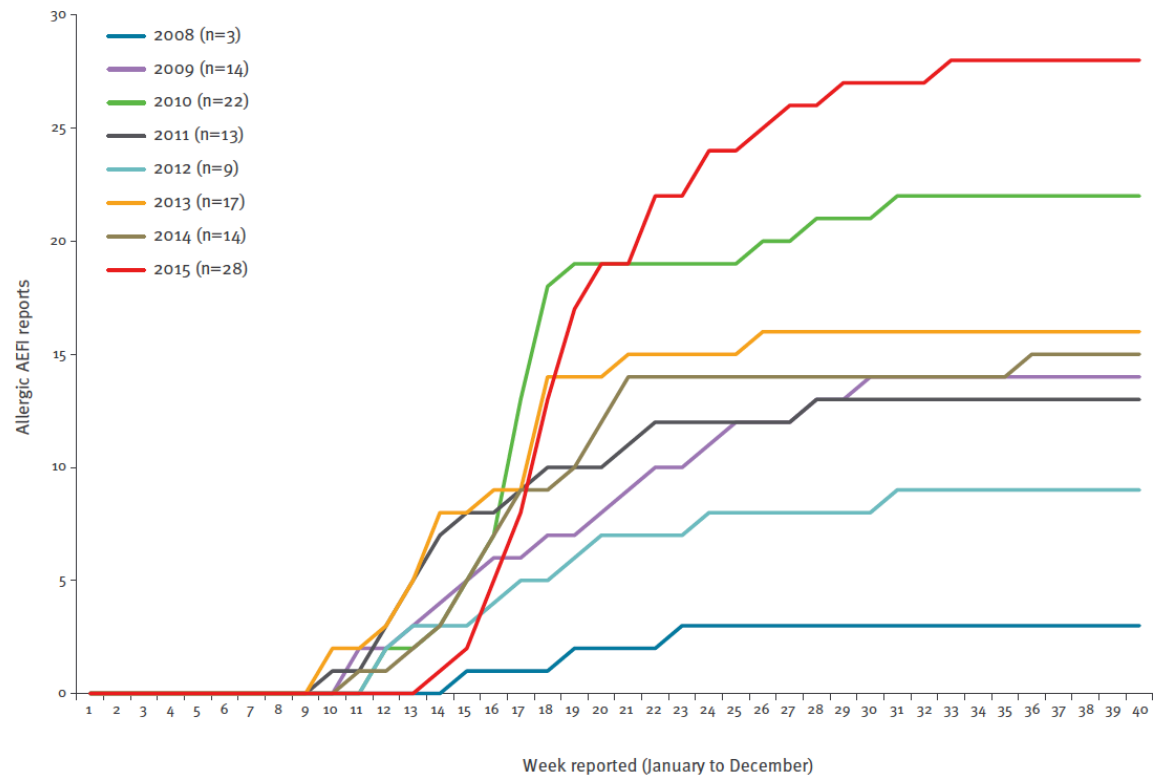
Data included in this analysis were restricted to the TIV brands used in the NIP in Victoria (Fluarix, GlaxoSmithKline; Fluvax, BioCSL; and Vaxigrip/Vaxigrip Junior, Sanofi Pasteur) and for which dose distribution data were available. AEFI reports received in 2015 were analysed by allergic AEFI categories, vaccinee age, sex, time to symptom onset and TIV brand. The frequency of reporting was assessed by calendar week and also realigned by week of seasonal influenza AEFI reporting commencement, as this varies each year depending on the NIP.

AEFI reporting risks (RR) were calculated using the number of vaccine doses distributed as the denominator. Doses distributed data were provided on request from the Victorian Department of Health and Human Services for 2011–2015 [9]. RR ratios were calculated, using AEFI reports received per 100,000 doses distributed.

Anaphylaxis AEFI were compared as proportion of all TIV-AEFI and as proportion of allergy-related AEFI as an indicator of clinical severity, with comparisons to combined data 2011–2014 using two-sample test of proportions with 95% confidence intervals.

FIGURE 2

Cumulative reports of allergy-related adverse events following immunisation with trivalent influenza vaccine, by week reported, Victoria, 2008–2015 (n = 120)



AEFI: adverse events following immunisation.

The numbers in the legend represent cumulative reports per year.

Results

Initial investigation

At 3 May 2015, 11 (25%) of the 44 TIV AEFI reports received were allergy-related; this was an increase from 15 (12%) of 128 reports received by SAEFVIC throughout 2014 (RR: 2.13, 95% confidence interval (CI): 1.00 to 4.56).

The national DAEN database was accessed but was unable to inform the investigation as data were available only to end of January 2015, before season commencement. Personal communication with other jurisdictions and review by the TGA and the Advisory Committee on the Safety of Vaccines (ACSOV) acknowledged the potential signal in Victoria, but agreed there was insufficient evidence of clinical severity to alter the risk-benefit of the ongoing influenza vaccination programme [10].

Ongoing monitoring remained suggestive of above-expected reporting of allergy-related AEFI, although

frequency of reporting decreased towards the end of May (Figure 1).

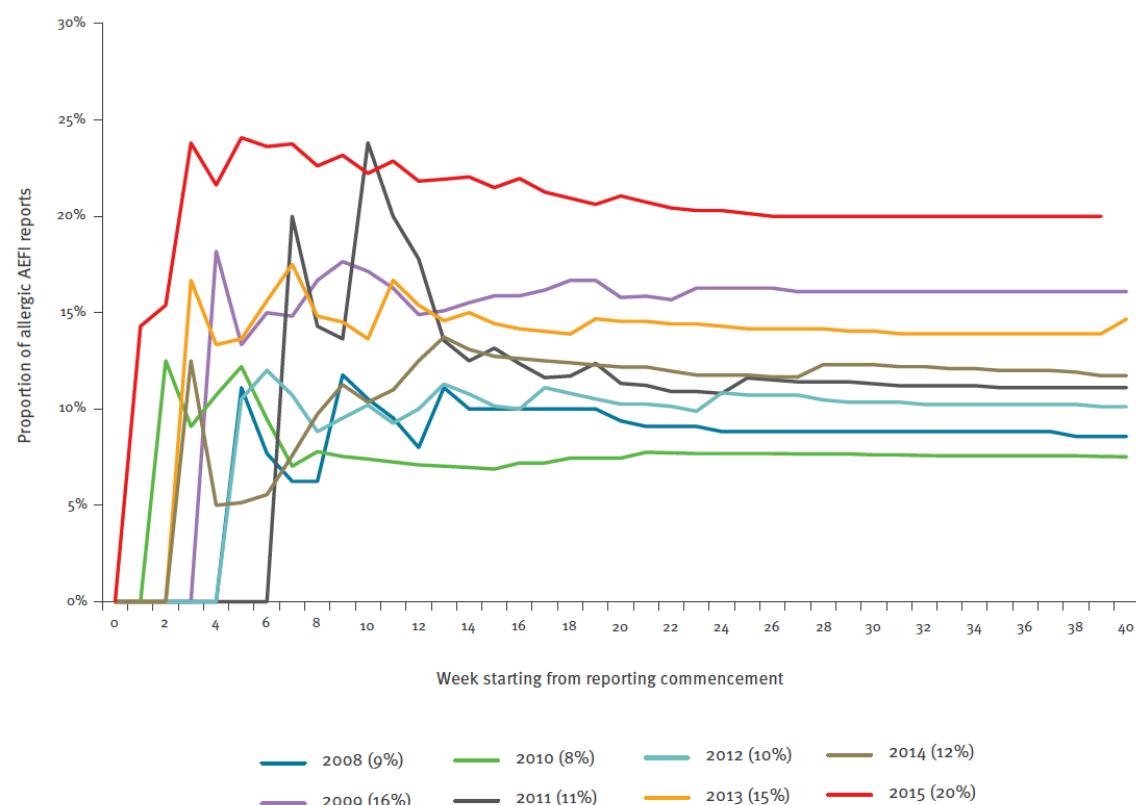
No increase was observed at any time during the 2015 season in the number or proportion of anaphylaxis cases, which peaked at six cases (21% [6/28] of allergy-related AEFI), when compared with four cases (27% [4/15]) reported in 2014 ($p = 0.70$).

End of season signal investigation

For the 2015 season SAEFVIC received 140 reports of AEFI with TIV, of which 28 (20%) were allergy-related. Vaccinee age ranged from 0 to 79 years (mean: 36 years), with all allergy-related cases aged over 5 years (6/28 aged 6–17 years and 22/28 aged ≥18 years, mean: 39 years). While females comprised the majority of reports (104/140, 74%), the proportion reporting allergy-related AEFI was similar in both males (7/36, 19%) and females (21/104, 20%) ($p = 0.92$; 95% CI: -0.14 to 0.16). Three-quarters (76%) of those experiencing allergy-related AEFI reported symptom onset within one-hour of vaccination and all within 10 hours.

FIGURE 3

Proportion of allergy-related adverse events following immunisation (AEFI) with trivalent influenza vaccines, by week from reporting commencement, Victoria, 2008–2015 (n = 1,010 total AEFI)



AEFI: adverse events following immunisation.

The y axis shows the proportion of allergy-related AEFI at the end of seasonal vaccination campaign.

The proportion of allergy-related AEFI with TIV of 20% (28/140) in 2015 was higher than in any previous year and significantly higher than the 12% (121/1,010) for all years 2008–2015 combined ($p = 0.008$; 95% CI 0.01 to 0.15) (Table 1).

The seasonal reporting pattern of overall TIV AEFI reporting in 2015 was similar to that seen in previous years (Figure 1). However, comparison of the number of allergy-related AEFI reported with previous years demonstrated the early steep rise and increased cumulative magnitude in reports (Figure 2), which was more clearly evident when realigned by weekly seasonal influenza AEFI reporting commenced in each annual period (Figure 3).

Final analysis at 2015 seasons end found the overall 2015 TIV AEFI RR of 11.8 reports per 100,000 vaccine doses distributed was no different to the RR of 11.1 per 100,000 for the four years 2011–2014 combined

(RR: 1.07, 95% CI: 0.88 to 1.29) (Table 1). However when comparing allergy-related AEFI with TIV, the RR in 2015 of 2.4 per 100,000 vaccine doses distributed was nearly double that of the combined risk of 1.3 in 2011–2014, (RR: 1.78, 95% CI: 1.14 to 2.80).

The observed variation in AEFI reports per 100,000 doses distributed by vaccine brands in 2015 was not significant either comparing individual brands, or when comparing Fluarix to the combined BioCSL Fluvax and Vaxigrip RR (RR: 1.89, 95% CI: 0.79 to 4.48) (Table 2). Anaphylaxis AEFI reports in 2015 did not differ from 2011 to 2014 combined data as a proportion of all AEFI (6/140 (4.2%) vs 9/453 (2.0%); $p = 0.13$) or proportion of allergy-related AEFI (6/28 (2.1%) vs 9/54, (1.7%); $p = 0.60$).

Discussion

On conclusion of the 2015 southern hemisphere TIV/ influenza season our study found a near-doubling of

TABLE 1

Trivalent influenza vaccine adverse events following immunisation reports, by category and comparison of proportion and adverse events following immunisation reports per 100,000 doses distributed, Victoria, Australia 2008–2015 (n = 1,010)

Year	All reports	Allergy reports n	Allergy reports % (95% CI)	Doses distributed	AEFI per 100,000 doses distributed	Allergic AEFI per 100,000 doses distributed
2015	140	28	20 (14–28)	1,186,417	11.8	2.4
2014	128	15	12 (7–19)	1,097,024	11.7	1.4
2013	116	17	15 (9–22)	1,095,217	10.6	1.6
2012	90	9	10 (5–18)	966,393	9.3	0.9
2011	119	13	11 (6–18)	932,246	12.8	1.4
2010	293	22	8 (5–11)	NA	NA	NA
2009	89	14	16 (9–25)	NA	NA	NA
2008	35	3	9 (2–23)	NA	NA	NA
2008– 2015	1,010	121	12% (10–14)	NA	NA	NA
2011– 2014	453	54	12% (9–15)	4,090,880	11.1	1.3

AEFI: adverse events following immunisation; CI: confidence interval; NA: not available.

annual generalised allergy-related AEFI compared with the 4 previous years in this investigation of passive surveillance reports, with no evidence of correlation with any specific vaccine brand or allergic symptom, nor a significant increase in anaphylaxis. Further studies would be required to confirm that the signal was more than a spurious increase in reporting, however we were not aware of any publicity or event that may have stimulated reporting. Our study demonstrated that the longitudinal data availability, combined clinical and epidemiological services of SAEFVIC were well placed to identify and conduct a rapid investigation of a possible signal event early in the influenza vaccination campaign and facilitate evidence-based decision making by the Australian national regulatory authority.

However, vaccine pharmacovigilance in Australia is limited by wide variation in AEFI surveillance systems across Australian health jurisdictions [11]. Data are not consistent in format, categorisation or method of analyses until final collation of jurisdictional reporting and classification according to standardised MedDRA terminology is completed by the TGA. National AEFI data are publicly accessible via the Database of Adverse Event Notifications (DAEN), but there is a 3-month lag in publication. Australia continues to strive towards stronger multi-jurisdictional vaccine pharmacovigilance collaborations and streamlined cohesion between the jurisdictional surveillance models.

Detecting signals as an increase in AEFI frequency from previous years is best achieved by comparing risk of AEFI in the exposed (vaccinated) population. However, in this scenario, cases were predominantly adults for whom there is little available data on the vaccinated (exposed) population as the vaccine register in Australia, the Australian Childhood Immunisation

Register (ACIR), is limited to vaccines administered to children aged less than 7 years [12]. Expansion of the Register in 2016 to all age groups for vaccines on the NIP or given in general practice will partially address this gap, but the register will not include vaccines administered in specialist clinics (e.g. Bacillus Calmette–Guérin, travel vaccines) [13] thus underlining the importance of spontaneous or passive surveillance collating AEFI reports for all vaccines administered and from all vaccine-recipient sub-groups [14].

To determine AEFI RR, we therefore used a proxy denominator of vaccine doses distributed. This is an approximation of the exposed population as usage (and wastage) is unknown and may therefore lead to underestimation of RR. Reports of AEFI with non-NIP TIV brands were excluded from the final investigation in all years as numbers were small and vaccine doses distributed data were not readily available. Exclusion of these non-NIP TIV reports and non-specific potential allergy-related symptoms such as itchiness or undefined rash means that this summary is a conservative approach to the signal magnitude.

Non-specific AEFI such as the allergy-related reactions reported in 2015 can give rise to subjective variations in categorisation, although these would be consistent in inter-year comparisons. Brighton Collaboration definition criteria were applied for the serious AEFI of anaphylaxis [15], which showed no significant increase from previous years. The observed increased proportion of allergy-related AEFI may equally indicate a decrease in non-allergic reports; although there is no specific reason that non-allergic reporting would be depressed and no drop in the number of non-allergy-related reports was observed. Furthermore our analysis does not consider temporal co-circulation of environmental or infective allergic triggers; however,

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Conflict of interest

None declared.

Authors' contributions

HJC contributed to the study design, conducted data analysis and interpretation of results and drafted the manuscript. NWC contributed to the study design and reviewed and contributed to the manuscript draft. MAR contributed to the data analysis, result interpretation and reviewed and contributed to the manuscript draft. JPB contributed to the study design and reviewed and contributed to the manuscript draft.

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6.5 Publication: AEFI in older persons

Short report

Adverse events following vaccination of older people may be under-reported

Hazel J Clothier^{1,2}, Nigel W Crawford^{1,2}, Melissa Russell², Jim P Buttery^{1,3,4}

Adverse events following immunisation (AEFIs) in Australia are monitored by diverse jurisdictional passive surveillance systems that report to the national database, established primarily for detecting safety problems with childhood vaccinations. Supplementary, active AEFI surveillance systems, such as AusVaxSafety (operated by the National Centre for Immunisation

Adverse events following immunisation (AEFIs) reported to SAEFVIC, July 2007 – June 2016, by age group

	Age at vaccination				Total
	60–69 years	70–79 years	80–89 years	≥ 90 years	
AEFI reports	345	244	51	5	645
Sex (women)	252 (73%)*	158 (65%)	33 (65%)	4 (80%)	447 (69%)
Reactions†					
Localised	240 (70%)	169 (69%)	27 (53%)	3 (60%)	439 (68%)
Systemic‡	66 (19%)	28 (11%)	9 (18%)	1 (20%)	104 (16%)
Fever	53 (15%)	28 (11%)	6 (12%)	0	87 (13%)
Gastrointestinal	50 (14%)	31 (13%)	5 (10%)	0	86 (13%)
Musculoskeletal	41 (12%)	33 (14%)	1 (2%)	2 (40%)	76 (12%)
Allergic	28 (8%)	30 (12%)	2 (4%)	1 (20%)	61 (9%)
Headache	30 (9%)	15 (6%)	1 (2%)	0	46 (7%)
Inflammatory/immune	21 (6%)	8 (3%)	1 (2%)	1 (20%)	31 (5%)
Respiratory	14 (4%)	3 (1%)	3 (6%)	1 (20%)	21 (3%)
Cardiac	9 (3%)	7 (3%)	0	0	16 (2%)
Neurological	8 (2%)	4 (2%)	1 (2%)	0	13 (2%)
Other§	54 (16%)	36 (15%)	13 (25%)	1 (20%)	104 (16%)
Total	614	386	74	8	1082
Serious AEFIs, number	38	28	5	0	71
Proportion (95% CI)	11.0% (7.9–15%)	11.5% (7.7–16%)	9.8% (3.2–21%)		11.0% (8.7–14%)
Visited emergency department	18	16	0	0	34
Proportion (95% CI)	5.2% (3.1–8.1%)	6.6% (3.8–10%)	—	—	5.3% (3.8–7.3%)
Admitted to hospital, number	14	18	3	0	35
Proportion (95% CI)	4.1% (2.2–6.7%)	7.4% (4.4–11%)	5.9% (1.2–16%)	—	5.4% (3.8–7.5%)
Attended clinic, number	12	5	0	0	17
Proportion (95% CI)	3.5% (1.8–6.0%)	2.0% (0.7–4.7%)	—	—	2.6% (1.5–4.2%)
Vaccines†					
Influenza	210 (61%)	121	31 (61%)	3 (60%)	365 (57%)
Pneumococcal	166 (48%)	145	18 (35%)	3 (60%)	332 (51%)
Diphtheria/tetanus/pertussis booster	45 (13%)	21	3 (6%)	0	69 (11%)
Zoster	0	0	1 (2%)	0	1 (2%)
Other	16 (5%)	10	1 (2%)	0	27 (4%)
Total	437	297	54	6	794

SAEFVIC = Surveillance of Adverse Events Following Vaccination in the Community. * In one case, sex was not reported. † Multiple responses possible. ‡ Includes lethargy and malaise. § Includes drug administration errors (21 cases). ◆

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Short report

Research and Surveillance) request AEFI information by automated SMS and email messages after selected vaccinations. Understanding AEFI reporting patterns for older people is important for identifying safety problems in this group, particularly following the introduction of a zoster vaccine program targeting 70–79-year-old people in November 2016.¹

During July 2007 – June 2016, the Victorian enhanced passive AEFI surveillance service, Surveillance of Adverse Events Following Vaccination In the Community (SAEFVIC),² received 645 reports for people aged 60 or more (6.5% of all reports), a mean of 72 reports per year; 69% concerned women, and pneumococcal or influenza vaccines were the most frequently implicated vaccines (697 of 794 [88%]). The most frequent AEFIs were localised reactions (40.6% of all reactions; 95% confidence interval [CI], 37.6–43.6%); serious AEFIs were reported in 11% of cases (95% CI, 8.7–14%), and 5.4% of reported patients (95% CI, 3.8–7.5%) were hospitalised. Increasing age was not associated with higher frequencies of serious AEFIs or seeking medical attention (Box).

Two deaths were reported, unlikely to have been vaccine-related: a single vehicle accident after an uneventful influenza vaccination, and a post-vaccination diagnosis of acute disseminated encephalomyelitis. As a result of high annual influenza vaccination coverage in this population, coupled with age-related baseline mortality rates, deaths coincident with vaccination are likely to be more frequent in older people; robust investigation and causality assessment are therefore critical.³

Given that each year an estimated 75% of Australians aged 65 or more receive influenza vaccine, and many also receive pneumococcal vaccine, AEFI reporting for older people was less frequent

than anticipated. In 2013, fewer AEFIs per influenza vaccine dose were reported for Australians over 65 than for those aged 18–65 years.⁴ Despite having more comorbidities, older Australians also reported fewer serious AEFIs in an earlier study of all age groups.⁵ The apparent under-reporting may reflect adverse events being perceived as normal in older people and therefore not linked with recent vaccinations, a higher threshold for reporting, or reduced access to reporting channels.

Analysing hospital admissions may increase case ascertainment, particularly for serious AEFIs. The expansion of AusVaxSafety in 2017 to include all age groups may also increase reporting by prompting associating events with recent vaccination,⁶ but surveillance via mobile phone messaging in this age group may be unreliable.

Other methods of detection may be needed for AEFIs in older people. Improving case ascertainment and using vaccination data from the Australian Immunisation Register, which has recorded vaccinations for all age groups since 2016, will enable more sensitive and reliable surveillance, maintaining the overall safety of the National Immunisation Program.

As new vaccine programs are introduced for older people, vaccine pharmacovigilance in this age group must be improved. AusVaxSafety active surveillance is an important first step.

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Chapter 7: Signal detection

“A principal concern of vaccine pharmacovigilance is the timely detection of adverse events following immunisation (AEFI) that are novel by virtue of their clinical nature, severity and/or frequency”(314).

7.1 Chapter introduction

This PhD aims to optimise passive AEFI surveillance in Victoria: one objective of which is to detect, investigate and validate vaccine safety signals. The evaluation of SAEFVIC (Chapter 5) and signal investigation studies (Chapter 6) demonstrated that the SAEFVIC system had good utility for signal investigation and validation. However, the studies presented in both Chapters also identified a gap in capacity for *de novo* signal detection in the absence of prior clinical suspicion. This Chapter addresses that gap by exploring opportunities for signal detection and providing the evidence-base to shape the path forward.

This Chapter provides a literature review on what a signal is and describes options for signal detection with passive AEFI surveillance, using available data sources within the Victorian setting. Sections 7.4.1 and 7.4.3 specifically set the background for the two studies described in this chapter that were developed to address particular vaccine pharmacovigilance issues current at the time, as well as to further our knowledge in the area.

The first study presented in this chapter aims to investigate the utility of routine hospital administration data for calculating background rate estimates of conditions that may arise as AEFI, specific to the Victorian setting. Following similar methodology developed in the UK in 2009(58), this study was the first to employ such methods in Australia. This was timely to inform the soon-to-be-implemented human papillomavirus vaccine (HPV) program in adolescent boys, for which Australia was a world-leader(315). By providing background estimates of expected reporting of severe

neurological conditions following immunisation, anticipated vaccine safety concerns could be alleviated.

The second study presented in this chapter aims to provide proof-of principle for using signal hypothesis generation methodologies that are relevant and practical to implement. The study explored application of an industry-standard calculation of disproportionality—the proportional reporting ratio (PRR) —to the SAEFVIC dataset. Successful in demonstrating PRR utility to detect two known vaccine safety signal events, the study provided the evidence-base for establishing routine signal detection using passive AEFI surveillance data. PRR was subsequently integrated as routine practice within SAEFVIC and was instrumental in demonstrating a signal event of severe neurological adverse events occurring in 2018 was likely due to increased volume of influenza vaccine administration as opposed to change in reactogenicity(185). These findings are discussed further in *Chapter 8: SAEFVIC maturation*.

These studies—and ongoing explorations for signal detection that have continued beyond the scope of the PhD—have been presented at various conferences (Appendix 2) and/or with contributions as co-author (listed in *Chapter 1: Introduction*).

7.2 Research questions

7.2.1 Question 4: Can background rates of potential AEFI be estimated using Victorian hospital administration datasets?

The hypothesis was that routinely collected state health outcome data can be used to inform post-licensure safety surveillance of conditions that may be perceived as AEFI. The setting was chosen specifically to inform the worlds' first roll out of HPV to boys(315).

Publication: Clothier *et al.* Human papillomavirus vaccine in boys: background rates of potential adverse events. *Med J Aust.* 2013; 3;198(10):554-8

7.2.2 Question 5: Is proportional reporting ratio (PPR) a useful signal detection method for AEFI with Influenza vaccines?

The hypothesis was that a conventional signal detection algorithm (PPR) would adequately detect two known signal events in the SAEFVIC database. The aim was to 1) demonstrate proof-of-principle; 2) establish signal hypothesis generation methodologies that were relevant and practical to implement and; 3) offer insight for future studies into use of signal detection algorithm (SDA) to support vaccine pharmacovigilance in Australia.

Publication: Clothier *et al.* Early signal detection of adverse events following influenza vaccination using proportional reporting ratio, Victoria, Australia. PloS ONE. 2019; 14(11) doi:10.1371/journal.pone.022470

7.3 What is a signal?

“A principle concern of vaccine pharmacovigilance is the timely detection of adverse events following immunisation (AEFI) that are novel by virtue of their clinical nature, severity and/or frequency”(314).

The Council for International Organizations of Medical Sciences (CIOMS) defines a **safety signal** as ‘Information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verifactory action’(316). More generally the term “signal” in vaccine pharmacovigilance infers incidence of adverse events following immunisation (AEFI) occurring at a higher level than is normally expected and is synonymous with the term “outbreak” as applied to infectious diseases. The exact determination of what constitutes “higher than normal” is subjective and relies on the availability of a background expected incidence on which to make comparisons.

7.3.1 The role of Passive AEFI surveillance in signal detection

“The primary function of the AEFI monitoring system is to detect early warning signals and generate hypotheses about possible new vaccine adverse events or changes in frequency of known ones”(167).

The role of post-licensure passive AEFI surveillance has become increasingly recognised by regulatory authorities as an essential component of vaccine development(64). While pre-licensure activities provide the foundation for vaccine safety and efficacy, it is post-licensure surveillance that provides assurance vaccines are safe and effective in the real-world setting. Passive AEFI surveillance aims to provide assessment of potential safety issues that were not statistically significant in phase 3 trials; that trials were under-powered to detect; or occur in timeframes beyond the scope of pre-licensure trials(64).

The Australian national regulatory agency, the Therapeutic Goods Authority (TGA), states signal detection involves identifying patterns of adverse events associated with a particular vaccine, or combination of vaccines, that warrant further investigation: and that signals may arise from;

- i) a previously unrecognised safety issue
- ii) a change in the frequency or severity of a known safety issue, or
- iii) identification of a new at-risk group(317).

7.4 Opportunities for signal detection

7.4.1 Background rates

Adverse events may coincide temporally with vaccine administration, indeed it would be expected that they would occur coincidentally at a rate no different to that which occurs in the absence of vaccination(318). In an ideal world we would know the background incidence of conditions that might arise as an adverse event and thus be able to account for these expected temporal associations using the concept of observed to expected analyses(58, 318). However, as the range of mandated reportable conditions is limited, background rates of potential AEFI are largely

unknown. This is particularly so for clinically mild conditions: however, serious conditions requiring medical attention may be recorded in routine health datasets such as emergency department presentations or hospital admissions. Examples include Guillain Barré syndrome (GBS) or acute flaccid paralysis, where pathogenesis is associated with immune stimuli arising from natural infection and therefore also plausibly with immunisation(319).

An understanding of background rates of both common and rare potential AEFI therefore supports interpretation of post-licensure surveillance data, whereby increases above expected rates may be identified and generate signal hypotheses of potential vaccine-associated adverse events. Ideally background incidence would be estimated prior to exposure to the vaccine of interest and in populations that have similar demographic characteristics to the proposed vaccinated population. This is of particular relevance when considering introduction of a new vaccine—or introduction to a new population sub-group, where there is no vaccine-associated adverse event history beyond clinical trials(320, 321).

In 2013 Victoria faced such a scenario. The quadrivalent human papilloma virus vaccine (4vHPV) vaccination (Gardasil®) for prevention of cervical cancer had been introduced as a routine vaccination for adolescent females in 2007. In late 2011 vaccination of males was recommended as a cost-effective intervention and expansion of the routine program to include boys was planned to commence in 2013(322).

The introduction of 4vHPV to boys had the advantage of AEFI information from both pre-licensure clinical trials and post-licensure surveillance of AEFI in adolescent girls. However, background rates of potential AEFI presentations and consequent thresholds for safety flags should not be informed merely using data limited to one gender, or from other countries, as sex or geographical-related differences could cause misinterpretation of potential signals (320, 321). For example, multiple sclerosis, which has an unsubstantiated association with vaccines(323), has a preponderance for females with a trend for increasing female to male incidence ratio that varies geographically with a latitudinal gradient(324, 325).

Studies in the United Kingdom, and more recently in Canada, have shown how hospital datasets can inform on background rates of conditions that may be perceived as AEFI(58, 326): however, this method had not been explored in the Australian context.

In Victoria routinely collected population level health outcome administration data are available within two state-wide Victorian datasets: the Victorian admitted episodes dataset (VAED) recording hospital discharge data and; the Victorian emergency minimum dataset (VEMD) which records emergency department presentations. The attributes of these datasets have been described in *Chapter 3: Methods* and their utility for determination of background rates is presented in section 7.4.1 in this Chapter.

7.4.2 AEFI reporting

Passive AEFI surveillance is a primary source providing the breadth of data for signal detection of unanticipated changes in reporting trends.

Historically signal hypotheses were generated through the scrutiny of AEFI surveillance data by experts, a method appropriately described as a “time-consuming procedure whose reliability is unknown”(327) and akin to “finding a needle in the haystack”(328). This is particularly so as AEFI range from rare occurrences of severe manifestations to increased incidence or increased severity of a known, often frequently occurring, condition(28, 329). While rare events, particularly when clinically serious, can be detected through astute clinical observation or review of each individual report, increased incidence in a more common AEFI can be more difficult to detect (330, 331).

Monitoring of AEFI reporting frequencies may provide timely indication of reporting trends, especially if AEFI are reported promptly upon symptom onset. However, AEFI count data are influenced according to variations in quantity of vaccine administered, for example through program delivery cycles and changes to immunisation program schedules. The calculation of AEFI incident rates using vaccine administered data as the exposed population denominator would account for such variations. The use of rates and determination of the denominator is discussed below.

7.4.2.1 AEFI Incidence rates

Calculation of AEFI incident reporting as rates according to vaccine doses administered would account for quantitative variations in immunisation program delivery. However, population-based information systems or immunisation registers containing the exposed population denominator data for calculating incidence rates and relative risks are not commonly available to many passive AEFI surveillance systems, thus hampering the interpretation of AEFI reporting trends(113, 332). A survey of European countries identified only eight were operating national systems that met the US CDC definition of an immunisation information system (Denmark, Finland, Iceland, Ireland, Malta, the Netherlands, Norway and Romania) and six had none(333, 334). The WHO Vaccine Alliance (GAVI) have put out a call to action for improving the quality of immunisation data through electronic immunisation registries including individual-level health record systems(335).

In Australia, prior to 2016, vaccination registers were limited to children or specific programs for a prescribed range of vaccines(203, 336). Specifically, the Australian Childhood Immunisation Register (ACIR), established in 1996, holds records of vaccinations for children under age seven for a prescribed range of vaccinations, predominantly those on the National Immunisation Program (NIP). Although described as the world's first attempt in developing a near-complete population-based immunisation register, the ACIR had limitations in that records were not enduring—being held only to age 14—and vaccinations in late childhood, adolescents or adults were not captured(203): populations for which there are an increasing spectrum of targeted programs. Various jurisdiction school-based immunisation registers, including the national HPV register established in 2007(337), provided some additional data and adult vaccinated population data were estimated through data mining of health services databases or population surveys(203, 338).

During 2016 an Australian all-of-life immunisation register commenced as a progressive expansion of the children's register (ACIR) (see *Chapter 3: Methods* section 3.4.1) (339, 340). This Australian Immunisation Register (AIR) will provide a national register that records all vaccines given to all people in Australia(207). However, while the expanded register will provide an improved denominator, particularly for adults,

the known issue of under-reporting to registries(341-344) and timing of report processing to provide data in acceptable timeframe for signal detection and responsive action will remain(203, 345).

Active surveillance, whereby AEFI reporting is solicited from vaccine recipients, can meet the provisions for accurate rate calculation. However, it is resource intensive such that prudent economies of resource, time and finance lead to active surveillance being targeted to specific vaccines or vaccine recipient populations of interest(88). Australia's expanding capacity for active surveillance through the AusVaxSafety suite of systems is encouraging. However, each system currently retains varying restrictions in age, vaccine and symptoms for which the data are collected(94).

This inability to calculate AEFI incidence rates has been noted in several Australian studies involving investigations of AEFI(47, 173, 198, 307). It was acknowledged during the 2010 signal event of febrile seizures associated with one brand of seasonal influenza vaccine that lack of information concerning the number of vaccines administered—and therefore inability to measure the incident rate of adverse events—added to the reporting difficulties(9). The ministerial review by Stokes determined that, even retrospectively, Australia remained unable to determine the number of vaccines administered during this period(9).

In the absence of good measures of exposed population, studies have used a variety of proxy measures to assist interpretation of AEFI data, including drug sales, distributions and census data (346). Census data provides overall population data with demographic detail, however falsely elevates estimates of the exposed denominator through inability to exclude non-immunisation targeted cohorts and/or deficiencies in vaccine coverage.

7.4.2.2 Doses distributed as a proxy denominator

Vaccine doses distributed are commonly used by major systems like US Vaccine Adverse Event Reporting System (VAERS) for rate calculation in retrospective observational studies(347). For example, a recent review of post-licensure safety monitoring of quadrivalent human papillomavirus vaccine in the VAERS from 2009–2015 calculated crude reporting rates of AEFI reporting per million doses distributed to

characterise specified reactions and to quantify annual reporting trends over the study period(348). However, doses distributed offer an overestimation of doses administered and there is no provision of information on sex or age group of vaccine recipients. Furthermore, doses distributed data can show substantial variation or differential recording of data, thus limiting interpretation and jurisdictional or international comparisons(349, 350). However, an advantage of dose distributed data is the potential availability, should urgency require analysis before administered dose data have been recorded into a register.

As vaccines in Australia are predominantly delivered through the NIP, doses distributed data are held by the managing jurisdiction, thereby providing a potential data source for analyses. Doses distributed have been used as a denominator for annual (or periodic) analyses of SAEFVIC data (see *Chapter 4: SAEFVIC early years* and *Chapter 5: Informing pharmacovigilance*), however no review of data attributes or within-period variations have been conducted in the Victorian setting.

The utility of doses distributed as a proxy denominator for calculating AEFI incidence rates to facilitate timely signal investigation were therefore reviewed as a prelude to the studies presented in this Chapter. Doses distributed data were found to be readily available from the Department of Immunisation with minimal time lag (within a week of distribution). However, investigation found influences of delivery scheduling - for example school programs in term time and convenience of co-administering vaccines alongside influenza immunisation during the winter period. This limited the scope for time-critical analyses and therefore the use of doses distributed as a proxy denominator for real-time signal detection was not progressed. The findings were shared internally to ensure appropriate caution applied when interpreting rates using doses distributed presented at a granular level less than yearly.

An alternate approach is to use the number of AEFI reports themselves as the denominator and calculate proportional profiles for reactions or vaccines of interest. This proportionate approach has advantages from not requiring an external data source and may counteract some biases of variable reporting between datasets(328). Various algorithms for analysis have been developed.

7.4.3 Signal detection algorithms.

The concept of signal detection algorithms (SDA) permits filtering of large databases, comparing reporting for a particular vaccine-event combination relative to the rest of the data to provide observed and expected counts solely from within the dataset(351, 352). There are two main types of SDAs: those based on disproportionality analysis, and those based on multivariate modeling techniques such as logistic regression.

Disproportionality methodologies use analysis of 2×2 contingency tables to quantify the degree to which a vaccine-event combination co-occurs disproportionately compared to what would be expected if there were no association(351). Common methods include the proportional reporting ratio (PRR), reporting odds ratio (ROR), information component (IC) and empirical Bayes geometric mean (EBGM)(352). The framework for calculating disproportionality is shown in Table 8 and interpretations in Table 9(351, 353).

Table 8: Framework for calculation of disproportionality within a dataset(351)

	AEFI	Not AEFI	Total
Vaccine of interest	a	b	(a+b)
Not vaccine of interest	c	d	(c+d)
Total	(a+c)	(b+d)	(a+b+c+d)

The PRR and ROR use the other vaccines and events—at the exclusion of the vaccine-event pair of interest—as a comparator group and proxy for the background incidence for testing if there is an association(328, 354).

Table 9: Common measures of association for 2x2 tables in passive AEFI surveillance analysis(353)

Measure of association	Probabilistic interpretation
Reporting Ratio (RR)	$\frac{\Pr(\text{AEFI} \text{Vaccine})}{\Pr(\text{AEFI})}$
Proportional Reporting Ratio (PRR)	$\frac{\Pr(\text{AEFI} \text{Vaccine})}{\Pr(\text{AEFI} \text{notVaccine})}$
Reporting Odds Ratio (ROR)	$\frac{\Pr(\text{AEFI} \text{Vaccine}) / \Pr(\text{notAEFI} \text{notVaccine})}{\Pr(\text{AEFI} \text{notVaccine}) / \Pr(\text{notAEFI} \text{notVaccine})}$
Information Component (IC)	$\text{Log2} \frac{\Pr(\text{AEFI} \text{Vaccine})}{\Pr(\text{AEFI})}$

The proportional reporting ratio (PRR) is defined as: $\text{PRR} = [a/(a+b)]/c/(c+d)$ and is identical to the calculation of a relative risk (RR) from a cohort study. A PRR greater than 1 suggests that the adverse event is more commonly reported for individuals following the vaccine of interest, relative to the comparison vaccines. The higher the PRR, the greater the strength of the signal(328).

The reporting odds ratio (ROR) is defined as $\text{ROR} = (a/c)/(b/d) = ad/bc$, which is the same as calculation of an odds ratio (OR) from a case-control study.

Both RORs and PRRs provide measures of whether or not a signal is present and, if it is, give a broad indication of the strength of that signal(355). Values will be similar providing the assumption (as is usually the case) that “a” is a small proportion - the same argument is used to show that OR in a case control study approximates the RR. It is important to appreciate that although the calculations are the same, when used in

this context they do not actually estimate RR/ OR in a population, but estimate occurrence in a database(355).

These estimators can be completed by χ^2 -test (Yates correction) or calculation of confidence intervals, however this is for filtering of data, rather than determining “statistical significance” of the signal event in the clinical sense(351).

While the frequentist methods of PRR and ROR consider counts and proportions, the Bayesian methods take a probability compared to prior distribution approach.

With Information Component (IC) (Bayesian) and EBGM methods, an observed number of reports is compared with the expected number derived from all events and all vaccines (including the vaccine and event of interest): the assumption being that the observed and the expected numbers can be treated as independent(356). Both use the IC, which amounts to the log to the base 2 of the PRR(357)

WHO neural network method expresses expected number of reports (for drug and events) with assumption to have independent binomial distributions. whereas empirical Bayes assumes expected numbers of reports mentioning drug event is fixed and that the observed number of reports is generated by a Poisson distribution(357).

For all methods, the larger the fraction of the database represented by the vaccine (or event) of interest, the less independent is the observed from the expected number evaluated(358).

7.4.3.1 SDA interpretation

SDA are not appropriate for hypothesis testing. This is because signal detections are nonclinical and only highlight deviations from expected values—that is, reflect a disproportionality in reporting—without explaining whether these deviations are due to a causal linkage(329, 331).

Trigger levels for signal alerting may be standardised by applying thresholds as a measure of magnitude, however this requires decision rules on which to base the threshold of the chosen parameters. Choosing higher or lower thresholds changes

both the sensitivity of the screening and the number of false alarms produced and thus impacts efficiency of the signal detection process(359, 360).

There are two thresholds to consider when applying an SDA; firstly, a minimum case-count and secondly, that of the resulting ratio statistical determinant. As small counts of reports may give somewhat erratic results, a case-count threshold of minimum 3 reports related to the specific vaccine-event combination of interest is widely used(361). Studies by Slattery have shown that this may be increased up to threshold of 6 for well-established vaccines to improve specificity and work-load efficiency, with marginal loss of sensitivity(359).

Statistical determinant threshold conventions can be varied to local circumstances(328, 359), however, the widely used convention of the EV Guidelines is to use a PRR threshold of 2 and either a chi-square of 4 or the lower 97.5% confidence bound (PRR025))(359, 361).

Trends will be less important and harder to interpret once an adverse reaction is well-established and it has been shown that there is a reduction in precision for any method over the lifetime of a product(362). Likewise impact of “media bias” following publicity of an event may give rise to a sudden increase in reporting, and hence in the observed/expected ratio(221, 351). Therefore, in certain circumstances it may be appropriate to exclude certain reports from the expected (or observed) count that could cause dampening of vaccine-AEFI pair estimates, and possibly hide signals(351). Known very strong signals could be removed from the expected background used for comparison or clusters of observed reports arising from stimulated reporting, as might occur in response to regulatory action such as withdrawal of a product(363). An example in the Australian context is the strong signal of fever and febrile seizures with 2010 seasonal trivalent influenza vaccine with stimulated AEFI reporting following the federal response to withdraw of influenza vaccine for children(167, 364). Such removal of background signal or current stimulated observed events would best be done at a second stage as a sensitivity analysis.(351)

Frequency of analysis should consider the resources required and the generation of false positives: the World Health Organization conducts screening quarterly. A method

intended to specifically allow for repeated examination of the data is the sequential probability ratio test (SPRT), which has been applied to spontaneous databases with some evaluation(365). Use of interactive graphical displays of disproportionality, which enable the analyst to visually identify safety signals, may also affords insights into the data inaccessible by traditional analytic methods(366).

7.4.3.2 Choice of SDA

Although these SDAs have been used in pharmacovigilance for many years their performance characteristics remain incompletely defined(329, 331, 356, 367), particularly when translating from methods practiced in clinical trial setting to spontaneous reporting(368).

While there are various justifications for the benefits of individual SDAs (369-373), no single approach will be optimal in all situations(374-376). Outputs of different measures have been found to be broadly comparable both within and across spontaneous reporting databases(355, 362, 377) and a range of frequentist and/or Bayesian measures of disproportionality are used internationally(329, 367, 370, 378). Furthermore, the absolute performance of any one signal detection method may vary between adverse event databases and so cannot be assumed to translate to other databases(361, 362, 379, 380).

Exact comparisons of SDA performance characteristics are hampered by lack of gold standard signals. While the Observational Medical Outcomes Partnership (OMOP) has made gold standards for signal detection reactions (SDR) for drugs, none are for vaccines(329). A limited reference set of vaccine-adverse event pairs was proposed through the Global Research in Paediatrics (GRiP) project for use in comparing signal detection methods and systems in the paediatric population(381). The predominant documented vaccine pharmacovigilance events offering locally relevant reference signals are febrile and allergy-related AEFI related to seasonal influenza vaccines occurring in 2010 and 2015 respectively (8, 308, 312).

Ultimately choice of SDA should be guided by the Innovative Medicines Initiative PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) project, which recommended that “Choice of a

disproportionality statistic for signal detection should be primarily based on ease of implementation, interpretation and optimisation of resources”(380). As a main purported benefit of passive surveillance is the lower resource intensity and the stability of routine systems, the best signal detection methodologies will therefore be those that have equal low resource requirements, minimal specialist skill requirements and are easy to interpret(379). The effort undertaken should also ideally reflect the likelihood of finding a signal event and may also need to consider the likely clinical impact of the signal(361).

Within this thesis I chose to explore the PRR as the initial SDA to commence signal detection in SAEFVIC because it is a well-defined SDA that is simple to apply in practice and had some prior familiarity within Australia. Furthermore, PRR is a common starting point for SDA analysis in international systems(328, 359, 361). There are two well defined signal events within the lifespan of SAEFVIC surveillance, both involving influenza vaccines, which provide an excellent opportunity for pilot testing SDA and especially as influenza vaccines continue to require enhanced vigilance due to potential for variations in seasonal formulation reactogenicity(382).

7.4.3.3 SDA signal management

Signal detection is just one component of signal management. Signal management covers “all steps from detecting signals, through their validation and confirmation, analysis, prioritisation and assessment to recommending action, as well as the tracking of the steps taken and of any recommendations made”(383).

While SDAs are useful for indication of a potential signal, any hypotheses generated by disproportionality analyses must be investigated by more robust methods before influencing clinical decisions(384). It is important to appreciate that even when a highly inclusive search for such evidence is conducted there is a substantial fraction of signals for which no external supporting evidence can be found.(385)

The mathematical basis of measures of disproportionality do not obscure the numerous confounders and biases inherent in spontaneously reported surveillance data(352). For example, spontaneous reporting is prone to a disease-specific AEFI bias arising from preferential reporting of both live attenuated and, paradoxically, non-live

vaccines as the suspected cause of the disease/signs/symptoms related to the disease they should protect against(386, 387). Such a phenomenon may arise in misleading signal detections and should be considered during validation of disproportional associations(387).

In summary, SDAs cannot replace expert clinical review, signal strength does not necessarily correlate with medical significance and used alone SDAs are insufficient for regulatory action(388, 389). However, they can be helpful to focus attention when confronted with the difficult task of screening large numbers of vaccine–event combinations for potential signals(356). Vaccine pharmacovigilance therefore needs a multi-faceted approach with complimentary and overlapping systems synergising to maximise signal hypothesis generation, testing and validation.

7.5 Signal detection in Australia

Reporting of AEFI is not consistently mandated across Australia and indeed there is no one comprehensive surveillance system, therefore the application of signal detection methodologies is equally scattered and inconsistently applied(167).

At the national level, the TGA conducts weekly clinical review of line lists of reported AEFI as subjective screening for conditions of interest or potential concern. This is accompanied by two-monthly reviews of proportional reporting ratios (PRR) for collated national AEFI surveillance data(6, 390). Any signal hypotheses generated are investigated by clinical experts.

The lack of application of timely signal hypothesis generation methods to passive surveillance data was considered to directly contribute to the delay in response to early suspicions of the febrile seizure signal in young children that occurred in 2010, which in turn led to further vaccine administration with severe consequences(9). One recommendation made as an outcome of the review of this episode was for signal identification and investigation protocols to be developed(6).

In 2013 early exploration of signal detection methodologies was being attempted using SAEFVIC data(179), however, there were no presentations of other Australian signal

detection study findings, or standard operating procedures, available to offer guidance for use by jurisdictional surveillance systems.

There was therefore considerable interest in utilising database screening tools to supplement the crude inspection of lists of spontaneously reported vaccine-AEFI combinations and identify trends or associations worthy of further investigation (i.e., signals) embedded within a database consisting largely of background ‘noise’ (314). The effectiveness of detecting variations in reporting trends may be enhanced if routine monitoring systems were applied (329).

SAEFVIC, operational since 2007 with approximately 6,000 reports in 2013 and rising to 12,000 by 2017 when the exploration of PRR study commenced, was therefore of sufficient size and diversity to serve as a suitable background for evaluating disproportionate reporting (331).

As vaccine pharmacovigilance develops with the prospect of multi-jurisdictional expansion of the SAEFVIC model, it is timely to gain experience and insight into opportunities for signal detection using Australian data. In particular, ascertaining a baseline understanding of the applicability and utility of SDAs will inform future studies that may consider infographics for signal visualisation and review the strength-of-evidence for combining methods such as multivariate analyses and time-to-onset distribution to improve statistical signal detection (391, 392).

The two studies presented in this Chapter explored principles of signal detection using Victorian datasets to provide an underlying evidence-base for establishing a mechanism for routine signal detection and future explorations. Each study progressed our understanding of available datasets and increased our maturity in signal hypothesis generation. The impact of the study findings are described in *Chapter 9: Optimising SAEFVIC*.

Human papillomavirus vaccine in boys: background rates of potential adverse events

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Cervical cancer is the most common cancer affecting women in developing countries. It is caused by persistent infection with specific types of human papillomavirus (HPV).¹ Quadrivalent human papillomavirus (4vHPV) vaccine is a recombinant vaccine administered as a three-dose course to provide protection against four types of HPV (6, 11, 16 and 18).² The vaccine is highly efficacious for the four included types, of which 16 and 18 are reported to cause 70% of cervical cancers and 6 and 11 cause anogenital warts.^{1,3} 4vHPV vaccination was introduced under the Australian National Immunisation Program (NIP) in April 2007 for adolescent girls, with an initial catch-up program including women up to 26 years of age. The current ongoing funded program is only for girls in the first year of high school (aged 12–13 years). Recent data suggest that the 4vHPV vaccination program has caused a rapid decline in genital wart presentations in females,^{4,5} and there are early indications of a reduction in high-grade cervical dysplasias.⁶

Following advice from the Australian Technical Advisory Group on Immunisation, vaccination of males was recommended as a cost-effective intervention by the Pharmaceutical Benefits Advisory Committee in November 2011.⁷ Accordingly, 4vHPV vaccination for boys has been added to the Australian NIP, commencing in 2013 and targeting boys aged 12–13 years in a school-based program, with a catch-up program over 2 years for boys aged 14–16 years.^{7,8} The program aims to reduce the incidence of HPV disease in males, such as anogenital warts and anal intraepithelial neoplasia,⁹ and reduce sexual pathways of virus transmission. Australia will be the first nation to implement HPV vaccination for boys in a national program.

Vaccines, as with any medicine, have potential adverse reactions varying from mild and expected to rare and/or serious events. Vaccination may cause such events — the nature of adverse events following immuni-

Abstract

Objectives: To determine background rates of potential adverse events following immunisation (AEFI) before expansion of the quadrivalent human papillomavirus (4vHPV) vaccination program to adolescent boys.

Design, patients and setting: Retrospective analysis of hospital discharge data obtained from the Victorian Admitted Episodes Dataset and emergency department visit data obtained from the Victorian Emergency Minimum Dataset for boys aged 12 to < 16 years during the period 1 July 2004 to 30 June 2009.

Main outcome measures: Numbers of and incidence rates for Guillain-Barré syndrome, anaphylaxis, seizures, syncope and other potential AEFI from 1 July 2004 to 30 June 2009, and estimated numbers of events after 4vHPV vaccination assuming no association (other than temporal) with the vaccine.

Results: We estimated background rates of neurological and allergic events in adolescent boys to be 252.9 and 175.2 per 100 000 person-years, respectively. Assuming an 80% vaccination rate with three doses per person — which equates to 1 440 000 doses administered nationally per year in the first 2 years of the program — about 2.4 episodes of Guillain-Barré syndrome would be expected to occur in the 6 weeks following vaccination. Within 1 day of vaccination, about 3.9 seizures, 0.3 episodes of anaphylaxis and 6.5 acute allergy presentations would be expected.

Conclusions: Routinely collected health outcome administration data can inform postlicensure safety surveillance of target conditions that might be perceived as AEFI.

sation (AEFI) and the timing of onset after vaccination are important factors when assessing causation. Adverse events may also coincide temporally with vaccine administration by chance. To interpret postlicensure surveillance data, it is useful to know the background rates of common and rare potential adverse events before introduction of the vaccine.^{10,11} With this understanding, increases above background rates can be rapidly identified, which can assist with the evaluation and reporting of potential vaccine-associated adverse event rates.

The mass school-based introduction of female 4vHPV vaccination raised a number of well publicised initial safety concerns, including “scare” regarding potential episodes of anaphylaxis and multiple sclerosis after vaccination.^{12–14} In addition, a mass psychogenic reaction was seen in a Melbourne school vaccination environment,¹⁵ with syncope and syncopal seizures occurring in response to the vaccination process.¹⁶ Such spurious events may arise from the psychological impact of the vaccination process, particularly when using mass vaccination strategies in a school-based teenaged population.

Release of the 4vHPV vaccine to boys has the advantage of adverse event information from prelicensure clinical trials and postlicensure surveillance of adverse events arising from administration to adolescent girls. However, additional information on the background rates of potential adverse events in teenaged boys is critical for assessing the safety of this vaccination program.

Our aim was to explore the use of routinely collected information for estimating potential adverse event rates. We used population-level health outcome administration data to describe the background rates of potential AEFI before the introduction of 4vHPV vaccination for boys into the NIP in Australia, and to estimate numbers of a range of neurological, allergic and other events that can be expected following vaccination, assuming temporal association with administration of vaccine but no other association.

Methods

Two statewide Victorian datasets were accessed — the Victorian Admitted Episodes Dataset (VAED; hospital

discharge data) and the Victorian Emergency Minimum Dataset (VEMD; emergency department visit data) — both of which include International Classification of Diseases 10th revision Australian modification (ICD-10-AM) codes. The data included a unique identifier that enabled linking of individuals across the datasets, but were otherwise non-identifying, according to Victorian Department of Health data linkage protocols.¹⁷ Ethics approval for the study was provided by the VAED and VEMD data custodians.

Multiple records of the same event within a dataset or across datasets — for example, a person presenting at emergency who is subsequently admitted, or a person admitted to hospital who is then discharged to a different hospital or to home and who later returns with continuation of the same episode (with each presentation recorded as a separate event) — were linked via the unique identifier. All events occurring within 28 days of a previous event were combined into a single episode.

The data that we analysed comprised all episodes that occurred in boys aged 12 to <16 years and were recorded in the VAED and/or VEMD with one of the ICD-10-AM codes listed in Box 1 and an admission or presentation date from 1 July 2004 to 30 June 2009.¹⁸ Conditions selected for inclusion are rare adverse events, conditions that patients are likely to present to hospitals with after vaccination, and conditions that have previously been raised as potential sources of concern in Australia and overseas.^{10,19}

Age was taken to be the youngest age at which an episode occurred, and records were excluded from the analysis if sex was recorded inconsistently among records with the same unique identifier. Some records had more than one ICD-10-AM code, and these were preserved. Events with an interstate or overseas postcode were excluded, but those with “unknown” (8888 and 9988) and “of no fixed abode” (1000) postcodes were preserved under the assumption that these occurred in Victoria. Episodes that were ongoing from the 3 months before the study period, the washout

period (31 March to 30 June 2004), were also excluded.

Events were described as the number of episodes and the number of first events. An episode was considered a discrete event if it occurred more than 28 days after a prior event in the same individual, as patients were deemed to still be “at risk” of the same event during their recovery from an acute condition. First events were defined as the first time a condition was diagnosed in each patient during the study period. First events are more relevant for chronic conditions and episodes are more relevant for acute conditions.

We calculated background annual incidence rates as the number of events during the 5-year study period divided by the population at risk during this period, using Australian Bureau of Statistics 2006 mid-year resident population data for males.²⁰

The analysis was restricted to boys aged 12 to <16 years — the target age range for vaccination. We used these background rates to estimate the number of events expected within 1 day, 1 week and 6 weeks of vaccination per 100 000 vaccinees. We then estimated the expected number of events for each condition 1 day, 1 week and 6 weeks after vaccination across Australia following the introduction of 4vHVP into the NIP, assuming there is no association (other than temporal) with the vaccine.

Seasonal variation was analysed by graphing the number of first events or episodes by month of presentation. As the numbers of chronic neurological presentations in the study group were small, they were combined and compared with numbers of all-age presentations in males for individual neurological conditions. For multiple sclerosis, data were also presented omitting presentations in the first 12 months of the study period to assess the effectiveness of the study's 3-month washout period.

Results

The numbers of and incidence rates for potential AEFI in boys aged 12 to <16 years are shown in Box 2, and the estimated numbers of cases of potential AEFI per 100 000 adolescent boys

1 Conditions included in the study

	ICD-10-AM codes
Neurological	
Guillain-Barré syndrome*	G61.0
Transverse myelitis*	G37.3
Multiple sclerosis*	G35
Optic neuritis*	H46, G36.0
ADEM	G04.0
Bell's palsy	G51.0
Syncope	R55
Seizures	R56, R56.0, R56.8
Allergic	
Anaphylaxis	T78.2, T88.6
Urticaria	L50.0, L50.1, L50.9
Serum sickness	T80.6
Adverse effect of drug or medication†	T88.7
Other	
Adverse events	T78.8, T78.9, T88.1, T78.3
ICD-10-AM = International Classification of Diseases 10th revision Australian modification. ADEM = acute disseminated encephalomyelitis. * Conditions considered chronic. † Not otherwise specified.	

that would occur, even in the absence of vaccine, are shown in Box 3. Assuming an 80% vaccination rate with three doses per person — which equates to about 480 000 boys vaccinated and a total of 1 440 000 doses administered nationally per year in the first 2 years of the program — about 2.4 episodes of Guillain-Barré syndrome would be expected to occur within 6 weeks of vaccination. In addition, about 3.9 seizures and 6.5 acute allergy presentations would be expected to occur within 1 day of vaccination, including 0.3 episodes of anaphylaxis.

There was minimal seasonal variation in the occurrence of potential AEFI (Box 4, Box 5). However, repeating this analysis with a larger number of neurological presentations (using data for all age groups) revealed a notable peak in the number of multiple sclerosis presentations in July. This peak was reduced but not eliminated when the washout period was increased to 15 months (Box 4).

Discussion

Using statewide morbidity data, we estimated background rates of neurological and allergic events in adolescent boys in Victoria to be 252.9 and 175.2 per 100 000 person-years, respectively. Such adverse events

2 Numbers of and incidence rates for potential AEFI in boys aged 12 to < 16 years (Victoria, July 2004 – June 2009)

	First events		Episodes	
	No. of events	Incidence rate (95% CI) per 100 000 person-years	No. of events	Incidence rate (95% CI) per 100 000 person-years
Neurological				
Guillain-Barré syndrome	10	1.46 (0.56 to 2.37)	11	1.61 (0.66 to 2.56)
Transverse myelitis	2	0.29 (-0.11 to 0.70)	3	0.44 (-0.06 to 0.94)
Multiple sclerosis	2	0.29 (-0.11 to 0.70)	2	0.29 (-0.11 to 0.70)
Optic neuritis	4	0.59 (0.01 to 1.16)	6	0.88 (0.18 to 1.58)
ADEM	8	0.17 (0.45 to 1.90)	11	1.61 (0.66 to 2.56)
Bell's palsy	60	8.78 (6.56 to 11.00)	60	8.78 (6.56 to 11.00)
Syncopal	807	118.0 (109.9 to 126.2)	831	121.5 (113.3 to 129.8)
Seizures	666	97.4 (90.0 to 104.8)	830	121.4 (113.1 to 129.7)
Total	1516	221.7 (210.6 to 232.9)	1729	252.9 (241.0 to 264.8)
Allergic				
Anaphylaxis	49	7.17 (5.16 to 9.17)	51	7.46 (5.41 to 9.51)
Urticaria	620	90.7 (83.6 to 97.8)	647	94.6 (87.3 to 101.9)
Serum sickness	23	3.4 (2.0 to 4.7)	23	3.4 (2.0 to 4.7)
Allergic reaction	495	72.4 (66.0 to 78.8)	517	75.6 (69.1 to 82.1)
Total	1125	164.6 (154.9 to 174.2)	1198	175.2 (165.3 to 185.1)
Other				
Total	7	1.02 (0.27 to 1.78)	7	1.02 (0.27 to 1.78)

AEFI = adverse events following immunisation. ADEM = acute disseminated encephalomyelitis.

may be mistakenly assumed to be caused by vaccination, owing to temporal association, when the 4vHPV vaccination program is expanded to include adolescent boys.¹⁰ Postlicensure safety assessments of 4vHPV vaccine programs in adolescent girls have shown little evidence of increased risk of neuro-

logical and allergic adverse events after vaccination.^{3,21,22}

Expected rates of potential AEFI in recent studies vary widely, but direct comparisons are restricted because of differences in methods, health care systems and data collection and analyses.^{10,11,23} In particular, caution is required when using emergency pres-

entation databases as these may record preliminary diagnoses, rather than final diagnoses. Studies limited to analysis of ICD-10 coded data, such as ours, lack the rigour of diagnosis verification and conformity to standardised case definitions, although coding standards are maintained. Our study identified higher reporting rates for anaphylaxis compared with similar studies.^{10,11} While data aberrations are possible, marked increases in anaphylaxis rates Australia and the United States over the past two decades may play a part.^{24,25}

Background rates of potential AEFI and consequent thresholds for safety flags should not be informed merely using data on adolescent girls because sex-related differences could cause misinterpretation of potential signals.^{10,11} For example, the rate of adolescent boys presenting with a first multiple sclerosis event in the 6 weeks following vaccination would be expected to be one-third of the rate seen for adolescent girls assuming no relationship with vaccine other than temporal.²⁶

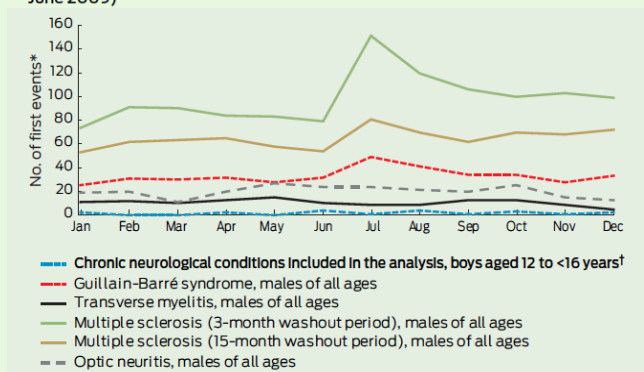
In our study, we used a 3-month washout period to attempt to remove the risk of categorising events as incident cases when they were part of a pre-existing illness than was ongoing from before the study period. However, the 3-month washout period did

3 Estimated numbers of cases of potential AEFI in vaccinated boys aged 12 to < 16 years, assuming no relationship with vaccine*

	No. of first events per 100 000 population			No. of episodes per 100 000 population		
	1 day	1 week	6 weeks	1 day	1 week	6 weeks
Neurological						
Guillain-Barré syndrome	0 (0.00–0.01)	0.03 (0.01–0.05)	0.17 (0.06–0.27)	0 (0.00–0.01)	0.03 (0.01–0.05)	0.19 (0.08–0.29)
Transverse myelitis	0 (0.00–0.00)	0.01 (0.00–0.01)	0.03 (0.00–0.08)	0 (0.00–0.00)	0.01 (0.00–0.02)	0.05 (0.00–0.11)
Multiple sclerosis	0 (0.00–0.00)	0.01 (0.00–0.01)	0.03 (0.00–0.08)	0 (0.00–0.00)	0.01 (0.00–0.01)	0.03 (0.00–0.08)
Optic neuritis	0 (0.00–0.00)	0.01 (0.00–0.02)	0.07 (0.00–0.13)	0 (0.00–0.00)	0.02 (0.00–0.03)	0.10 (0.02–0.18)
ADEM	0 (0.00–0.01)	0.02 (0.01–0.04)	0.15 (0.05–0.25)	0 (0.00–0.01)	0.03 (0.01–0.05)	0.19 (0.08–0.29)
Bell's palsy	0.02 (0.02–0.03)	0.17 (0.13–0.21)	1.01 (0.75–1.26)	0.02 (0.02–0.03)	0.17 (0.13–0.21)	1.01 (0.75–1.26)
Syncopal	0.32 (0.30–0.35)	2.26 (2.11–2.42)	13.57 (12.64–14.51)	0.33 (0.31–0.36)	2.33 (2.17–2.49)	13.98 (13.03–14.93)
Seizures	0.27 (0.25–0.29)	1.87 (1.73–2.01)	11.20 (10.35–12.05)	0.33 (0.31–0.35)	2.33 (2.17–2.48)	13.96 (13.01–14.91)
Total	0.61 (0.58–0.64)	4.25 (4.04–4.46)	25.50 (24.22–26.78)	0.69 (0.66–0.72)	4.85 (4.62–5.07)	29.08 (27.71–30.45)
Allergic						
Anaphylaxis	0.02 (0.01–0.03)	0.14 (0.10–0.18)	0.82 (0.59–1.05)	0.02 (0.01–0.03)	0.14 (0.10–0.18)	0.86 (0.62–1.09)
Urticaria	0.25 (0.23–0.27)	1.74 (1.60–1.87)	10.43 (9.61–11.25)	0.26 (0.24–0.28)	1.81 (1.67–1.95)	10.88 (10.04–11.72)
Serum sickness	0.01 (0.01–0.01)	0.06 (0.04–0.09)	0.39 (0.23–0.54)	0.01 (0.01–0.01)	0.06 (0.04–0.09)	0.39 (0.23–0.54)
Allergic reaction	0.20 (0.18–0.22)	1.39 (1.27–1.51)	8.33 (7.59–9.06)	0.21 (0.19–0.22)	1.45 (1.32–1.57)	8.70 (7.95–9.44)
Total	0.45 (0.42–0.48)	3.15 (2.97–3.34)	18.92 (17.82–20.03)	0.48 (0.45–0.51)	3.36 (3.17–3.55)	20.15 (19.01–21.29)
Other						
Total	0 (0.00–0.00)	0.02 (0.01–0.03)	0.12 (0.03–0.20)	0 (0.00–0.00)	0.02 (0.01–0.03)	0.12 (0.03–0.20)

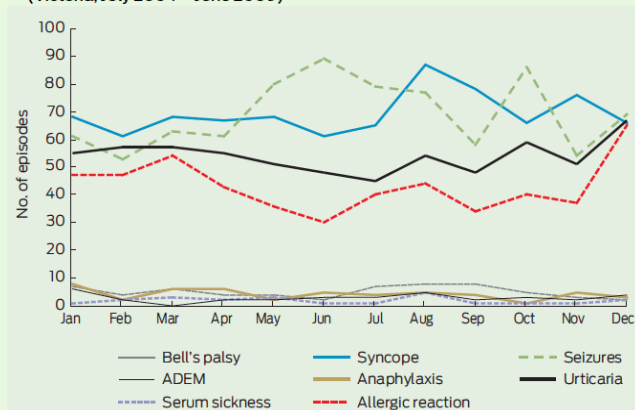
AEFI = adverse events following immunisation. ADEM = acute disseminated encephalomyelitis. * Data are based on one dose of vaccine per vaccinee.

4 Numbers of first events of chronic conditions, by month (Victoria, July 2004 – June 2009)



* Data are numbers of first events for chronic neurological conditions analysed in boys aged 12 to <16 years and numbers of presentations for individual neurological conditions in males of all ages.
† Conditions included were Guillain-Barré syndrome, transverse myelitis, multiple sclerosis and optic neuritis.

5 Number of episodes of acute conditions by month in boys aged 12 to <16 years (Victoria, July 2004 – June 2009)



ADEM = acute disseminated encephalomyelitis.

not remove this issue for multiple sclerosis. While our study showed little seasonal variation in potential AEFI, school-based vaccination programs are conducted in blocks (as convenient to the vaccine schedule and the school year), which may give rise to false signal detection. Specific investigation of appropriate washout periods, as well as seasonal variation in the occurrence potential AEFI and implementation of the vaccine program, must therefore be explored before conducting in-depth analyses for specific conditions or extrapolating data to other jurisdictions.

In Victoria, first-dose 4vHPV vaccine coverage for adolescent girls has

reached 80%,²⁷ but challenges of uptake and course completion by males may be anticipated.²⁸ If coverage for boys is less than 80%, the expected rates in our study should be recalculated to avoid erroneous alert thresholds.

The background rates of potential AEFI that we have estimated can be used to inform surveillance systems, health care providers and the community regarding health care events that may be temporally related to vaccination. In mass vaccination programs, where vaccine exposure is a common event in the target group, many incident acute health conditions will occur following vaccination, irrespec-

tive of causal association. While current passive surveillance system reporting is likely to underascertain postvaccination events, prior knowledge of expected numbers of events are valuable in helping determine whether reports or clusters of reports represent real safety flags that require urgent investigation.²⁶

Our data highlight the value of statewide and nationwide health datasets in providing information that can improve public safety. In addition to establishing background rates of diseases, international systems such as those in Denmark and the US, have been used to link vaccination databases to health care event databases, enabling direct investigation of potential associations with adverse events.^{29–31} These methods, conducted in accordance with state and federal privacy protections, offer a promising future for further improving vaccine safety in Australia.³²

Routinely collected state health outcome data can enable informed postlicensure safety surveillance of conditions that may be perceived as AEFI. When the 4vHPV vaccine program is expanded to adolescent boys, such data can be used for targeted active surveillance of potential vaccine safety flags.

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Competing Interests: Hazel Clothier and Jim Buttery are members of the Advisory Committee on the Safety of Vaccines.

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7.7 Publication: Early signal detection using PRR



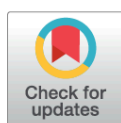
RESEARCH ARTICLE

Early signal detection of adverse events following influenza vaccination using proportional reporting ratio, Victoria, Australia

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Abstract

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Introduction

Timely adverse event following immunisation (AEFI) signal event detection is essential to minimise further vaccinees receiving unsafe vaccines. We explored the proportional reporting ratio (PRR) ability to detect two known signal events with influenza vaccines with the aim of providing a model for prospective routine signal detection and improving vaccine safety surveillance in Australia.

Methods

Passive AEFI surveillance reports from 2008–2017 relating to influenza vaccines were accessed from the Australian SAEFVIC (Victoria) database. Proportional reporting ratios were calculated for two vaccine-event categories; fever and allergic AEFI. Signal detection sensitivity for two known signal events were determined using weekly data; cumulative data by individual year and; cumulative for all previous years. Signal event thresholds of $PRR \geq 2$ and Chi-square ≥ 4 were applied.

Results

PRR provided sensitive signal detection when calculated cumulatively by individual year or by all previous years. Known signal events were detected 15 and 11 days earlier than traditional methods used at the time of the actual events.

Conclusion

Utilising a single jurisdiction's data, PRR improved vaccine pharmacovigilance and showed the potential to detect important safety signals much earlier than previously. It has potential to maximise immunisation safety in Australia. This study progresses the necessary work to

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establish national cohesion for passive surveillance signal detection and strengthen routine Australian vaccine pharmacovigilance.

Introduction

Criticism of adverse event following immunisation (AEFI) signal event detection in Australia has included that detection occurred relatively late, unnecessarily exposing further Australians to unsafe vaccines [1]. Typically, signals have been detected only following a reporter or surveillance team member describing an anecdotal impression of a change in AEFI presentations or reports [2].

The most notable event occurred in 2010 when increased incidence of fever and febrile seizures occurred following seasonal influenza vaccines [3, 4]. This was subsequently identified as arising from increased reactogenicity of one tri-valent influenza vaccine brand (Fluvax[®] bioCSL). The initial alert was made by Western Australia emergency department physicians. The vaccine was withdrawn 10 days later, but not before additional cases had occurred, including a prolonged febrile seizure resulting in profound disability in a previously healthy 11-month-old child [5]. The multi-million dollar compensation decision recognized the delays in reporting and state and federal response processes that were identified in an independent enquiry [1, 5].

A separate signal event occurred in 2015 when retrospective analyses of AEFI with seasonal influenza vaccines identified a probable increase in allergy-related AEFI [6]. In this instance, severity was fortunately insufficient to warrant modification of the program. Nevertheless, it highlighted continuing insensitivity of the Australian passive surveillance systems to detect AEFI signal events in a timely manner [2]. The welcome introduction of active surveillance systems has helped, however these can be costly, time consuming and usually focus on known potential risks (new vaccines, or high risk groups) [7]. The backbone of AEFI surveillance remains passive systems and it is critical they be utilised optimally for timely signal detection.

A “signal” can be defined as incidence of AEFI occurring at a higher level than is normally expected. Signal detection in vaccine vigilance requires a multi-faceted approach as AEFI range from a rare occurrence of a severe AEFI to increased incidence or increased severity of a known, often frequently occurring, AEFI [8, 9]. While rare but particularly serious events can be detected through review of each individual report or active surveillance, an increased incidence in a more common AEFI is often more difficult to detect [10, 11], and has been described as akin to “finding a needle in the haystack” [12].

If there is known high potential for a change in AEFI incidence, as demonstrated with febrile and allergy-related AEFI related to seasonal influenza vaccines [6, 13, 14], the extra resources and intensity of active surveillance may be warranted [7]. However, for unanticipated changes in reporting, passive AEFI surveillance can provide effective means of signal detection if routine monitoring systems are applied [9]. A benefit of passive surveillance is the lower resource intensity and the stability of routine systems. The best signal detection methodologies will be those that have equal low resource requirements, do not require extensive computational skills and are easy to interpret [15].

Statistical methods for pharmacovigilance signal detection are well established but their performance characteristics remain incompletely defined [9, 16, 17]. While there are various justifications for the benefits of individual methods [18–22], no single approach is optimal in all situations [23–25] and a range of frequentist and / or Bayesian measures of disproportionality

are used internationally [9, 16, 19, 26]. In Australia, the national regulator Therapeutic Goods Administration (TGA) conducts bi-monthly proportional reporting ratios (PRR) for collated national AEFI surveillance data accompanied by weekly clinical review of line lists [27, 28]. However, there are no published reports on their routine use in Australia, or evaluation of their ability to detect signal events. Investigation of these signal detection tools and applicability within the resource structure of Australian systems is therefore timely.

Proportional reporting ratio (PRR)

This analysis focusses on proportional reporting ratio as a measure of disproportionality [29, 30]; chosen because it is an established signal detection algorithm (SDA) in pharmacovigilance [31, 32] and easy and practical to employ. Moreover it was an approach recommended in the response to national review into the management of a significant adverse event [33, 34].

The PRR is defined as the ratio between the frequency with which a specific adverse event is reported for the vaccine of interest (relative to all adverse events reported for the vaccine) and the frequency with which the same adverse event is reported for all vaccines in the comparison group (relative to all adverse events for vaccines in the comparison group). Although the PRR is an established measure, the definition of the comparator group used in calculations can vary, hence it is important to evaluate its performance prior to implementation in a new dataset.

We explore the PRR SDA as a simple to use, well defined SDA on passive vaccine AEFI surveillance data from the Victorian state vaccine safety service, SAEFVIC, using influenza vaccines as an example with the aim of providing a model for using an SDA and improving pharmacovigilance in Australia.

Objectives

To apply PRR to routine SAEFVIC surveillance data for specific AEFI with seasonal influenza vaccines and

- Determine the time period for data calculation sufficient to meet case count requirements
- Determine ability to detect known safety signals
 - a. 2010 fever/febrile seizures (Fluvax[®] brand specific)
 - b. 2015 allergic reactions
- Investigate impact of vaccine brand and age subgroup analyses on signal detection
- Ascertain generation of other potential / spurious signals

Methods

SAEFVIC is approved under the auspices of the Human Research Ethics Committee, Royal Childrens Hospital, Victoria to manage the clinical and public health surveillance database in compliance with national and jurisdictional privacy legislation (No. 37194). Data for this study were used within the public health surveillance functions for which it is approved. No patient identifiers were included in the extraction fields to generate the PRR.

Data source

Data from AEFI reports submitted to SAEFVIC database from January 2008 to December 2017 (as at 4 April 2018) were extracted by reported date, imported and analysed in Microsoft Power BI (Version 2.56.5023.2021, March 2018) [35].

Annual reporting periods for calendar week 10 to 40 were chosen to coincide with seasonal influenza vaccine program, although it was noted that in 2015, week 16 was the first week of reporting due to late commencement of the seasonal vaccination program [36].

Seasonal influenza vaccines

In Australia annual influenza vaccination is recommended for anyone six months of age and older, with persons aged 65 years and over, pregnant women and those who suffer chronic conditions eligible for free vaccine under the National Immunisation Program [37]. Seasonal influenza vaccines have changed across the years and may be funded differently for different target groups (e.g. children / health care workers). Reports for all seasonal influenza vaccines were combined for analyses, except where signal investigation of brand specific reactogenicity were performed. Where junior formulations were reported, they were grouped with the parent brand for analysis. Monovalent pandemic influenza vaccines H1N1Pdm2009 were excluded.

AEFI reactions

AEFI reactions are categorised by SAEFVIC immunisation nurses according pre-determined case definitions based on symptom description [35]. We created two adverse event groups colating AEFI relating to fever or allergic reactions (below).

- **Fever** (fever unmeasured, fever $\geq 38 < 40$, fever ≥ 40 and febrile seizure)
- **Allergy-related** (allergic reaction generalised, urticaria, anaphylaxis, angioedema)

Calculations

Proportional reporting ratio were calculated according to a 2x2 table (Table 1).

$$PRR = [a/(a+b)]/[c/(c+d)]$$

Chi-square (ChiSq) calculated as [12, 38]:

$$\chi^2 = \frac{(ad - bc)^2(a + b + c + d - 1)}{(a + b)(c + d)(a + c)(b + d)}$$

At 1 degree of freedom and a 5% error the tabulated value is 3.84.

Empirical thresholds were applied [12, 39], being:

- a minimum vaccine-event case-count (a) of 3
- signal alert threshold of $PRR \geq 2$
- statistical significance test of $ChiSq \geq 4$

Proportional reporting ratios were calculated for seasonal influenza vaccines with each of the adverse event-pair groups (fever and allergic reactions).

Table 1. Vaccine and adverse event 2x2 contingency table.

	AEFI of Interest	Other AEFI	Sum
Vaccines of interest	a	b	a+b
Other vaccines	c	d	c+d
Sum	a+c	b+d	a+b+c+d

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Three time period analyses were tested comparing the influenza vaccine-event ratio with the rationale that cumulative data would provide larger sample size for disproportionality assessment:

1. By week reported in that week alone
2. Cumulative by week in that individual year, and
3. Cumulative by week with all previous years data.

Signal detection

Analyses were undertaken to ascertain if PRR would have assisted detection of known/suspected signal events (sensitivity):

1. 2010 febrile event [3]
2. 2015 allergy event [6]

Brand subgroup analysis

If a signal was suggested ($PRR \geq 2$ and $ChiSq \geq 4$), the PRR was calculated for influenza vaccines as a specific subgroup, whereby each of that seasons individual influenza brands (as a ratio to the other influenza vaccine brands used in that year) to ascertain brand specific contribution to the increased PRR [38].

Age subgroup analysis

Two age groups were defined as children (0–4 years) and 5 years and older reflecting the Australian National Immunisation Program [37]. PRR were calculated using single year and all previous year denominator data to ascertain impact of age subgroup on signal detection and signal magnitude.

Past signal subanalysis

It was considered possible that inclusion of increased reporting from signal events in the cumulative all-years denominator may reduce the proportional ratio and mask a signal in subsequent years. Therefore we re-examined the data by excluding 2010 and 2015 from the respective cumulative all-year denominator analyses for fever and allergic reaction AEFI in calculations for each year following the known signal event.

Signal hypothesis generation

For each signal investigated the number of weeks with PRR above threshold and the estimated proportion for which a signal could be confirmed or for which an investigation could/should have been initiated was calculated.

Results

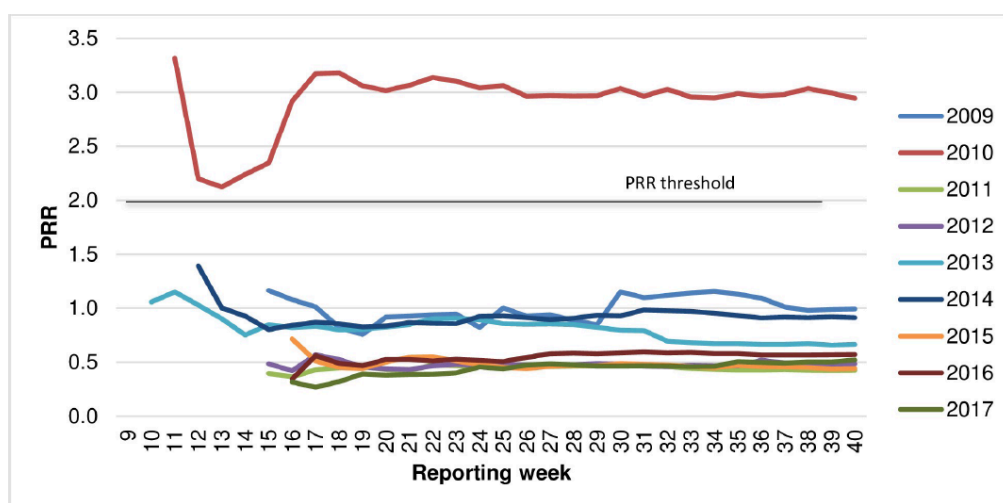
A total of 12,152 AEFI reports were accessed of which 1649 (13.6%) related to administration of a seasonal influenza vaccine (Table 2). There was higher reporting for females receiving influenza vaccines (male:female ratio 1:2.2) than with all vaccines (male:female ratio 1:1.2) reflecting the funded influenza vaccine program for healthworkers, who are predominantly female. The mean time to report was 4 days with 95% of all reports received within 6 months. Reports by influenza vaccine brand are provided in supplementary data (S1 Table).

PRR calculation by time period

Reporting week. Due to low case numbers reported in any one week, the threshold of a ≥ 3 was reached irregularly and in some years not at all, resulting in inconsistent reporting of PRR for both fever and allergic AEFI categories. We therefore progressed to cumulative analyses.

Cumulative by week and individual year. Monitoring of data cumulatively in each year provided case numbers consistently above the calculation threshold ($a \geq 3$) for PRR calculation. For Influenza vaccines and fever reactions, a $PRR \geq 2$ was attained only in 2010 when in fact the PRR was >2 and $ChiSq >4$ in all of the 17 weeks of reporting (Fig 1).

For influenza vaccines and allergic reactions, signal threshold of $PRR \geq 2$ and $ChiSq \geq 4$ was attained in the first two weeks of reporting in 2011 before subsiding below threshold level as the number of reports received increased. Signal thresholds were reached consistently across all reporting weeks in 2015 (Fig 2).



Note: No fever AEFI were reported in 2008

Fig 1. PRR cumulative (individual year) for Influenza vaccines and fever AEFI, by reported year and week, 2008–2017.

<https://doi.org/10.1371/journal.pone.0224702.g001>

Table 2. Summary of influenza vaccine AEFI reports received by SAEFVIC, Victoria 2008–2017.

Year	AEFI reports	Influenza (% of all reports)	Influenza reports with fever AEFI (% of Influenza reports)	Influenza reports with allergy-related AEFI (% of Influenza reports)
2008	843	40 (4.7%)	0 (0.0%)	4 (10.0%)
2009	1121	95 (8.5%)	7 (7.4%)	15 (15.8%)
2010	989	317 (32.1%)	217 (68.5%)	22 (6.9%)
2011	1091	178 (16.3%)	21 (11.8%)	21 (11.8%)
2012	887	108 (12.2%)	12 (11.1%)	12 (11.1%)
2013	1200	132 (11.0%)	31 (23.5%)	19 (14.4%)
2014	1327	140 (10.6%)	29 (20.7%)	16 (11.4%)
2015	1406	163 (11.6%)	17 (16.6%)	36 (22.1%)
2016	1451	216 (14.9%)	26 (12.0%)	26 (12.0%)
2017	1837	260 (14.2%)	28 (10.8%)	20 (7.7%)
Total	12152	1649 (13.6%)	398 (24.1%)	191 (11.6%)

<https://doi.org/10.1371/journal.pone.0224702.t002>

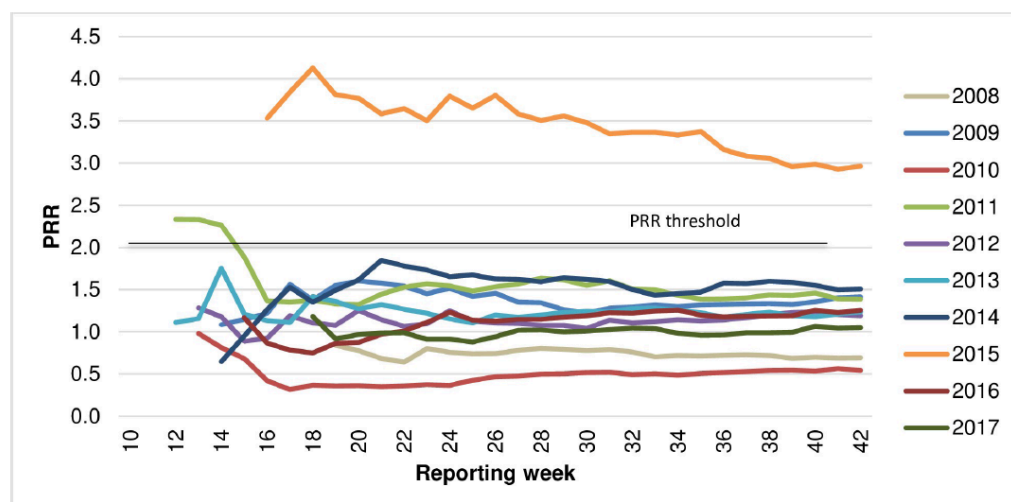
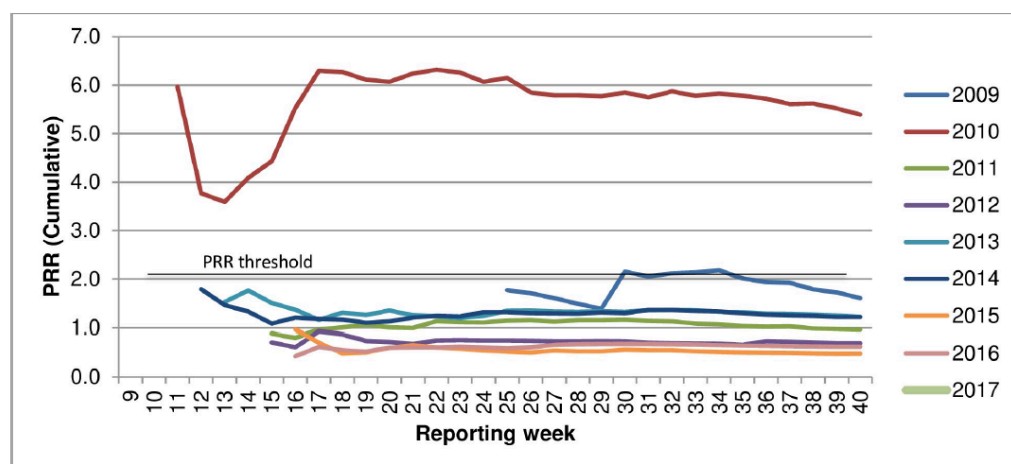


Fig 2. PRR cumulative (individual year) for Influenza vaccines and allergy-related AEFI, by reported year and week, 2008–2017.

<https://doi.org/10.1371/journal.pone.0224702.g002>

Cumulative by week and all previous years data. Both signals were detected using cumulative data for all years available (i.e., proportion of all other vaccines with the AEFI of interest in all previous years to the same reporting week time point) (Figs 3 and 4).

A comparison of PRR and ChiSq calculated using single year data or using all previous years data demonstrated variable effect on the signal magnitude (Table 3). When using all-years data in the denominator compared to the single year data, the magnitude of PRR and ChiSq significance more than doubled for the 2010 signal of influenza vaccines and fever reactions but—while still above signal thresholds—almost halved for the 2015 signal of influenza vaccines and allergy AEFI.



*In 2009, for weeks with $PRR \geq 2$ and $ChiSq$ was < 4

Fig 3. PRR cumulative (all previous years) for influenza vaccines & fever, by year.

<https://doi.org/10.1371/journal.pone.0224702.g003>

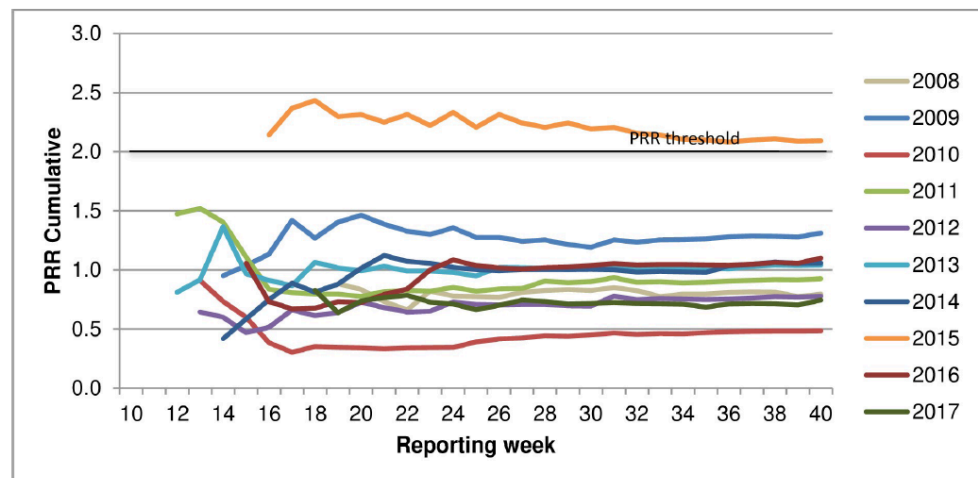


Fig 4. PRR cumulative (all previous years) for influenza vaccines & allergy, by year.

<https://doi.org/10.1371/journal.pone.0224702.g004>

Sensitivity and subgroup analyses

2010 fever signal. In 2010 a signal would reasonably have been indicated by at least week 13 (using single year data; likely earlier with cumulative all-years data), which equates to 28 March 2010. At this time point the PRR = 2.12 with ChiSq 5.32 (Fig 5). This was 15 days earlier than the alert raised through clinical observation (12 April) and 26 days before the child influenza program was suspended nationally (23 April) (Fig 6).

Sub-analysis comparing individual influenza vaccine brands with the other brands, for fever AEFI in 2010 shows that the proportional reporting of fever with Fluvax[®] was significantly higher than the other brands in use that year (Fig 7).

Sub-analysis by age group using single year data brought higher magnitude (PRR 5.74, ChiSq 15.88) and earlier detection (calendar week 12, March 21, 2010) in the 0–4 age group. However, case count threshold was not reached for PRR calculation in 2008 and 2009 and was delayed in the remaining years by between 3–8 weeks compared to analyses across all ages. In the 5 years and older age subgroup signal magnitude was increased (PRR = 3.28, ChiSq 13.22) but was delayed by 2 weeks till calendar week 15 (first week calculable). The increased magnitude was more pronounced using cumulative all previous year data PRR 8.72, ChiSq 24.15, however the 2 week delay remained.

2015 allergy signal. In 2015 the PRR was consistently >2 from onset of reporting, with ChiSq reaching >4 (8.2) in week 16 (PRR 3.51) which equates to April 19 2015. This was 11 days earlier than the alert raised through clinical observation (1 May) (Fig 8).

Sub-analysis by age group did not facilitate signal detection in 2015. Case count in the 0–4 year age subgroup reached threshold for calculation in only three of the 10 years under

Table 3. Comparison of results using single year data or all previous year data for 2010 and 2015 signal detection^a.

Reporting week ^a	2010 Febrile AEFI signal				2015 Allergy-related AEFI signal			
	Single year		All data		Single year		All data	
	PRR	ChiSq	PRR	ChiSq	PRR	ChiSq	PRR	ChiSq
1 st week	3.32	6.96	5.97	17.15	3.51	8.69	2.13	3.22
2 nd week	2.20	4.73	3.77	14.49	3.82	18.87	2.36	8.30
3 rd week	2.12	5.32	3.59	16.81	4.11	29.91	2.43	13.27
4 th week	2.24	8.80	4.09	29.68	3.79	33.32	2.29	15.17
5 th week	2.34	15.87	4.43	54.48	3.76	36.86	2.30	17.66
6 th week	2.92	52.31	5.53	158.18	3.57	34.30	2.25	16.65

^aData presented in consecutive weeks starting from commencement of reporting in that year.

(For 2010 this is calendar weeks 11–16 and in 2015 weeks 16–21)

<https://doi.org/10.1371/journal.pone.0224702.t003>

investigation (2010, 2012 and 2016) and not at all in the signal event year of 2015. Signal threshold was reached in 2015 for the 5 years and older age subgroup, but one week later and at a lower magnitude (PRR = 2.48) compared to analysis across all ages. Cumulative analysis using all previous year data did not reach signal detection thresholds in either age subgroup.

Sub-analysis comparing individual influenza vaccine brands with the other brands, for allergic AEFI in 2015 shows that the proportional reporting of allergic AEFI with Vaxigrip[®], Sanofi Pasteur and Influvac[®], Solvay Pharmaceuticals were significantly higher than for Fluvax[®] and Fluarix[®], GlaxoSmithKline that year (Fig 9).

Sub-analysis removing signal year data from the all previous years cumulative denominator when calculating PRR for subsequent years did not elicit any additional signal detections.

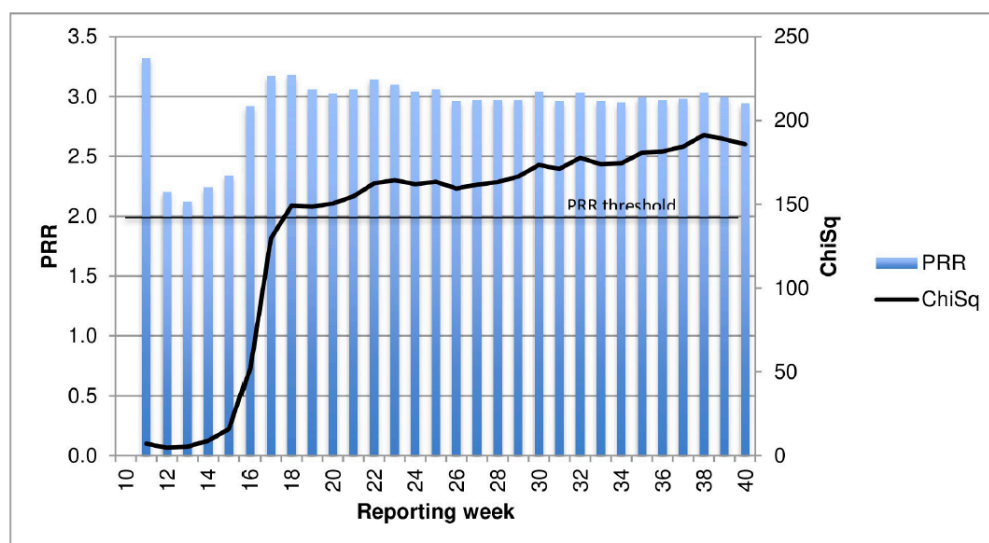


Fig 5. PRR cumulative and ChiSq for influenza vaccines and fever reactions by reporting week, 2010.

<https://doi.org/10.1371/journal.pone.0224702.g005>

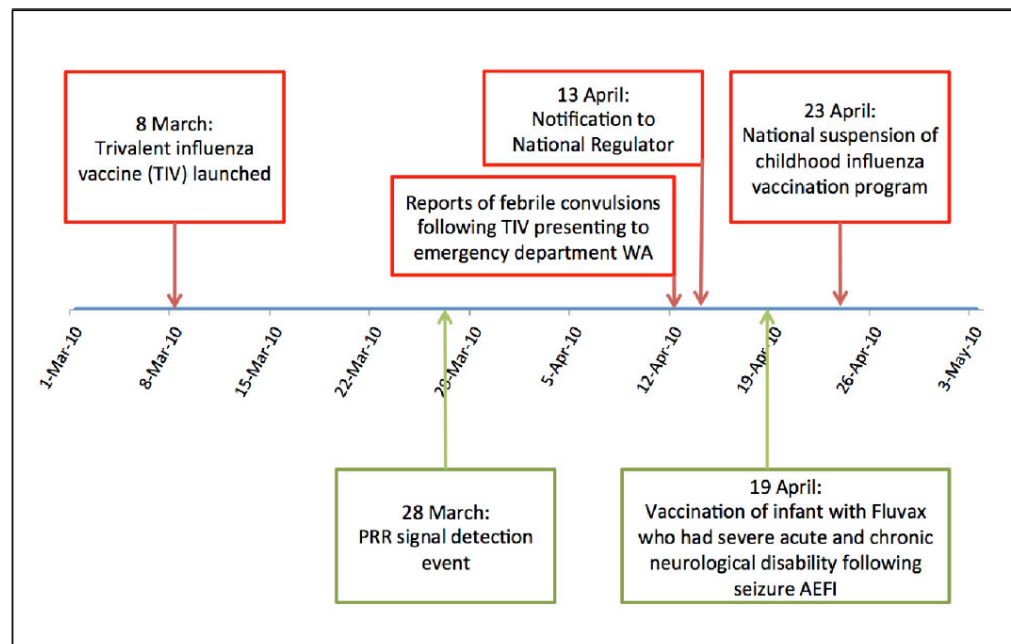
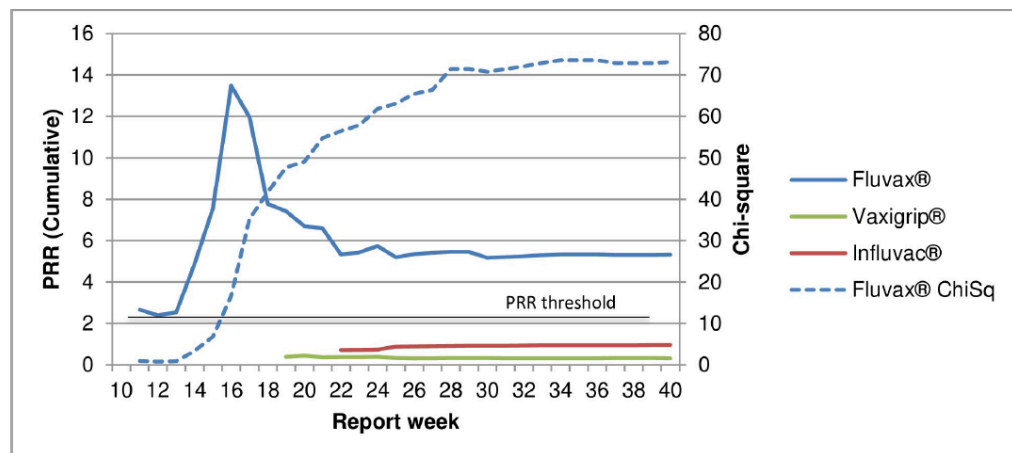


Fig 6. Timeline of 2010 influenza vaccine and fever AEFI signal detection.

<https://doi.org/10.1371/journal.pone.0224702.g006>



Fluarix® was not available in 2010

Fig 7. PRR by influenza brand to other influenza vaccines, fever AEFI, 2010.

<https://doi.org/10.1371/journal.pone.0224702.g007>

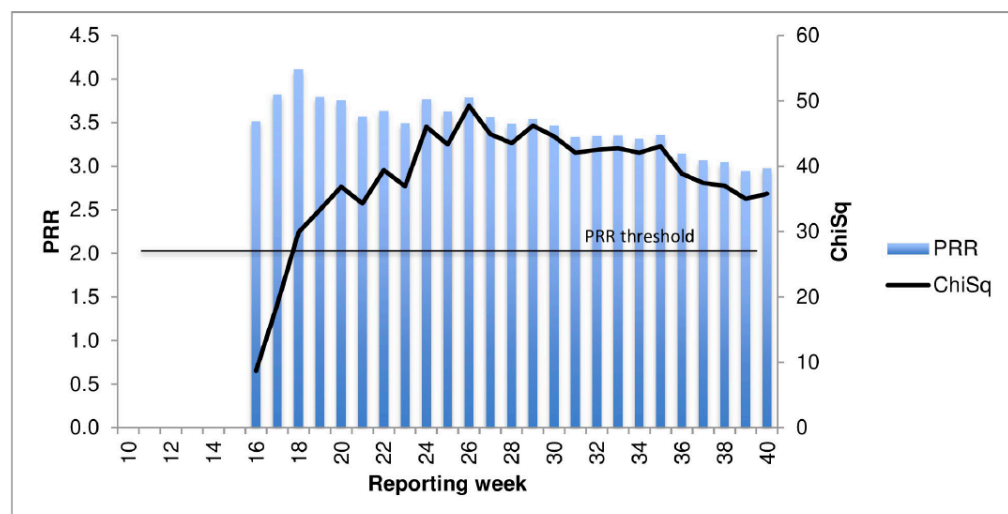


Fig 8. PRR cumulative and ChiSq for influenza vaccines and allergic reactions by reporting week, 2015.

<https://doi.org/10.1371/journal.pone.0224702.g008>

Signal hypothesis generation

This analysis intended to document the number of weeks in which PRR and ChiSq reached signal threshold levels of ≥ 2 and ≥ 4 respectively, and correlate the proportion that matched with known events (positive detection) as well as to indicate the proportion of weeks when an investigation could have been suggested (hypothesis generation). The data were calculated for each week and for each reporting year as single year data and as all previous years data. Signal thresholds, aside from the two known events, were reached only in the first two weeks (weeks 13 and 14) of seasonal surveillance in 2011.

The analysis for Influenza vaccines and fever AEFI was repeated for all subsequent years, excluding 2010 data, and did not produce any additional reporting weeks reaching $\text{PRR} \geq 2$.

Outcomes

- PRR identified the two known signals of influenza vaccines and fever / allergic reaction
- Statistical evidence hypothesised a signal 15 and 11 days earlier than actual alert dates respectively
- Cumulative data period influences signal magnitude depending on AEFI association to vaccine
- PRR sub-analysis by vaccine brand supports hypothesis of brand specific signals
- Using PRR generated one signal hypothesis requiring further investigation for signal validation

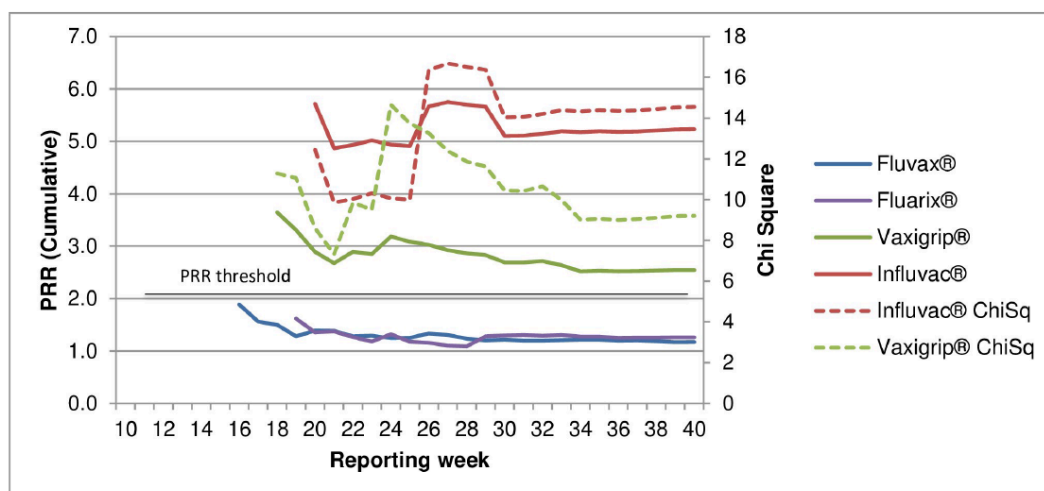


Fig 9. PRR by influenza vaccine brand to other brands, allergic AEFI, 2015.

<https://doi.org/10.1371/journal.pone.0224702.g009>

Discussion

This retrospective analysis demonstrated PRR as a feasible and applicable signal detection algorithm for two known influenza vaccine signal events. If cumulative PRR analysis had been in use at the time, we would have been able to identify the febrile signal in 2010 and allergy signal in 2015 much earlier than was possible by signal monitoring methods in place at those time points. Earlier signal detection and investigation implicitly enables earlier action if warranted, which in 2010 could have prevented many children receiving an unsafe vaccine. In 2015, it would have helped clarify the risk-benefit information and improve consumer confidence to continue with vaccination.

While the longevity of the SAEFVIC database with over a decade of data benefited cumulative calculations, a single year of data sufficed for effective signal detection. This is important for newly established datasets. It is also an important performance requirement if monitoring new vaccines (e.g. Zostavax[®] Merck vaccines), or new brands or formulations (e.g. Gardasil[®]9 Seqirus) or population subgroups (e.g. in pregnancy) as it may not be appropriate to include disparate historical AEFI reporting data in the comparator group.

There was discordant impact on efficiency of signal detection when using cumulative data from all previous years compared to data from a single year. In 2010 with fever AEFI the signal was magnified, but in 2015 with allergy AEFI the signal diminished. This may occur as fever is a common AEFI with many vaccines but allergy-related AEFI occur more frequently with influenza vaccines due to the multiple antigens and the manufacturing process being in eggs with small amounts of egg albumin retained in influenza vaccines [40]. The inclusion of higher numbers of allergy-related reports from previous years in the denominator therefore diminishes the signal.

Analysis by population or categorical subgroups (e.g. age, gender or geographic area) has potential to increase sensitivity for signal detection but may also mask signals [38]. Constraints can arise through small case numbers leading to a delay in reaching calculation threshold and consequently signal detection opportunities being equally delayed. However, jurisdictional funding in recent years as well as the July 2019 Pharmaceutical Benefits Advisory Committee recommendation for seasonal influenza vaccination of children aged 6 months to 5 years to

be included in the National Immunisation Program [41], is likely to boost numbers in this age group and therefore increase the utility and sensitivity of age subgroup analyses [42].

The population under surveillance is all vaccinees and when operating prospectively it will not be known in which age group a signal may arise in, therefore it is appropriate to analyse across the whole population routinely, as well as by subgroup [38].

This study hypothesises that Vaxigrip[®] and Influvax[®] vaccine brands flagged in the 2015 allergy-related signal event, which is in contrast to the findings in the previous investigation, which concluded there was no implication of a specific brand [6]. The previous analysis however, was limited to calculating brand-specific reporting rate per 100,000 doses distributed; the rates of which did not differ significantly between brands. Furthermore, as Influvac[®] was not a Department of Health funded vaccine in that year, dose distribution data were not available and so Influvac[®] could not be included in the brand-specific analyses in that study.

The paucity of spurious signals in our study should be interpreted with caution as this study was limited to a narrow scope of influenza vaccines and only two AEFI categories. Other studies indicate the norm is to find a substantial fraction of signals, albeit for which no external supporting evidence can be found, even when a highly inclusive search for such evidence is conducted [43]. Spurious signals are likely to be detected if PRR were applied to all vaccine-AEFI event pairs occurring in the database, which would be extensive. This study used calculation and signal threshold determinants with precedence from earlier studies [12, 38]. Further exploration of these arbitrary detection thresholds may be required as changes in the standard threshold for the count of drug-event combinations can result in a substantial variation in efficiency of the signal detection process. The European Medicines Agency found a threshold of five compared to a threshold of three (as we used) gave a reduction of 25% in false positive signals in return for a loss of 12% in true signals detected early [39].

Strengths for this proof-of-principle study were the decade of data available and presence of two confirmed signal events of differing magnitude contained within. Limitations included the small number of case-event pairs, particularly in non-signal years; testing on only two signals, both involving the same vaccine group (influenza vaccines) and; the absence of documented false signals within the dataset and non-generation of spurious signals meaning an inability to examine the algorithm performance with false-positive signals. The potential for prospective analyses to inform signal detection must also be viewed commensurate with known limitations of passive surveillance systems: namely under-reporting—particularly of reactions perceived as mild—and the time lag from symptom onset to report submission. However, it is worth noting that in this study, simulating reality as data were extracted according to date reported, the safety signal was still generated well ahead of the historical clinical recognition.

To mature signal hypothesis generation, we plan to integrate PRR as a routine prospective signal detection platform with automated calculations updated weekly providing an “alert” table presenting any vaccine-event pairs reaching the pre-defined threshold and statistical significance levels for epidemiological review. This will provide signal hypothesis generation as a first step in comprehensive signal management process. Even though this will be performed on the SAEFVIC Victorian state-level data it has relevance for Australian vaccine safety nationally as SAEFVIC contributes approximately 45 per cent of all AEFI reporting to the national AEFI database [44].

Further studies to incorporate and compare performance characteristics with Bayesian algorithms and multivariate modeling techniques are required [9, 45], however the final choice of SDA should be made in the context of meeting the Innovative Medicines Initiative PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) project recommendation that “Choice of a disproportionality statistic for signal detection should be primarily based on ease of implementation, interpretation and optimisation of resources” [15].

Conclusion

The PRR algorithm is relatively easy to implement and analyse. Utilising a single jurisdiction's data, PRR identified a loud (febrile) and a quieter (allergy) signal in the SAEFVIC data set. There is no reason to think it would not be as successful prospectively as it has been shown to be retrospectively. We believe the PRR should be routine in SAEFVIC and in any national adverse event surveillance system that evolves.

The implementation of signal detection algorithms in routine Australian vaccine pharmacovigilance has the potential to detect important safety signals much earlier than previously, keeping immunisations in Australia as safe as possible and helping maintain community and provider confidence.

Supporting information

S1 Table. AEFI reports by Influenza vaccine brand and year reported, 2008–2017, SAEFVIC.
(DOCX)

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Author Contributions

Conceptualization: Hazel J. Clothier, Heath Kelly, Jim P. Buttery.

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Writing – original draft: Hazel J. Clothier.

Writing – review & editing: Hazel J. Clothier, Jock Lawrie, Melissa A. Russell, Heath Kelly, Jim P. Buttery.

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Chapter 8: SAEFVIC maturation

8.1 Chapter introduction

Surveillance is defined as “information for action”: therefore, while reporting on outcomes of research studies remains the foundation of scientific publications, it is equally important to inform on the outputs of routine surveillance(253).

This Chapter provides a descriptive epidemiological overview of SAEFVIC surveillance and data outputs at the conclusion of this PhD, presented as a publication summarising SAEFVIC in 2018. This publication expands on the surveillance report of 2012—documenting the early years of SAEFVIC and presented in *Chapter 4: SAEFVIC early years*(179).

This publication provides evidence of the incorporation of the findings from this PhD into the routine practices of SAEFVIC surveillance and overall maturation of the system. Notable elements are SAEFVICs capacity to report on routine signal monitoring and signal detection, which led to SAEFVIC stimulation of the national regulators to initiate investigations into issues of vaccine safety. The report describes investigation of a signal event of increased reporting of serious neurological adverse events (SANE), which was concluded to be an aberration arising from increased administration of influenza vaccines and clearly establishes the benefit of integrating the PRR method explored in *Chapter 7: Signal detection* into routine surveillance practices(231).

While reviewing the educational arm of SAEFVIC was not a component of this PhD, the improved capability of SAEFVIC surveillance to inform on vaccine safety issues has directed the development of educational resources and facilitated the desired outcome of “information for action”. Together these actions support consumer confidence and overall improvement to vaccine pharmacovigilance in Victoria and Australia.

This study affirms that SAEFVIC has been strengthened to achieve its stated objectives, is informing on vaccine pharmacovigilance effectively and that national expansion is progressing.

8.2 Research aim

To provide a descriptive epidemiological overview of SAEFVIC surveillance and data at the conclusion of this PhD and demonstrate maturation of routine surveillance processes in Victoria.

8.2.1 Publication: SAEFVIC in 2018

Clothier *et al.* SAEFVIC: Surveillance of adverse events following immunisation (AEFI) in Victoria, 2018. *Communicable Disease Intelligence* 2020;44(1-27)

Annual report

SAEFVIC: Surveillance of adverse events following immunisation (AEFI) in Victoria, Australia, 2018

Hazel J Clothier, Jock Lawrie, Georgina Lewis, Melissa Russell, Nigel W Crawford and Jim P Buttery

Abstract

Background

SAEFVIC is the Victorian surveillance system for adverse events following immunisation (AEFI). It enhances passive surveillance by also providing clinical support and education to vaccinees and immunisation providers.

This report summarises surveillance, clinical and vaccine pharmacovigilance activities of SAEFVIC in 2018.

Methods

A retrospective observational cohort study of AEFI reports received by SAEFVIC in 2018, compared with previous years since 2008. Data were categorised by vaccinee demographics of age, sex, pregnancy and Indigenous status, vaccines administered and AEFI reactions reported. Age cohorts were defined as infant (0–12 months); young child (1–4 years); school-aged (5–17 years); adult (18–64 years); and older person (65+ years). Proportional reporting ratios were calculated for signal investigation of serious adverse neurological events with all vaccines and with influenza vaccines. Clinical support services and educational activities are described.

Results

SAEFVIC received 1730 AEFI reports (26.8 per 100,000 population), with 9.3% considered serious. Nineteen percent ($n = 329$) attended clinical review. Annual AEFI reporting trends increased for infants, children and older persons, but were stable for school-aged and adult cohorts. Females comprised 55% of all reports and over 80% of reports among adults. There were 17 reports of AEFI in pregnant women and 12 (0.7%) in persons identifying as Indigenous Australians. A possible signal regarding serious adverse neurological events (SANE) was detected, but was not supported by signal validation testing. A clinical investigation is ongoing. Two deaths were reported coincident to immunisation with no evidence of causal association.

Conclusion

SAEFVIC continues to provide robust AEFI surveillance supporting vaccine safety monitoring in Victoria and Australia, with new signal detection and validation methodologies strengthening capabilities.

Keywords: Vaccine safety, adverse events, immunisation, surveillance, pharmacovigilance

Introduction

Surveillance of Adverse Events Following Vaccination In the Community (SAEFVIC) is a public health partnership initiative of the Victorian Immunisation Program funded by the Victorian Government Department of Health and Human Services. AEFI surveillance is an essential component of post-licensure vaccine safety monitoring and aims to detect rare, late onset or unexpected safety signal events. SAEFVIC has been in operation since May 2007. It comprises a central reporting enhanced passive surveillance system integrated with clinical services and is focused on adverse events following immunisation (AEFI) identification for the state of Victoria.¹

Innovative aspects of SAEFVIC include integration of surveillance with jurisdictional clinical services, enabling timely comprehensive follow-up of individual cases including enriching case information with subsequent clinical reviews. This model has also been associated with an increase in reporting rates.² Responsive education on immunisation for healthcare professionals, parents and the public is provided through the Melbourne Vaccine Education Centre (MVEC) online initiative.³

This is the first report describing SAEFVIC data and service delivery since 2012, and the first report following the system evaluation conducted in 2015.^{2,4} It provides important baseline background as the SAEFVIC model expands through uptake by other jurisdictions and leading towards a harmonised national AEFI surveillance platform across Australia. The AEFI data received by SAEFVIC are reported to the Therapeutic Goods Administration (TGA) and entered into their searchable database of adverse event notifications (DAEN). National reports of AEFI using these collated data are prepared by the National Centre for Immunisation Research and Surveillance (NCIRS) and published annually.⁵

SAEFVIC undertakes quarterly reporting to the Immunisation Advisory Committee of the Victorian Government Department of Health and Human Services and is the home of the Australian Adverse Events Following Immunisation Clinical Assessment Network, AEFI-CAN. This report collates and summarises SAEFVIC surveillance activity from 1 January to 31 December 2018 and provides, with comparisons to previous years where relevant: 1) descriptive analyses of AEFI reports for vaccines administered in Victoria; 2) an analysis of serious AEFI; 3) a summary of signal detection and investigation activities; and 4) an outline of the continuing development of educational and clinical services provided by SAEFVIC.

Methods

This retrospective observational cohort study describes AEFI reported to SAEFVIC, Victoria, Australia from 1 January to 31 December 2018 and provides comparisons to AEFI reported in the preceding decade, 2008–2017. Data presented in this report may differ from other reports for the same period as records are continually updated and may be re-categorised following clinical review or for specific analyses.

AEFI data source

Reports are entered into SAEFVIC for any AEFI reported in Victoria (reporter with Victoria postcode) for vaccine administered anywhere (including overseas) regardless of causality assessment, providing the AEFI occurred after vaccination. Reports may include immunisation errors that do not result in a reaction or historical events reported for investigation due to concern for future vaccinations.

SAEFVIC is an integrated AEFI reporting system, including passive reports voluntarily received from immunisation providers (medical practitioners, nurses and pharmacists) and from consumers (vaccinees or their guardians). Since 2016, SAEFVIC has additionally recorded and integrated reports submitted from active surveillance where the event has resulted in a

medical attendance. Active surveillance means reports have been solicited through either a search of records or a prompted response, and in Victoria are obtained through two systems: 1) the Paediatric Active Enhanced Disease Surveillance (PAEDS) hospital sentinel system,⁶ which seeks admission information for selected serious childhood conditions, particularly vaccine preventable diseases and potential AEFI; and 2) the AusVaxSafety network, which uses SMS prompts to elicit information on AEFI from vaccinees within 7 days of immunisation.⁷ All reports encountered through PAEDS with a relevant vaccination history are entered into the SAEFVIC database. However, of those reports encountered through AusVaxSafety, only those that are identified as being AEFIs temporally associated with vaccines, resulting in a medical attendance, are entered and it requires the general practitioner (GP) or practice to consent to forwarding the events to the Victorian vaccine safety team at SAEFVIC.

Definitions

An Adverse Event Following Immunisation (AEFI) is defined as any untoward medical occurrence that follows immunisation but does not necessarily have a causal relationship with the administration of the vaccine. The adverse event may be a sign, symptom or defined illness. This represents a temporal association and does not necessarily have a causal relationship with the vaccine.

AEFI reactions are recorded as signs and symptoms described by the reporter using general medical terminology. Reactions may be further categorised according to standard case definitions, where available and as determined by the Brighton Collaboration, Australian Immunisation handbook or SAEFVIC in hierarchical order as previously described.¹ A case may report more than one AEFI reaction.

An AEFI is determined as serious (SAEFI) if the report indicates a reaction that: resulted in death; was life threatening; required in-patient hospitalization or prolongation of an existing

hospitalization; resulted in persistent or significant disability/incapacity; caused a congenital anomaly/birth defect; or was deemed medically important by SAEFVIC clinicians.⁵ A life-threatening event is an event or reaction in which the vaccinee was at risk of death at the time of the event/reaction; it does not refer to an event/reaction that hypothetically might have caused death if it were more severe (e.g. anaphylaxis).

Shoulder injury related to vaccine administration (SIRVA) is a term used to describe a syndrome of pain, inflammation and restricted movement that can arise when the position of the needle is too high causing injury.⁶

Serious adverse neurological events (SANE) include transverse myelitis, optic neuritis, multiple sclerosis and Guillain-Barré syndrome (GBS).

A signal is defined as an increase in AEFI reporting above that which is expected and may be an arbitrary determination through clinical perception or breaching a statistical calculation threshold (see below for proportional reporting ratio calculation and thresholds).

Data categories

Reporter type is recorded by the vaccine administering profession or consumer: the category of consumer includes reports submitted by the vaccinee or their parent or guardian.

Vaccines administered are recorded by brand name but were grouped by antigen for the purpose of analysis. A case may receive multiple vaccines in one encounter, therefore any AEFI reaction described is recorded in association with each vaccine administered at that encounter.

Age groups were determined as best fit to the National Immunisation Program (NIP) age groups of infant 0–12 months, young child 1–4 years, school-aged 5–17 years, adult 18–64 years and older person 65+ years.⁸

Analyses

Data were extracted and analysed using Microsoft Power BI (version 2.71.55523.941, July 2019).⁹ Reports were analysed as counts, proportions of reports received and proportions by age-group and vaccinee demographics.

Reports per 100,000 population were calculated using Victorian mid-year population estimates obtained from the Australian Bureau of Statistics (ABS); specifically the 2018 mid-year estimates *Regional Population Growth*ⁱ and mid-year projections for 2018 by age and sex, Victoria.¹⁰

The long-term average for serious AEFI reporting was calculated as the proportion of serious AEFI reported using the sum data from the preceding decade (2008–2017).

Reporting rates per 100,000 doses administered were calculated using Australian Immunisation Register (AIR) recorded administered doses for each age group in 2018, collated by vaccine brand as at the date of extraction (24 July 2019).

Signal investigation methods included comparison of reporting frequency trends and calculation of proportional reporting ratio (PRR). PRR is calculated for vaccine-reaction pairs using a 2×2 table convention where $PRR = \frac{\text{Observed}}{\text{Expected}}$. Thresholds were defined as $PRR \geq 2$ and chi-squared (χ^2) ≥ 4 .

Ethical approval

Approval was granted by the Royal Children's Hospital Human Research Ethics Committee for this registered database (Number 37194).

Results

Reports received

SAEFVIC received a total of 1730 AEFI reports during 2018 (Box 1).

The 1,730 AEFI reports to SAEFVIC submitted during 2018 was a slight decrease on the 1,802 received in 2017 but was still higher than any other previous year (Figure 1). This equates to a reporting rate of 26.8 per 100,000 population per annum. The proportion of reports meeting the definition of serious AEFI was 9.3%, which was less than the long-term average, across the preceding decade, of 12.4% ($p = 0.008$). Despite fluctuating overall reporting, the annual proportion of serious AEFI has decreased across the last three years, from a peak of 13.6% in 2015.

Serious AEFI

Of the 1730 reports, 9.3% ($n = 161$) met the definition of serious, of which 48 (29.8%) had been admitted to hospital and a further 100 (62.1%) attended an emergency department without admission. The majority of serious AEFI were reported in infants (31.7%; 51/161) and children (34.6%; 55/161). As a proportion of the AEFI within each age group, infants had the highest frequency of a serious AEFI being reported (14.8%; 51/344) (Table 1).

Two deaths temporally associated with vaccine administration were reported: an older Australian administered influenza vaccine in the general practice setting was reported deceased later the same day with cause of death attributed to a history of cardiac disease; and the death of an infant from neurological sequelae secondary to disseminated infection was noted to have received routine vaccines 2 weeks prior. These deaths showed no evidence of causal association.

Reporting modality

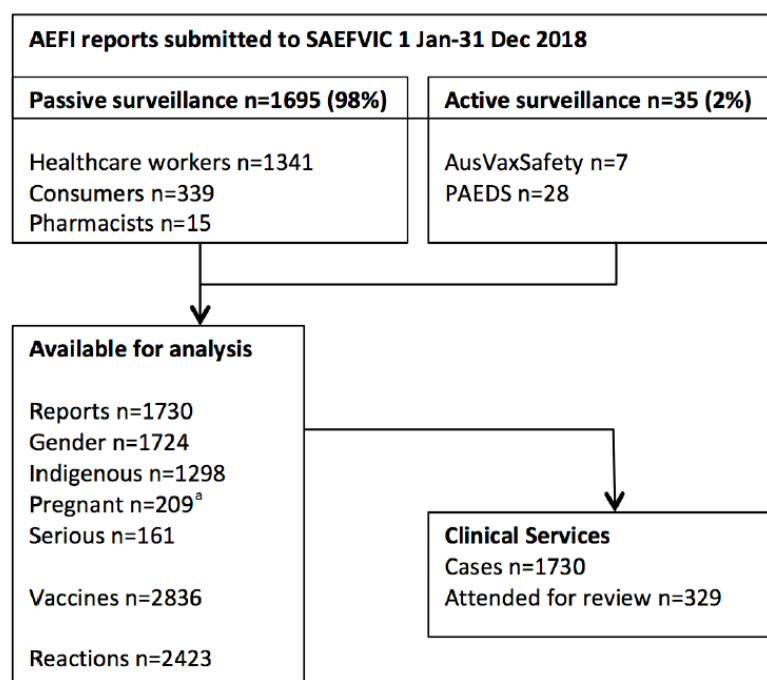
Online reporting continues to be the favoured modality of report submission, stabilising at just over half of reports received (53.4%), followed by telephone (22.5%) and fax reporting (23.0%) (Figure 2).

Reporter type

Reports were submitted predominantly by health/immunisation providers (doctors 23.6%,

i <https://www.abs.gov.au/Population>

Box 1: Flow diagram of reports available for analysis, SAEFVIC 2018



a Pregnancy is positively reported for adult females (i.e. +ve or blank)

nurses 49.7%), with consumers (either the vaccinee or the parent or guardian) contributing approximately one-fifth of reports (20.0%). The proportion of consumer reporting has remained consistent across the last three years.¹¹ Fifteen reports (0.9%) related to vaccines administered by a pharmacist (which compares with 11 in 2017 and 3 in 2016, the year pharmacist administration commenced) (Figure 3).

Active surveillance [PAEDS & AusVaxSafety]

The proportion of reports from active surveillance remained low at 2.0% (35/1730) and related to a broad range of vaccines administered. Just over half of active surveillance reports (18/35; 51.4%) were for serious AEFI, which is consistent with PAEDS being hospital-based surveillance and the selective entering of only those active surveillance cases requiring follow-up reported through AusVaxSafety.

Age and sex distribution

The young child age group (1–4 years) formed the largest proportion of AEFI reports (Figure 4), consistent with reporting across all previous years (Figure 4). While the trend for increased reporting was observed across all age groups, it was more pronounced in young children and older persons. The increased reporting in older persons aligns with initiation of the Zoster vaccine program commencement in November 2016. Reporting for school-aged children increased in 2013 commensurate with expansion of the HPV program from girls only to both sexes, but has since remained stable across the last three years (Figures 5).

Figure 1: AEFI reports and reports per 100,000 population, by year, SAEFVIC, Victoria, 2008–2018

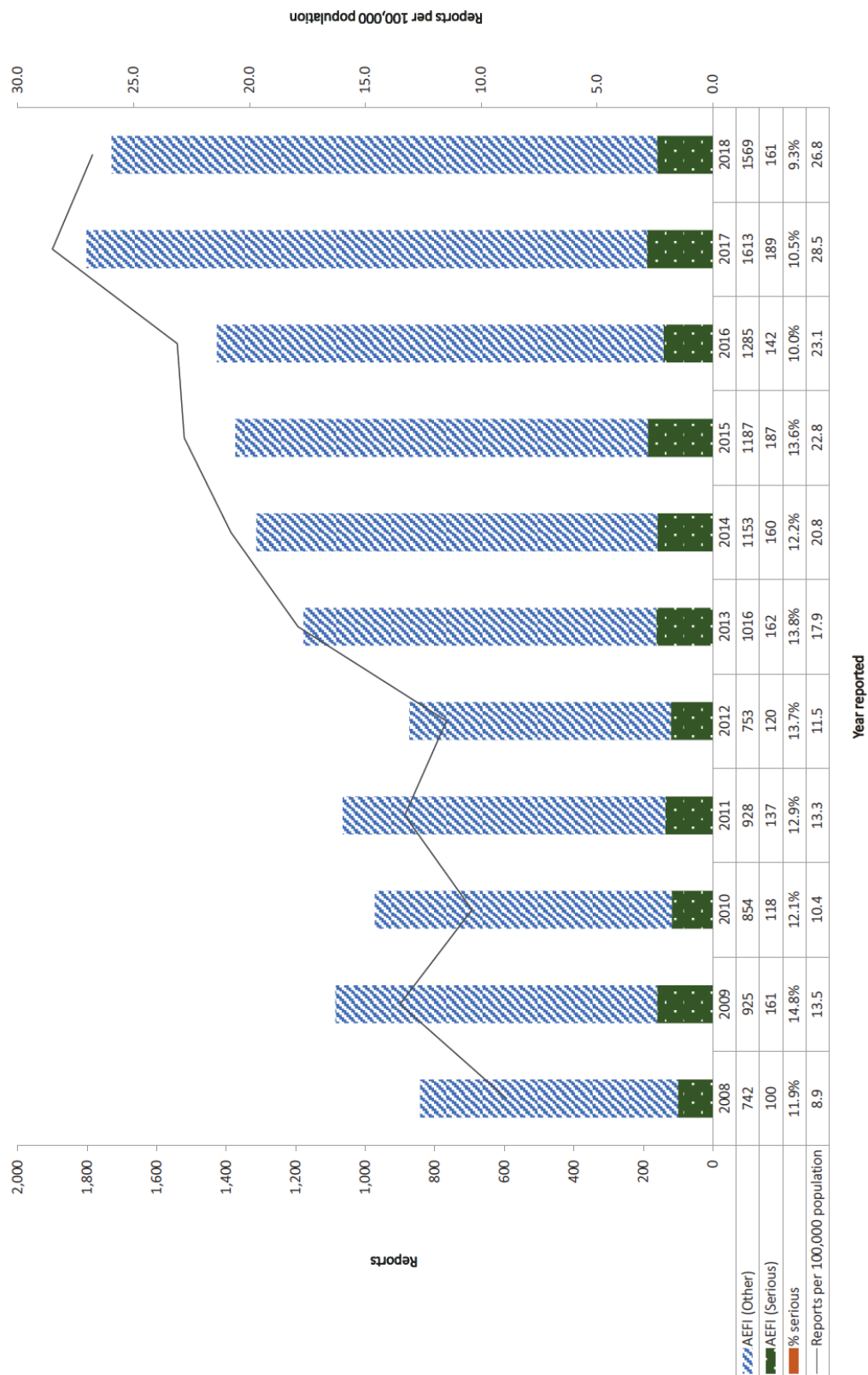


Figure 2: Proportion of AEFI reporting modality, by year, SAEFVIC, Victoria 2008–2018

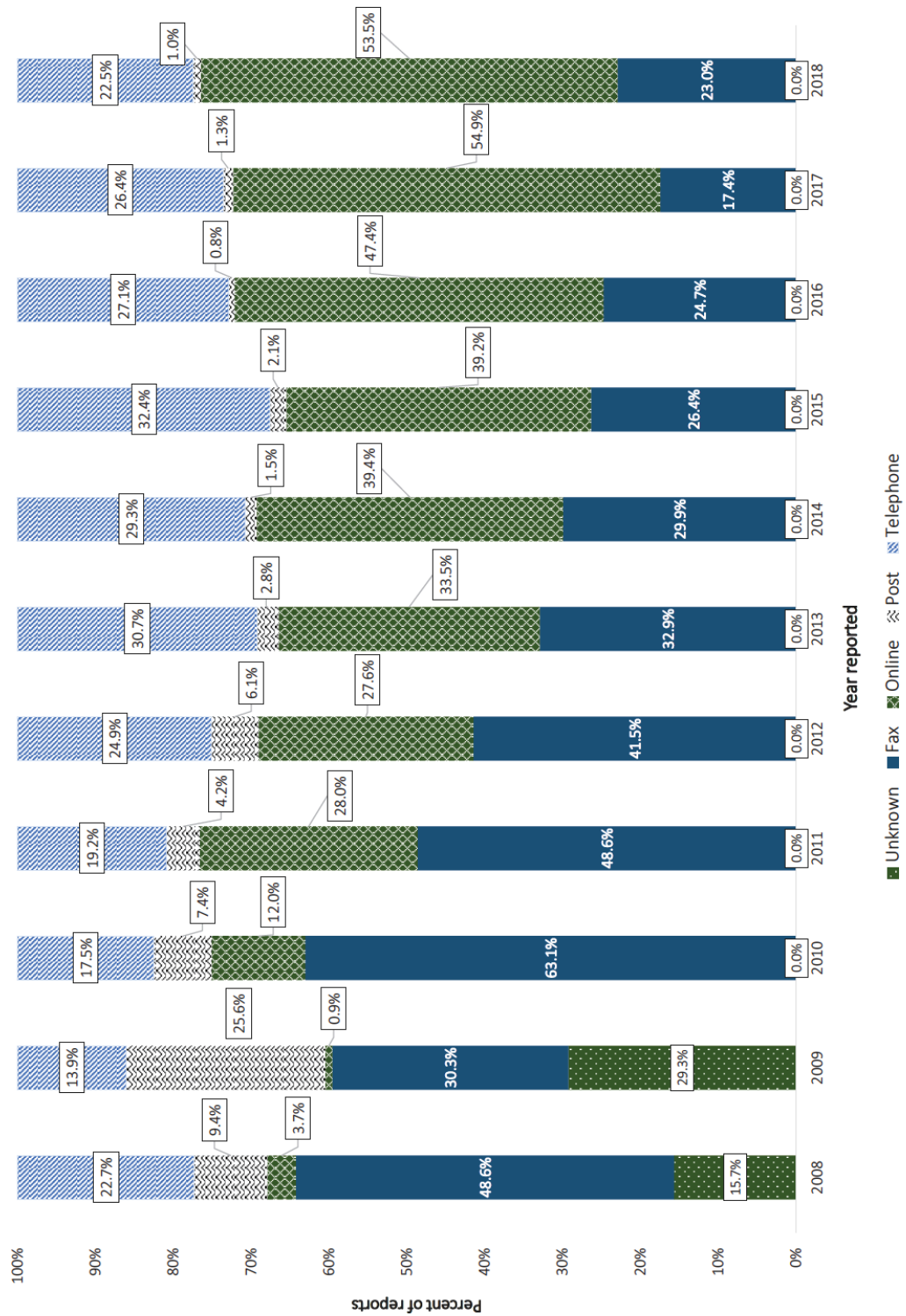


Figure 3: Proportion of AEFI reports by reporter type, by year, SAEFVIC, Victoria 2008–2018

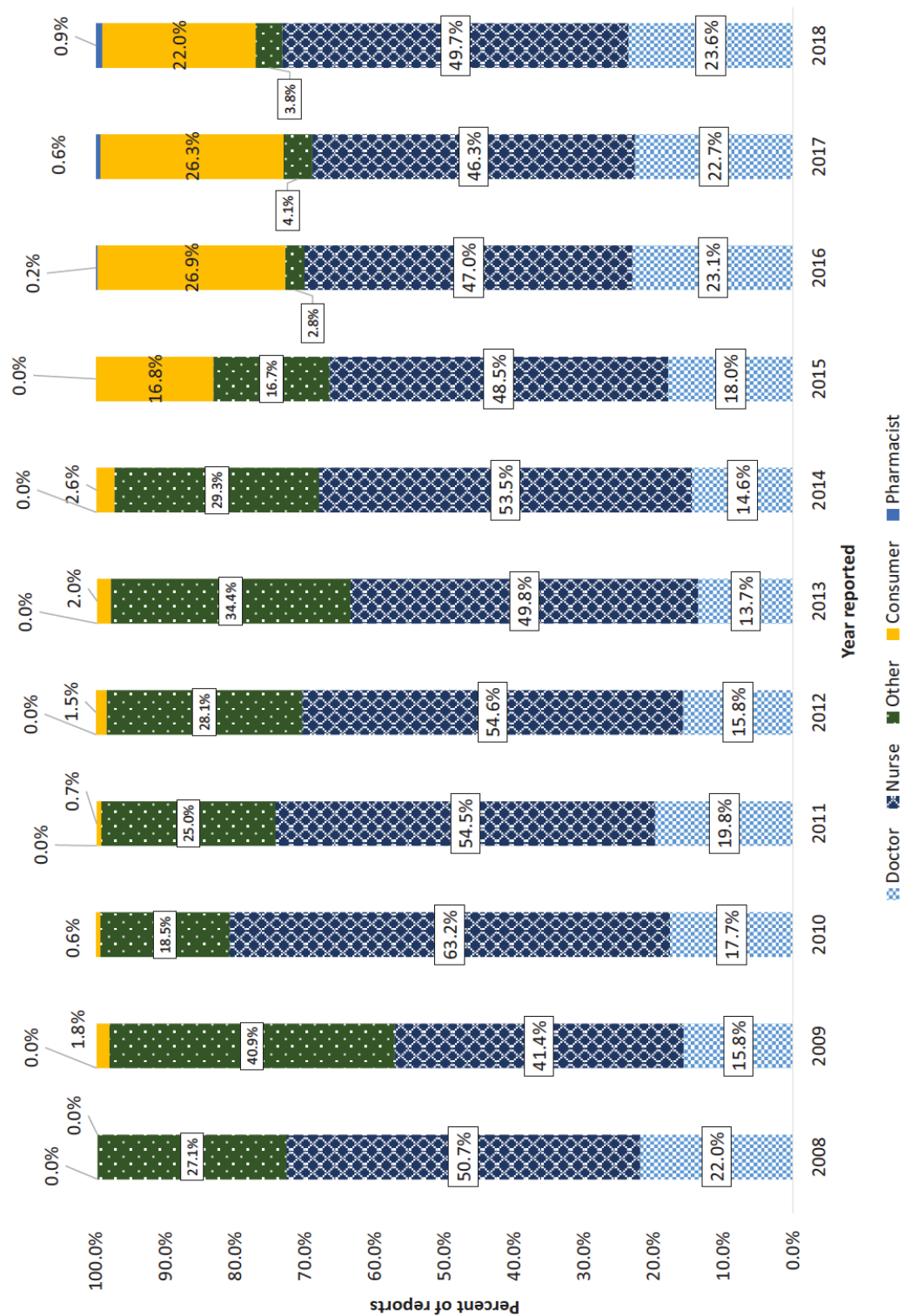
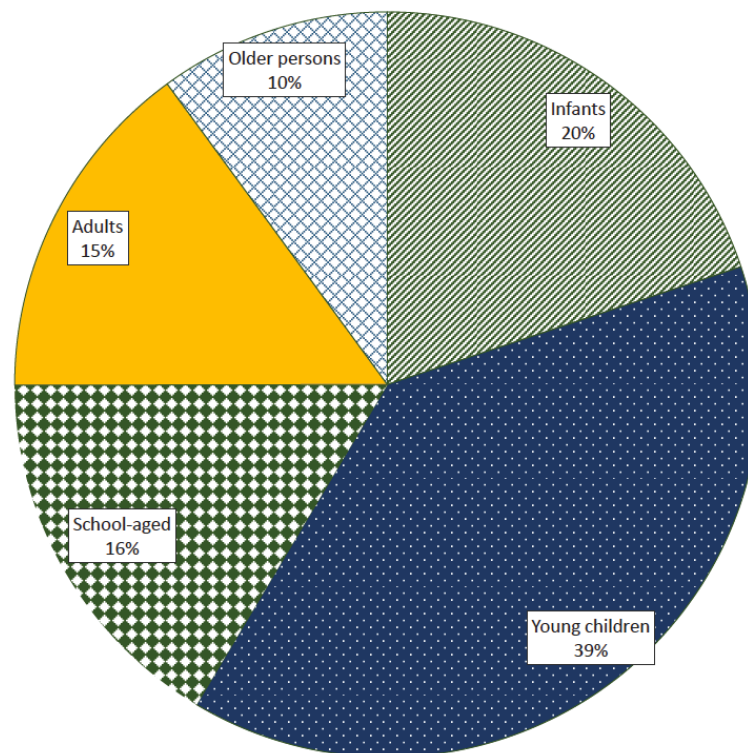


Figure 4: Proportion of AEFI reports received, by age group, SAEFVIC, Victoria, 2018



Overall just over half of all reports were for females (55.0%), however this varied by age group. In the infant and young child age groups, reporting was mostly even between the sexes (Table 1). However, females accounted for 81.0% of AEFI reports in adults (18–64 years) and for 66.1% of reports for older persons (65+ years).

At-risk populations

Routine capture of subgroup demographics e.g pregnancy and Aboriginal and/or Torres Strait Islander (Indigenous Australians) status commenced in 2016. In 2018, Indigenous status was reported for 75% of reports, with 0.7% being from persons identifying as Indigenous Australians. This proportion is similar to the Victorian Aboriginal and/or Torres Strait Islander population estimate of 0.8% (2016 census data).¹⁰

Seventeen reports were for AEFI during pregnancy, which was 8.1% (17/209) of reports received for adult females (aged 18–64).

Vaccines

A total of 2,836 vaccines were administered to the 1,730 persons reporting an AEFI, a median of two per vaccination encounter. The young child vaccines, DTP and MMR/MMRV, were the most frequently reported (Figure 6, Table 2).

Figure 5: AEFI reports received by age group and year reported, SAEFVIC, Victoria 2008–2018

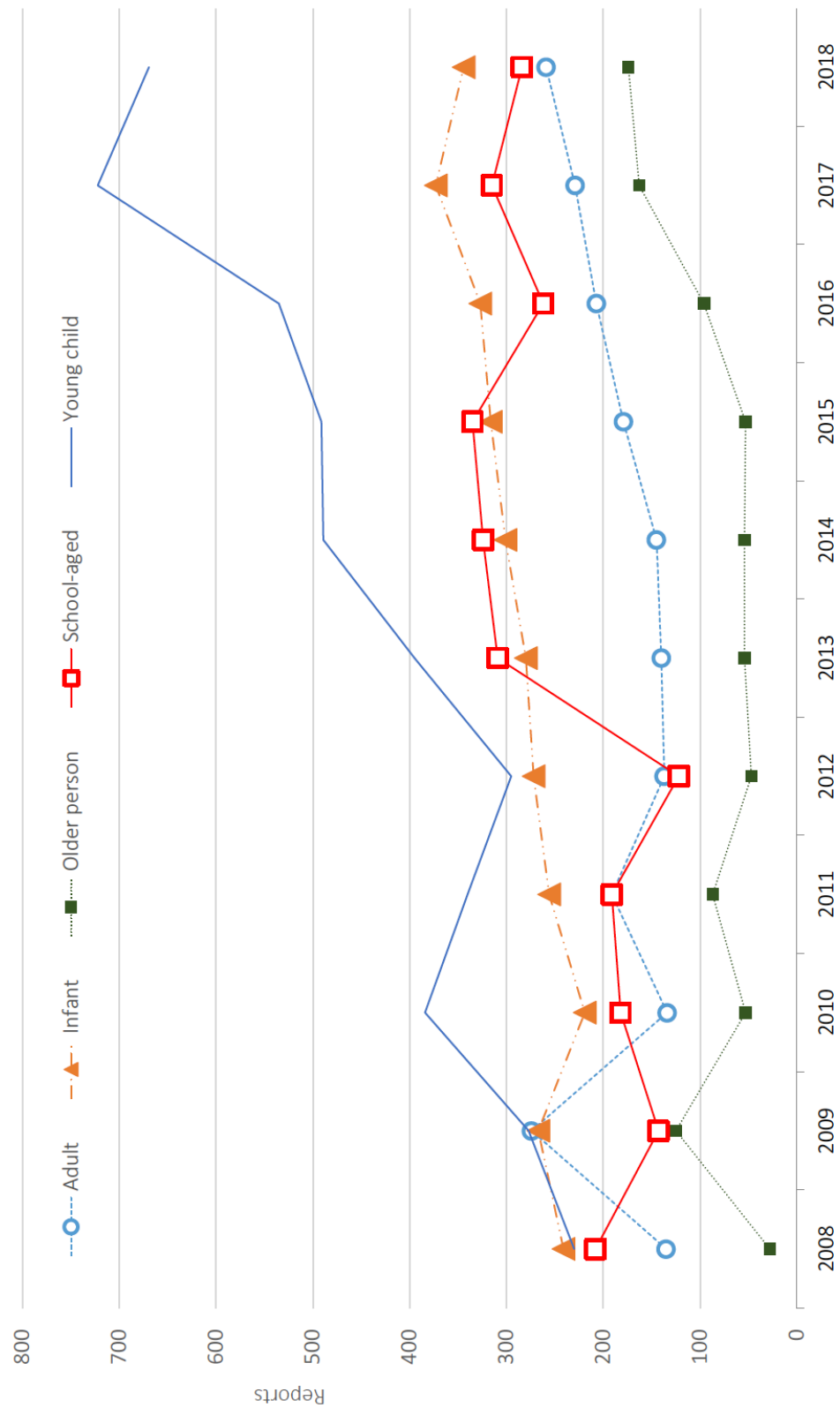


Table 1: AEFI reports by 'serious' category, age group, and sex,^a SAEFVIC, Victoria, 2018

	AEFI reports								
Age group (years)	Total				Male		Female		
		Per 100,000 population	Serious AEFI n	Serious AEFI %	Cases	Per 100,000 population	Cases	Per 100,000 population	
<1	344	408.8	51	14.8%	173	400.4	169	412.8	0.97
1-4	669	203.5	55	8.2%	360	213.0	308	192.9	1.10
5-17	284	28.4	19	6.7%	136	26.5	146	30.1	0.88
18-64	259	6.4	21	8.1%	49	2.4	209	10.2	0.24
65+	174	17.6	13	7.5%	59	12.9	115	21.7	0.59
Total	1,730	26.8	161	9.3%	777	24.3	947	29.0	0.84

^a Sex was not recorded for 6 cases

Table 2: AEFI reports by NIP schedule and vaccine, Victoria, 2018

National Immunisation Schedule (NIP) vaccines			
Age group	Vaccine antigen	Reports (n)	Reports per 100,000 doses administered
Infant <12 months (n = 344)	Hepatitis B (birth)	3	80.0
	DTP IPV Hib Hep B	245	123.5
	Pneumococcal	228	141.2
	Rotavirus ^a	210	176.7
	Influenza	38	120.2
	Meningococcal B	25	176.3
Young child 1–4 years (n = 669)	Measles Mumps Rubella +/- Varicella (MMR or MMRV)	305	188.6
	Pneumococcal ^b	68	218.7
	Meningococcal	110	131.4
	DTP	370	–
	Influenza	94	–
	Meningococcal B	48	–
	TB	18	–
School-aged 5–17 years (n = 284)	HPV	125	–
	Influenza	65	–
	DTP	84	–
	Meningococcal	34	–
Adult 18–64 years (n = 259)	DTP ^c	38	–
	Pneumococcal ^d	11	–
	Influenza ^e	154	–
Older person 65+ yrs (n = 174)	Pneumococcal	55	–
	Shingles	44	–
	Influenza	80	–

a Rotavirus vaccine used is Rotarix, with a 2-dose schedule (2 and 4 months), with last dose recommended by 24 weeks of age

b 12-month routine dose commenced 1 July 2018

c Pregnant women

d Indigenous Australian or medically at risk

e Not in NIP but recommended for at risk/healthcare workers.

Table 3: AEFI reactions reported (>20 reports & selected conditions in italics) by age group, SAEFVIC, 2018^{a,b}

Reaction reported	Infant	% of Infant reports	Child	% of Child reports	School-aged	% of School-aged reports	Adult	% of Adult reports	Older person	% of Older person reports	Total reactions	% of Total reactions
Injection site reaction (minor)	21	4%	168	20%	45	11%	43	10%	45	17%	322	13.3%
Rash	68	14%	112	13%	41	10%	16	4%	10	4%	247	10.2%
Drug errors	44	9%	83	10%	34	9%	27	6%	27	10%	215	8.9%
Injection site reaction (severe)	7	1%	128	15%	23	6%	18	4%	18	7%	194	8.0%
vomiting	34	7%	39	5%	13	3%	16	4%	6	2%	108	4.5%
Fever (unspecified)	18	4%	34	4%	11	3%	13	3%	18	7%	94	3.9%
Fever (> 38; < 40)	25	5%	49	6%	9	2%	3	1%	1	0%	87	3.6%
Urticaria/hives	22	5%	31	4%	13	3%	14	3%	4	1%	84	3.5%
Pain in limb	5	1%	2	0%	22	6%	23	5%	18	7%	70	2.9%
Lethargy	4	1%	13	2%	15	4%	19	4%	17	6%	68	2.8%
Diarrhoea	34	7%	16	2%	5	1%	4	1%	5	2%	64	2.6%
Vasovagal episode	0	0%	14	2%	43	11%	6	1%	0	0%	62	2.6%
Irritable	41	9%	18	2%	1	0%	1	0%	0	0%	61	2.5%
Nausea	1	0%	3	0%	17	4%	19	4%	14	5%	54	2.2%
Headache	2	0%	1	0%	14	4%	12	3%	9	3%	38	1.6%
Angioedema	6	1%	6	1%	4	1%	14	3%	5	2%	35	1.4%
Respiratory symptoms	5	1%	8	1%	1	0%	14	3%	7	3%	35	1.4%
HHE	31	7%	3	0%	0	0%	0	0%	0	0%	34	1.4%
Dizziness	1	0%	1	0%	11	3%	15	3%	5	2%	33	1.4%
Paraesthesia	0	0%	2	0%	4	1%	17	4%	6	2%	29	1.2%
Myalgia	3	1%	0	0%	5	1%	9	2%	7	3%	24	1.0%
Fever (>40)	2	0%	19	2%	1	0%	0	0%	0	0%	22	0.9%

Reaction reported	Infant	% of Infant reports	Child	% of Child reports	School-aged	% of School-aged reports	Adult	% of Adult reports	Older person	% of Older person reports	Total reactions	% of Total reactions
Influenza-like-illness	1	0%	1	0%	2	1%	12	3%	6	2%	22	0.9%
Pallor	8	2%	1	0%	3	1%	1	0%	0	0%	21	0.9%
Anaphylaxis	2	0%	4	0%	2	1%	7	2%	1	0%	16	0.7%
GBS	0	0%	3	0%	1	0%	1	0%	1	0%	6	0.2%
Optic neuritis	0	0%	0	0%	3	1%	0	0%	0	0%	3	0.1%
Transverse myelitis	1	0%	0	0%	0	0%	2	0%	0	0%	3	0.1%
Total reactions	472		837		399		445		270		2,423	
% of all reactions	19.5%		34.5%		16.5%		18.4%		11.1%			

a The above table presents counts and percentages of reactions reported; a person may report more than one reaction.

b Highlighted values indicate reactions with higher reporting in a particular age-group variation.

c Hypotonic-hyporesponsive episode; definition is restricted to children aged < 2years.

Figure 6: Frequency of reports by vaccine group and age group, 2018

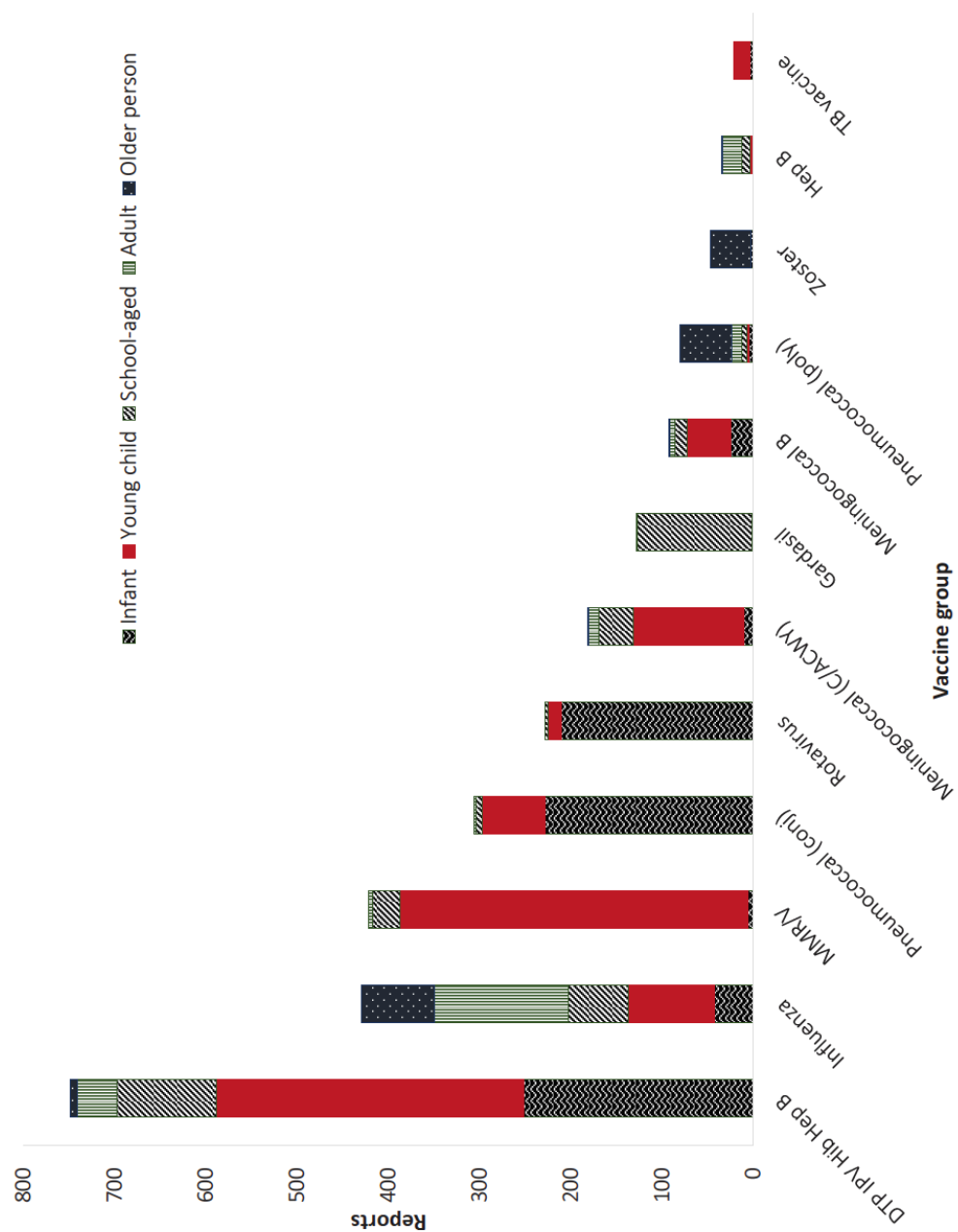


Table 4: Summary of reported immunisation errors and implicated vaccines, SAEFVIC, 2018

Immunisation error description	Reports	Commonly implicated vaccines
Vaccine administered outside of prescribed age range	68	Seasonal influenza vaccines (75.0%, 51/68) Rotavirus vaccines (17.6%, 12/68)
Incorrect vaccine administered	63	12 and 18 month routine vaccines
Repeat dose/s administered	66	Zoster vaccine (27.3%, 18/66)
Expired vaccine	17	
Minimum interval not observed	8	
Diluent only	6	Infanrix-hexa (100%, 6/6)
Other	12	
Total reports	241	Seasonal influenza vaccines 22.8% (55/241) Zoster vaccine (10.0%, 24/241)

Table 5: Targeted monitoring for vaccine pharmacovigilance, SAEFVIC, 2018

Vaccines / population	Monitoring period	Reason for targeted monitoring	Findings
Influenza	Annual seasonal Mar–Oct	Seasonal changes to strain with past history of AEFI signal events	Hypothesised increase in serious adverse neurological events (SANE)—likely attributable to increased administration of influenza vaccines. Ongoing review of cases in collaboration with TGA.
Meningococcal ACWY Menactra*	2017–2019	New vaccine introduced to the Victorian school-based program for funded ACWY meningococcal vaccine.	AEFI reporting has decreased to 5 or fewer reports per month from a peak of 29 reports in August 2017. This is consistent with early increased reporting patterns following introduction of a new vaccine. ¹²
BCG	2014–2018	Vaccine strain changes and restricted provider permissions.	2018 saw the lowest reporting for 3 years. This is consistent with reduced BCG vaccine administration resulting from provider restrictions <i>in situ</i> during 2018. ¹³
Zoster	2016–2018	New vaccine introduced for 70–79 year olds Death following administration to an immunocompromised person. ¹⁴	AEFI reporting has decreased to fewer than 5 reports per month, from a peak of 20 in March 2017, consistent with increased reporting patterns following introduction of a new vaccine at that time. Noted immunisation errors of administration to immunocompromised persons and inadvertent administration of second dose. Improved education to immunisation providers was instigated. Monitoring of shingles post Zostavax* is routinely included in AEFI-CAN.
Pharmacist administered	2016–2019	Victorian Pharmacist-Administered Vaccination Program	Small number of reports and most common is for minor injection site reactions.

AEFI reactions

The 1,730 AEFI reports described 2,423 reactions (a vaccine recipient may describe multiple AEFI reactions) of which 255 were included in the 160 reports meeting the definition of serious adverse event from immunisation (SAEFI).

The distribution and frequency of reactions listed in AEFI reports for 2018 (commonly reported and selected conditions) are shown in Table 3. Minor/common/expected injection site reaction was the most frequently reported reaction overall (13.3%; $n = 322/2,423$) as well as for each age group category.

There were some notable variations in the age-group proportional reporting with higher proportions seen for injection site reaction (severe) in young children (15%); vasovagal episodes in school-aged children (11%) and fever (unspecified) in older people (7%). Two reactions were reported in much higher frequency within specific age groups; hypotonic-hyporesponsive episode (HHE) was reported exclusively in infants, which is a specification of the case definition of HHE being diagnosable in those < 2 years; 86% of fever > 40 °C occurred in young children; and vasovagal episode (syncope or faint) in school-aged children accounting for 69% of vasovagal reports.

Drug / immunisation errors

SAEFVIC received 210 reports of immunisation errors, involving administration of 241 vaccines (more than one vaccine was administered with an error at some encounters). The highest number of reports were for young children ($n = 80$). As a proportion of all SAEFVIC reports received for a given age group, drug errors were most commonly reported in older persons (27/174; 15.5%).

The most frequently-implicated vaccines with immunisation error reports were the seasonal influenza brands which, when grouped together, accounted for 22.8% (55/241), predominantly for administration to a person outside of the

vaccine-brand-registered prescribing age range. The next most frequently-implicated vaccine was live attenuated Zoster vaccine (Zostavax[®]) (10.0%; 24/241), for which the immunisation errors were predominantly associated with inadvertent administration of additional doses (19/24; 79.2%). There was one drug error (1/24; 4.2%) where Zoster vaccine was inadvertently administered to an immunocompromised patient (with no AEFI outcome noted); a marked improvement on 2017, when 9 such incidents were reported (9/39; 23.1%).

Repeated administration of routine vaccines was the most commonly-reported error, often accompanied by an explanation of the recipient having given unreliable information on their vaccination history; followed by vaccines administered outside of the prescribed age range (notably seasonal influenza vaccines, as above, and rotavirus vaccines) and the wrong vaccines being administered. There were 6 reports of Infanrix-hexa[®] being administered as the pre-filled diluent only syringe, without being reconstituted with the Hib pellet. The 'other' category comprises a range of uniquely reported errors such as later discovering the recipient had been pregnant at the time of immunisation, spilling the vaccine, vomiting after administration of rotavirus vaccine and one report of immunisation in a school setting without correct consent forms. Immunisation errors are summarised in Table 4. (Note that cold chain breachesⁱⁱ are predominantly reported to the Department of Immunisation.)

Targeted monitoring

SAEFVIC conducts targeted monitoring of AEFI for specific vaccines, for specific reactions, or when programmatic changes occur that may have potential for increased risk of a signal or have heightened attention within the community. These are summarised in Table 5.

ii Cold chain breach is the exposure of vaccines to temperatures outside the recommended range of 2 °C to 8 °C.

Signal investigations

SAEFVIC initiated investigation into two signal hypotheses that were raised initially by clinical immunisation staff perceiving an increase in reporting. It is important to note that these investigations do not infer causality but are included here as an indication of SAEFVIC's role in examining issues of potential vaccine safety in our jurisdiction.

Serious adverse neurological events (SANE) are known and rare AEFI, particularly with influenza vaccines,¹⁵ but they can also occur with temporal association to vaccines without causal association.^{16,17} Cases reported in 2018 encompassed a broad spectrum of ages (paediatric and adult) and vaccines. The proportional reporting ratio of SANE in 2018 (across all vaccines) was significantly higher than in previous years (PRR = 2.51, $\chi^2 = 6.78$). However, when calculating the PRR limited to influenza vaccines alone, SANE reporting in 2018 was not disproportionately increased (PRR = 1.57, $\chi^2 = 0.48$). The increase in number of reports was therefore hypothesised to be a consequence of increased influenza vaccine administration in 2018. This signal hypothesis was reported to the TGA and is the subject of an ongoing national review, supported by AEFICAN.

SAEFVIC perceived an increase in reporting of limb pain, restricted movement and bursitis during 2018, suggestive of shoulder injury related to vaccine administration (SIRVA). Following this increase in Victorian (SAEFVIC) notifications, the TGA was alerted and a review, conducted by the Advisory Committee on Vaccines, was initiated.¹⁸ This resulted in the development of new resources by both the Melbourne Vaccine Education Centre (MVEC) and the Australian Government Department of Health, which led a national educational initiative on correct injection technique included in the Australian Immunisation Handbook (April 2019). Resources are available via the MVEC websiteⁱⁱⁱ.

iii <https://mvec.mcri.edu.au/immunisation-references/shoulder-injury-related-to-vaccine-administration>

Reported SIRVA cases are undergoing a clinical review for diagnostic confirmation, with symptom follow-up and long term outcomes to be determined.

System innovations

During 2018, SAEFVIC transitioned analysis of data to Microsoft Power Business Intelligence (PowerBI) software.⁹ This permits simpler and more rapid processing of data accompanied by visual presentation. Enhanced semi-automated signal monitoring processes using frequentist and Bayesian methodologies are being explored.

Tabulations of vaccine-event pairs reaching signal hypothesis threshold levels using proportional reporting ratios (PRR) and Bayesian algorithms are generated weekly and reviewed to determine whether an investigation may be warranted. We are developing a ranking system to classify new signal detections, to identify increases in magnitude of known signals, and to undertake automated notification of identified signals.

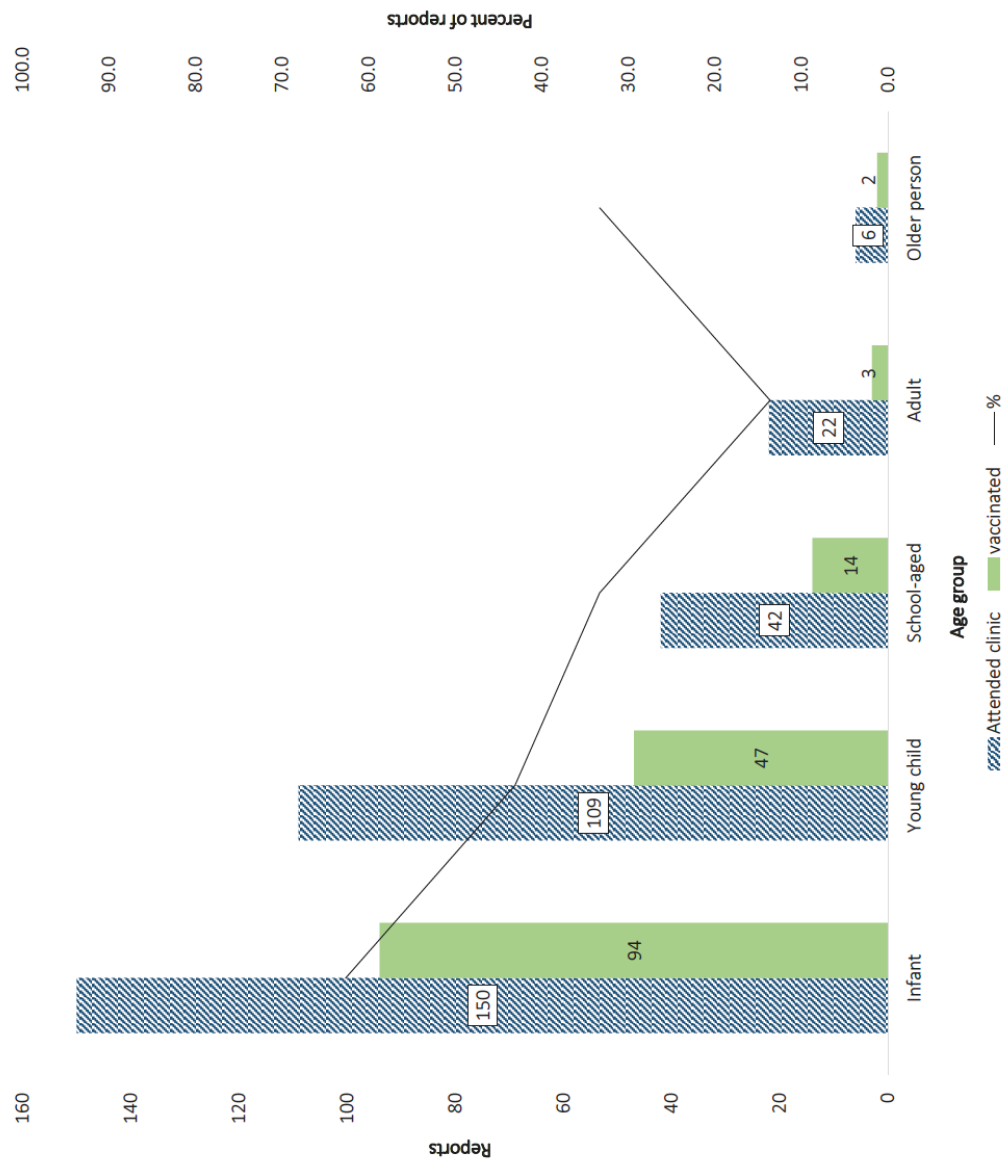
SAEFVIC service delivery

SAEFVIC surveillance is integrated with clinical service delivery. All AEFI reports are reviewed by an immunisation nurse with follow-up conversation with the vaccinee (or parent or guardian) to confirm the AEFI reaction. For serious AEFI, or if the vaccinee has reduced confidence in further vaccinations, a specialist clinical review is offered.

Clinical review

One fifth (329/1,730) of all cases attended specialist clinical services for review at either of two tertiary hospitals (Royal Children's Hospital or Monash Health), via Telehealth or at regional services by arrangement. One hundred and sixty such cases (48.6%) received onward vaccination via these services (Figure 7), with 61 being vaccinated under high-level supervision in day (n = 31) or overnight (n = 30) admission

Figure 7: Clinic attendance and further vaccination by age group, SAEFVIC, 2018



settings. Note that not all clinic attendees would require further vaccination at the clinic attendance timepoint.

Immunisation advice

The SAEFVIC team responded to 3,140 phone calls during 2018, a 5% increase compared to 2017 ($n = 2,987$). Two additional short-term information services for immunisation providers and public/ consumers were provided in 2018, funded by the Victorian Government Department of Health and Human Services. The first was a 10-week telephone immunisation advice line providing expert advice on all NIP vaccines and particularly regarding: 1) recently-introduced federal and jurisdictional legislation¹⁹ restricting access to kindergarten and family payment benefits for unvaccinated children, called 'No Jab No Play, No Jab No Pay'; 2) the Victorian Immunisation Program; and 3) the AIR. This was followed by 6-week clinical support via email providing immunisation advice on all NIP vaccines (paediatric and adult); the seasonal influenza program; immunisation catch-up requirements by age; advice around the Victorian immunisation schedule and vaccine eligibility criteria; changes to the National Immunisation Program; and other advice as relevant.

AEFI Clinical Assessment Network (AEFI-CAN)

AEFI-CAN is a national vaccine safety network coordinated by SAEFVIC, providing a collaborative approach to clinically assess and manage individual patients following serious or unexpected adverse events following immunisation. SAEFVIC leads national monthly teleconferences to discuss clinical cases of interest. A national database (with some funding support through AusVaxSafety) is being developed with capacity to harmonise AEFI data collation across jurisdictions for these serious clinical AEFI cases, seen in specialist immunisation clinics. In support of this initiative, SAEFVIC reviewed the case definitions used for AEFI surveillance and prepared a report for discussion as first

steps towards uniform reporting across jurisdictions reporting. As a national network, this will improve data transfer with the Therapeutic Goods Administration and enhance assessment of serious AEFI.

During 2018, AEFI-CAN has led clinical reviews of: shingles cases temporally associated with Zostavax[®]; SANE with seasonal influenza vaccines; and SIRVA. AEFI-CAN has also supported the Commonwealth-led education campaign on vaccine administration techniques (see references above). The network of specialist immunisation clinics is also being utilised to discuss 'No Jab No Pay' special exemptions with the Commonwealth.

Education

SAEFVIC seeks to develop and strengthen communication about important vaccine safety issues among both public and healthcare professional stakeholders and to provide information to support the management of any adverse events or concerns about vaccine safety.

Melbourne Vaccine Education Centre (MVEC)

The **Melbourne Vaccine Education Centre** web-based initiative^{iv} provides up-to-date immunisation information for healthcare professionals, parents and the public.^v SAEFVIC, working in collaboration with the Victorian Government Department of Health and Human Services, has successfully achieved accreditation for MVEC as a World Health Organization Vaccine Safety Net approved website. Vaccine Safety Net websites have been evaluated by the World Health Organization and meet the Global Advisory Committee on Vaccine Safety (GACVS) criteria for good information practices.²⁰

iv <http://www.mvec.vic.edu.au>

v for example, <https://mvec.mcri.edu.au/immunisation-references/nip-schedule-changes-july-1-2018-faqs>

Clinical Vaccinology Updates (CVU)

The Clinical Vaccinology Updates (CVU) are a series of educational conferences providing an opportunity for immunisation providers and healthcare professionals, from Victoria and interstate, the opportunity to meet and discuss vaccines, vaccine preventable disease epidemiology and vaccine safety. Two symposiums in 2018 attracted over 400 attendees including general practitioners, nurse immunisers, pharmaceutical representatives and healthcare providers.

CVU presentations are publicly available as a resource accessible by all health professionals and interested members of the public on the Melbourne Vaccine Education Centre (MVEC) website.^{vi}

Discussion

AEFI reporting in Victoria was 26.8 per 100,000 population in 2018, comparable to 2017 and represents a tripling since SAEFVICs first full year of operation in 2008. SAEFVIC Victoria is now the highest AEFI reporting jurisdiction nationally, with the second highest reporting rate by population.²¹ The increased reporting, both in number and by population, is likely indicative of improved case ascertainment rather than increase in vaccine reactogenicity. This conclusion is supported by the decreasing proportion of reports deemed serious. The high number of reports received by SAEFVIC means that Victoria's contribution to Australian national AEFI reporting is considerable, comprising 41.5% of all reports nationally in 2017—the most recently-published national report available—and triple that of New South Wales (25.3 to 8.7 AEFI reports per 100,000 population respectively), despite the similar jurisdictional population size of both states.²¹ Comparative national and jurisdictional data are accessible online from the Australian Government Department of Health, Therapeutic Goods

Administration Database of Adverse Event Notifications (DAEN), however restricted by a 90 day access lag.²²

Age-group vaccine-specific AEFI reporting rates were estimated using records of administered vaccines from the AIR, which was established in 2016 as an all-of-life expansion of the previous age-restricted Australian Childhood Immunisation Register (ACIR). AEFI reporting is predictably higher in Victoria than other jurisdictions as a result of the higher case ascertainment achieved through the SAEFVIC surveillance model. However, further rate elevations were notable in reporting for non-NIP vaccines such as meningococcal B in children and non-universal vaccines administered in adult age groups. This is anticipated as a consequence of under-reporting for non-NIP administered doses into AIR, widely attributed to a lack of incentive payments for notification.²³ For this reason vaccine AEFI reporting rate estimations were not presented in this report beyond the infant age group. As AIR becomes established and systems for automated extraction of immunisation data from primary care software expand to include all encounters, regardless of funding drivers (for vaccine administration and/or data recording into AIR), AEFI reporting rate calculations will become more reliable.

SAEFVIC provides vaccine safety insight into several important areas: antenatal; Indigenous Australians; specialist provider programs; and for individual vaccine programs. Routine capture of information on pregnancy and Indigenous status commenced in 2016. AEFI reporting for persons identifying as Indigenous (0.7% of reports in 2018) is commensurate with the Indigenous population in Victoria. However, the number of reports received for immunisations administered in pregnancy was low, at only 8% of reports from adult females. Eighty per cent of adult reports were for females, reflecting the NIP in this adult age group that targets predominantly vaccination in pregnancy and seasonal influenza vaccine in healthcare workers who are also predominantly female. This is an important contribution to AEFI surveil-

vi <http://www.mvec.vic.edu.au/clinical-vaccinology-update-2018/>

lance in pregnancy, which is acknowledged as a global priority especially as new vaccines are introduced to this cohort.^{24,25} Integration with active surveillance, whereby activities can be specifically directed to populations of interest, will further strengthen monitoring of vaccine safety for population subgroups.^{26,27}

The pharmacist administration of vaccines program commenced in 2016 with provisions for seasonal influenza vaccines. The number of AEFI reports received for pharmacist administered vaccines in 2018 was small and predominantly for minor injection site reactions, reflective of findings in the Western Australia pharmacist program that commenced earlier in 2014.²⁸ In September 2018 the program was expanded, authorising appropriately trained and registered pharmacists to administer measles-mumps-rubella (MMR) vaccine, along with influenza and pertussis-containing vaccines, to people aged 16 years and over subject to some exclusions. In 2019 we would expect to see an increase in AEFI reporting for pharmacist administered immunisations as the volume of vaccines administered through this pathway increases. The AIR does not record the immunisation provider so an alternative source of denominator data is required to accurately assess vaccine safety from this program.

Global bacillus Calmette–Guérin (BCG) vaccine supply shortages have resulted in frequent changes in BCG vaccine availability via the national authorised prescriber process, with recent transition to ‘19A regulations’ for approval to supply alternative brands within public health justifications.¹³ There is disparate jurisdictional administration of BCG and reporting on BCG AEFI, with such reporting predominantly from Victoria and Northern Territory; this is further exacerbated by low reporting in 2018, partially related to vaccine availability issues.^{29,30} SAEFVIC is currently comparing reporting by BCG vaccine product to inform future policy decision-making as BCG vaccine availability evolves.

As the largest contributor to AEFI reporting nationally,²¹ scrutiny of SAEFVIC surveillance data is likely to provide the earliest potential for signal hypothesis generation. In 2018 SAEFVIC referred suggestive signal events for SANE and SIRVA for further consideration by the national regulator (TGA). Additional innovations such as the incorporation of SAEFVIC data into business intelligence software, allowing improved visualisation, characterisation, mapping and statistical transformation, has enhanced our ability to understand and communicate our findings, as well as automating many of these processes to reduce delay.

Limitations of passive surveillance remain applicable to SAEFVIC and should be considered when drawing conclusions from these data. While reporting is presented as rates per population to provide trend estimation, they cannot be interpreted as AEFI incidence rates due to known ubiquitous under-reporting and biases associated with passive surveillance.^{31,32} Equally, AEFI are reported alongside all vaccines administered at a single encounter and cannot therefore be concluded as attributable to each individual vaccine. Vaccine program delivery scheduling is influenced by school terms, convenience and vaccine distribution constraints. These impact on AEFI reporting patterns and therefore seasonality is not analysed as part of this report.

While passive AEFI surveillance is subject to under-reporting,^{31,32} we believe SAEFVIC has established a strong balance for ascertaining serious AEFI and representative data for common or mild AEFI. Case ascertainment is further supported through inclusion of AEFI notified in Victoria through the active surveillance platforms of PAEDS and AusVaxSafety, the advent of which have improved immunisation safety surveillance in Australia.^{33,34} As an example, AusVaxSafety had almost 74,000 solicited participant-reported outcomes post-influenza vaccination recorded in 2017, with 6.6% reporting adverse events.³⁴ One third of the 300 AusVaxSafety sentinel sites were within

Victoria.^{vii} AEFI requiring medical attention identified from the active surveillance pathways are incorporated into the SAEFVIC comprehensive state-based vaccine safety system. However, with only 2.0% of AEFI reported to SAEFVIC acquired through the partner active surveillance systems, effective passive AEFI surveillance remains crucial, particularly to detect rare, unexpected or delayed events post-immunisation. Through integrating surveillance platforms, our aim is to provide a comprehensive vaccine safety system that captures all serious AEFI and supports clinicians and patients through specialist immunisation clinical review where indicated.

SAEFVIC's unique platform of surveillance integrated with clinical services is further complemented by the MVEC education website, enabling responsive action to emergent vaccine safety issues. For example, enhanced monitoring of Zoster vaccine and analyses of the opportunistic reporting of drug administration errors, facilitated identification of several addressable issues such as Zoster vaccine administration in contraindication to immunocompromised persons. This led to development of new educational resources for immunisers.^{viii} Vaccines continue to be administered in contravention of age and interval guidelines, particularly with influenza vaccines, raising demand for strategies to minimise age and interval violations.

The facility of the MVEC website for reactive and responsive publication and dissemination of resources meets the needs of immunisers and the increasing demand of community for directly accessible information.³⁵

SAEFVIC continues to evolve as a leader in AEFI surveillance, providing a broad spectrum of pharmacovigilance services to community, immunisation providers and regulators. The SAEFVIC platform is now adoptable by other jurisdictions as an independent data silo or with collaborative reporting and analytic services.

Goals for the future are to formalise robust amalgamated processes for signal detection and to substantiate Victorian and national clinical support services through MVEC and AEFI-CAN. Ongoing optimisation of data visualisation and signal detection algorithms incorporating not just AEFI reports but also alternate health datasets will help ensure jurisdictional and national immunisation programs remain among the safest in the world.

Conclusion

SAEFVIC received 26.8 per 100,000 population reports in 2018, a tripling of the annual reporting rate since its inception, with no unexpected increases in the frequency or severity of AEFI reporting. Potential signal events were closely monitored with serious adverse neurological events (SANE) and SIRVA referred for national consideration but with no ongoing signal verified. Passive surveillance is useful for informing vaccine safety pharmacovigilance and for detecting potential safety signals. Integration with clinical services enhances the capacity for signal investigation and provides extended opportunity for collaborations to enhance pharmacovigilance nationally.

vii www.ausvaxsafety.org.au/our-work/active-vaccine-safety-surveillance

viii <https://mvec.mcri.edu.au/immunisation-references/zoster/>

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Chapter 9: Optimising SAEFVIC

9.1 Chapter Introduction

The overarching objective of this research was to optimise SAEFVIC for the detection, investigation and validation of vaccine safety issues necessary for informing vaccine pharmacovigilance and to support the expansion of SAEFVIC for use in other Australian jurisdictions.

The specific research aims were to:

- **Evaluate** the current SAEFVIC surveillance system ability to meet its stated objectives
- **Demonstrate** that SAEFVIC data can be used to inform vaccine pharmacovigilance
- **Explore and apply** concepts to develop signal detection capacity for SAEFVIC
- **Optimise** SAEFVIC: specifically to support expansion of SAEFVIC to other jurisdictions and thus improve immunisation safety in Australia.

This research was important because vaccines are a cornerstone of public health; saving millions of lives each year and robust vaccine safety surveillance is essential to ensure an effective safe vaccination program. Moreover, with Australia an “early adopter” of vaccines, our safety knowledge informs both nationally and internationally(13). Prior vaccine safety challenges occurring within Australia had highlighted the need to improve adverse event surveillance, with SAEFVIC proposed as a suitable model(6, 9). However, despite this recommendation there had been no comprehensive evaluation on whether SAEFVIC met its stated objectives or was fit for purpose, leaving a gap in knowledge and evidence that this research aimed to address. Working within SAEFVIC while undertaking these studies created the opportunity for me to capture vaccine safety issues as they arose, meet the challenges and translate findings directly into action, bringing credence to the proposition of SAEFVIC as a model for AEFI surveillance and actualisation of the expansion of SAEFVIC as a national platform for AEFI surveillance in Australia.

In this Chapter I present a summary of the salient findings from my thesis and describe the transformational impact on SAEFVIC, vaccine safety policy and more broadly on Australian vaccine pharmacovigilance. This is followed by an overview of the strengths and limitations of this thesis, which segues to aspirational opportunities for future epidemiological studies in the field. The chapter concludes with a summary of the achievements my doctoral research has made towards improving immunisation safety in Victoria and Australia and therefore answering the final research question of:

Question 6: How have the findings of this PhD been incorporated to optimise SAEFVIC?

9.2 Optimising SAEFVIC

“An ideal vaccine safety and effectiveness monitoring system should be flexible and sustainable, able to quickly detect possible vaccine-associated events, distinguish them from programmatic errors, reliably and quickly evaluate the suspected event and its association with vaccination and, if associated, determine the benefit-risk of vaccines to inform appropriate action”(393).

Australia is traditionally an early adopter of vaccines and has a comprehensive funded national immunisation program with enviable immunisation coverage rates, further consolidated through a strong policy stance of linking family benefit payments and education enrolment to immunisation with the “No jab no pay, No jab no play” policy(13, 195, 394). Therefore, Australian vaccine pharmacovigilance should be an equal key contributor to global vaccine safety. However, the discordant national AEFI surveillance—indeed, in some jurisdictions being almost absent—has been identified as sub-optimal, leaving Australia lagging behind the contribution of other major continent players such as the US and Europe(9, 167).

The studies I have completed within this thesis have progressed closure of this gap through their contribution to scientific literature on vaccine safety surveillance; the strengthening of the SAEFVIC AEFI surveillance system and; establishment of AEFI signal detection into routine practice. The outcomes of my doctoral research have not only contributed to knowledge, but translation of the findings have enhanced SAEFVIC

as a comprehensive and effective AEFI surveillance system and impacted directly to strengthening Australian and global vaccine safety.

The contribution and impact of each component of my research is discussed in the following sections.

9.2.1 Descriptive epidemiology

Expansive descriptive epidemiology of AEFI surveillance in Victoria was provided at two time-points, 2012 and 2018 (*Chapters 4: SAEFVIC early years and 8: SAEFVIC maturation*), being the bookends of this doctoral research period. Additional detail on data and system attributes were articulated in the evaluation of SAEFVIC (Chapter 5).

These descriptive works directly address concerns, raised by Bonhoeffer *et al.* in 2005(395), of inconsistencies in the reporting of AEFI in vaccine safety publications by providing a structured format for presenting AEFI data in Victoria. Analyses of data document trends over more than a decade of AEFI surveillance. Further, they contribute to addressing the growing demand for improved transparency in defining the underlying data upon which research studies using routinely collected data are based(396).

The depth of the descriptive epidemiological studies of 2012 and 2018, accompanied by the evaluation of SAEFVIC attributes and the description of data sources contributing to vaccine safety surveillance presented in *Chapter 3: Methods*, provide transparency in reporting of pharmacoepidemiological data.

This strengthening in reporting was timely as standardised guidelines for reporting on routinely collected data were developed, concomitantly to these doctoral studies, with the “**R**eporting of studies **C**onducted using **O**bservational **R**outinely collected health **D**ata” (ReCORD) statement being published in 2015(397). These guidelines arose through the increasing recognition of issues identified in research using routine data, particularly inadequacies in the description of database characteristics(396). The ReCORD guidelines are separate and beyond the pre-existing “**S**trengthening the **R**eporting of **O**bservational Studies in **E**pidemiology” (STROBE) statement, which provides more general guidelines for reporting observational studies(398). ReCORD

was developed to provide best practice standards for the reporting of research using routinely collected health data: a category that includes SAEFVIC AEFI data.

Despite the demand for best practice standards to be followed, a review of the reporting quality of evaluation studies using routine pharmacovigilance data identified that ReCORD and STROBE did not capture the complexities of pharmacoepidemiology (PE)(399). The guidelines were therefore extended into the RECORD-PE statement, published in 2018(400). This statement provides a 15-item checklist to be used in parallel with the ReCORD and STROBE guidelines to ensure transparency in reporting of pharmacoepidemiology studies.

The publications arising from my doctoral work will, therefore—individually and in combination—support future research studies’ compliance with the STROBE, ReCORD and ReCORD-PE statements. Specifically, the rigour in detailing the underlying data and providing documentation within this thesis assures understanding of the population in which analyses of AEFI are undertaken and in particular explores the complexity of measuring incidence in the absence of an exposed population denominator.

The descriptive studies also address a different theme: that of making data available to stakeholders, in particular provision of feedback to those who are relied upon to provide the initial reports and to health consumers(298, 401). At the outset of this doctoral work, SAEFVIC as a surveillance system lacked routine feedback to stakeholders, with the only routine reporting being to the “parent” funding agency, the Department of Health and Human Services, Victoria. Publishing the descriptive epidemiology and surveillance system processes has facilitated stakeholder access to AEFI surveillance outputs. At this stage the feedback is still “static”: being presented in summary published reports(1, 179). However, bringing data into the public domain with standardised presentation of AEFI data has progressed enabling of broader dissemination of surveillance outputs. The aspiration is to develop an online platform with access to dynamic system description, data and interpretations, including end-user interactive infographics(254, 402).

9.2.2 SAEFVIC evaluation

Chapter 5: SAEFVIC evaluation provided a rigorous structured evaluation of SAEFVIC. This was the first evaluation of SAEFVIC and remains the only systematic evaluation of an AEFI surveillance system across Australia to date. Therefore this evaluation provides a benchmark not only for SAEFVIC but also for AEFI surveillance nationally.

The SAEFVIC evaluation, established to determine if the system met its stated objectives, identified two major deficiencies: firstly, gaps in data collection fields and secondly; a lack of signal detection capability. The gap in data collection fields was imminently amendable and actioned accordingly. These amendments enabled collection of important data on immunisation target groups and/or risk factors. This specifically improved the capacity for surveillance to inform on AEFI in targeted vaccine programs to Indigenous Australians and vaccine delivery in pregnancy, a recognised global priority for AEFI surveillance(403). Updates to the database included incorporating reports received via active surveillance, making it an integrated system while still permitting disaggregation of data by report source (active/passive and the specific active surveillance system origin) for analyses.

An extension study that evolved out of the evaluation explored the contribution to AEFI surveillance arising from consumer-reporting as a data source(230). The findings informed policy that accepting consumer reporting was beneficial as a means of increasing the volume of reporting without eroding capture of serious AEFI reports(230). It is anticipated that consumer reporting will increase as community awareness of AEFI and empowerment to engage with surveillance systems increases, for example through active surveillance and consumer access to online reporting portals(94, 404). Therefore these findings provide a foundation for future studies reviewing the impact that higher volume of reporting brings(405). While it may be assumed that the power for signal detection will increase commensurate with increased reporting(406), some studies examining this element have concluded that both aggregate and disaggregate analytics are appropriate, as jurisdictional or reporter-type specific analyses can give information not visible in collated reporting(306, 407).

In the global context, the SAEFVIC evaluation provided evidence that Victoria—and therefore Australia—met the WHO minimal reporting requirement for indication of a functional AEFI reporting system, being defined as 10 AEFI reported per 100,000 surviving infants(108, 408). It also provided quantified evidence that SAEFVIC—and therefore Australia—has the potential to inform on rare to extremely rare AEFI(406). Grahame-Smith *et al.* proposed the number of patients one would need to observe in order to have a 95% chance of detecting an AEFI, given a specified incidence of the reaction (Table 10)(409). Reviewed against this measure, the quantity of reports now held within the SAEFVIC dataset—reaching over 16,000 patient records as of 2019 year-end—are sufficient (with 95% confidence) to detect 3 events of a rare (1 in 2000) AEFI. As SAEFVIC currently contributes approximately 40% of national AEFI data and continues to expand, SAEFVIC therefore provides a significant contribution to the national capacity to detect 1 event of an extremely rare (1 in 10,000) AEFI among the approximately 40,000 AEFI reports held.

Table 10: Number of observations to detect 1,2 or 3 adverse events(409)

Expected incidence of adverse reaction	Observations to detect 1, 2 or 3 events		
	1	2	3
1 in 100	300	480	650
1 in 200	600	960	1300
1 in 1000	3000	4800	6500
1 in 2000	6000	9600	13000
1 in 10000	30000	48000	65000

The demand for evaluation of public health surveillance systems is not only to inform economic efficiency to justify continuation, but also in determining the comprehensiveness of data on which policy and practice decisions are made(254, 256, 410). The literature review presented in Chapter 5—accompanying the SAEFVIC evaluation—describes an array of evaluation guidelines gaining traction in the pharmacovigilance field and therefore offers opportunities to expand the evaluation lens as the discipline evolves(302).

9.2.3 Informing pharmacovigilance

Chapter 6: Informing pharmacovigilance presented evidence of SAEFVIC informing vaccine pharmacovigilance by bringing together three exhibitions across a spectrum of investigations and provides a foundation for emerging AEFI surveillance analytic methodologies.

This collection of work provided a two-pronged achievement; an overall demonstration of how passive AEFI surveillance can be used to inform on vaccine safety issues for policy, program expansion and gaps in knowledge; but also, each study had stand-alone impact through the findings presented, which are individually described below.

9.2.3.1 Investigating a vaccine safety signal

In the first study presented in Chapter 6, SAEFVIC data were analysed to investigate an increase in reporting of allergic AEFI that occurred in 2015(308). While addressing the concern at hand, the study also iterated the findings from the SAEFVIC evaluation of the paucity for routine signal detection. While the 2015 signal investigation was well supported by SAEFVIC data, it could only provide comprehensive findings on conclusion of the influenza vaccination season(308). Nevertheless, this study had immediate impact on national immunisation policy/decision-making in that year and prospectively into adjunct surveillance program development. SAEFVIC raised the initial alert to the national regulator (TGA) leading to the data and potential signal being discussed by the national Advisory Committee for the Safety of Vaccines (ACSOV). Thus my doctoral research was a major contributor to the information used to determine national program policy and confidence to continue with the immunisation program (Box 8)(313, 411).

Box 8: Extracts from ACSOV meeting statements, June and October 2015(313, 411)

ACSOV meeting statement, Meeting 8, 11 June 2015

“ACSOV was advised that the TGA had begun an investigation into an observed increase, compared to previous years, in reports of Immune System Disorders (ISD) following the administration of the 2015 influenza vaccines. The percentage of reported ISD adverse events following immunisation (AEFIs) with the influenza vaccine compared to the total number of reported AEFIs following influenza vaccine had risen from 12% (2013) and 13% (2014) to 21% in 2015 (as at 8 May 2015).”

ACSOV meeting statement, Meeting 9, 23 October 2015

“Overall, the data suggested an increase in allergy related AEFI, but the signal was not strong and this did not have any significant programmatic or clinical implications. The committee agreed it was reassuring that similar conclusions had been independently reached by the TGA and SAEFVIC although each used a different method for coding the reported adverse events.”

The study also had broader impact in that it corroborated the findings of the expert reviews by Stokes and Horvath of deficiencies in signal detection and furthermore, demonstrated the lack of progress achieved since those reports were published in 2011(9, 167). This body of evidence was instrumental in the national active AEFI surveillance collaboration *AusVaxSafety*, initially funded in 2014 to provide active seasonal influenza surveillance in children aged <5 years, being expanded to include all ages(94).

9.2.3.2 Investigating a vaccine quality issue

The second investigation presented in Chapter 6 demonstrated how SAEFVIC was able to inform on a drug error: namely a possible faulty BCG vaccine batch arising through a breach in manufacturing process quality(311). While the investigation provided comfort that no safety issue was identified due to the quality breach, it did identify limitations in data capture to inform on batch-related issues(307). These findings

supported the enacting of national policy for use of an unregistered vaccine, giving confidence for the approval to implement the 19A regulations enabling provisions for specialist providers to supply alternative brands within public health justifications(412). These provisions maintained BCG vaccine for high-risk groups during a prolonged period of global BCG vaccine shortage(413).

Subsequent similar studies, profiling BCG vaccine strain alternatives as they have become available to the market, have since been published(414). Although stating national Australian figures, results predominantly comprise Victorian/SAEFVIC data: as Victoria and the NT are the major contributors to BCG administration, with SAEFVIC consequently the major data repository of AEFI data(349, 413).

9.2.3.3 Inform on representativeness

The third investigation presented in Chapter 6 sought to address suggested disparity in case ascertainment by age group identified as an issue during the evaluation of SAEFVIC (Chapter 5). This finding was expanded as a specific analysis exploring reports of AEFI in older persons. The potential under-reporting in this age-group, and therefore gap in representativeness of surveillance data, was confirmed(229). This was significant because a newly funded vaccine program was being introduced into this older person age-group (Zoster vaccine to 70–79 year olds from 1 November 2016)(415). Therefore, it was important to provide evidence that existing passive AEFI surveillance systems were likely to under-represent older persons and thus were insufficient to provide the comprehensive vaccine safety information required. This evidence was instrumental in guiding the funding for expansion of the AusVaxSafety active surveillance system to include Zostervax® recipients (70–79 age-group) for the first two years of the funded vaccination program—monitoring over 18,000 recipients with no signal detected—and also inclusion of shingles into AEFI-CAN, as shingles would not be adequately monitored through SAEFVIC(416, 417).

9.2.4 Signal detection

Lack of *de novo* signal detection, or application of routine signal detection methods to generate signal hypotheses, was identified in the evaluation of SAEFVIC (Chapter 5).

This finding was further confirmed through the 2015 influenza vaccine allergy-related AEFI signal investigation (*Chapter 6: Informing pharmacovigilance*), as SAEFVIC had limited ability to give timely information on the vaccine safety issue as it unfolded(15, 308).

These issues were examined through two avenues; as background rates and exploration in the use of a signal detection algorithm, tested for competency on two known signal scenarios. Findings were presented in *Chapter 7: Signal detection*, defining the term signal as used in the pharmacovigilance context and describing options for signal detection with passive AEFI surveillance, using available data sources within the Victorian setting.

9.2.4.1 Background rates

The first study presented in *Chapter 7: Signal Detection* highlighted the value of routine administrative health datasets to provide information for the benefit of public safety(215). The baseline rates of potential AEFI, as produced from this study, were subsequently used to inform a program of enhanced clinical monitoring of severe AEFI undertaken by the recently established AEFI Clinical Alert Network (AEFI-CAN)(180).

Similar principles of calculating background rates have recently (2019) been used in Canada to investigate three rare AEFI conditions of immune thrombocytopenia, Kawasaki disease and multiple sclerosis(326). In this study the average annualised incidence of multiple sclerosis in adolescents aged 11–17 years was 0.8 per 100,000 across the 2005–2014 study period(326). This rate was higher than in our study (0.29 per 100,000), however our study was restricted to boys, for whom it is known have an approximately one-third lower incidence risk of multiple sclerosis compared to girls(325). This affirms the relevance in conducting sex-specific AEFI studies(287).

While the study presented in this thesis provided proof-of-principle in using routine health data to inform vaccine safety, at the time (2013), technologies and permissions for real-time efficient linked data analyses were not yet established sufficiently to enable integration into routine practice. However, these fledgling moves in using health care datasets have provided a foundation for future research integrating data-linkage and data-mining methodologies with routine health care data(93). This is

exciting as studies establishing background rates of diseases in Denmark and the US have followed on to demonstrate how linking routine health care event databases to immunisation databases can enable direct investigation of potential associations of immunisation with adverse events(418-420). The future opportunities of data-linkage are further discussed below in section 9.4.1.

9.2.4.2 Proportional Reporting ratio (PRR)

The second investigation presented in *Chapter 7: Signal Detection* detailed the novel use of a signal detection algorithm, the proportional reporting ratio (PRR), on AEFI data with evidence of signal detection capability proven on two known signal events(231). While this publication has not yet been cited in further works (as it was published shortly before submission of this thesis) the work has informed significant development in signal detection within SAEFVIC.

Integration of routine PRR into the SAEFVIC surveillance system has been established and expanded beyond influenza vaccine AEFI monitoring to encompass all vaccine-AEFI reaction pairs. Evidence of this improved capability for signal detection is presented in *Chapter 8: SAEFVIC maturation*, describing an increase in proportional reporting of serious adverse neurological events (SANE) following immunisation, which SAEFVIC alerted to the national regulators for further investigation. SAEFVIC was able to provide some reassurance by demonstrating the increased PRR dissipated when assessed within influenza vaccines as a subset. This indicated that the signal arose from an increase in volume of influenza vaccine administration rather than a vaccine safety issues *per se*, alleviating alarm(185). The evidence of the PRR foundational research and publication conducted as part of this doctoral work gave confidence to the use of PRR in practice.

SAEFVIC capability in signal detection has progressed exponentially since the 2010 febrile seizure with influenza vaccine signal event(312): it is now more assured to detect signals, earlier and with more confidence. Post-doctoral research continues to build upon the signal detection algorithm concept with exploration of mixed effects models, enhancing signal visualisation and automated alerting for AEFI-vaccine pairs

breaching signal thresholds, providing leadership in this field in both Victoria and Australia(93, 421).

9.2.5 Microsoft PowerBI

The practicality of implementing routine timely signal detection was a motivation in transporting SAEFVIC analytic processes into Microsoft Power Business Intelligence software (PowerBI)(236). While the algorithm calculations were not particularly complicated, the challenge lay in how to incorporate into routine practice the complexity of calculating multiple vaccine-event pair possibilities among over 16,000 reports to be examined in a repetitive ongoing process. PowerBI makes this manageable: the template points to the data with updates in real-time; permits interrogation of data parameters such as reaction, vaccine, demographic or time period; is nested with statistical functionality, and; provides a visual dashboard to aid interpretation(236).

The move to PowerBI brought with it the associated incremental impact of sophisticated visualisation of AEFI surveillance data and reporting platforms facilitating sharing with other jurisdictions as SAEFVIC methodology is adopted. This leads well towards the aspiration for a user-interfaced interactive dashboard to monitor vaccine risk in near real-time(247, 402).

9.3 Thesis strengths and limitations

Limitations inherent to passive AEFI surveillance are numerous and well documented(190). They include; under-reporting; inconsistencies in data quality, particularly capture of patient demographic characteristics and vaccine batch information; gaps in representativeness of AEFI reporting, by vaccine, reaction or patient demographic; influence of media attention (including social media) on reporting practices, and; complexity of concomitantly administered vaccines limiting attribution of an AEFI to a single vaccine(222). These aspects of data bias and confounding ubiquitous to passive surveillance are presented in *Chapter 3: Methods* as they underpin research in pharmacovigilance. Where limitations were specifically

encountered in—and in some instances were the focus of—investigations conducted as part of this thesis, they are described within their individual Chapter publications.

In this Chapter section the overarching strengths and limitations thematic through the thesis are discussed in the context of considerations to ameliorate such limitations through further studies or advancements in pharmacovigilance.

9.3.1 Length of study period

The research aim was to optimise SAEFVIC: a term that, rather than having a finite end point, is an open-ended continuum. Conducting this body of work part-time over a seven-year study period provided strength by enabling investigations to be responsive to actual events as they arose and for translation and embedding the findings into practice. However, studies conducted in the earlier years lacked the flexibility and ease of data manipulation and visualisation utilised in later studies following the move to PowerBI.

9.3.2 Denominator

A predominant limitation in this research using passive surveillance data was the absence of an accurate vaccine administered denominator and therefore inability to provide the preferable epidemiological rigour of calculating rates. This limitation and the proxy-alternate data sources used to provide denominator estimates was described in detail in *Chapter 3: Methods*. It is anticipated that this limitation will be mitigated in the foreseeable future as the Australian Immunisation Register gains momentum and timely automated methods of data linkage between the AIR and the array of data sources being investigated as having potential to support AEFI surveillance are actualised(93, 297). The timing of this, however, is yet to be determined as a recent audit of the AIR concluded there is still work required to ensure more reliable transmission of immunisation encounters to the AIR to improve accuracy of coverage data(210).

9.3.3 Data comparability

SAEFVIC was established using clinical-based case definitions to record AEFI reactions. There is strength in this clinical attribute, particularly as the potential for misclassification bias of reactions reported is partially addressed in SAEFVIC by specialist clinical reviews and adherence to the growing range of standardised case definitions of the Brighton Collaboration¹(115, 116). However, multiplicity in clinical terminology can bring limitations such as potentially diluting signal detection as similar conditions are given alternate, albeit legitimate, names; for example bloody stools, melaena or hematochezia. Diversity in nomenclature also brings constraints to comparing and/or collating data across jurisdictions, nationally and internationally. This was particularly evident in the investigation of allergy-related AEFI in 2015 as the SAEFVIC clinical terms of anaphylaxis, generalised allergic-reaction and urticarial rash were not entirely compatible with the national regulator (TGA) AEFI classification of “immune system disorders”(308, 313, 411).

Work external to this PhD was undertaken to bring national-level agreement to clinical case definitions. The next phase, currently underway, is to use standardised hierarchical systems of medical terminology to support consistency in adverse events classification. This will enable generalisability of statistical analyses, information exchange and comparison of analyses across jurisdictions, nationally and internationally(269, 422). While there are several ontologies, two with prominence in pharmacovigilance and Australia are; the Medical Dictionary for Regulatory Activities (MedDRA)(269), and; the Systematized Nomenclature of Medicine – Clinical Terms (SNOMED)(270).

MedDRA is a “medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products”, including

¹ As announced on the 21st of May 2019, the Brighton Collaboration will be dissolved as a Partnership under Swiss law and reconstituted as a programme of the Task Force for Global Health (TFGH; www.taskforce.org).

vaccines(269). SNOMED is a broad structured vocabulary of medical terms for documenting and reporting clinical content in health records and is considered to be “the most comprehensive, multilingual clinical healthcare terminology in the world”(270, 422). MedDRA is commonly used in pharmacovigilance, including in Australia (TGA DAEN) and the US (VAERS)(423, 424). SNOMED is used in more than eighty countries and is the endorsed preferred national clinical terminology for Australia(425-427).

SAEFVIC—being data-rich with over a decade of data captured—will have the benefit of maintaining the high-level clinical descriptive information, ascertained through individual clinical review, alongside the soon-anticipated consistency of coded data using one, or both of the systems described above. Once the ontological mapping is defined, it can be applied retrospectively to the entire data collection, thus facilitating investigation of any rare or new events arising. Having both clinical and coded data is important as while some adverse events have clear diagnoses and consistent coding within records, others with non-specific symptoms or syndromes may lead to varied coding and low positive predictive value(428).

9.3.4 Information bias

Information bias is a universally accepted limitation of passive surveillance reporting, visualised with the notification pyramid (see *Chapter 3: Methods*)(183). Information bias may arise in each of the reporting layers dependent on perception of AEFI, equitable access to, or propensity to use, healthcare services (under-ascertainment) as well as health-care provider failure to report (under-reporting)(183, 190).

Furthermore, particularly when reporting is passive, periodic motivation to report, for example, through media attention, may impact on case ascertainment with variable representative consistency(221, 248). A good example of the correlation of media and adverse event reporting was evident with reporting of AEFI with HPV vaccines(221, 429).

One strategy is to consider opportunities to estimate (and therefore potentially rectify) the extent of under-ascertainment and under-reporting, however this should be in the context of potential gain in information/value against the additional resources

incurred. An alternative strategy is to increase or triangulate AEFI case ascertainment with capture through alternative pharmacovigilance systems such as active surveillance or data-linkage with other health data sources. There is considerable opportunity to expand and explore this arena through adaptation of methods with experience in infectious disease notification such as community surveys, capture-recapture and modelling(190, 430).

Capture of active surveillance reporting into the passive SAEFVIC system, initiated through data field upgrading as an output of the SAEFVIC evaluation, partially addresses under-reporting for early onset AEFI. Onward studies are being undertaken to use routine health care data for signal detection and exploration of alternate health data sources that may capture and value-add to pharmacovigilance(93).

9.3.5 Confounding

Inherent to observational studies, particularly those using highly information-biased spontaneous/passive reporting systems, are that they generate hypotheses of causation through observation of associations and are not investigatory of causation(42, 183, 226).

However, within this there is unmeasured interference through confounding by indication—that is, confounding as a vaccine, or even vaccine brand, may be selectively administered to population groups targeted for a health or occupational demographic characteristic that may then confound susceptibility for developing an AEFI, a particular type of AEFI, or severity of the AEFI (see *Chapter 3: Methods*).

Contemporary epidemiological methods of directed acyclic graphs (DAGs) have potential to assist in the consideration of such confounding relationships in surveillance, but have not been fully explored(431). DAGS would need to be drawn with care, from the population level (immunisation eligible or administered) through to the “exposed” group of AEFI being recognised and reported. The aim being to look at finding the indication confounding to control for when estimating reported AEFI effects(432). Remembering that in this context the causal effect is between the

indication (condition or risk) for immunisation, vaccine selection and reporting an AEFI and not to draw conclusions of a causal relationship between vaccine and AEFI.

The applied nature of adverse event surveillance, however, may not require such determination of confounding detail, rather acceptance of missing variables, bias and confounding as “real-world data”(433)(see section 9.4.2 below). This paradigm moves beyond theoretical perspective into practical methods, accepting a degree of subjective expert judgement, that are applicable and relevant to clinical practice(227, 434, 435).

9.3.6 Data analysis

Recognising that these doctoral studies provided first steps in the use of signal detection algorithms on SAEFVIC (and Australian) pharmacovigilance data requires diligence in continuing to look at limitations of the method and setting in which it was studied.

PRR signal detection capability was tested against two well-documented signal events; being the 2010 observed increase in frequency of fever AEFI and the 2015 lower magnitude signal of allergy-related AEFI(308, 312). However, despite the strength of having known signals on which to investigate detection methods, they are both high frequency events. Fever is one of the top five most commonly reported AEFI and although allergy-related AEFI are less common, they are still not infrequent AEFI(186). Recent signal simulation studies in Australia on this topic were equally constrained to examination on the known high volume signal events(436).

A known limitation in measures of disproportionality is the masking effect of influential vaccine-events—either as prior signal events, differential reactogenicity, or domination by frequency. Attempts to unmask the disproportionality effect by, for example, data exclusion, regression or stratification, can either uncover or cover signal detections and therefore should be conducted as supplementary analyses, not as alternative analyses(437, 438).

Preliminary explorations of these potential masking elements were included in this thesis through; the PRR studies sub-analyses excluding prior known signal events and

measuring the effect of stratification by age (<5 years and adult) on signal magnitude, and; in the 2018 investigation of SANE, stratification within influenza vaccines as a vaccine group. These explorations are being continued in post-doctoral and parallel studies using novel Bayesian mixed effect models.

Care is therefore needed not to over-generalise findings on different scenarios. As signal events in this thesis were predominantly based on high frequency vaccines (influenza) with large record numbers (fever and allergy)(439), methods may not be appropriate for new vaccines or infrequently administered vaccines where there are few past records and/or few exposed on which to base disproportionality assessments. Doing so leads to a risk of false negative or failure to detect signals, especially for rare AEFI. Restricting analyses to the subset of interest, if numbers permit, or applying alternative methods such as self-control-case series may be considered (as discussed further in section 9.4.2)(440).

This limitation in generalisability is particularly important (pertinent) if using methods of disproportionality to monitor novel vaccines for which there is no equivalent vaccine history in the dataset, such as the future potential non-virus rapid deployment pandemic vaccines(441).

Concomitant vaccine administration hampers our ability to tease out the individual culprit vaccine, but studies also need to consider potential for drug-drug interaction. In polypharmacy situations, each vaccine may induce adverse events, but there is also the potential for vaccine-vaccine interactions to increase the risk of AEFI(442).

Concomitant non-vaccine pharmaceutical use is not recorded in SAEFVIC therefore cannot be used for interrogation of vaccine-drug interactions.

As a final thought—currently the focus is on surveillance ability to detect signals and initiate action to intercept a safety issue. There is value in strengthening a shift to the broader intangible benefit of surveillance information that does not lead to action: the concept of valuing surveillance safety information through continuum of non-signal periods, and rather than the propensity for publishing the bad news stories, we should give equal value to the good news/non-events(443). This is particularly so in light of WHO calling vaccine hesitancy as one of the top ten threats to global health in

2019(34). In summary, we should forcefully promote the ability of high quality data to offer reassurance and effective communication—including mitigating misinformation from the avalanche of online media—important for consumer confidence as a primary function of surveillance in itself(444, 445).

9.3.7 Generalisability

The high volume and proportion to population of AEFI reporting to SAEFVIC provides confidence that the broad epidemiological descriptors and surveillance outputs are generalisable to the immunised population of Victoria. Furthermore, as the NIP is in the most part a nationally consistent immunisation regimen, and SAEFVIC provides almost half of all reports, there is a degree of comfort in assuming generalisability to the whole of Australia. As the national consortium of jurisdictions utilising the SAEFVIC model grows, this generalisation will be affirmed.

However, as discussed above among limitations and in *Chapter 3: Methods*, caution should be exercised before generalising findings based on broad populations to niche demographics and vice versa. Findings may not consistently extrapolate beyond that in which they are studied, as was evidenced in the sex-variant presentation of multiple sclerosis(307, 326). Recent studies have also shown significant differences in reactogenicity with trivalent influenza vaccines among individual groups based on sex, age and ethnicity(424, 446). Divergence in AEFI profiles between vaccine types is intuitive, however, generalisability between same-antigen vaccine brands also requires consideration(446), of which Australia is poignantly cognisant since the 2010 Fluvax® brand-specific febrile seizure event(176).

9.4 The future

Opportunities for the continued optimisation of SAEFVIC and expansion of pharmacovigilance more broadly have been described in each section above. However, we should look beyond incremental improvements towards aspirational advances in vaccine safety and creation of new opportunities to elevate the benefit-risk of immunisation.

9.4.1 “Big data” and artificial intelligence

The review by Horvath proposed that future developments in e-health would provide opportunities to improve the capacity for vaccine surveillance to collect data on vaccine administration and adverse events and should be considered a key priority(6). Likewise, limitations discussed relevant to this thesis—particularly under reporting and gaps in reporting for specific age groups—also direct towards considering the size and power of datasets and the potential advantages of increased volume and diversity in records relevant to adverse events, immunisation and health more broadly(406).

Data-linkage brings the potential to combine information and increase the volume of data-points available for analysis. Recognition of this potential is evidenced in global growth in data-linkage programmes, including the now decades-old Vaccine Safety Datalink in the US(296), which enables direct calculation of AEFI incidence through AEFI reporting being linked to vaccination records(447).

Within Australia there is long-standing recognition that direct linkage of immunisation registers with health outcome data would create opportunities for rapid, effective vaccine-safety investigations(203, 204): and further, that this would be internationally beneficial considering Australia’s history of being an “early adopter” of new vaccines(13). However, disparate and convoluted processes within Australian systems for accessing data (including authority to access) have compromised feasibility to conduct timely vaccine safety surveillance or epidemiological investigations(448).

Creating sizeable databases, or combinations of datasets, to give more records and therefore investigative power, is leading into the emerging field of “big data”(406, 449), whereby the high volume and highly varied data of electronic datasets, registries and social media are being interrogated for public health surveillance(450-452).

Exploration of signal detection methodologies using social media such as Facebook and Twitter and internet-based query are gaining popularity(450, 453). The high “noise” in big data, however, can be burdensome: a 3-year European study concluded social media for general signal detection was not recommended for this reason, although did suggest potential added value for studies in niche areas such as pregnancy

outcomes(454). Enhancements to adverse event recognition algorithms may broaden the scope for use of social media in pharmacovigilance(454).

Such large volumes of data, particularly unconstrained free text in social media, bring logistical issues challenging resources of human analysis and therefore use for pharmacovigilance signal detection(455). Thus there is a move towards the computational science domain of machine learning and artificial intelligence for management of “big data”(456).

This shift will bring new considerations into the context of system evaluations, bringing a need to move beyond measures of achieving objectives and maintaining economic value, but also to expand the boundaries of evaluation to include focus on “the dynamic and networked structure of information systems, on the contribution of diverse data, and on the added value of combining qualitative and quantitative information”(443).

9.4.2 “Methodological frontiers”

Extending beyond identifying signal events of frequency and rare AEFI there is a need for surveillance methods applicable to capture trends in at-risk or targeted immunisation groups such as pregnant women, diverse ethnicities and those with underlying co-morbidities. Likewise, increasing multi-vaccine schedules necessitates methods capable of investigating vaccine combinations, in addition to individual vaccines(428). These issues have recently been examined by Dodd *et al.* on behalf of the GACVS and presented in the position paper “Methodological Frontiers in Vaccine Safety: Qualifying available evidence for rare events, use of distributed data networks to monitor vaccine safety issues, and monitoring the safety of pregnancy interventions”(428).

The increasing advocacy for antenatal immunisation requires not only comprehensive AEFI surveillance during pregnancy and for pregnancy outcomes but also brings challenges in onward surveillance of AEFI arising in the child. Identification of the mother-child linkage in databases—or even dedicated antenatal immunisation registries(457)—is needed and especially such that time-distant AEFI presentations

among gestationally-immunised children can be captured and/or investigated(428, 458).

Surveillance for rare events requires large datasets or linked datasets to provide the data volume to capture rarities. It also requires the need to perceive the event as an AEFI: that is, consideration of recall bias in reduced perception of an association with immunisation for AEFI that occur distant in time from the immunisation: a bias likely exacerbated further when frequency in occurrence is low(428, 459). Longevity of data for retrospective searching of such events is beneficial, however the initiative to investigate may not always be statistical in origin but require intuition and astute observation of cases, linked with vaccination history(428).

Self-controlled study designs are gaining popularity to address these challenges of investigating safety based on observational data and within the domain of real-life immunisation practices, including concomitant vaccination(440, 460, 461).

Population-based health datasets each have their own vagaries in misclassification errors and bias in data(188). Therefore, appreciating the underlying data characteristics, presuming they are described, is essential when utilising methods that combine data from these error and bias prone datasets. This is particularly relevant with the accessibility to free-text fields in electronically held health administration datasets, encouraging their inclusion in large data analytics(462). Statistical models are increasingly being employed to attempt to correct for errors when combining such healthcare and electronic medical records(463).

This use of “real-world data” and “real-world evidence” is being embraced as the new state-of-art for safety assessments, taking the focus beyond reliance on randomised controlled trials for regulatory health decision-making(433). The European Medicines Agency has developed the “OPTIMAL” framework specifically to guide integration of real-world evidence in decision-making(464). As standards of rigour in observational studies continue to evolve and improve, embedding innovation into the evolution lifecycle in pharmaceutical development and deployment will become the norm(465).

The finesse will come through the “methodological frontiers” of exploring new designs, incorporating combinations of data mining, revised statistical methods being melding together with the ideas and data-analytic technologies from computational science of artificial intelligence and machine learning to better exploit large observational databases and “big data”(222, 466, 467).

9.4.3 Advancing vaccine deployment

Robust post-marketing surveillance clearly has benefits for existing immunisation programs but may also influence future vaccine development and the path of initiation into the market phase. In situations where disease risk is high and vaccine efficacy is sufficiently demonstrated, individuals may be more tolerant of some uncertainty in vaccine safety in order to progress an immunisation program(468, 469). For example, consider this in the context of Ebola vaccines(470, 471) or the demand for rapid vaccine development and deployment to avert a pandemic(441, 472).

In such a situations it may be reasonable to shift the emphasis of safety data collection from the pre-clinical trials to the post-marketing phase(302, 471). In the USA this concept is being explored as a pilot project for “adaptive licensing” whereby the national regulator (FDA) will consider a benefit–risk evaluation approach for release of pharmaceuticals, including vaccines(473). Likewise in Europe, the “*Innovation in Medicine Initiative*” has begun project called “*Advance*, to build a framework to rapidly deliver data on the benefits and risks of vaccines in actual use”(402, 474). Europe is testing a lifecycle approach aiming to streamline risk-benefit evaluation, from pre-market through to robust post-market safety, in the context of increasing regulatory flexibility towards enabling “adaptive licensing” of pharmaceuticals(475).

These strategies are controversial(183, 468). However, advances in vaccinology technology with non-viral mRNA vaccines that combine beneficial attributes of live-attenuated vaccines while avoiding some of the inherent safety limitations, make rapid generation of vaccine candidates and timely deployment a reality(472). The aspirational goal to deploy pandemic vaccines within days of discovering new virus strains is discussed in Ulmer’s eloquently titled “Vaccines 'on demand': science fiction or a future reality?”(17).

Never more has this aspirational vision been more pertinent than now as this thesis is submitted in the midst of a pandemic crisis with real prospect of development of “COVID-19 vaccines at pandemic speed”(16).

9.5 Conclusion

My doctoral research has been instrumental in identifying gaps; testing the hypothesised strategies and; offering the evidence-base to incrementally improve and optimise the SAEFVIC surveillance system.

The program of work from this thesis has demonstrated SAEFVIC as an effective and sustainable monitoring system, able to quickly detect AEFI signal events, reliably evaluate the event and therefore inform policy decision-making such that actions appropriate to the benefit-risk of vaccines can be made.

My studies have directly contributed to policy decisions for implementation and/or continuation of immunisation programs; incorporation of automated PRR analysis of AEFI in Victoria and Western Australia, and; expansion of funding for active AEFI surveillance to include older persons and a broader range of vaccines. In addition my research has informed further collaborative studies in vaccine pharmacovigilance, particularly in advancing signal detection through an integrated multimodal system.

Communicating my thesis research outputs regarding surveillance system attributes, opportunities and outcomes for vaccine safety, through the publications and conference presentations has ensured confidence in SAEFVIC and facilitated uptake of the AEFI surveillance platform by other jurisdictions. This has ultimately improved vaccine pharmacovigilance nationally and assisted in ensuring the safety of immunisation in the Australian community.

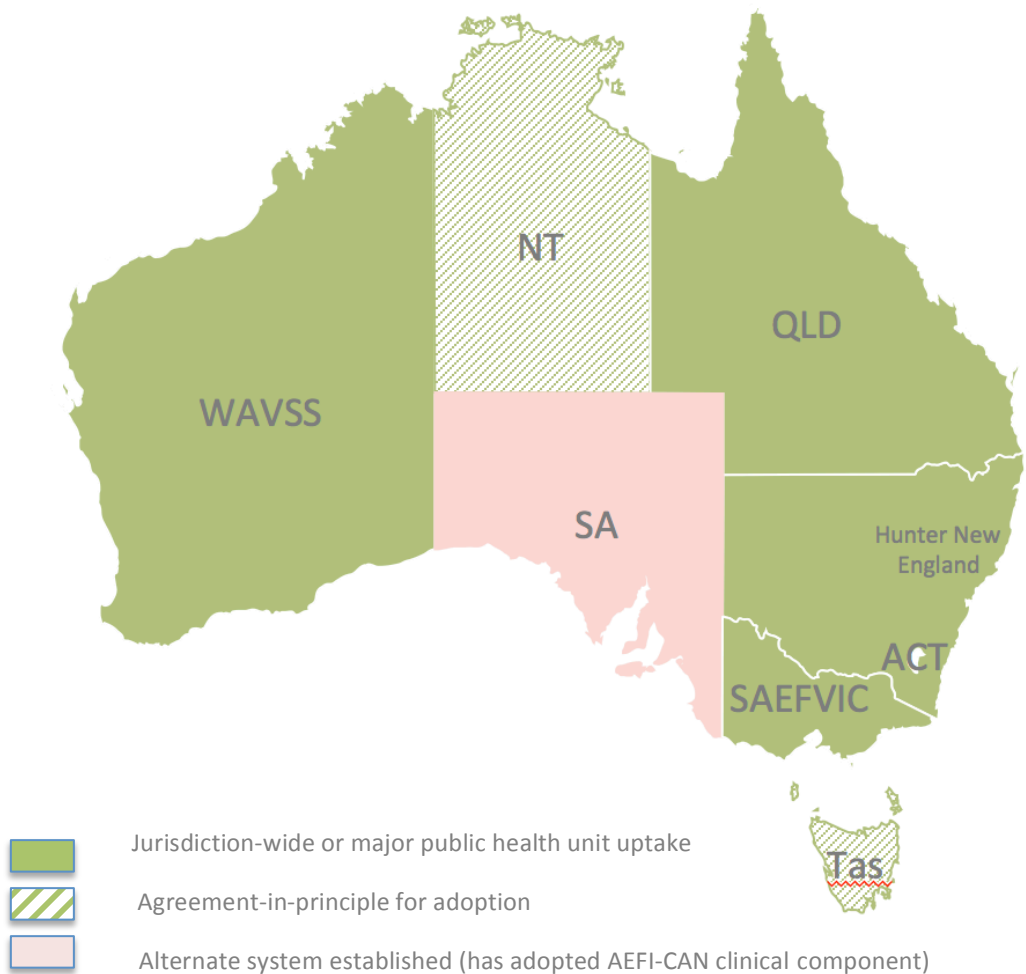
9.5.1 SAEFVIC as a national AEFI surveillance system

A premise for my doctoral research, in addition to strengthening pharmacovigilance, was to optimise SAEFVIC in anticipation of expansion to form a national AEFI surveillance platform. On conclusion of this body of work (2020) SAEFVIC provides leadership in the national AEFI surveillance arena, being the highest reporting

jurisdiction and consistently contributing over 40% of all AEFI reported nationally(170, 187). Furthermore, the SAEFVIC system has been expanded as the passive AEFI surveillance system used by Western Australia (WAVSS)(476), the Australian Capital Territory (ACT), selected public health units in NSW and Queensland and agreements are well-progressed with Northern Territory and Tasmania (Figure 11)(185).

The national expansion of the SAEFVIC system enables data consistency from the point of reporting; data collection; facilitates clinical verification—particularly for serious AEFI through the AEFI-CAN network—and comparability in analyses. While data are currently held in jurisdictional privacy-protected silos, there are opportunities for collaborative reporting and aggregation of data for signal detection. The balance of maintaining jurisdictional independence compared to the value of higher reporting has been previously discussed and will be an interesting aspect in analysis as this collaborative network moves forward(306).

Figure 11: Schematic of Australian jurisdictions adopting SAEFVIC surveillance system



9.5.1.1 *SAFEVAC and SAFESIG*

The leadership capability of SAEFVIC is in an expansion phase. SAEFVIC was established as a surveillance system with integrated clinical support services to provide for the immunisation needs of the individual as well as inform vaccine safety in Victoria(1). Through this doctoral research and other parallel and subsequent research activities, there is a growing transformative element for informing vaccine pharmacovigilance more broadly. The intention is to build on this capability and leadership through an expanded branch of SAEFVIC, nominally called SAFEVAC. SAFEVAC will provide guidance in the methodological side of AEFI surveillance and provide an umbrella platform for multi-jurisdictional research collaborations and presentation of findings.

The expanded surveillance capacity for signal detection, initiated through my doctoral work, is now being combined with ongoing development of the signal detection arm of SAEFVIC—newly designated as SAFESIG—building a consortium of data sources which can be explored for potential contribution to provide early signal detections(93). Recent explorations include post-immunisation re-presentations to general practice; emergency department presentations for both post-immunisation events and generically for syndromes that may arise following immunisation (for example, anaphylaxis)(188) and; data-mining of calls to medical helplines such as “Nurse-on-call”(93). As each of these are pre-existing administrative datasets, there are opportunities to automate extraction and conduct real-time monitoring, reducing information bias by precluding the need to identify the event as an AEFI and undertake the action of reporting.

These are exciting new developments, some of which will see their first airing at the forthcoming Public Health of Association of Australia (PHAA) Immunisation conference to be held in Perth, Western Australia in June 2020.

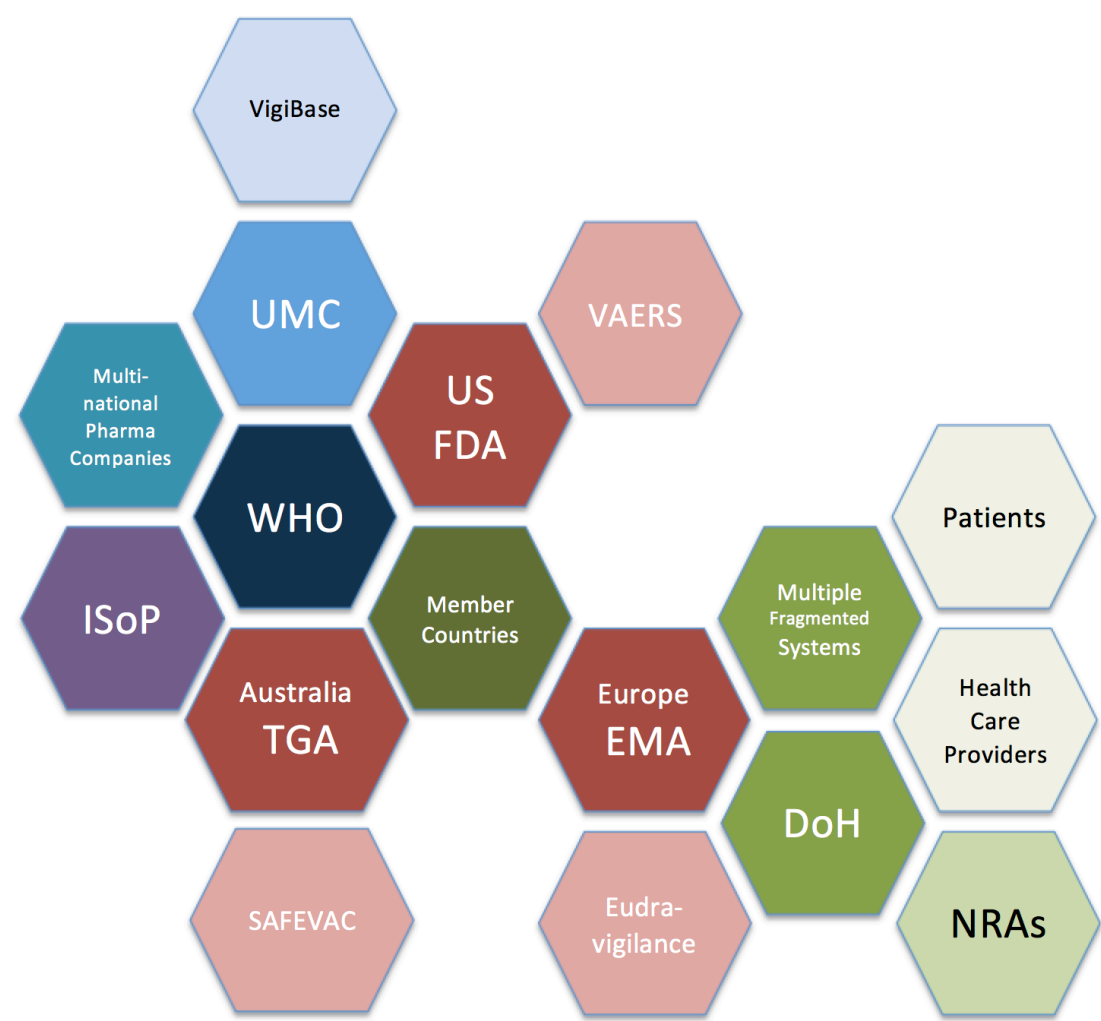
9.5.2 Contribution to global vaccine safety

SAEFVIC contributes greater than 40% of national AEFI data and with its semi-national expansion at conclusion of this PhD, is the major player in Australian AEFI

pharmacovigilance. Therefore, achieving the objective of my thesis in optimising SAEFVIC has ensured Australian pharmacovigilance meets global standards and expectations of a national AEFI surveillance system. With current ontological studies strengthening data compatibility for national and international collation it is anticipated that there will be further building of national collaborations, as well as links into international activities, including the World Health Organization’s UPPSALA monitoring centre and the Global Vaccine Safety Observatory(119, 477).

The literature review (Chapter 2) of this thesis provided a schematic outlining the global interaction of vaccine safety components (Figure 2 in Chapter 2). We propose to restate the international interactions, confident in highlighting Australia’s southern hemisphere leadership in informing vaccine pharmacovigilance and contribution to global vaccine safety surveillance (Figure 12).

Figure 12: Aspirational schematic of global bodies in pharmacovigilance



9.5.3 Finale

My doctoral research has provided practical findings that have been translated into action and embedded into SAEFVIC. Real-time investigation of vaccine safety issues has informed policy decisions on immunisation program delivery and ensured community confidence. Description of the system epidemiology has provided a foundation for research integrity. Individual studies have identified opportunities for improvement, guided amendments to data collection to better inform on at-risk populations; tested and implemented routine signal detection; established contemporary reporting and visualisation leading to an integrated surveillance platform supporting national expansion.

SAEFVIC is now embedded in four of the nine Australian jurisdictions—soon to be six—which markedly increases national capability to provide “comprehensive and effective post-licensure AEFI surveillance critical to maintain confidence in immunisation and inform evidence-based policy for vaccine safety”(1).

Put simply, SAEFVIC is leading Australia as a major southern hemisphere partner in global AEFI surveillance and ultimately making immunisations safer. I am proud to have made such a major contribution to this development through my doctoral research.

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Appendix 1

This article, published in 2011 and prior to this doctoral research, provides a foundational overview of the SAEFVIC surveillance system.

A1.1 Surveillance of adverse events following immunisation: the model of SAEFVIC, Victoria

Clothier HJ, Crawford, NW, Kempe A, Buttery, JP

Communicable Diseases Intelligence, 2011; 35(4):294-298

Short reports

SURVEILLANCE OF ADVERSE EVENTS FOLLOWING IMMUNISATION: THE MODEL OF SAEFVIC, VICTORIA

Hazel J Clothier, Nigel W Crawford, Ann Kempe, Jim P Buttery

Abstract

State-based adverse events following immunisation (AEFI) reporting systems in Australia demonstrate marked regional differences in surveillance methodologies and reporting rates. To improve AEFI services in Victoria, Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) was established in 2007. SAEFVIC comprises a central reporting enhanced passive surveillance system integrated with clinical services. AEFI may be reported by phone, fax or on-line. Immunisation nurse specialists follow up all reports, coupled with physician review as required. Supervised re-vaccination in a hospital environment, when appropriate, helps ensure clinical support for vaccinees, families and health-care providers. The *Brighton Collaboration*, the *Australian Immunisation Handbook* and in-house case definitions are used to categorise AEFI reports. In the first 3 years (2007–2010) of operation 3,265 reports were received, describing 4,293 AEFI. The number of reports received increased annually over the 3-year period. Seventy-six per cent of AEFI met one of 52 established case definitions and the remainder were recorded verbatim: 22% of reported AEFI were considered severe. Of 1,086 persons reporting an AEFI in 2009, 356 (36%) attended for a clinical consultation and 325 (83%) were revaccinated, of which 114 were day stay or overnight patients. Enhanced passive AEFI surveillance using integrated clinical services has been shown to improve adverse event reporting with reporting rates in Victoria increasing from 2.6 per 100,000 in 2003 to 13.5 per 100,000 per annum in 2009. This report describes the SAEFVIC service model and summarises outcomes and lessons learnt in the first 3 years of operation. *Commun Dis Intell* 2011;35(4):294–298.

Keywords: Surveillance, adverse event, immunisation, vaccine safety

Introduction

The international definition of an adverse event following immunisation (AEFI) is 'an unwanted or unexpected event following the administration of a vaccine(s). AEFI may be caused by a vaccine(s) or may

occur by coincidence: that is, it would have occurred regardless of vaccination'. AEFIs also include conditions that may occur following the incorrect handling and/or administration of a vaccine.

In Victoria prior to 2007, AEFI surveillance was conducted as a passive system whereby reports were sent directly to the Adverse Drug Reaction Unit (ADRU) in the Therapeutic Goods Administration (TGA) and reviewed by the Adverse Drug Reactions Advisory Committee (ADRAC), now replaced by the Advisory Committee on the Safety of Medicines (ACSOM). This system was known to be insensitive and AEFI events appeared to be significantly under-reported: the overall reporting rate per 100,000 population in 2002 being 2.6 in Victoria, compared with the Australian Capital Territory (22.5 per 100,000) and South Australia (10.8 per 100,000) where enhanced surveillance systems were already in place.^{1,2}

In May 2007, under contract with the Victorian Department of Health, an enhanced passive surveillance system known as Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) was initiated. SAEFVIC comprised a partnership led by the Murdoch Childrens Research Institute, with the Royal Children's Hospital, the Victorian Infectious Diseases Service at the Royal Melbourne Hospital and Monash Medical Centre. The service continues to provide Victorian-wide enhanced passive surveillance integrated with a clinical support service. Patients and their families, and immunisation service providers can access advice and support from expert immunisation nurses and physicians. The objectives of the system were to: increase the number of AEFI reports, to maximise confidence in the immunisation program for those who have experienced AEFI, and importantly, to provide clinical feedback directly to vaccinees and the AEFI reporters. Effective clinical communication is paramount for SAEFVIC to function effectively.

Aims

SAEFVIC aims to provide increased early detection and appropriate rapid response to AEFI in adults and children, integrated with clinical support for reporting health care workers and patients/families.

The intention is to enhance the passive surveillance of all significant or rare AEFI, regardless of causality. The surveillance information is used to detect vaccine safety 'signals', prompt action and maintain confidence in immunisation programs. This collaboration aims to deliver a system with world-leading sensitivity for Victorian health authorities to rapidly detect and research vaccine safety concerns, whether they are new trends or just temporally associated events.

This report describes the Victorian SAEFVIC service model and summarises outcomes in the first 3 years of operation.

Methods

Reporting

AEFI may be reported by phone, fax or, as of 2010, on-line. SAEFVIC encourages reporting from health care professionals, including immunisation providers and accepts self or parent reports. Reports sent by the vaccine service-provider directly to the TGA are re-directed back to SAEFVIC. Once assessed by a SAEFVIC immunisation nurse all reports are forwarded to the TGA.

Follow-up

Accredited immunisation nurses follow up all reports of AEFI and discuss with reporters the nature of the AEFI, any ongoing concerns and strategies for future vaccinations. Informed consent to contact the vaccinee or their guardian is normally provided at the time of the report or at the time of follow-up. The initial contact is by telephone and a minimum of three attempts made, before a letter is sent to the reporter to advise SAEFVIC has been unable to follow-up with the case.

Clinical review

All persons reporting a serious AEFI (requiring hospitalisation or having ongoing sequelae) or those who have concerns about future vaccinations are offered the option to attend a clinical review with a medical specialist. Clinics are available on a weekly basis at the Royal Children's Hospital and on a fortnightly basis at Monash Children's Hospital. In addition, there are monthly adult vaccine safety clinics in two tertiary centres, the Royal Melbourne Hospital and the Monash Medical Centre. Clinic appointments are on average for 30 minutes and are organised so that revaccination, if indicated, is possible at the time of the appointment. These may be provided in the hospital clinic under medical or nursing supervision if required. Supervised vaccination may be within the clinic, as a day patient or supported by an overnight admission depending on the severity and time of onset of previous AEFI.

For rural areas, SAEFVIC clinicians can liaise with a local clinician to provide a more convenient consultation option.

Passive surveillance

AEFI are recorded using standard case definitions where available (currently $n=52$), in the following order: the *Brighton Collaboration* ($n=23$),³ the *Australian Immunisation Handbook* ($n=22$)⁴ and then the definitions derived by SAEFVIC from published literature ($n=7$). The remaining AEFI are recorded verbatim using standard medical terminology where possible for consistency. Regular analysis for quarterly reporting to the Victorian Department of Health is conducted and case reports of points of interest are published in the Immunisation newsletter.

Additional analysis is conducted as required in response to local, national or international concerns or in response to possible safety signals or unusual trends noticed in the AEFI data. AEFI rates are calculated by the type of vaccine delivered for those vaccines recorded on the Australian Childhood Immunisation Register (ACIR). This means the analysis is limited to children under 7 years of age and will be affected by any under-reporting to ACIR.⁵ Additional calculations are possible if appropriate denominator data are available, for example the Department of Health records of vaccine doses distributed.

SAEFVIC contributes to national AEFI surveillance by forwarding reports to the TGA. As an additional vaccine safety review, SAEFVIC also reviews all TGA AEFI summaries forwarded to each state, in collaboration with the Immunisation Section of the Victorian Department of Health.

Data analysis

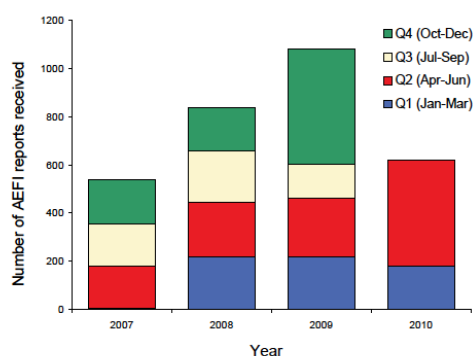
AEFI reported to SAEFVIC from 1 July 2007 to 30 June 2010 were analysed by number, AEFI symptoms reported and population-based reporting rate. Clinical review data were analysed for reports received for the calendar year 2009. Analyses were conducted using Microsoft Excel and STATA 11.0. Australian Bureau of statistics estimated resident population data were used to calculate AEFI rates.

Results

For the 3-year period July 2007 to June 2010, 3,265 reports describing 4,293 AEFI were received. Between 1 and 6 separate AEFI case definitions were extracted in relation to each report received. A total of 5,648 vaccines were administered to the subjects of AEFI reports in the 3 year period with between 1 and 5 vaccines included in each of the AEFI reports in this period. The number of reports

received increased in each 12-month period, from 804 in 2007–2008 to 1,336 in 2009–2010. There was a notable increase observed in the fourth quarter of 2009 and second quarter of 2010 (Figure 1). The first increase coincided with the release of the H1N1 2009 pandemic influenza vaccine (PANVAX®) and the second increase coincided with the release of the trivalent seasonal influenza vaccine when more febrile seizures in children were noted (Figure 1).⁶

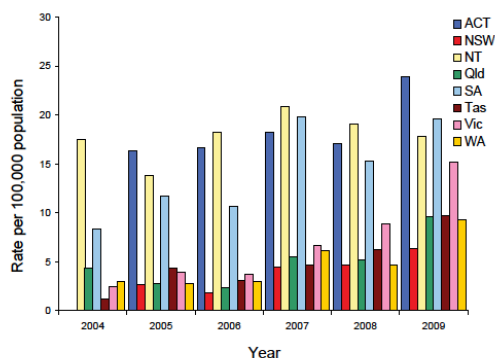
Figure 1: Number of adverse events following immunisation reports received, SAEFVIC, May 2007 to July 2010, by year and quarter



AEFI reporting rates per 100,000 population increased from baseline reporting rates of 2.6 per 100,000 in 2003, prior to SAEFVIC commencing operation, to 13.5 per 100,000 per annum in 2009 (Figure 2).^{7,8}

Of all 4,293 AEFI reports, 3,262 (76%) were classified according to previously discussed case definitions. The most frequently reported AEFI were: injection site reactions (minor, common or expected) 987

Figure 2: Adverse events following immunisation reporting rates per 100,000 population, 2003 to 2009, by state or territory^{7,8}



(23%); fever ($\geq 38^{\circ}\text{C}$) 472 (11%); rash 429 (10%); urticaria 300 (7%); and vasovagal episode 215 (5%). Of all 4,293 AEFI reports, 944 (22%) were considered serious (requiring hospitalisation or having ongoing sequelae). Of the serious AEFI reported there were 26 cases of anaphylaxis, 16 intussusception and 32 afebrile seizures. Three deaths were reported following vaccination. The deaths were due to ovarian cancer, sudden infant death syndrome and a car accident. Review by SAEFVIC clinicians of the 3 deaths did not support a likely aetiological association between vaccination and subsequent death.

An increased proportion of reports received by SAEFVIC related to people who required advice prior to vaccination. These types of reports increased from one in 2008 to 75 or 10% of all reports received in the first 6 months of 2010. The main concern raised related to the influenza vaccine for individuals with a past history of egg allergy. These reports are recorded on the database as 'non-events' in order to provide clarity that no adverse event has occurred.

Of the 1,086 people for whom AEFI were reported in 2009, 356 (36%) attended for clinical review. Of the 41 people who presented in 2009 with concerns prior to receiving vaccine, 33 (80%) also attended for clinical review. Of 356 clinic attendees, 325 (83%) continued with vaccination, 95 (26%) were vaccinated in a hospital setting and 19 (6%) were admitted as day or overnight patients for additional monitoring.

In 2010, most of the AEFI reports were sent directly to SAEFVIC from across Victoria, with only 2 reports being redirected back from the TGA. This was a decrease compared with the 85 reports (19% of all reports received) in 2007, which was the first year of the program.

Discussion

In the 3 years following the establishment of SAEFVIC as a dedicated Victorian passive AEFI surveillance system, the number of AEFI reported increased. The Victorian AEFI reporting rate of 13.8 per 100,000 population, is now closer to that of similar sized states.⁸

Scheduled and ad hoc analyses of data have identified and permitted further investigation of potential immunisation concerns arising during the review period. In 2007, following introduction of the 4-valent human papillomavirus (4vHPV) vaccine, SAEFVIC investigated potential signals such as an event of mass psychogenic illness occurring in school-aged girls following administration of the 4vHPV vaccine⁹ and later a review of all cases of syncope and seizures post the 4vHPV vaccine.¹⁰ SAEFVIC has reported on rare AEFI cases such as 4vHPV vac-

cine associated lipoatrophy, measles-mumps-rubella vaccine associated orchitis, and prolonged rotavirus vaccine excretion in an infant diagnosed with severe combined immunodeficiency.^{11–13} SAEFVIC has also been involved in supporting active surveillance of intussusception following rotavirus vaccine.¹⁴

Offering vaccination under an appropriate level of supervision permits adequate medical support in the event of a recurrence and appears to improve parental, adult vaccinee and community confidence, in the immunisation program. Stringent clinical review and monitoring for recurrence of AEFI has enabled SAEFVIC to provide evidence-based advice for administration of vaccine to infants experiencing apnoea as an AEFI.¹⁵ Most importantly, it also allows us to document the risk of recurrence of AEFI; an area where current evidence is sparse.

In the absence of a more systematic, centralised, national AEFI surveillance system, we believe SAEFVIC presents a suitable model for enhanced passive surveillance of AEFI. The link between the reporting system and access to individualised clinical advice and possible vaccination or re-vaccination under medical supervision in those with a previous AEFI, provides an incentive for the initial reporting of AEFI. A vaccine safety service was established in Western Australia based on the SAEFVIC model.

SAEFVIC has an advisory board of stakeholders including local government, immunisation nurses, physicians and general practitioners. The board meets annually and assists us to improve the reporting system, the clinical service, and communication strategies. The introduction of new vaccines to the National Immunisation Program such as HPV, rotavirus and monovalent H1N1 vaccine, meant the service has had to adapt rapidly and has been greatly enhanced through the electronic reporting function introduced in 2010. Future enhancements being considered are to improve the compatibility with other state reporting systems, reporting AEFI rates by vaccines administered and maximising reporting from immunisation providers.

Conclusion

Enhanced passive AEFI surveillance linked to an integrated clinical immunisation service has been shown to improve AEFI reporting within Victoria and has contributed to the detection and investigation of both potential and actual AEFI signals.

Acknowledgements

We gratefully acknowledge the contribution of SAEFVIC staff past and present, in particular Susan

Rogers, Sonja Elia, Jenny Royle, Theresa Lazzaro, Miranda Pellisier, Julie-Anne Quinn and Georgie Lewis.

We also acknowledge our SAEFVIC Advisory Board and the Immunisation Section, Department of Health, Victoria.

Conflict of interest

NWC and JPB have acted as chief investigators for epidemiological studies sponsored by vaccine manufacturers (CSL) and serological testing (Merck). Industry sourced honoraria for sitting on advisory boards (NWC), data safety monitoring boards (JPB), lecturing (NWC) and travel expenses for attendance at scientific meetings, are paid directly to an administrative fund held by Murdoch Childrens Research Institute.

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Appendix 2

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A2.1.1 When volume counts: investigating a spike in serious adverse neurological events following immunisation

Hazel J Clothier, Jock Lawrie, Nigel W Crawford and Jim P Buttery

Public Health Association Australia Immunisation Conference, Perth, June 2020

Background

Serious adverse neurological events (SANE) are known rare adverse events following immunisation (AEFI), particularly with influenza vaccines. They can also occur with temporal association to immunisation without causal association. In 2018 a spike in SANE reported to SAEFVIC, the Victorian AEFI surveillance system, was observed, triggering a signal investigation.

Methods

AEFI reported to SAEFVIC from 2008-2018 were analysed using Microsoft Power BI. SANE were defined as reports of acute disseminated encephalitis, Guillain Barré syndrome, multiple sclerosis, optic neuritis or transverse myelitis. Epidemiology was described by case demographics and vaccines administered. Weekly reporting and annual comparisons were analysed as counts, reports per vaccine doses distributed and as proportional reporting ratio (PRR) across all vaccines and the influenza vaccines subgroup. Signal thresholds were $PRR \geq 2$ and Chi-squared ($ChSq$) ≥ 4 .

Results

SAEFVIC received 12 reports of SANE in 2018, higher than any previous year of reporting (range 0 to 7). SANE were reported for paediatric and adult vaccinees receiving a broad range of vaccines. The PRR of SANE across all vaccines was significantly higher in 2018 compared to previous years (PRR 2.51, $ChSq$ 6.78). However, influenza vaccine subgroup analyses dissipated the 2018 SANE reporting disproportionality signal (PRR 1.57, $ChSq$ 0.48).

Conclusion

PRR is a useful tool to for investigating AEFI reporting signals. The increased frequency of SANE reports observed in 2018 was hypothesised to be a consequence of increased influenza vaccine administration. This signal was reported to the Therapeutic Goods Administration and is the subject of a national clinical case review.

A2.1.2 Improving vaccine safety surveillance using business intelligence software: Victoria, Australia

Hazel J Clothier, Jock Lawrie, Melissa A Russell and Jim Buttery

New Zealand Immunisation Conference, Auckland, September 2019

Background

SAEFVIC, the vaccine safety surveillance system of Victoria, Australia, commenced in 2007. A structured evaluation in 2018 demonstrated improved reporting of adverse events following immunisation (AEFI) and utility of the data for the investigation and validation of AEFI signals. However, it also highlighted limitations in de novo signal detection. We explored application of proportional reporting ratio (PRR) as an industry- standard signal detection algorithm, validated performance on two known signal events and integrated with business intelligence software to provide a platform for visualisation and detection of AEFI signal events

Methods

Passive AEFI surveillance reports from 2008-2017 relating to seasonal influenza vaccines were accessed from the SAEFVIC database. PRRs were calculated for two vaccine-event categories: fever and allergic AEFI. Signal detection sensitivity for two known signal events were determined using cumulative data by individual year and cumulative for all previous years. Signal event thresholds of $PRR \geq 2$ and Chi-square ≥ 4 were applied. Data were analysed using Microsoft Power business intelligence software (Power BI).

Results

PRR provided sensitive signal detection when calculated cumulative by year or by all previous years. Known signal events were detected 15 and 11 days earlier than traditional methods used at the time of actual events. Sub-analysis by vaccine brand supported hypotheses of brand-specific signals. Analysis in Power BI provided effective and efficient visualisation and interpretation.

Conclusion

Use of business intelligence software simplified automation of signal detection and aided visualisation for rapid interpretation. PRR identified a loud (febrile) and quieter

(allergy) signal in the SAEFVIC data. Incorporating these routinely offers opportunities to improve vaccine pharmacovigilance and detect important safety signals much earlier than previously.

A2.1.2.1 Presentation

SAEFVIC

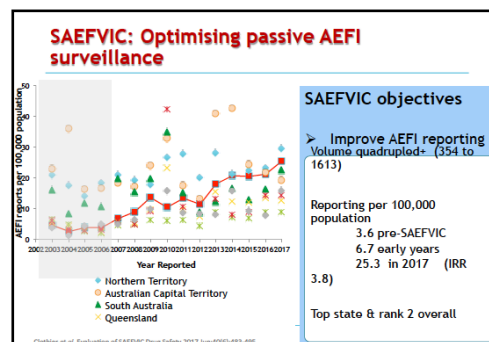
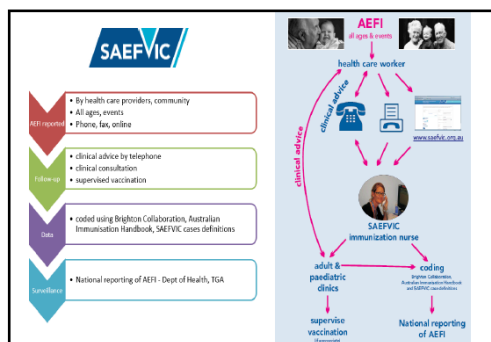
Improving vaccine safety surveillance using business intelligence software: Victoria, Australia

Hazel Clothier
Jock Lawrie, Nigel Crawford, Melissa Russell, Jim Buttery

SAEFVIC: Surveillance of Adverse Events following Vaccination in the Community

- Enhanced passive AEFI surveillance
- All ages integrated with clinical support

Clothier et al. The model of SAEFVIC. CDI



SAEFVIC: Optimising passive AEFI surveillance

SAEFVIC objectives

- Improve AEFI reporting
- Detect, validate & inform

Signal Validation & inform - excellent
Regular reporting to stakeholders
Facilitate research & policy direction

Signal detection - opportunities
Lack of new detection initiated on clinical suspicion
No routine statistical algorithm

Adverse events following vaccination of older people may be under-reported

SAEFVIC: Optimising passive AEFI surveillance

SAEFVIC objectives

- Improve AEFI reporting
- Detect, validate & inform on AEFI signals
- Maintain consumer Individual Confidence - Good

Clinical review ~30%

The decline in the number of people getting the influenza vaccine is a startling trend that is unnecessarily jeopardising peoples' health.

2010 AEFI event - Fluvax® fever & febrile seizure

Flu vaccination ban goes national after fever, convulsions in children

CHRIS THOMSON
April 23, 2010



P K Armstrong et al. BMJ Open 2011;1:e000010

SAEFVIC

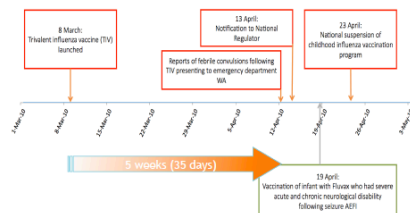
2010 AEFI event - Fluvax® fever & febrile seizure



Saba Botton: 11 months

SAEFVIC

2010 AEFI event - Fluvax® fever & febrile seizure



P K Armstrong et al. BMJ Open 2011;1:e000010

SAEFVIC

SAEFVIC

Faster detection of real problems...

Decade of data ✓

Analytic methods ?

Visualisation ?



Proportional Reporting Ratio

	AEFI of interest	Other AEFI	Sum
Vaccines of interest	a	b	a+b
Other vaccines	c	d	c+d
Sum	a+c	b+d	a+b+c+d

$$PRR = \frac{a/(a+b)}{c/(c+d)}$$

Thresholds:

- a minimum vaccine-event case-count (a) of 3
- signal alert threshold of PRR ≥ 2
- statistical significance test of ChiSq ≥ 4

"Relative risk"

Disproportionality

Computationally

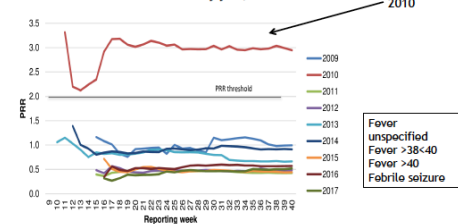
uncomplicated

Precedence in EU/US

SAEFVIC

Proportional Reporting Ratio

Influenza vaccines & febrile AEFI by year, 2008-2017



Note: No fever AEFI were reported in 2008

SAEFVIC

PRR - Influenza vaccines and febrile AEFI

2010 vs all-previous years

2010 by Influenza vaccine band

SAEVIC

Timeline of events:

- 1-Mar-09
- 8-Mar-09: Trivalent influenza vaccine (TIV) launched
- 13-Apr-09: Notification to National Registrar
- 23-Apr-09: National suspension of childhood influenza vaccination program
- Reports of febrile convulsions following TIV presentation to emergency department (VA)
- 19 children with severe acute and chronic neurological disability following seizure (AEI)
- 5 weeks (from start of reports to suspension)
- 3 weeks (from suspension to identification of children)

Outcome: 19 children with severe acute and chronic neurological disability following seizure (AEI)

Source: *Outlier of early signal detection with PRR, submitted to PlosOne*

SAEFCV

Proportional Reporting Ratio

Influenza vaccines & allergy-related AEFI by year, 2008-2017

PRR

PRR threshold

Reporting week

2015

2008
2009
2010
2011
2012
2013
2014
2015
2016
2017

Anaphylaxis
Allergic reaction-general
Urticaria/allergic rash

PRR - Influenza vaccines and allergic AEFI

2015 vs all-previous years

Report week	Fluorix PRR	Chik PRR
10	3.5	0.2
11	3.5	0.2
12	3.5	0.2
13	3.5	0.2
14	3.5	0.2
15	3.5	0.2
16	3.5	0.2
17	3.5	0.2
18	4.0	0.2
19	3.5	0.2
20	3.5	0.2
21	3.5	0.2
22	3.5	0.2
23	3.5	0.2
24	3.5	0.2
25	3.5	0.2
26	3.5	0.2
27	3.5	0.2
28	3.5	0.2
29	3.5	0.2
30	3.5	0.2
31	3.5	0.2
32	3.5	0.2
33	3.5	0.2
34	3.5	0.2
35	3.5	0.2
36	3.5	0.2
37	3.5	0.2
38	3.5	0.2
39	3.5	0.2
40	3.5	0.2
41	3.5	0.2
42	3.5	0.2
43	3.5	0.2
44	3.5	0.2
45	3.5	0.2
46	3.5	0.2
47	3.5	0.2
48	3.5	0.2
49	3.5	0.2
50	3.5	0.2
51	3.5	0.2
52	3.5	0.2
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54	3.5	0.2
55	3.5	0.2
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57	3.5	0.2
58	3.5	0.2
59	3.5	0.2
60	3.5	0.2
61	3.5	0.2
62	3.5	0.2
63	3.5	0.2
64	3.5	0.2
65	3.5	0.2
66	3.5	0.2
67	3.5	0.2
68	3.5	0.2
69	3.5	0.2
70	3.5	0.2
71	3.5	0.2
72	3.5	0.2
73	3.5	0.2
74	3.5	0.2
75	3.5	0.2
76	3.5	0.2
77	3.5	0.2
78	3.5	0.2
79	3.5	0.2
80	3.5	0.2
81	3.5	0.2
82	3.5	0.2
83	3.5	0.2
84	3.5	0.2
85	3.5	0.2
86	3.5	0.2
87	3.5	0.2
88	3.5	0.2
89	3.5	0.2
90	3.5	0.2
91	3.5	0.2
92	3.5	0.2
93	3.5	0.2
94	3.5	0.2
95	3.5	0.2
96	3.5	0.2
97	3.5	0.2
98	3.5	0.2
99	3.5	0.2
100	3.5	0.2

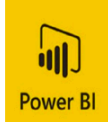
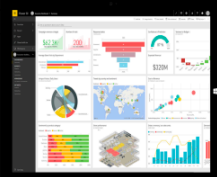
2015 by Influenza vaccine brand

Reporting week	Fluorix PRR	Fluorix-4 PRR	Influenza PRR	Influenza-Chik PRR
101113	1.5	1.5	1.5	1.5
111113	1.5	1.5	1.5	1.5
121113	1.5	1.5	1.5	1.5
131113	1.5	1.5	1.5	1.5
141113	1.5	1.5	1.5	1.5
151113	1.5	1.5	1.5	1.5
161113	1.5	1.5	1.5	1.5
171113	1.5	1.5	1.5	1.5
181113	1.5	1.5	1.5	1.5
191113	1.5	1.5	1.5	1.5
201113	1.5	1.5	1.5	1.5
211113	1.5	1.5	1.5	1.5
221113	1.5	1.5	1.5	1.5
231113	1.5	1.5	1.5	1.5
241113	1.5	1.5	1.5	1.5
251113	1.5	1.5	1.5	1.5
261113	1.5	1.5	1.5	1.5
271113	1.5	1.5	1.5	1.5
281113	1.5	1.5	1.5	1.5
291113	1.5	1.5	1.5	1.5
301113	1.5	1.5	1.5	1.5
311113	1.5	1.5	1.5	1.5
321113	1.5	1.5	1.5	1.5
331113	1.5	1.5	1.5	1.5
341113	1.5	1.5		

Business Intelligence Software

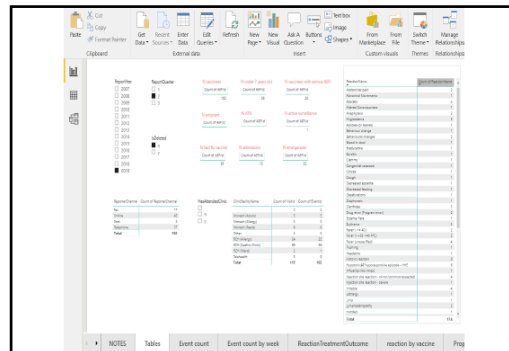
Any data, anywhere, any time

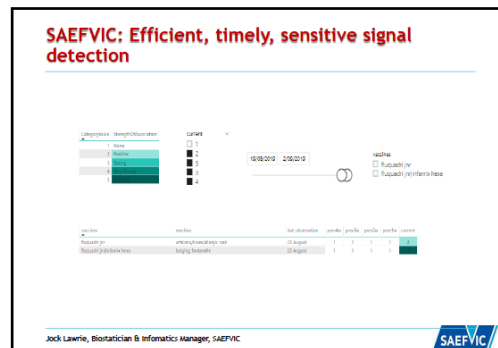
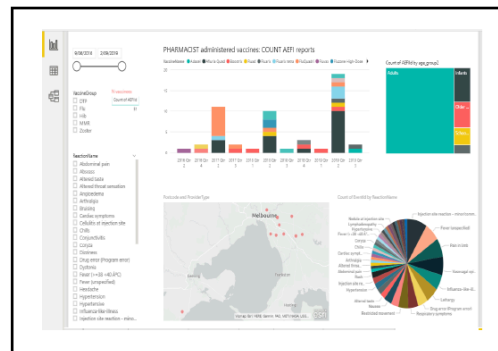
Power BI is a cloud-based business intelligence tool that gives you a collection of data from different business data sources. It allows you to create and share interactive reports and dashboards with your team. It also allows you to create and share reports and dashboards with your team. It also allows you to create and share reports and dashboards with your team.



<https://powerbi.microsoft.com/en-us/>

SAEVC





A2.1.3 SAEFVIC: Impact of implementing enhanced passive surveillance for adverse events following immunisation

HJ Clothier, NW Crawford, M Russell, H Kelly, JP Buttery

Public Health Association Australia Immunisation Conference, Adelaide, 2018

Background

Following concerns regarding low reporting rates of adverse events following immunisation (AEFI) in Victoria, the Victorian DHHS funded a collaborative partnership to conduct enhanced passive AEFI surveillance system, integrated with clinical services, commencing 2007.

Objective

To evaluate “SAEFVIC” surveillance against its stated objectives at commencement: improve AEFI reporting; provide AEFI signal detection; and maintain consumer confidence in vaccination .

Methods

We conducted a retrospective structured desktop evaluation of AEFI reporting received by SAEFVIC from 2007–2014.

Results

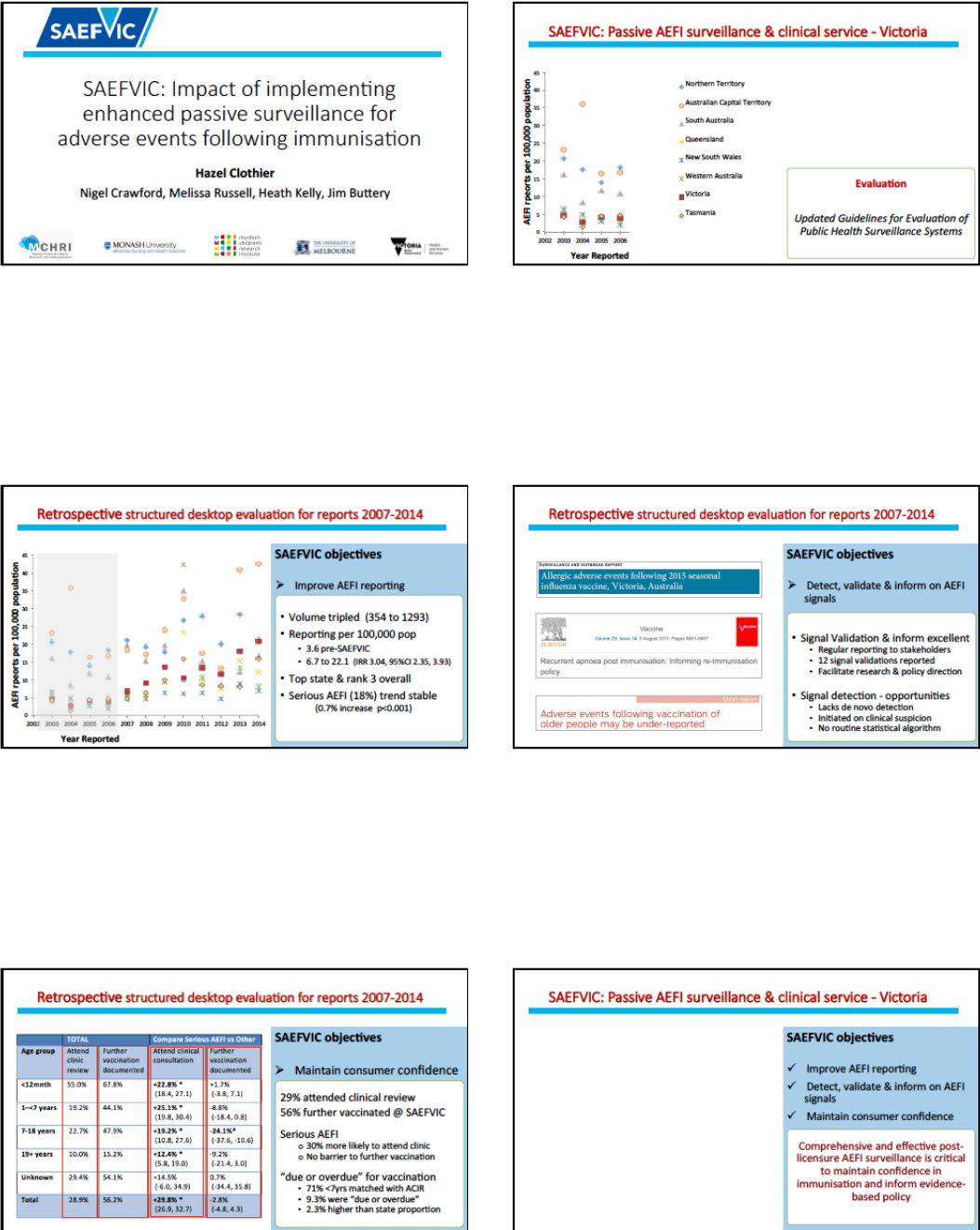
AEFI reporting tripled since SAEFVIC commenced in 2007 (IRR 3.04; 95%CI 2.35, 3.93), raising Victoria to the lead jurisdiction by AEFI reports and rank third by reporting rate nationally. Data were utilised to investigate potential signal events and inform vaccine policy. Signal detection required clinical suspicion by surveillance nurses, or prior vaccine-specific concerns. A majority of patients experiencing AEFI continued with further vaccinations successfully, with vaccination post-AEFI documented for 56% (95%CI 54.1, 58.4) and the proportion of children due or overdue for vaccination only 2.3% higher for those reporting AEFI compared to the general population. No other metrics to measure the contribution of SAEFVIC to consumer confidence were identified.

Conclusion

SAEFVIC has improved AEFI surveillance, facilitated signal detection, investigation and validation, and supported revaccination after AEFI. Further work is needed to determine impact upon consumer confidence in immunisation. Expansion of the

system nationally through AusVaxSafety and the AEFI-Clinical Assessment Network will improve capacity and capability of vaccine pharmacovigilance, particularly through data consistency and linkage across jurisdictions and with the Therapeutic Goods Administration.

A2.1.3.1 Presentation



A2.1.4 Pharmacovigilance of allergic adverse events following 2015 seasonal influenza vaccination, Victoria

Hazel Clothier, Nigel Crawford, Melissa Russell, Heath Kelly, Jim Buttery

Public Health Association Australia Immunisation Conference, Brisbane, June 2016

Background

The Victorian vaccine safety surveillance service, SAEFVIC, was alerted to a possible increase in allergy-related adverse events following immunisation (AEFI) with trivalent influenza vaccines (TIV) in week two of the 2015 influenza vaccine program. We describe SAEFVICs investigation to define the signal event and inform on risk-benefit for continuation of the vaccine program.

Analysis

Allergy-related AEFI were defined as anaphylaxis, angioedema, urticaria or generalised allergic reaction. Using this definition we analysed the AEFI reports received in 2015 to those in previous years by influenza vaccine brand; vaccinee age and time to symptom onset and reported as proportions and reporting risk (RR) per 100,000 vaccine doses distributed.

Results

The initial investigation in May showed an increased proportion of allergy-related AEFI compared to the whole of 2014 (25% vs 12%) reported predominantly in adults. While the overall 2015 AEFI with TIV reporting risk of 11.8 reports per 100,000 doses distributed was similar to 2011–2014 combined data, we identified a near-doubling risk for allergy-related AEFI. The allergy-related reporting risk in 2015 being 2.4 compared to the combined risk of 1.3 in 2011–2014, when comparable data were available, with the difference being 1.78 (95%CI 1.14, 2.80). No difference by brand or increase in anaphylaxis (n=6) was identified.

Conclusion

Early suspicion and timely investigation confirmed a marginal increase in generalized allergy-related AEFI occurring in adults with no correlation to any specific vaccine brand or indication of severe clinical outcomes above historical AEFI reporting parameters. Such demonstrations of effective vaccine pharmacovigilance are paramount for ensuring the safety of vaccination programs.

A2.1.4.1 Presentation

Murdoch Childrens Research Institute
Gipster Lab, South St John

Allergic adverse events following 2015 seasonal influenza vaccination Victoria

Hazel Clothier
Nigel Crawford
Melissa Russell
Jim Buttery

SAEFVIC

Murdoch Childrens Research Institute
Gipster Lab, South St John

Seasonal influenza vaccination



- April to September
- Targets at-risk groups
- Tri-valent vaccines (3 brands)

Increased monitoring

- febrile seizure in <5yr olds (2010)
- egg allergy reactions

SAEFVIC

Murdoch Childrens Research Institute
Gipster Lab, South St John

Adverse Event Following Immunisation (AEFI)

Vaccine product related	• Local reaction at injection site
Vaccine quality defect	• Manufacturing contamination
Immunisation administration error	• Adult dose administered to a child • Failure to mix diluent
Anxiety-related	• Vasovagal syncope in adolescents
Coincidental	• Fever from a circulating viral infection (temporal association)

SAEFVIC

Murdoch Childrens Research Institute
Gipster Lab, South St John

AEFI surveillance in Victoria

- AEFI reported
- Follow-up
- Clinic option
- Cases defined
- Surveillance



SAEFVIC

Murdoch Childrens Research Institute
Gipster Lab, South St John

Initial signal alert

May 3rd 2015 (week 2)
Immunisation nurses observation
"increase in allergic AEFI reports"

44 AEFI-TIV reports

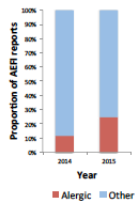
- 11 allergic type reactions
- Most (89%) were adults
- Different vaccine brands



SAEFVIC

Murdoch Childrens Research Institute
Gipster Lab, South St John

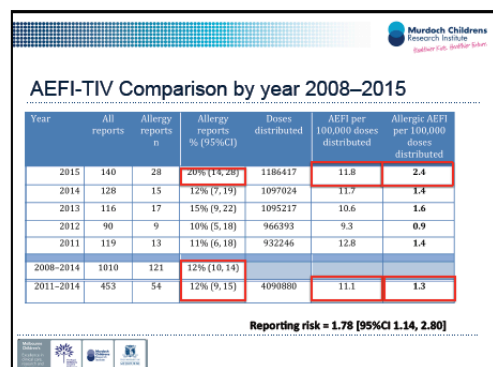
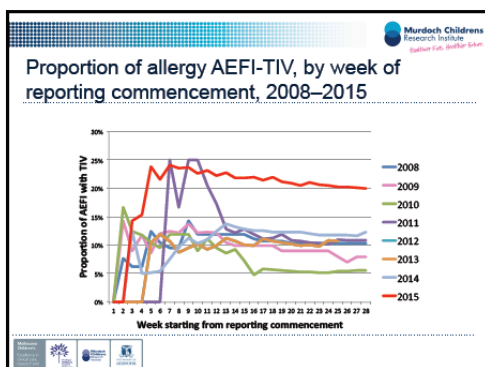
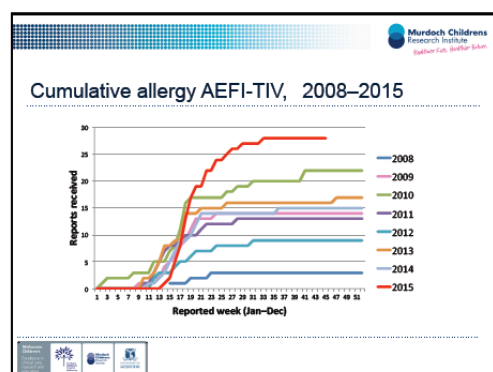
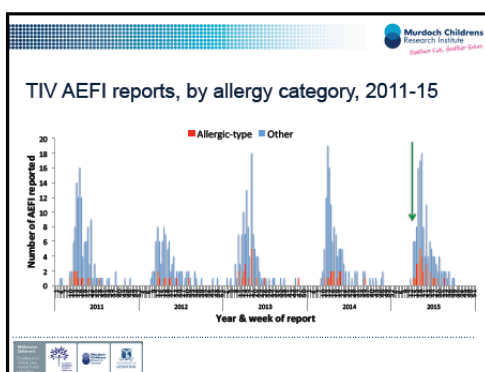
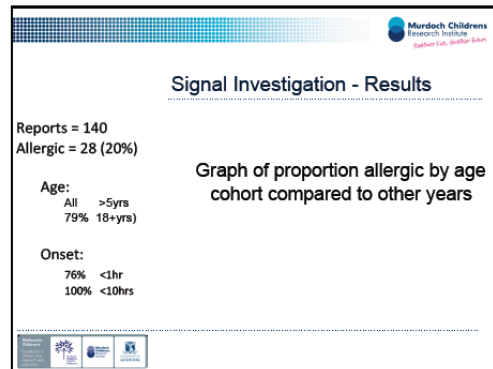
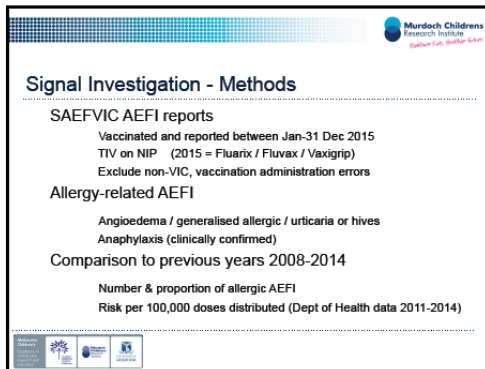
Preliminary investigation & Action

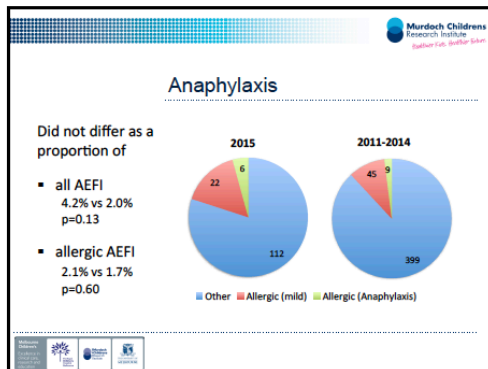


? Increase in AEFI reports	NO
? Increase in allergy AEFI	YES
25% vs 12% in 2014	
RR 2.13 [1.00, 4.56 95%CI]	
? Increase in anaphylaxis	NO
21% vs 27% [p=0.70]	
? Other jurisdictions	MAYBE

ACSOV: Further investigation needed to confirm a signal
No urgent program action indicated

ACSOV meeting statement, Meeting 8, 11 June 2015
<https://www.ssa.gov.au/acsov/meeting-statement>





AEFI-TIV in 2015 – comparison by vaccine brand

Brand	All reports	Allergic reports (n, %)	Anaphylaxis	Vaccine doses distributed	AEFI reports per 100,000 doses distributed	Allergic AEFI reports per 100,000 doses distributed	Comparison of Fluorix to other brands RR (95% CI)
Fluarix**	36	7 (19%)	2	212605	16.9	3.3	reference
Fluvax*	44	8 (18%)	2	586250	7.5	2.4	2.41 (0.90, 6.44)
Vaxigrip* (inc. inv)	43	9 (21%)	2	387562	11.1	2.3	1.42 (0.53, 3.79)
Brand unknown	17	4 (24%)	0	n/a	n/a	n/a	
Total	140	28 (20%)	6	1186417	11.8	2.4	

* Fluorix* was the funded vaccine for Victorian HCW in 2015

- ### Signal investigation - Discussion
- Challenge to monitor & compare AEFI risk
- Seasonal vaccination program timing varies
 - Brand distribution varies by year and target population
 - No register of all vaccination encounters
 - Active surveillance targets <5yrs
 - Timeliness of national data availability has limitations
 - Variation in jurisdictional surveillance methodologies
- Influenza vaccine pharmacovigilance
- ~Annual vaccine strain variation
 - Adoption of quadrivalent vaccines
 - Reactogenicity variability (even within stable manufacturing)
 - Timely information to inform risk profile

Conclusion

Sensitive pharmacovigilance

Mild allergic signal event

- Generalised allergic symptoms
- Across all utilised brands
- Risk-benefit for vaccination maintained

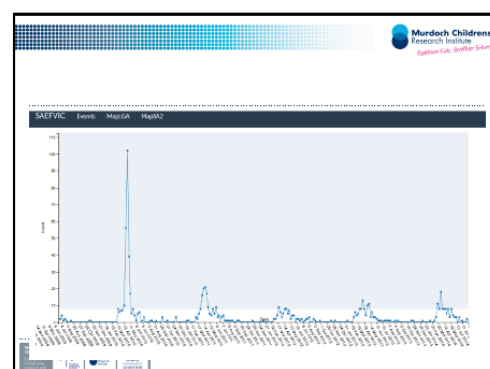
Variable reactogenicity & strain variation necessitates effective seasonal influenza vaccine pharmacovigilance

Allergic adverse events following 2015 seasonal influenza vaccination Victoria

Hazel Clothier

Nigel Crawford
Melissa Russell
Jim Buttery

SAEFVIC



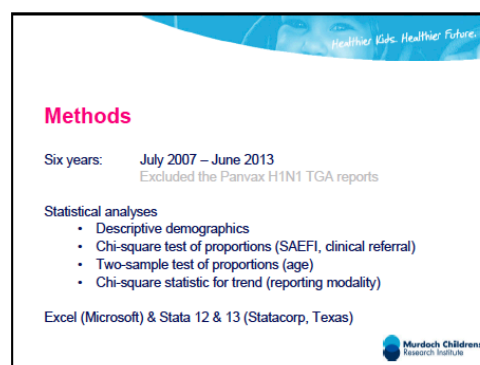
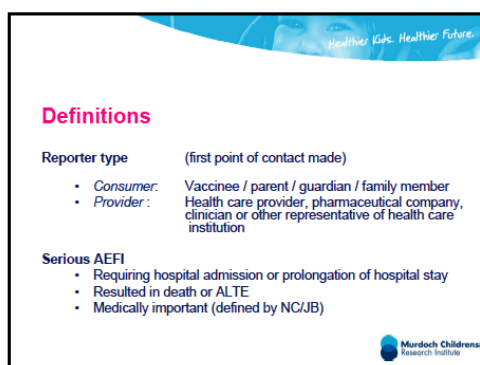
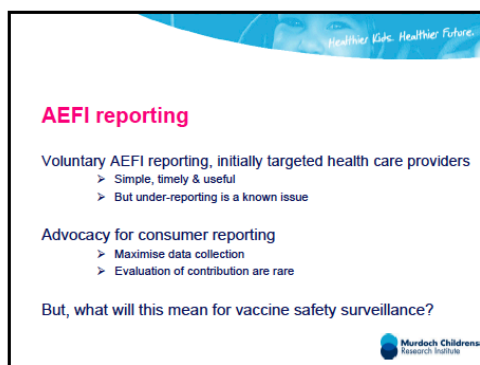
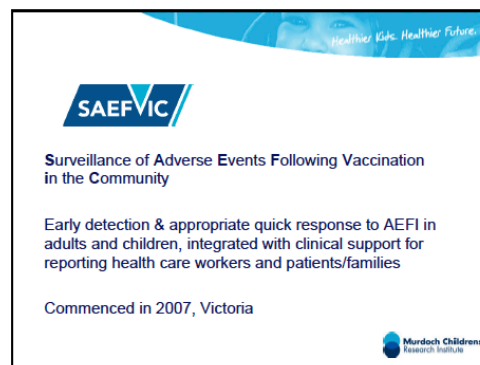
A2.1.5 Consumer adverse event reporting strengthens vaccine safety surveillance

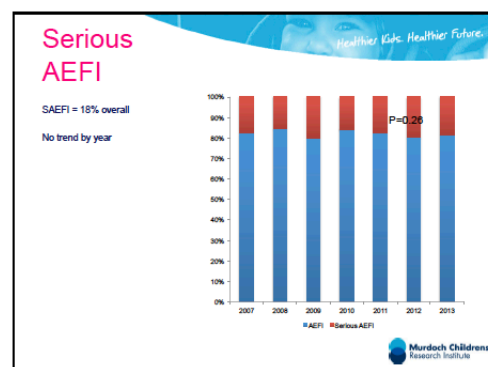
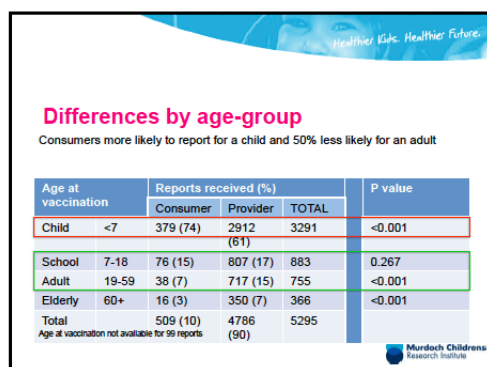
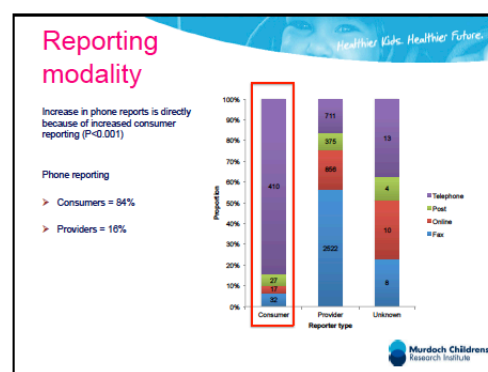
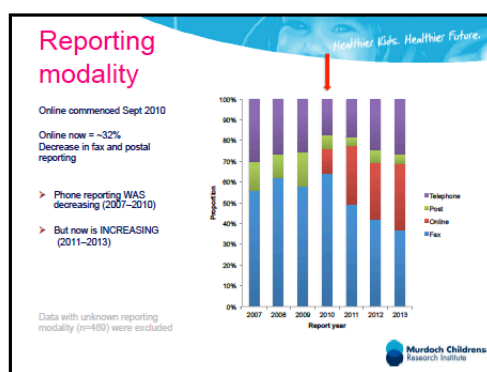
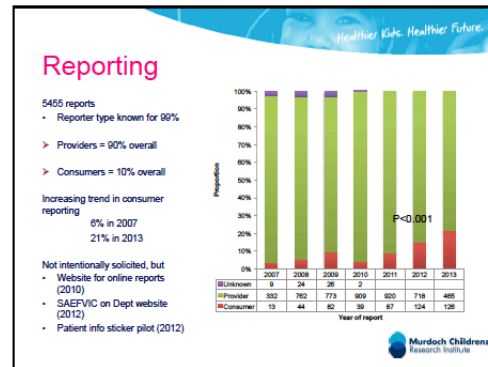
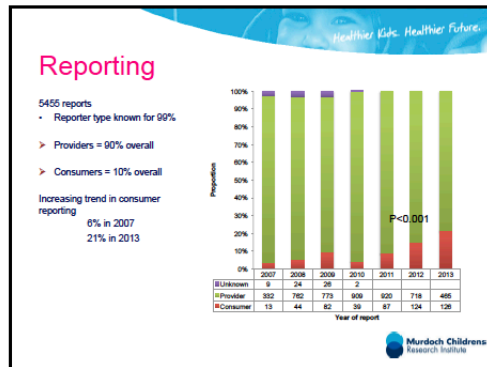
Hazel J Clothier, Selvaraj G, Easton M, Lewis G, Crawford NW, Buttery JP

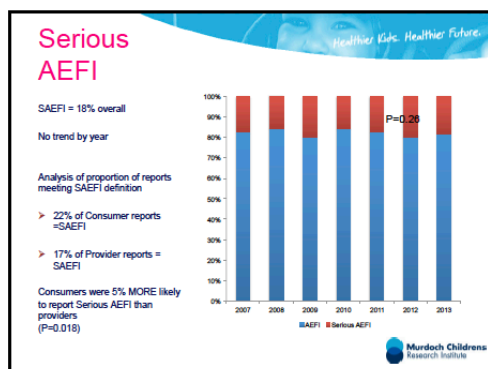
Public Health Association Australia Immunisation Conference, Darwin, June 2014

Surveillance of adverse events following immunisation (AEFI) is an essential component of vaccine safety monitoring. The commonly utilized passive surveillance systems rely predominantly on reporting by health care practitioners (HCP). We reviewed six years of adverse event reports received in Victoria between July 2007–June 2013 to ascertain the contribution of consumer (vaccinee or their guardian) reporting to vaccine safety monitoring and to inform future surveillance system development directions. Categorical data included were: reporter type, AEFI reported, serious AEFI and vaccinee age cohort. Chi-square test and two-sample test of proportions were used to compare categories; trend changes were assessed using linear regression. Consumer reporting increased over the six years, reaching 21% of reports received in 2013 ($P<0.001$), most commonly for children aged less than seven years. Consumers were 5% more likely to report serious AEFI than HCP ($P=0.018$) and 10% more likely to access specialist clinical review ($P<0.001$). Although online reporting to SAEFVIC has increased to 32% overall since its introduction in 2010, 85% of consumers continued to report by phone. This study identified that unsolicited consumer reporting provides a valuable contribution to vaccine safety monitoring.

A2.1.5.1 Presentation







Specialist clinical referral

Attended by 30% (n=1629) of persons reported with an AEFI

Consumer reported AEFI were 10% more likely to attend (30% vs. 20% P<0.001)

Age at vaccination		Attended clinical review (%)		P value
		Consumer	Provider	
Child	<7	86%	75%	<0.001
School	7-18	8%	15%	0.005
Adult	19-59	3%	7%	0.026
Elderly	60+	1%	1%	0.850
Unknown		2%	2%	0.905
Total (no.)		203	1406	

Murdoch Childrens Research Institute

- ## Findings
- Consumer reporting already entrenched in vaccine safety surveillance
- Young children (but not adults)
 - Telephone reporting
 - Resources, availability, overlap with other helplines
 - Does not just increase minor/common AEFI
 - Higher proportion of Serious AEFI
- Murdoch Childrens Research Institute

- ## Future?
- Progress with consumer AEFI reporting
 - Determine impact on signal generation
 - Combined generated more signals (Avery, UK)
 - But some signals may be lost
 - Consider reporting demographic profiles
 - Ethnicity, AEFI perception, experience
 - Australian-born compared to overseas-born
 - Resources & collaboration
 - Expand online system to be consumer friendly
 - Explore other technology, e.g SMS, apps
 - Clinical services, telehealth
- Murdoch Childrens Research Institute

Acknowledgements

AEFI reporters, providers & consumers
SAEFVIC team

SAEFVIC is funded by Department of Health and is a collaboration between

- Murdoch Childrens Research Institute,
- Royal Children's Hospital and
- Monash Health

Hazel Clothier is the recipient of an Australian Postgraduate Award Scholarship

Murdoch Childrens Research Institute

A2.1.6 HPV vaccine in boys: what are the pre-existing 'background' rates of potential adverse events?

Clothier HJ, Lee KJ, Crawford NW, Sundararajan V, Buttery JP

Australian Society of Infectious Diseases Conference, Canberra, May 2013

Introduction

In November 2011 the quadrivalent human papillomavirus (4vHPV) program was recommended to expand to adolescent males, commencing July 2012. The experience of school-based 4vHPV implementation to adolescent girls in 2007 brought a flurry of AEFI reporting, including mass psychogenic illness and syncopal seizures. We used Victorian state-held databases to determine expected background rates of neurological and allergic AEFI that would occur in the absence of HPV vaccine.

Methods

The Victorian Admitted Episodes and Emergency Minimum Datasets were used to estimate the number and rate of admissions and emergency visits for ICD-10AM codes including Guillain Barre syndrome (GBS), anaphylaxis, seizures and syncope in boys aged 9–20 years during the 5-year period (2004–2009). Episodes occurring more than 28 days since last discharge were considered as discrete events. Incidence rates were calculated and used to estimate the expected number of events post-vaccine assuming no association with vaccine.

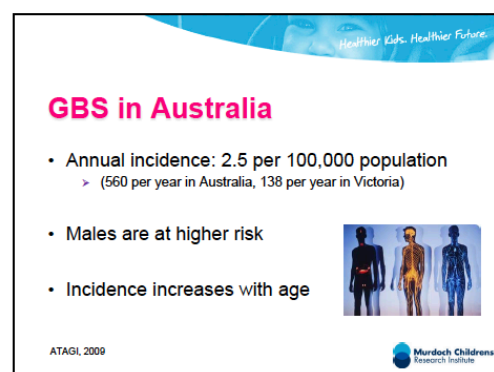
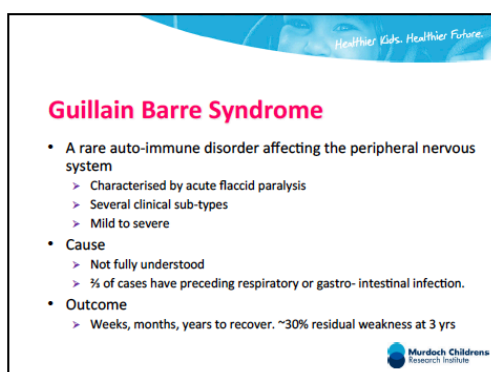
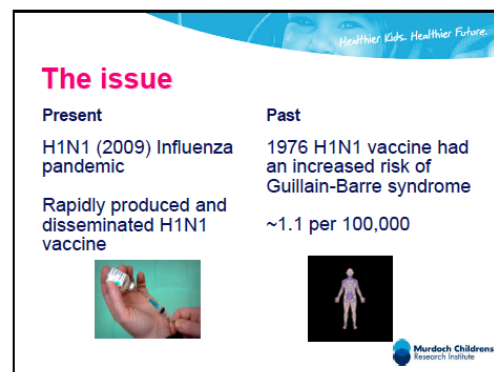
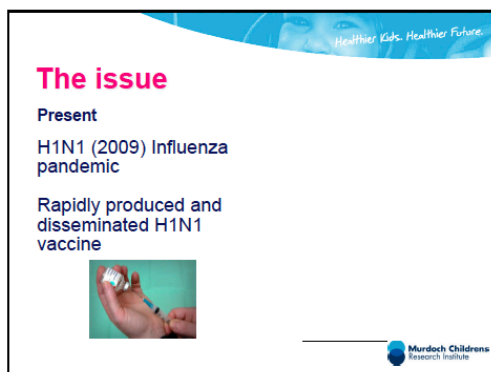
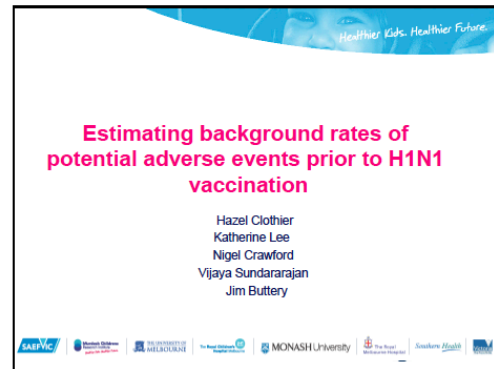
Results

Assuming an 80% vaccination rate with 3 doses per person and an estimated 480,000 males immunised nationally for each of the first 2 years of the program, approximately 2.9 episodes of GBS are expected in the 6 weeks following vaccination each year. Within 24 hours of vaccination, approximately 4.5 seizure and 7.3 acute allergy presentations are expected, including 3.0 episodes of anaphylaxis.

Conclusion

State health outcome administrative data are useful in informing post-licensure safety surveillance of target conditions that may be perceived as AEFI.

A2.1.6.1 Presentation



Estimating background rates

AIM:

Determine the expected number of admissions and emergency presentations for specific neurological and allergic events that would have occurred even in the absence of any vaccination

Methods

- VAED & VEMD data sources
- 1 July 2004 – 30 June 2009

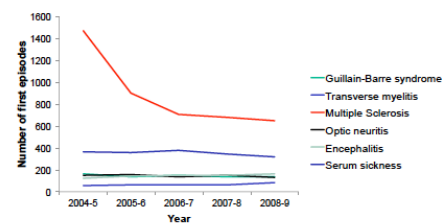
ICD-10-AM codes

Group	Condition	ICD10-AM
Neurological	Guillain-Barre Syndrome	G61.0
	Transverse myelitis	G37.3
	Multiple sclerosis	G35
	Optic neuritis	H46, G36.0
	ADEM	G36
	Peripheral neuritis in pregnancy	O28.8
	Bell's Palsy	G51.0
	Syncope	R55
	Seizures	R56.R56.0, R56.9
	Encephalitis	G04.0, G04.2 to 4.9
	Anaphylaxis	T78.2, T78.3, T78.4
	Urticaria	L50.0, L50.1, L50.9
Allergy	Serum sickness	T80.6
	Allergic reactions NOS	T88.7
Other	Adverse events	T78.8, T78.9, T88.1

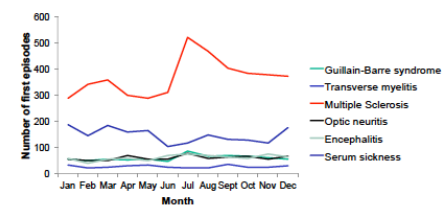
Methods

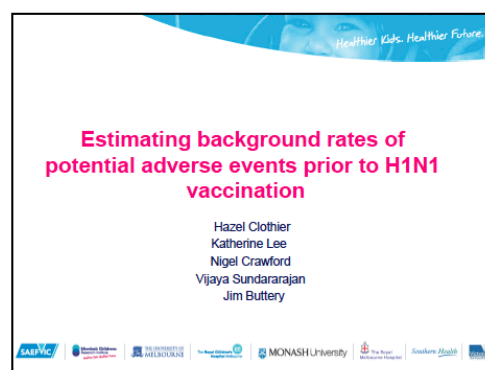
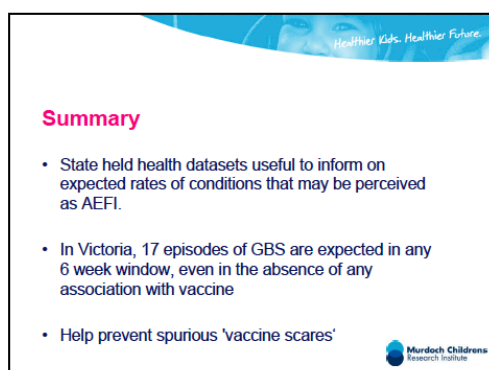
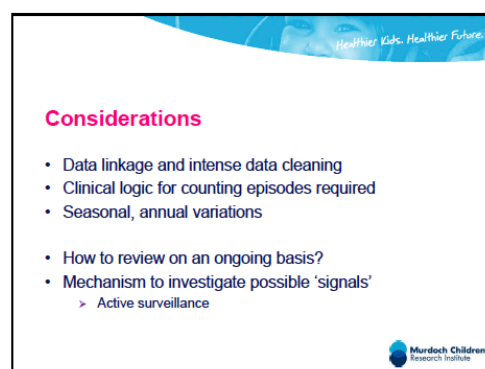
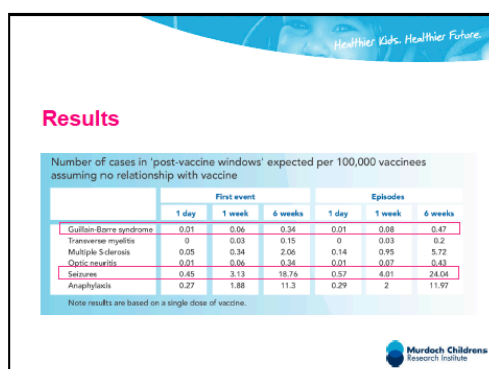
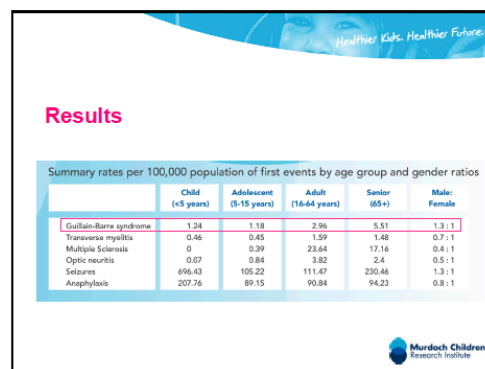
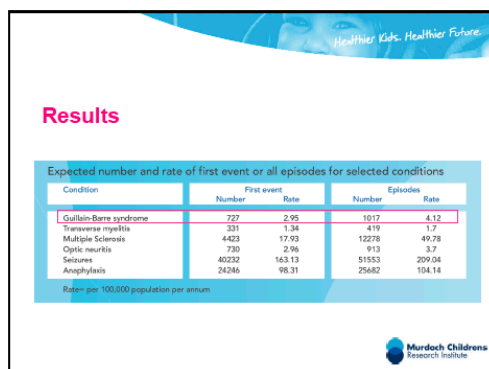
- VAED & VEMD data sources
- 1 July 2004 – 30 June 2009
 - Data linkage to unique entries
 - Logical & clinical timeframes for repeat episodes
 - First ever episode
 - All episodes
- ABS mid year population, Victoria, 2006

Annual variation



Seasonal variation





A2.1.7 Partial tip, unknown iceberg: bcg vaccine adverse events in victoria

Clothier HJ, Hosking LM, Crawford NW, Lewis G, Quinn J, Buttery JP

Australian Society of Infectious Diseases Conference, Canberra, May 2013

Introduction

In Australia, Bacillus Calmette-Guérin (BCG) vaccine is recommended for individuals at high risk for *Mycobacterium tuberculosis* (TB) infection. Batch variation, immune response and adverse events following immunisation (AEFI) are well described. Local reactions and progression to the characteristic BCG scar are common. Serious complications are rare. The recall of four BCG vaccine batches secondary to issues with the monitoring system for environmental contamination at the Canadian manufacturing plant prompted a review of AEFI reported following BCG vaccine administration. In Victoria, AEFI are reported to SAEFVIC, an immunisation safety collaborative service combining enhanced passive surveillance with integrated clinical services.

Methods

AEFI reports post BCG were extracted from the SAEFVIC database by report date from July 2007–June 2012. The number of multidose vials distributed was obtained from Department Health Victoria.

Results

Fifty-nine cases describing 67 AEFI were reported. Only one-quarter were reported within 30 days of symptom onset (mean 75 days, range 0–574 days). Batch number was reported in 21 (36%) cases with four relating to recalled batches. Provider details were unavailable for 78% of cases. Abscess was the most frequently reported AEFI (n=31), three of which followed incorrect dose or administration site, followed by Lymphadenopathy (n=20). Number of doses administered was not available due to no consistent database for BCG and unknown number of doses (0–10) used per vial distributed.

Conclusion

BCG AEFI were poorly and incompletely reported, hampering ability to investigate any potential AEFI signal. BCG administration is now restricted in Victoria to

specialist provider sites to ensure correct administration, documentation and adequate, timely AEFI management and reporting.

A2.1.7.1 Presentation



BCG withdrawal June 2012

- Sanofi-Aventis Australia Pty Ltd has recalled batches of its Bacillus Calmette-Guerin vaccine amid concerns its sterility cannot be assured because of an “environmental monitoring excursion” during manufacture



Methods

- Adverse events following immunisation (AEFI) in Victoria are reported to SAEFVIC
- AEFI reports post-BCG were extracted from the SAEFVIC database by report date from July 2007–June 2012

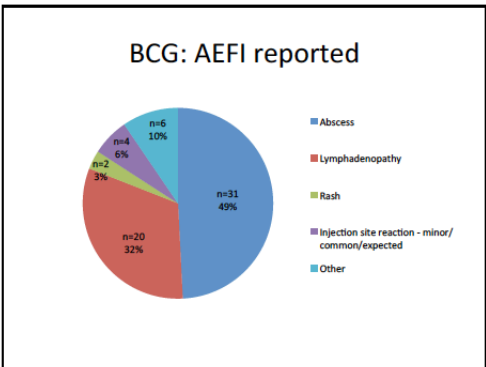
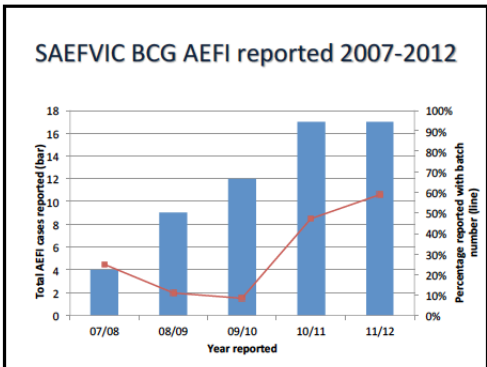


www.saeftvic.org.au

SAEFVIC BCG AEFI n=59

- male/female : 40/19
- age at vaccination
 - mean: 2.66 years
 - median: 0.90
 - range: 0.06-22.78
- time to report
 - % within 30 days of symptom onset
 - Mean: 75 days
 - Range: 0-574days
- batch number
 - reported in 21 (36%) cases
 - > four relating to recalled batches





Left anterior axillary lymphadenopathy



BCG AEFI reported : recalled batches

- BCG Connaught- 4 batches used since April

Batch	AEFI	Reactions
C3787AA	1	Lymphadenopathy
C3787AC	3	Abscess (n=2), lymphadenopathy, nodule at injection site
C3787AE	0	N/A
C3787AG	0	N/A

- Doses administered not known
 - Not recorded in ACIR
 - Poor vaccination records for overseas vaccinated cases
 - 10 doses per vial



Pragmatics: BCG

- BCG Connaught strain replaced with BCG Denmark strain
 - Denmark higher rate disseminated disease in HIV
 - ?other AEFI
 - 100 dose vials rather than 10 dose
- BCG administration now restricted in Victoria to specialist provider sites



Conclusion

- Abscess / lymphadenopathy = 80% of AEFI
- No correlation between AEFI and recalled batches
- BCG AEFI poorly and incompletely reported

The consistent and timely reporting of batch numbers in BCG vaccine administration is identified as a critical requirement for accurate attribution of AEFI events



A2.2 Poster presentations

A2.2.1 Examining the relationship between AEFI reporting and vaccine coverage

Public Health Association Australia Immunisation Conference, Adelaide, June 2018

Examining the relationship between AEFI reporting and vaccine coverage

Hazel J Clothier^{1,2,3}, Jock S Lawrie^{1,2}, Nigel W Crawford^{1,4}, Jim P. Buttery^{1,2,5,6}

¹ Monash Centre for Health Research & Implementation, School of Public Health & Preventative Medicine, Monash University, Clayton, Victoria, ² SAEFVIC, Murdoch Childrens Research Institute, Melbourne, Victoria, ³ School of Population & Global Health, University of Melbourne, Melbourne, Victoria, ⁴ Department of Paediatrics, University of Melbourne, Melbourne, Victoria, ⁵ Department of Infection & Immunity, Monash Children's Hospital, Melbourne, Australia, ⁶ The Ritchie Centre, Hudson Institute of Medical Research, Melbourne, Victoria

HYPOTHESIS

Adverse event reporting may have a relationship with vaccine coverage either correlating by volume of vaccine administered or inversely correlating where consumer confidence and vaccine coverage is lower.

BACKGROUND

Regional variations in public and provider confidence in immunisations may be reflected in vaccination coverage. This has been described anecdotally at both local and national levels. We wished to explore whether this may be reflected in AEFI reporting behaviour regionally within Victoria.

SAEFVIC is an enhanced passive surveillance system for vaccine pharmacovigilance in Victoria operating since mid-2007

METHODS

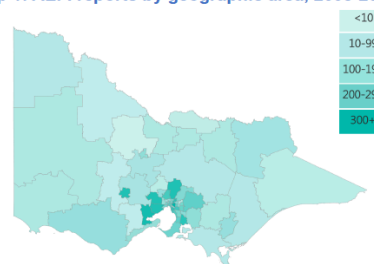
AEFI data from reports submitted to SAEFVIC from 2008-2017 were extracted and analysed using Power BI software (Box).

Each AEFI report defines a specific vaccination event and describes vaccines administered, patient demographics and subsequent adverse reactions. Vaccinee residential postcodes were approximated to geographic area using ABS postcode concordance tables.

Population estimates and data that defined geographic area were accessed from the Australian Bureau of Statistics (ABS) and 2017 annualised vaccine coverage data as the percentage of children fully immunised at age 12 months, 24 months and 60 months according to the National Immunisation Program Schedule, obtained from the Australian Government Department of Health.

AEFI reports were mapped by ABS statistical area (SA3) level as i) count of AEFI reports (Map 1) and ii) AEFI reporting rate per 100,000 person-years (Map 2). AEFI reporting rate in 2017 for children under 5 years was compared to vaccine coverage (shown by immunisation age cohort) for the same year as a visual estimation of the relationship between AEFI reporting and vaccine coverage (Figure 1).

Map 1: AEFI reports by geographic area, 2008-2017



Map 2: AEFI reporting rate per 100,000 person-years and geographic area, 2008-2017

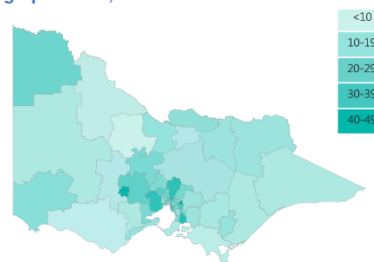
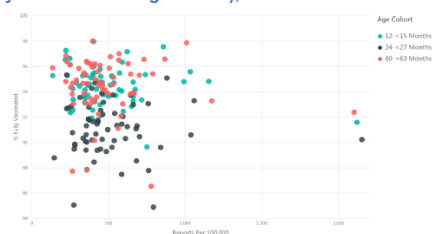


Figure 1: AEFI reporting rate and vaccination coverage (by immunisation age cohort), 2017



CONCLUSION

Adverse event reporting is an important component of vaccine pharmacovigilance. Our findings indicate that AEFI reporting can be encouraged without detrimental impact on consumer confidence and vaccine coverage.



POWER BI

Microsoft Power Business Intelligence is an interactive data visualisation tool that can ingest data from multiple sources, join and format them and enable visualisation in one place. The tool enables rapid creation of tables, charts and maps, as well as analyses on filtered data.

DISCUSSION

AEFI reporting to SAEFVIC is broadly geographically representative across the State. Marginally higher AEFI reporting rates were observed from Metropolitan and Regional areas.

Comparison of AEFI reporting rates with vaccine coverage for children aged under five years demonstrated a likely volume-based relationship with the outlying lower AEFI reporting rates associated with areas of lower vaccine coverage.

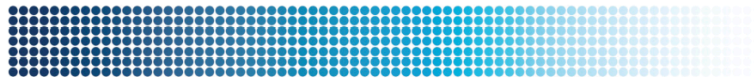
The hypothesis that higher AEFI reporting was associated with lower vaccination coverage as a result of poor consumer confidence was not demonstrated.

Using tools such as Power BI has strengthened capacity to examine AEFI data with other immunisation data sources and enhances utility of routine surveillance to inform program delivery.

1. SAEFVIC www.saeftvic.com.au
2. Australian Bureau of Statistics www.abs.gov.au/Population <http://data.abs.gov.au/10130/Totalbyregion>
3. <https://beta.health.vic.gov.au/resources/publications/vic-childhood-immunisation-coverage-data-by-sa3>

A2.2.2 Partial tip, unknown iceberg: adverse events following immunisation with BCG vaccine

Australian Society of Infectious Diseases Conference, Canberra, May 2013



HPV vaccine in boys: background rates of potential adverse events

Hazel J Clothier^{1,2}, Katherine J Lee^{3,4}, Vijaya Sundararajan⁵, Jim P Buttery^{1,6}, Nigel W Crawford^{1,4,7}

¹ SAEVIC, Murdoch Childrens Research Institute
² Department of Population and Global Health, The University of Melbourne
³ Clinical Epidemiology and Biostatistics Unit, Murdoch Childrens Research Institute
⁴ Department of Paediatrics, The University of Melbourne
⁵ Department of Medicine, Southern Clinical School, Monash University
⁶ Department of General Medicine, Royal Children's Hospital Melbourne
⁷ Paediatric Infectious Diseases Unit, Monash Children's Hospital, Department of Paediatrics, Monash University

Introduction

In 2013 Australia will become the first nation to expand the National Immunisation Program of HPV vaccination for adolescent girls to boys. Quadrivalent human papilloma virus (4vHPV) vaccine is highly efficacious for the four HPV genotypes reported to cause 70 per cent of cervical cancers (16 and 18) and anogenital warts (6 and 11).

Monitoring for any adverse events following immunisation (AEFI) is a crucial part of the program as vaccines, like any medicine, have potential adverse reactions as well as adverse events that may coincide temporally with vaccine administration by chance.

In anticipation of expansion of the 4vHPV program to adolescent boys, we explored the use of routinely collected population level health outcome administrative data to determine expected rates for a range of allergic and neurological conditions that may be mistakenly assumed to be caused by immunisation due to temporal association¹.

Methods

Data comprised all episodes of conditions of interest (see Table 1) occurring in boys aged 12–<16 years recorded in the Victorian admitted episodes dataset (VAED) and the Victorian emergency minimum dataset (VEMD) between July 2004 to June 2009.

Table 1: ICD10-AM coded conditions and group classification

Group	Condition	ICD-10-AM
Neurological	Guillain-Barré syndrome	G61.0
	Transverse myelitis	G37.3
	Multiple sclerosis	G35
	Optic neuritis	H45, G36.0
	Acute disseminated encephalomyelitis	G04.0
	Bell's palsy	G51.0
	Syncope	R55
Allergy	Seizures	R56.0, R56.8
	Anaphylaxis	T78.2, T88.6
	Urticaria	L50.0, L50.1, L50.9
	Serum sickness	T80.6
Other	Adverse effect of drug or medication – Not otherwise specified	T88.7
	Adverse events	T78.8, T78.9, T88.1, T78.3

Shaded conditions are considered chronic.

Episodes ongoing from the three months prior to the analysis period, "the wash-out period" (March–June 2004), were excluded.

Multiple episodes for the same event were combined into a single episode. Episodes were considered discrete events if occurring more than 28 days after a prior event in the same individual for acute conditions or described as the first time a condition was diagnosed in each patient.

Incidence rates were calculated and used to estimate the expected number of events post-vaccine assuming no association with vaccine, with an 80% immunisation uptake.

Seasonal variation was presented as the number of first events or episodes by month of presentation. For multiple sclerosis, data were also presented omitting presentations in the first 12 months of the study period in order to view the effectiveness of the studies 3-month wash-out period (Figure 1).

Results

The key results are detailed in Tables 2 and 3.

Table 2: Number and incidence rates (per 100,000 population) of events in males aged 12–<16 years old, Victoria, as captured in the two databases

	First events*		Episodes	
	No. of events	Rate	No. of events	Rate
Guillain-Barré syndrome	10	1.46	11	1.61
Transverse myelitis	2	0.29	3	0.44
Multiple sclerosis	2	0.29	2	0.29
Optic neuritis	4	0.59	6	0.88
ADDEM	8	0.17	11	1.61
Bell's palsy	60	8.78	60	8.78
Syncope	807	118.0	831	121.5
Seizures	665	97.4	830	121.4
Neurological Total	1516	221.7	1729	252.9
Anaphylaxis	49	7.17	51	7.46
Urticaria	620	90.7	647	94.6
Serum sickness	23	3.4	23	3.4
Allergic reaction	495	72.4	517	75.6
Allergy Total	1125	164.6	1198	175.2
Other	7	1.02	7	1.02

* First event means the first time this condition was diagnosed in each patient within the specified time period.

Table 3: Uses the data above to estimate the number of cases expected per 100,000 male adolescent population that would present, even in the absence of vaccine

	First event			Episodes		
	1 day	1 week	6 weeks	1 day	1 week	6 weeks
Guillain-Barré syndrome	0.00	0.03	0.17	0.00	0.03	0.19
Transverse myelitis	0.00	0.01	0.03	0.00	0.01	0.05
Multiple sclerosis	0.00	0.01	0.03	0.00	0.01	0.03
Optic neuritis	0.00	0.01	0.07	0.00	0.02	0.10
ADDEM	0.00	0.02	0.15	0.00	0.03	0.19
Bell's palsy	0.02	0.17	1.01	0.02	0.17	1.01
Syncope	0.32	2.26	13.57	0.33	2.33	13.98
Seizures	0.27	1.87	11.20	0.33	2.33	13.96
Neurological Total	0.61	4.25	25.50	0.69	4.85	29.08
Anaphylaxis	0.02	0.14	0.82	0.02	0.14	0.86
Urticaria	0.25	1.74	10.43	0.26	1.81	10.88
Serum sickness	0.01	0.06	0.39	0.01	0.06	0.39
Allergic reaction	0.20	1.39	8.33	0.21	1.45	8.70
Allergy Total	0.45	3.15	18.92	0.48	3.36	20.15
Other	0.00	0.02	0.12	0.00	0.02	0.12

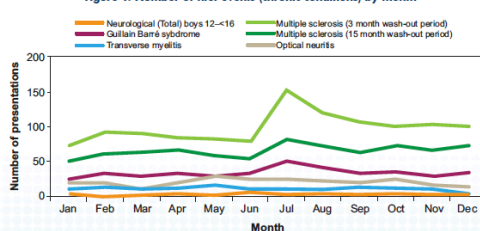
Note: Results estimated number of cases based on a single dose of vaccine

Calculating rates

- Assuming an 80 per cent vaccination rate with three doses per person and an estimated 480,000 males immunised nationally per year, approximately 2.4 episodes of GBS would be expected in the 6 weeks following vaccination.
- Approximately 3.8 seizures and 6.5 acute allergy presentations would be expected within 24 hours of vaccination, including 0.3 episodes of anaphylaxis.

There was minimal seasonal variation in the presentation of potential acute AEFI investigated. However, when neurological presentations were viewed across all age-groups and therefore larger number of presentations, multiple sclerosis had a notable increase in July–September. This seasonal peak was reduced, but not eliminated, when the wash out period was increased to 15 months (Figure 1).

Figure 1: Number of first events (chronic conditions) by month



Discussion

In large vaccine implementations, where vaccine exposure is a common event in the target group, many incident acute health conditions will present following vaccination, irrespective of any causal association.

'Background rate' studies assist national vaccine safety monitoring as prior knowledge of 'expected' numbers of cases is invaluable in helping determine whether reports or clusters of reports represent real safety flags requiring urgent investigation².

Currently published data are limited to adolescent females, raising the risk of sex-related differences potentially leading to misinterpretation of potential signals¹.

In Victoria, 4vHPV first dose vaccine coverage for adolescent girls has reached 80 per cent³, however challenges of uptake by males and completion of the course may be anticipated. If true coverage for boys is found to be less than 80 per cent the expected rates per 100,000 vaccinees in this study should be recalculated to avoid an erroneous alert threshold.

Specific investigation of appropriate wash-out periods, as well as seasonal variations in both the presenting condition and vaccine program delivery, must be fully explored prior to in-depth analyses for specific conditions or extrapolations to other jurisdictions.

Conclusion

This study highlights the value of state health datasets to inform post-licensure safety surveillance of expected rates of conditions that may be perceived as adverse event following immunisation ahead of the expansion of the 4vHPV program and assist in targeted active surveillance for potential vaccine safety flags.

Acknowledgement

The authors acknowledge Dr Lalitha Sundaresan of the Victorian Department of Health for initial data extractions.

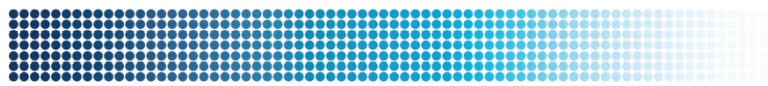
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A2.2.3 Human papillomavirus vaccine in boys: background rates of potential adverse events

Australian Society of Infectious Diseases Conference, Canberra, May 2013



Partial tip, unknown iceberg: BCG vaccine adverse events in Victoria

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² School of Population & Global Health, University of Melbourne
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⁴ Monash Immunisation, Monash Medical Centre
⁵ Infectious Diseases, Monash Children's Hospital
⁶ Department of Paediatrics, Monash University, Melbourne

Introduction

Tuberculosis (TB), caused by *Mycobacterium Tuberculosis* (Mtb), is a leading cause of death worldwide. Asymptomatic infection affects approximately one-third of the world's population, with 5–10 per cent developing clinical disease (1). In Australia, intradermal Bacillus Calmette-Guérin (BCG) vaccine is recommended for individuals at high risk for TB (2). There are six widely used strains of the original vaccine; in Australia the Sanofi Pasteur BCG has been used. Almost all vaccinations are associated with mild local reactions, with the formation of a papule with progression to the characteristic BCG scar. Serious complications are rare (1).

In June 2012 an urgent recall of four batches (C3787AA, C3787AC, C3787AE and C3787AG) of the Sanofi Pasteur BCG was issued by the Therapeutic Goods Administration (TGA) following a possible breach in sterility at the Canadian manufacturing plant. Implicated batches had already been distributed for administration in the Victorian community; the adverse effects of which have not been identified.

This study was conducted to assess any reported adverse events following administration of the recalled batches in Victoria.

Methods

In Victoria, adverse events following immunisation (AEFI) are reported to SAEFVIC, an immunisation safety collaborative service combining enhanced passive surveillance with integrated clinical services. AEFI reports post-BCG were extracted from the SAEFVIC database by report date from 01 July 2007–31 June 2012. Each AEFI case reported one or more adverse reactions. The reports were of varying degrees of completion.

Results

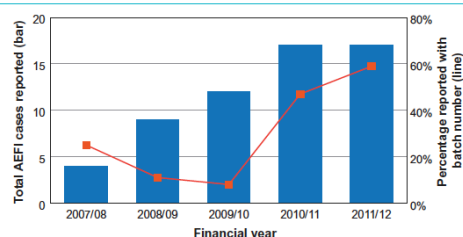


Figure 1. AEFI cases reported and percentage reported with batch number

Fifty-nine AEFI cases were reported, with the following characteristics:

- Forty males, 19 females (ratio 1:0.48)
- Median age: 11 months (range 22 days – 22 years)
- Seven had been co-administered with other vaccines
- One-quarter were reported within 30 days of symptom onset (mean 75 days, range 0–574 days)
- Batch number was reported in 21 (36%) cases with four relating to recalled batches (Table 1)
- Provider details were available for 13 (22%) case.

Table 1. Recalled batches AEFI in Victoria

Batch	AEFI	Reactions
C3787AA	1	Lymphadenopathy
C3787AC	3	Abscess (n=2), lymphadenopathy, nodule at injection site
C3787AE	0	N/A
C3787AG	0	N/A

Four AEFI cases were reported with vaccination administration errors; these have been included in the data set. However, vaccine administration error was also termed as a reaction in these cases, and has therefore been excluded as a reported reaction.

The number of doses administered was not available due to the absence of a consistent database for BCG, and unknown number of doses (0–10) used per multidose vial distributed.

Results continued

There were 63 reactions reported in the 59 AEFI cases (Figure 2):

- Abscess was the most frequently reported reaction (n=31), followed by lymphadenopathy (n=20)
- Of the AEFI cases with a recorded batch number (n=21), no reaction type was unique to the cases involving recalled batches (n=4)
- There were five reaction types unique to the AEFI cases without a recorded batch number (n=38).

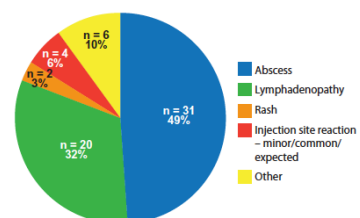


Figure 2. Reported reactions



Figure 3. Reaction showing left anterior lymphadenopathy

Outcomes

With the current reporting system no correlation can be made between reactions and specific recalled batches due to incomplete reporting of BCG batch numbers. Although there were no reactions unique to the set of AEFI cases involving a recalled Sanofi Pasteur batch, there were reactions unique to the set of cases without a recorded batch number. It is therefore possible that reactions within this set were associated solely with recalled batches, but this cannot be known without complete batch numbers. BCG administration is now restricted in Victoria to specialist provider sites to ensure correct dose capture, administration and documentation, as well as adequate, timely AEFI management and reporting. BCG Danish strain is currently being used due to a worldwide shortage, with higher AEFI rates reported in some settings than the Sanofi strain.

Conclusion

BCG AEFI were poorly and incompletely reported. The majority of cases (64%) were reported without batch information, hampering ability to investigate any potential AEFI signal. The consistent and timely reporting of batch numbers in BCG vaccine administration is identified as a critical requirement for accurate attribution of AEFI events.

REFERENCES

1. World Health Organization. BCG vaccine. WHO position paper. *Weekly Epidemiological Record*. 2004;79(4):27–38
2. National Tuberculosis Advisory Committee. The BCG vaccine: information and recommendations for use in Australia. *Communicable Diseases Intelligence*. 2006;30:109–15



Name (Vaccinee):

CONSENT FOR SAEFVIC TO CONTACT VACCINEE/ PARENT/ GUARDIAN

- ☐ Full consent was obtained from the vaccinee/ parent/ guardian
- ☐ Consent to report, but do not contact vaccinee/ parent/ guardian

Signature _____

Date ____/____/____

VACCINES ADMINISTERED

Date of Vaccination ____/____/____ Unknown ☐

Antenatal Vaccination ☐

Time ☐☐: ☐☐ AM/PM Unknown ☐

Weeks of Gestation _____

Vaccine	Dose No.	Batch Number	Injection Site (Please specify)
	☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	
	☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	
	☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	
	☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	

REACTION DETAILS (include medical history if relevant)

Time elapsed between administration of the vaccine and the onset of symptoms (e.g. 3 minutes/ 4 days)

- ☐ Minutes ☐ Hours ☐ Days ☐ Weeks ☐ Unknown

Detailed description of reaction including timing of events:

TREATMENT (tick one or more boxes and specify details)

- ☐ Unknown ☐ GP assessment
- ☐ None or symptomatic (e.g. paracetamol) only ☐ Hospital emergency at _____
- ☐ Parent help-line ☐ Hospital Admission at _____
- ☐ Nurse assessment # Days _____ Unknown ☐
- ☐ Other (please specify) _____

Details:

OUTCOME

How long did the symptoms last? ☐ Minutes ☐ Hours ☐ Days ☐ Weeks ☐ Unknown
(e.g. 3 minutes/ 4 days)

Detailed description of outcome ☐ Unknown

A3.1.2 Online reporting form

AEFI-CAN Reporting - Demo

Welcome, hazel.clothier

Logout

[Instructions](#) | [My Profile](#) | [Report Event](#) | [Search Reports](#) | [Administration](#)

Reporter Details

Reporter

Vaccinee

Immunisation Provider

Vaccines Administered

Reaction and Treatment

Submission

Reporter Details

First Name: *

Ms

hazel

Surname: *

clothier

Type of Professional: *

Other

epidemiologist

Reporter Setting:

-- Select --

Organisation: *

SAEFVIC

Address: *

SAEFVIC

Suburb: *

melbourne

State: *

VIC

Postcode: *

3000

Phone: *

Mobile

0421900113

Email Address:

hazel.clothier@mcri.edu.au

Save and Next >

Vaccinee Details

Reporter

Vaccinee

Immunisation Provider

Vaccines Administered

Reaction and Treatment

Submission

Vaccinee Details (Child or Adult)

Same as Reporter Details

First Name: *

--

Surname: *

Birth Date:

Gender: *

☐ Male ☐ Female ☐ Neither ☐ Unknown

Medicare Number:

ATSI Status: *

-- Select --

Parent / Guardian Details:

First Name:

--

Surname:

Address: *

Suburb: *

State: *

-- Select --

Postcode: *

Phone 1: *

-- Select --

Phone 2:

-- Select --

Email Address:

Medical History:

Medication History:

Immunisation History:

< Previous

Save and Next >

Cancel

Vaccinee Details

Reporter

Vaccinee

Immunisation Provider

Vaccines Administered

Reaction and Treatment

Submission

Vaccinee Details (Child or Adult)

Same as Reporter Details

First Name: *

Ms

Jane

Surname: *

Doe

Birth Date:

Gender: *

☐ Male ☒ Female ☐ Neither ☐ Unknown

Medicare Number:

ATSI Status: *

Unknown

Parent / Guardian Details:

First Name:

--

Surname:

Address: *

the house

Suburb: *

town

State: *

VIC

Postcode: *

3999

Phone 1: *

Mobile

0400400400

Phone 2:

-- Select --

Email Address:

Medical History:

XYZ

Medication History:

XYZ

Immunisation History:

As stated

< Previous

Save and Next >

Cancel

Vaccines Administered

Reporter Vaccinee Immunisation Provider Vaccines Administered Reaction and Treatment Submission

Vaccines Administered Related to AEFI

Vaccination Date: 05/04/2020 ☐ Antenatal Vaccination
☐ Unknown Weeks of Gestation:
Vaccination Time: 02 : 02 PM
hour min AM/PM
☐ Unknown

Vaccine *	Dose No *	Batch No (if known)	Injection Site
Infanrix hexa	1	XYZ	Right Deltoid
Quadracel	3	123	Right Buttock
-- Select --			-- Select --
-- Select --			-- Select --
-- Select --			-- Select --
-- Select --			-- Select --

Description of the vaccines (if uncertain or not listed above):

Immunisation Provider Details

Reporter Vaccinee Immunisation Provider Vaccines Administered Reaction and Treatment Submission

Immunisation Provider Details

☐ Same as Reporter Details ☐ Unknown Vaccination Venue:
Type of Provider: Community Clinic Organisation: SAEFVIC
Other: Address: SAEFVIC
First Name: Ms hazel Suburb: melbourne
Surname: clothier State: VIC
Type of Professional: Other Postcode: 3000
Other: epidemiologist Phone: Mobile 0400400400
Email Address: hazel.clothier@mcri.edu.au

< Previous Save and Next > Cancel

Reaction and Treatment

Reporter Vaccinee Immunisation Provider Vaccines Administered Reaction and Treatment Submission

Reaction

Time elapsed between the administration of the vaccine and onset of the symptoms: 4 mins 1 hours 0 days 0 weeks ☐ Unknown

Detailed description of the reaction including timing of events: *

Description as given by the case

Treatment (tick one or more boxes)

Treatment: ☒ Known ☐ Unknown *

☒ None or symptomatic (e.g. paracetamol) only

☐ Helpline

☐ Nurse assessment

☐ GP assessment

☐ Hospital emergency at

☒ Hospital admission at hospital

Days: ☐ Unknown

☐ Other:

Details:

Outcome

How long did the symptoms last? 0 mins 2 hours 0 days 0 weeks ☐ Known
☒ Unknown but Ongoing
☐ Unknown but Resolved

Detailed description of the outcome: *

☐ Unknown

Description as given

< Previous Save and Next > Cancel

Submission

Reporter	Vaccinee	Immunisation Provider	Vaccines Administered	Reaction and Treatment	Submission
----------	----------	-----------------------	-----------------------	------------------------	------------

Consent

I, the reporter, have obtained the following consent from the vaccinee, parent or guardian to report this AEFI and for their local public health unit or specialist immunisation clinic to contact them.

Date: 05/04/2020

- ☒ Full consent was obtained
☐ Consent to report but NOT to contact was obtained
☐ Consent is not required*/impracticable
*only in those jurisdictions where reporting is mandatory

< Previous Submit Cancel

A3.3 AEFI report clinical assessment form

Office Use

Standard AEFI ID: Z2004-000017
Status: Submitted

Submitted: 5/04/2020 8:02 PM by hazel clothier
Last modified: 5/04/2020 8:02 PM by hazel clothier

Reporter	Vaccinee	Immunisation Provider	Vaccines Administered	Reaction and Treatment	Submission	Office Use	Attachments
----------	----------	-----------------------	-----------------------	------------------------	------------	------------	-------------

Reactions

Reaction(s):	Other reaction(s):	Tick if minor/ common/expected:
Allergic reaction (generalised)	dizziness	☒
Brachial neuritis		☐
-- Select --		☐
-- Select --		☐
-- Select --		☐

Assessment

This is an: *	☒ Event ☐ Non-Event	Status: *	In Progress
Assessment:	☐ Certain ☒ Possible ☐ Not related	How reported?:	Online
Risk Group(s):	☐ Special Risk Group	Report Date:	05/04/2020
Previous AEFI Id:	☐ Had Previous AEFI	AEFI Location:	VIC
		Surveillance Type:	☐ Active Surveillance -- Select --

TGA Integration

Was original notification from TGA?:	☐ Yes ☒ No ☐ Unknown	Sent to TGA?:	☒ Yes ☐ No ☐ Unknown
TGA Event Number:		Date sent to TGA:	05/04/2020

Follow-Up

Follow up attempts:	☒ 1 ☐ 2 ☐ 3 ☐ Lost to follow up	Notes:	Clinical immunisation nurse notes
Letter sent to parent?:	☐ Yes ☐ No ☐ Unknown		
Attended clinic:	☐ Yes ☐ No ☒ Unknown		

Delete Event Print Event

Save Changes

Clinic Visits

Created	Clinic	Visit Date	Status	Report Code	Report Date
Add Clinic Visit					

A3.4 Clinical visit record

Clinic Visit - Booking

Booking

Vaccinee

Vaccination Plan

Follow Up

Feedback

Attachments

Booking

Visit Date: *
05/04/2020

Clinic Location: *
Demo Clinic

Booking Status: *
Booked

Appointment letter sent:
☒ Yes ☐ No ☐ Unknown

Clinic form:
☐ Yes ☒ No ☐ Unknown

Immunised:
☒ Yes ☐ No ☐ Unknown

UR Number:
hospital UR number

Return to Event

Save and Next >

Clinic Visit - Vaccinee

Booking

Vaccinee

Vaccination Plan

Follow Up

Feedback

Attachments

Vaccinee Details (Child or Adult)

First Name: *
Ms Jane

Surname: *
Doe

Birth Date:
06/04/2015

Gender: *
☐ Male ☒ Female ☐ Neither ☐ Unknown

Medicare Number:

ATSI Status: *
Unknown

Parent / Guardian Details:
First Name:
Mr John

Surname:
Doe

Address: *
the house

Suburb: *
town

State: *
VIC

Postcode: *
3999

Phone 1: *
Mobile 0400400400

Phone 2:
-- Select --

Email Address:

Medical History:
XYZ

Medication History:
XYZ

Immunisation History:
As stated

Return to Event

< Previous Save and Next >

Clinic Visit - Vaccination Plan

Booking

Vaccinee

Vaccination Plan

Follow Up

Feedback

Attachments

Vaccination Plan

Vaccine *	Dose No *	Batch No (if known)	Date	Clinic Location	Other Clinic
Prevenar 13	1			Demo Clinic	
Quadracel	2			Allergy Ward	
-- Select --				-- Select --	
-- Select --				-- Select --	
-- Select --				-- Select --	

Follow up appointment: *
☒ Yes ☐ No ☐ Unknown

If yes specify: *
allergy

Precautions regarding future vaccination: *
☐ Yes ☒ No ☐ Unknown

Notes:
Medical review notes

Medical Tests:
☒ Medical Tests
skin test

Return to Event

< Previous Save and Next >

Clinic Visit - Follow Up

Booking

Vaccinee

Vaccination Plan

Follow Up

Feedback

Attachments

Follow-Up Post Immunisations (if given)

Phone Call: ☒ Yes ☐ No ☐ Unknown

Date (if yes): 05/04/2020 

Time (if yes): 08 : 18 AM
hour min AM/PM

Any further significant adverse events post vaccination?

☐ Yes ☒ No ☐ Unknown

New AEFI Event ID:

Details:

Follow up notes

[Return to Event](#)

[< Previous](#) [Save and Next >](#)