MONASH University

# Syndromic vaccine safety surveillance: an alternative approach for vaccine safety signal detection

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BSc (Public Heath)

MPH (Epidemiology and Biostatistics)

A thesis submitted for the degree of Doctor of Philosophy at

Monash University in 2021

Monash Centre for Health Research and Implementation

School of Public Health and Preventive Medicine

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### Notice 1



Notice 2

## Abstract

### Background

Post-licensure vaccine safety monitoring (PVSM) is an essential requirement in vaccination programs that aims to detect not only rare, late-onset or unexpected adverse events following immunisation (AEFI) that are less likely to be detected in pre-licensure vaccine trials but also changes in frequency of known AEFI. Traditionally, PVSM has been undertaken by systematic analyses of AEFI predominantly reported via spontaneous reporting systems (passive surveillance). However, there are actual instances that have showed that reliance on passive surveillance alone could delay or hinder the detection of possible AEFI signals due to selective reporting and under-reporting. In recent years, electronically available routine health data have offerred an alternative source to conduct ongoing active AEFI surveillance to improve early detection of AEFI signals.

### Aims

The overarching aim of this thesis was to assess the potential use of near real-time capable aggregated and syndromic healthcare data generated from different levels of healthcare provision to facilitate the timely detection of vaccine safety problems.

### Methods

A systematic review of healthcare data-based post-licensure vaccine safety studies was conducted to summarise the nature of the data sources and methodological approaches that were used. Nearly a decade of healthcare data collected routinley during telephone consultations, general practice (GP) consultations and emergency department visits in Victoria, Australia were used to answer the research questions addressed in the studies presented in Chapters 4, 5 and 6. For the studies presented in Chapters 4 and 5, a univariate time-series

analysis was performed to examine the temporal patterns of the number of AEFI-related telephone calls and the rate of post-vaccination GP consultation, the two syndromes studied. Statistical signal detection algorithms, the Farrington surveillance algorithm and the cumulative sum chart were used to identify possible unusual increases of the syndromes. Two historically known AEFI signals that occurred in Australia in 2010 and 2015 were considered and used to evaluate timeliness and sensitivity. For the study presented in Chapter 6, positive predictive values were estimated to evaluate the validity of selected emergency department diagnostic codes to identify anaphylaxis following vaccination.

**Results**

The systematic review demonstrated that ongoing AEFI surveillance using routine healthcare data has led to the early detection of several vaccine safety signals, with experience to date largely limited to the United States. The system used linked data and paired immunisation records with diagnostic medical information generated mainly from hospital settings. The study presented in Chapter 4 revealed that the telephone helpline dataset was also a potential and timely data source for vaccine safety signal monitoring. Additionally, the AEFI-related call time series correlated well with weekly spontaneous AEFI reports, ranging in annual cross-correlation coefficients between 0.38 and 0.66. AEFI-related telephone calls changes preceded spontaneous AEFI reports by zero to two weeks. Further, an unprecedented increase in AEFI-related calls in 2010 corresponded with the 2010 confirmed febrile seizures signal, with a two-week time advantage to indicate the event. The GP consultation data study presented in Chapter 5 also demonstrated that temporal pattern analysis of rate of post-vaccination GP consultations can potentially indicate the unusual occurrence of AEFI-related healthcare visits, especially early-onset AEFI.

## Conclusion

Syndromic surveillance based on routine healthcare data collected during telephone helpline and GP consultations, together with existing AEFI systems, can potentially enhance the timely detection of AEFI signals. These near real-time available data have the potential to be incorporated jurisdictionally and in Australia nationally.

## General Declaration for Thesis including Published Works

Declaration for thesis based on conjointly published or unpublished work

Monash University

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations, the following declarations are made:

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

This thesis includes four manuscripts in total. Three manuscripts—two original articles and a systematic review—were published in peer-reviewed journals, and the remaining original manuscript has been in press for publication. The core theme of the thesis is to assess the potential use of routinely collected syndromic healthcare data to assist adverse events following immunisation signal detection in the context of multimodal vaccine safety signal detection approaches. The ideas, development and writing of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Public Health and Preventive Medicine, Monash Centre for Health Research and Implementation at Monash University under the supervision of Professor Jim Buttery, Professor Allen Cheng and Dr Joanne Enticott.

The inclusion of co-authors reflects that the work came from active collaboration among researchers and acknowledges input into team-based research.

My contribution to the work in Chapters 2, 4, 5 and 6 is presented in the following table.

| Thesis chapter | Publication title | Status | Nature and % of student contribution | Nature and % of co-authors' contribution* | Co-author(s) Monash student status* |
|---|---|---|---|---|---|
| 2 | Use of routinely collected electronic healthcare data for post licensure vaccine safety signal detection: a systematic review | Published in *BMJ Global Health* in 2019 | Literature search, data extraction, analysis and interpretation, conceptualisation and writing of manuscript, critical revision approval of final draft for publication (75%) | 1) Jim Buttery: guidance, ideas, review of and input into manuscript (15%)<br>2) Allen C Cheng: review of and input into manuscript (5%)<br>3) Jock Lawrie: review of and input into manuscript (5%) | No for all |
| 4 | Use of telephone helpline data for syndromic surveillance of adverse events following immunization in Australia: A retrospective study, 2009 to 2017 | Published in *Vaccine* in 2020 | Conception and design of the study, data analyses, manuscript writing, critical revision and approval of final draft for publication (75%) | 1) Jim Buttery: guidance, ideas, review of and input into manuscript (15%)<br>2) Allen Cheng: review of and input into manuscript (3%)<br>3) Joanne Enticott: review of manuscript (2%)<br>4) Jock Lawrie: data analysis support and review of and input into manuscript (5%) | No for all |
| 5 | Post-vaccination healthcare attendance rate as a proxy measure for syndromic surveillance of adverse events following immunisation: a validation study | Published in *Australian and New Zealand Journal of Public Health* | Conception and design of the study, data analyses, manuscript writing, critical revision and approval of final draft for publication (75%) | 1) Jim Buttery: guidance, ideas, review of and input into manuscript (15%)<br>2) Allen C Cheng: review of and input into manuscript (3%)<br>3) Joanne Enticott: review of and input into manuscript (2%)<br>4) Jock Lawrie: data analysis support and review of and input into manuscript (5%) | No for all |
| 6 | Positive predictive value of ICD-10 codes to detect anaphylaxis due to vaccination: a validation study | Published in *Pharmaco-epidemiology Drug Safety* in 2019 | Conception and design of the study, data analyses, manuscript writing, critical revision and approval of final draft for publication (75%) | 1) Jim Buttery: guidance, ideas, review of and input into manuscript (15%)<br>2) Allen C Cheng: review of and input into manuscript (5%)<br>3) Aimy H.L.Tran: medical record review and input into manuscript (5%) | No<br>No<br>Yes |

I have renumbered the sections of Chapter 5 to ensure consistent presentation. However, the sections and page numbers of Chapters 2, 4 and 6 have not been renumbered as they have been inserted as they appeared in publication.

**Student's name:** Yonatan Moges Mesfin

**Student's signature:** _____ **Date:** 23/02/2021

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author, I have consulted with the responsible author to agree on the respective contributions of the authors.

**Main supervisor's name:** Professor Jim Buttery

**Main supervisor's signature:** _____ **Date:** 23/02/2021

## List of Publications

Listed below are my first-author publications that are relevant to the period of candidature:

1. **Mesfin YM**, Cheng AC, Lawrie J, Buttery J. Use of routinely collected electronic healthcare data for post licensure vaccine safety signal detection: a systematic review. BMJ Glob Health. 2019;4(4):e001065. DOI: 10.1136/bmjgh-2018-001065 (Chapter 2)
2. **Mesfin YM**, Cheng AC, Enticott J, Lawrie J, Buttery J. Use of telephone helpline data for syndromic surveillance of adverse events following immunization in Australia: A retrospective study, 2009 to 2017. Vaccine. 2020;38(34):5525–31. (Chapter 4)
3. **Mesfin YM**, Cheng AC, Enticott J, Lawrie J, Buttery J. Post-vaccination healthcare attendance rate as a proxy measure for syndromic surveillance of adverse events following immunisation: a validation study. Australian & New Zealand Journal of Public Health (in press) (Chapter 5)
4. **Mesfin YM**, Cheng AC, Tran H.L. A, Buttery J. Positive predictive value of ICD-10 codes to detect anaphylaxis due to vaccination: a validation study. Pharmacoepidemiol Drug Saf. 2019;28:1353–60. DOI: 10.1002/pds.4877 (Chapter 6)

## List of Conference Presentations

Listed below are manuscripts that were accepted for conference presentations. However, the conferences have been postponed due to the COVID-19 pandemic.

1. **Mesfin YM**, Cheng AC, Enticott J, Lawrie J, Buttery J. Use of telephone helpline data for syndromic surveillance of adverse events following immunization in Australia: a retrospective study, 2009 to 2017.
    a. International Congress on Infectious Diseases (ICID), Kuala Lumpur, Malaysia, postponed for 2021
    b. National Immunisation Conference, Perth, Australia, postponed for 2021
2. **Mesfin YM**, Cheng AC, Enticott J, Lawrie J, Buttery J. Post-vaccination healthcare attendance rate as a proxy measure for syndromic surveillance of adverse events following immunisation: A validation study using CUSUM chart.
    a. National Immunisation Conference, Perth, Australia, postponed for 2021

## Grants and Scholarships

Listed below are the scholarships and funding relevant to the period of candidature.

| | |
|---|---|
| 2018 | Monash University Postgraduate Travel Grant<br>(To attend the Practical Pharmacoepidemiology short course, London School of Hygiene & Tropical Medicine, UK) |
| 2017–20 | Monash University Graduate Scholarship and Monash University International Postgraduate Research Scholarship |

## Professional Roles during Candidature

| | |
|---|---|
| 2019–Present | Teaching associate/tutor, School of Public Health and Preventive Medicine, Monash University, Australia |
| 2020 | Reviewed abstracts submitted to the World Congress of Epidemiology |
| 2020 | Peer reviewer: Epidemiology |

## Coursework and Short Courses

Listed below are course works, short course and professional development completed during candidature.

| Year | Coursework or short course |
|---|---|
| 2019 | **PhD Completion Masterclass**<br>Monash University |
| 2020 | **Introduction to Time Series Analysis and Forecasting in R**<br>Udemy |
| 2020 | **Data Science: Data Mining & Natural Language Processing in R**<br>Udemy |
| 2019 | **Introduction to R Statistical Software**<br>Monash University |
| 2019 | **Introduction to REDCap**<br>Monash University |
| 2019 | **Presenting your Research with Confidence When English is your Second Language**<br>Monash University |
| 2018 | **Intensive Writing Course for Science Communication**<br>Monash University |
| 2018 | **Practical Pharmacoepidemiology short course**<br>London School of Hygiene & Tropical Medicine, UK |
| 2017 | **Introduction to STATA 14 Statistical Software**<br>Monash University |
| 2017 | **Implementation Science Masterclass**<br>Monash Centre for Health Research & Implementation, Monash University |
| 2017 | **Advanced Statistical Method for Clinical Research—MPH5270**<br>Monash University |
| 2017 | **Systematic Reviews and Meta-Analysis—MPH6239**<br>Monash University |
| 2017 | **Ethics and Good Research Practice Training**<br>Monash University |
| 2017 | **Advanced Database Searching for Systematic Review**<br>Monash University |
| 2017 | **Ethics and Good Research Practice**<br>Monash University |
| 2017 | **Introduction to Intellectual Property**<br>Monash University |
| 2017 | **Vaccine Safety Basics**<br>WHO e-Learning course |

## Acknowledgements

First and foremost, all praise to the most high God and his mother, the holy Virgin Mary!

Second, I am extremely grateful to my primary supervisor, Professor Jim Buttery, for providing me all-round support to complete my PhD thesis. Without his timely, constructive feedback through each stage of my study, it would not have been possible to complete this research. I am also indebted to his commitment, and he continuously strengthened me when I was down and stressed. I am also grateful to my co-supervisors, Professor Allen Cheng and Dr Joanne Enticott, for their guidance and thoughtful feedback throughout my candidature.

Third, I give a special thank you to Dr Jock Lawrie for his unreserved support, especially with data analyses, throughout my candidature. I am also thankful to Professor Helen Skouteris for all her considerate guidance and encouragement, especially in difficult times. I would like to acknowledge Kathryn Daly and Meredith Mascetta for their positive attitude and support regarding the administrative issues. To Aimy Tran, I truly appreciate your contributions as co-author and for providing feedback on the manuscripts' written English.

Fourth, this research was supported by an Australian Government Research Training Program (RTP) Scholarship, without which my PhD would not have been possible.

Finally, I cannot forget to thank my family (my parents and siblings) for their unconditional love and steadfast support during an intense PhD journey. I also thank my friends Dr Kelemu Tilahun, Dr Tekito Kassew, Dr Adugna Dagne, Dr Estifanos Baye and Ms Biruktawit Ashebr, for their unwavering support and close friendship.

Capstone Editing provided copyediting and proofreading services, according to the guidelines laid out in the university-endorsed national 'Guidelines for Editing Research Theses'.

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## List of Abbreviations

| | |
|---|---|
| AEFI | adverse events following immunisation |
| AEs | adverse events |
| AFI | anaphylaxis following immunisation |
| AusVaxSafety | Australia's near real-time AVSS |
| AVSS | Active Vaccine Safety Surveillance |
| CIOMS | Council for International Organizations of Medical Sciences |
| COVID | coronavirus disease |
| CUSUM | cumulative sum |
| ED | emergency department |
| GP | general practice |
| HPV | human papillomavirus |
| ICD-CM | International Classification of Disease Clinical Modification |
| IMPACT | Canadian Immunization Monitoring Program ACTive |
| LLR | log likelihood ratio |
| NOC | Nurse-On-Call |
| NRVSS | near real-time vaccine safety surveillance |
| OPR | Office of Product Review |
| PAEDS | Paediatric Active Enhanced Disease Surveillance |
| PHNs | Primary Health Networks |
| POLAR | Population Level Analysis and Reporting |
| PSS | passive surveillance system |
| PVSS | post-licensure vaccine safety surveillance |
| PVSM | post-licensure vaccine safety monitoring |
| SAEFVIC | Surveillance of Adverse Events Following Vaccination In the Community |

| | |
|---|---|
| SNOMED | Systematised Nomenclature of Medicine |
| SSS | Syndromic Surveillance System |
| TGA | Therapeutic Goods Administration |
| TIV | trivalent influenza vaccines |
| VPD | vaccine-preventable diseases |
| VSD | Vaccine Safety Datalink |
| WA | Western Australia |
| WHO | World Health Organization |

## Structure of the Thesis

### Chapter 1: Introduction

This chapter provides a general description of vaccine pharmacovigilance, with a particular focus on post-licensure safety surveillance and the rationale to conduct this program of work.

### Chapter 2: Systematic Review

This chapter presents a systematic review that was undertaken to summarise the literature on signal detection of AEFI using electronic healthcare data, with a particular focus on data sources, the methodological approach and statistical analysis techniques.

### Chapter 3: Research Methods

This chapter briefly describes the data sources, study design and statistical analyses used to answer the four research aims that comprised this thesis.

### Chapter 4: Telephone Helpline Data Use for Syndromic Surveillance of Adverse Events Following Immunisation

This chapter presents a retrospective study that aims to evaluate the potential use of telephone helpline data to augment existing adverse events following immunisation surveillance systems.

### Chapter 5: Use of Primary Healthcare Data for Syndromic Surveillance of Adverse Events Following Immunisation

This chapter presents a retrospective observational cohort study that analysed aggregated general practice consultation data to assess whether the syndrome ‘post-vaccination healthcare attendance rate’ can be used as a proxy measure to detect the unusual occurrences adverse events following immunisation.

**Chapter 6: Use of Emergency Department Data for Syndromic Surveillance of Adverse Events Following Immunisation**

This chapter presents a validation study that aimed to evaluate the validity of selected diagnostic codes used in an emergency department setting for identifying anaphylaxis following vaccination.

**Chapter 7: Conclusions and Future Directions**

This chapter summarises the main findings of the thesis and presents the findings' implications.

# CHAPTER 1: INTRODUCTION

## 1.1 Vaccination success

Vaccination is one of the most successful and cost-effective public health interventions and has led to dramatic reductions in rates of hospitalisation, deaths and disability due to vaccine-preventable diseases (VPD).[1-3] Vaccination programs provide protection against more than 20 life-threatening diseases and prevent between two and three million deaths across all age groups annually.[1, 4, 5] Additionally, the World Health Organization (WHO) estimated that a further 1.5 million deaths could be avoided each year by increasing the coverage of existing vaccines.[5] Notably, new vaccines that target more than 24 diseases are being developed, including multiple vaccines against severe acute respiratory syndrome coronavirus-2, which was being developed rapidly at the time of writing.[6, 7] Ensuring the safety of those who receive vaccines and upholding public confidence in vaccines are key to improve vaccination coverage and to maximise the benefit of vaccination programs.[8]

## 1.2 Safety of vaccines

Prior to licensure and public use, vaccines are evaluated extensively for safety during pre-clinical evaluation and clinical trials, with development typically lasting from 8 to 10 years (Figure 1.1).[9, 10] However, like all medicines, vaccines are not free from risk, and adverse events (AEs) can occasionally occur after vaccination (referred to as adverse events following immunisation( AEFIs)). The majority of AEFI are mild and rapidly self-limiting; however, on rare occasions, serious AEs may occur.[11-13] For example, febrile convulsions following seasonal influenza vaccines in 2010, and intussusception following the tetravalent rhesus–human reassortant rotavirus vaccine (RRV-TV) in 1999.[14, 15] In recent decades, public concern regarding AEFI has increased as the incidence of VPD has declined. Additionally, as vaccines are given to healthy individuals—predominantly children—public expectation of vaccine

safety is high.[1, 16] Therefore, any real or perceived concerns regarding vaccine safety can undermine public confidence in a vaccine and, if not managed in a timely manner, can lead to vaccine hesitancy and drop in vaccination coverage (as exemplified by the cases of diphtheria–tetanus–whole-cell-pertussis vaccine and human papilloma virus vaccine in England and Japan respectivly).[12, 13, 17-20] In 2019, the WHO declared vaccine hesitancy—defined as 'the reluctance or refusal to get vaccinated despite the availability of vaccines'—one of the top 10 threats to global public health.[5]

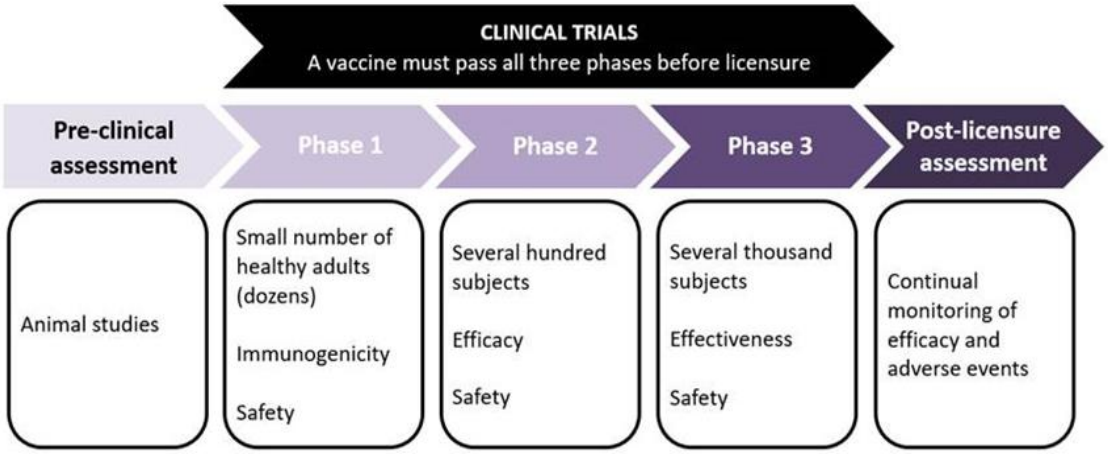


Figure 1.1. Vaccine development pathway: preclinical assessment, clinical trials and post licensure assessment [10, 21, 22]

The Council for International Organizations of Medical Sciences (CIOMS) defined an AEFI as:

> any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine and it can be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.[23]

Notably, not all AEFI are related causally to the vaccine itself; hence, an AEFI can be categorised into one of five following reaction types:

1. Vaccine product–related reaction: an AEFI that is caused or triggered by the inherent properties of the vaccine product.
2. Vaccine quality defect–related reaction: an AEFI that is caused or triggered by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.
3. Immunisation program error–related reaction: an AEFI may occur following the inappropriate handling, prescribing and administering of a vaccine (e.g., due to failure to keep vaccine in cold chain).
4. Immunisation anxiety–related reaction: an AEFI that arises from anxiety regarding the immunisation (e.g., fainting due to fear of the injection).
5. Coincidental reaction: the AEFI would have occurred regardless of vaccination (e.g., concomitant malaria or upper respiratory tract infections can cause fever).[9, 23]

Therefore, safety evaluation and monitoring for vaccines are continued after licensure, including while the vaccines are in use in immunisation programs; this is referred to as vaccine pharmacovigilance.[24] According to the CIOMS, vaccine pharmacovigilance is defined as:

> the science and activities related to the detection, assessment, understanding and communication of AEFI and other or immunization related issues and the prevention of untoward effects of the vaccine or immunisation.[23]

Monitoring the safety of licensed vaccines in real-world practice is important, particularly to identify rare, late-onset or unexpected AEs that could not be identified in pre-licensure studies.[25, 26] Specifically, pre-licensure clinical trials often have limited ability to detect rare AEFI (with a frequently of < 1/10,000 doses), AEFI that occur in specific population groups that are often excluded from clinical trials—such as pregnant women and patients with comorbidities—or AEFI with delayed presentation.[8, 25, 27] Several approaches can be used to

assess the safety of vaccines post-licensure (also called postmarketing), including post-approval (phase IV) trials and observational studies, but most approaches rely predominantly on post-licensure vaccine safety surveillance (PVSS).

### 1.3 Post-licensure vaccine safety surveillance

PVSS aims to detect possible safety problems that may be related to vaccination as early as possible to initiate timely risk assessment and response, not only ensuring the safety of those who receive the vaccines but also maintaining public confidence in vaccination programs. Generally, each country's national vaccination program, in collaboration with national regulatory authorities, is responsible for establishing and continuing PVSS.[9, 27]

In general, vaccine pharmacovigilance comprises four key steps, which are not necessarily sequential, as follows:

1. AEFI signal detection (hypothesis generation), which is merely an indication that something might be wrong and warrants further investigation. According to WHO, a vaccine safety signal is '*reported information on a possible causal relationship between an adverse event and a vaccine, the relationship being unknown or incompletely documented previously. The information can arise from one or multiple sources*.'[16]
2. AEFI signal strengthening, which is an intermediate stage and sometimes can be performed together with the signal confirmation. In this stage, available findings from different sources are researched, or additional studies are conducted to determine if further evaluation of the signal identified in step one is needed.
3. AEFI signal confirmation, which is the stage at which the identified signals are assessed rigorously using classic epidemiological methodologies to draw a conclusion regarding the presence or absence of a suspected causal association between an AE and a vaccine.

4. AEFI causality assessment, which is the systematic review of data regarding an AEFI case to determine the likelihood of a causal association between the event and the vaccine(s) that were received. Causality assessment of an AEFI considers five general principles, including temporal relation, biological plausibility, specificity, consistency and strength of association (see Figure 1.2).[9, 16, 28, 29]

Signal detection is an initial step in the practice of PVSS, but it also remains crucial in initiating a quick investigation and timely response to any AEFI signals. This thesis focused on AEFI signal detection exclusively. AEFI signals can be obtained from a wide range of sources, including from literature reviews and pre-licensure clinical trials, but are obtained principally from AEFI surveillance systems (passive/active).[16, 30] The different approaches used at each stage of AEFI surveillance are described in Figure 1.2.

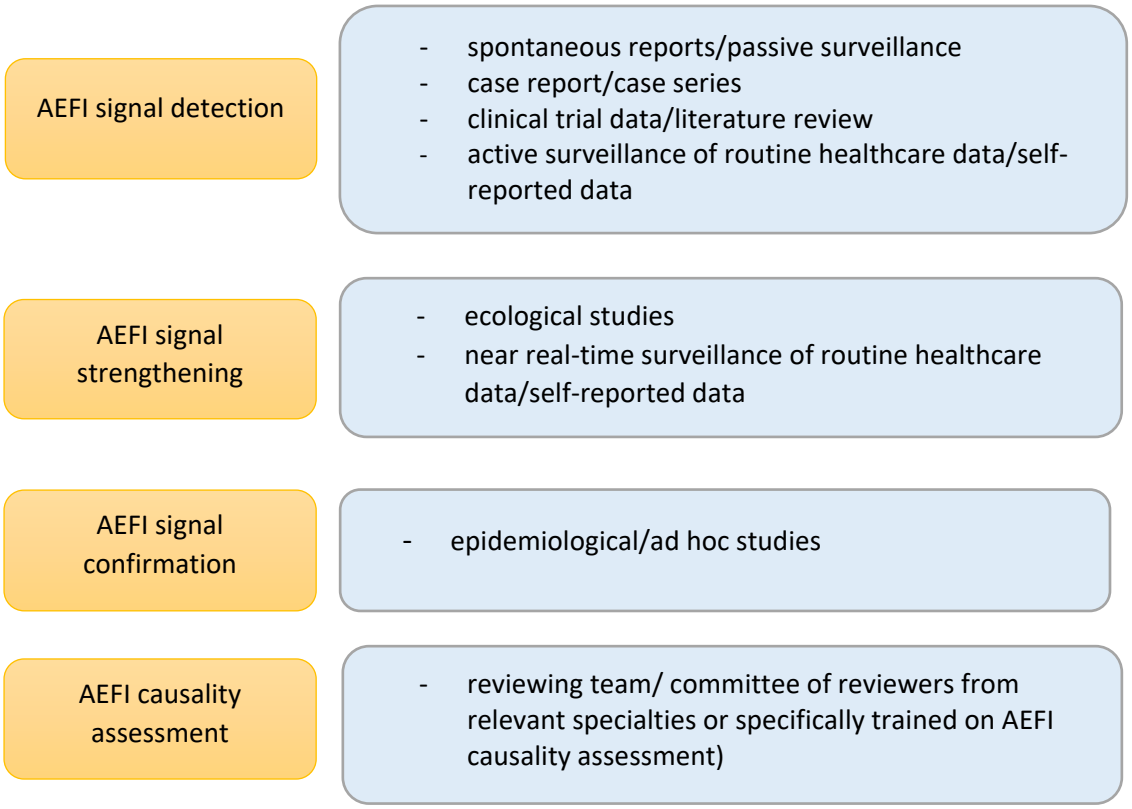


Figure 1.2. Post-licensure vaccine safety monitoring basic steps and potential data sources for each step [29, 31]

### 1.3.1 Passive surveillance systems

Passive (spontaneous) surveillance system (PSS) is the sole approach to post-licensure safety monitoring for vaccines in most countries, specifically for the purpose of signal detection. [32-34] The WHO also considers PSS as a minimal infrastructure for monitoring AEFI despite the fact that 36% of its member countries—the majority of which were from low-to-middle-income countries—did not have a functional PSS, according to a report in 2018.[35, 36] Of note, there have been developments by the Global Vaccine Safety Initiative (WHO vaccine safety blueprint I and II) towards strengthening vaccine safety signal detection capacity, mainly by carring out active surveillance in addition to PSS.[37-39] PSS rely on spontaneous reports of AEFI from anyone in the community, but the reports mainly come from healthcare workers and consumers (i.e., vaccinated individuals and their caregivers).[1, 30] With a broad population coverage, PSS has the potential to detect rare and unexpected AEFI, as well as increased rates of known AEFI.[30, 40] For example, in 1999, the link between intussusception and the human-rhesus reassortant rotavirus vaccine (RotaShield) was first detected through the United States's (US) passive Vaccine Adverse Event Reporting System (VAERS).[41] Other examples demonstrating the usefulness of PSS to detect new or rare AEs were when VAERS found an increased risk of febrile seizures among young children after influenza vaccine (Fluzone®) during the 2010–2011 season, and anaphylaxis after receiving the First Dose of Pfizer-BioNTech COVID-19 Vaccine in 2020-2021.[42, 43]

In Australia—although unsupported by legislation in some jurisdictions— AEFI are reportable events.[44] Any suspected AEFI should be reported to the national regulatory agency Therapeutic Goods Administration (TGA) Office of Product Review (OPR) either directly or via the jurisdiction-based health authority.[44, 45] TGA's OPR plays a vital role in collecting and analysing nationally reported AEFI.[44] Additionally, some jurisdictions have established an enhanced PSS aimed to improve the detection and reporting of AEFI. For example, in Victoria,

AEFI are reported to Surveillance of Adverse Events Following Vaccination In the Community (SAEFVIC). SAEFVIC provides clinical support and information to those who have experienced AEFI and aims to increase not only the likelihood of reporting but also consumers' confidence in immunisation.[46] West Australia have a similar system (WAVSS) which has been modelled from SAEFVIC.

Despite its indispensable importance, PSS has well-known limitations, including under-reporting, reporting bias and inability to determine AEFI incidence rates due to lack of appropriate denominator data (vaccine doses administered).[30] Reliance on passive AEFI surveillance alone may hinder (or delay) the detection of potential vaccine safety signals (e.g. the 2010 febrile convulsions in Australia) or delay the timely response to false and measliding claims of a link between vaccines and adverse reaction (e.g. the human papillomavirus (HPV) vaccination crisis in Japan), which can ultimately cause unnecessary exposure to a potentially unsafe vaccine or loss of public confidence in vaccination.[17, 40, 47-49] Studies showed that the public vaccination uptake in the respective countries following the incidents was declined significantly.[19] Notably, this is most concerning when introducing a new vaccine (or seasonal strain change) with a mass vaccination program, such as seasonal influenza vaccination, as it was significantly demonstrated in Australia in 2010.

To breifly describe the above two events, there was an unprecedented increase in rates of fever and febrile seizures in young children after administering trivalent influenza vaccine (TIV), specifically associated with BioCSL Fluvax™ and Fluvax Junior™.[15, 49] Unfortunately, the event was not detected by national or jurisdictional PSS until emergency department (ED) clinicians in Western Australia (WA) raised concerns six weeks after commencing the vaccination program (Figure 1.3). Finally, a country-wide suspension of administering the influenza vaccination to children under five years of age was implemented on 23 April 2010 and since then, BioCSL's Fluvax™ or Fluvax Junior™ is not recommended for use in children

< five years.[15] On the otherhand, in Japan in 2013, safety concerns were rasied through media reports, not from the government health regulatory body, that associated the HPV vaccine with diverse adverse events, including chronic pain and motor impairment. Eventaully, in June 2013, two months after the vaccine introduced for routine use in the national immunization program for girls aged 12–16 years, the Japanese Government suspended the proactive use of HPV vaccine in the national immunisation program.[17, 19] At the timing of writing this thesis, despite further investigations confirmed no link between HPV vaccination and the suspected AEs mentioned above and calls by WHO to resume active recommendation of the HPV vaccine, the proactive use of the vaccine in the national immunisation program remains suspended in Japan.

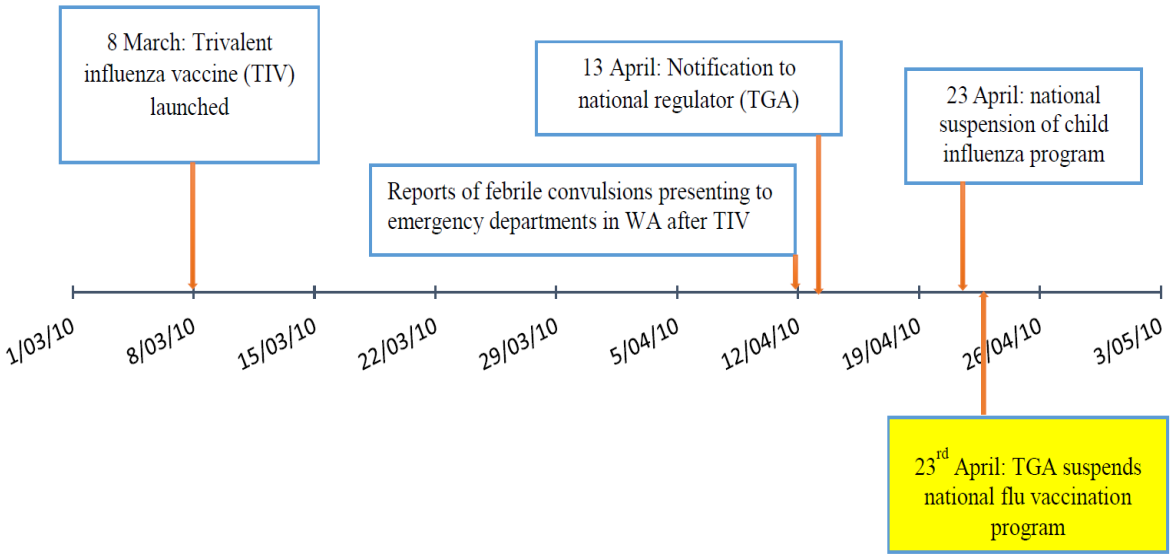


Figure 1.3. Timeline of detection of fever and febrile convulsions following influenza vaccination in 2010, Australia

### 1.3.2 Active vaccine safety surveillance

Vaccine safety signals are also monitored for using Active Vaccine Safety Surveillance (AVSS), which aims to complement, rather than replace, PSS. The CIOMS Working Group on Vaccine Safety define AVSS as ‘a data collection system that seeks to ascertain as completely

as possible the number of AEFI in a given population via a continuous organized process'.[30] AVSS typically provides more detailed and less biased data to enable accurate estimates of AEFI incidence, but it traditionally requires substantial expertise and resources. Hence, the use of AVSS has historically been limited largely to monitoring pre-specified AEFI for newly licenced vaccines.[30, 50] The CIOMS Working Group also recommended the use of AVSS either if a new vaccine was introduced with limited safety data or if a vaccine was introduced in a country for the first time.[30]

There are a variety of approaches for AVSS, but they can be classified broadly into self-reported data–based (also called participant-centred) [50, 51] and electronic healthcare data-based AVSS. [52] In participant-centred AVSS, information regarding vaccination and medical illness (possible AEFI) is collected by surveying healthcare providers or cohorts of vaccinated individuals or their caregivers directly via telephone interview, SMS and email.[50] Conversely, healthcare data–based AVSS analyses databases of medical records (routinely collected healthcare data) available electronically at different levels of healthcare provision or healthcare data collected by trained health workers at selcted hopitals (targeted hospital-based AVSS).[53, 54] Two examples of targeted hospital-based AVSS are the Canadian Immunization Monitoring Program ACTive (IMPACT)[55] and Paediatric Active Enhanced Disease Surveillance (PAEDS) in Australia.[46, 56] The main objective of targeted hospital-based AVSS is to identify pre-selected AEFI of sufficient severity that require hospital admission, such as acute flaccid paralysis, intussusception and febrile seizures.[56] A classic example of AVSS based on large healthcare data is the Vaccine Safety Datalink (VSD) in the US.[52, 53, 57] Notably, the US also uses complementary AVSS, kown as Post-Licensure Rapid Immunization Safety Monitoring (PRISM), which monitors vaccine safety using a database of health insurance claims.[58]

### 1.3.3 Near real-time vaccine safety surveillance

Due to the advancement of signal detection statistical tests and automated data extraction tools, some countries have been able to establish near real-time vaccine safety surveillance (NRVSS) that aims for early AEFI signal detection.[59, 60] The typical feature of NRVSS is that data are examined at repeated points over time using sequential statistical methods to estimate and test the association between a vaccine and potential AEs.[59, 60] Australia's near real-time AVSS, AusVaxSafety,[51] and the VSD in the US [57] are the two best-known examples of NRVSS. These systems update data and conduct analyses weekly.

AusVaxSafety was established in Australia in 2014 following the 2010 influenza vaccine safety incident and aimed to facilitate early detection of possible AEFI.[51] AusVaxSafety utilises solicited information reported directly from a cohort of those receiving vaccines (or their caregivers) in the days following vaccination. Essentially, using information extracted from selected immunisation clinics across Australia (at the time of writing, > 360 sentinel sites, predominantly general practices [GPs]), AusVaxSafety sends an automated SMS or email to individuals who were vaccinated at their clinic asking whether they had experienced any AEs within three days of vaccination (a 'Yes' or 'No' question). If an individual's answer is 'Yes', further questions will follow to gather detailed information regarding the event, including whether they attended medical care for the event (used by AusVaxSafety as a surrogate for severity).[51] AusVaxSafety has monitored the safety of seasonal influenza vaccines administered to all ages since 2017, and no AEFI signal was identified.[51, 61] At the time of writing, the safety of the following vaccines was being monitored under the AusVaxSafety:

- the seasonal influenza vaccine in people aged six months and older (data analyses are conducted weekly)

- the human papillomavirus (HPV) vaccine in adolescents aged 11–14 years (data are analysed fortnightly)
- a booster vaccine containing pertussis (whooping cough) in pregnant women (data are analysed monthly)
- the meningococcal ACWY vaccine in adolescents aged 14–19 years (data are analysed fortnightly).[51]

In the US, active surveillance for vaccine safety—mostly for newly licensed vaccines—is conducted using the population-based healthcare database, VSD. VSD is a collaborative project between the Centers for Disease Control and Prevention and 9 health maintenance organisations across the US.[52, 53] Essentially, in this system, pre-specified possible AEs (medical outcomes of outpatient visits, emergency room visits or hospitalizations) and vaccine pairs are monitored using linked data extracts from vaccination registries and medical records from the participated health maintenance organisations.[53, 62] Since 2005, the VSD has allowed several AEFI signals to be identified and has been utilised to review safety signals.[63-65]

As this thesis specifically examines aspects of AEFI signal detection using routinely collected healthcare data, details of routinely collected healthcare data–based NRVSS—including the VSD—are presented in Chapter 2.

### 1.4 Thesis rationale

AEFI signal detection in Australia has relied largely on self-reported information (spontaneous or solicited). As noted previously, passive (spontaneous) reporting systems are limited by under-reporting and reporting bias. Conversely, AusVaxSafety potentially takes weeks to accrue a sufficient sample size and lacks the power to detect rare AEs, and its scope is limited to participating sites. Similarly, the scope of PAEDS is limited to AEs that are severe enough to require hospital admission to participating hospitals (eight children's hospitals at time of

writing). However, Australia has not yet established an AEFI surveillance system that integrates routine healthcare data. Further, although existing healthcare data–based AVSS systems (including the VSD) have improved AEFI signal detection considerably, they are often conducted using diagnostic data from clinical settings, with the primary emphasis on suspected (pre-identified) AEFI.[66]

As the main objective of AEFI surveillance systems is to highlight vaccine safety issues at the earliest possible time, multimodal surveillance systems that integrate information on AEFI from all relevant sources, including from non-clinical sites, are essential.[67] Figure 1.4 summarises the different levels of healthcare services in Australia. Increasigly, healthcare services are being actively delivered via telehealth and online, which create an opportunity to reach out to those who live in rural and remote areas.[68, 69] In Australia, a registered, nurse-led telephone helpline service has been in operation since 2008, where nurses use computerised clinical algorithms to respond to callers and provide them with advice or information.[69] AEFI (occurring at any age) is a specific clinical algorithm listed within the options nurses can choose from.To the researchers' knowledge, no country has integrated telephone helpline data into existing AEFI surveillance systems.

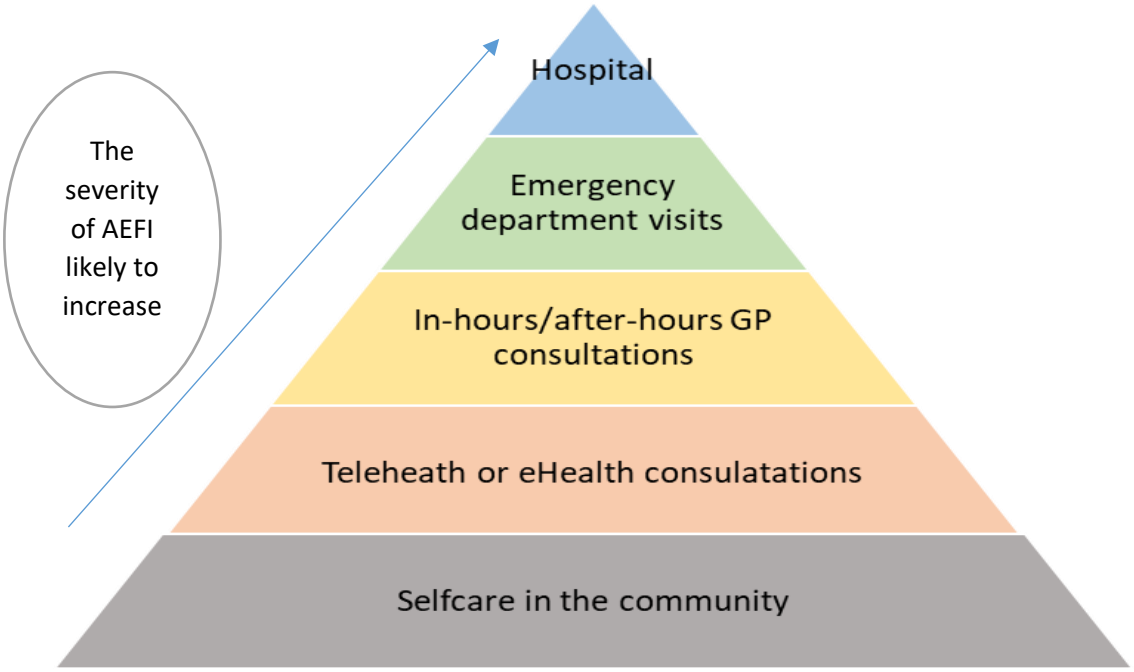


Figure 1.4. Potential electronic health data sources at different stages of healthcare visits

Outside pharmacovigilance, syndromic surveillance system (SSS) complements traditional public health surveillance systems and has proved useful in providing an early warning of increased disease activity, such as influenza-like illnesses and gastroenteritis.[70, 71] SSS is the real-time (or near real-time) collection, analysis, interpretation and dissemination of health-related data.[72] A key foundation of SSS is that it uses readily available information from clinical and/or non-clinical sources to help identify public health problems as early as possible to enable immediate action; the data are collected mostly for purposes other than surveillance.[72] Data are often aggregated into syndromic indicators based on pre-diagnostic clinical information (symptoms and clinical signs) or proxy measures (e.g., absenteeism, drug sales) that occur before the diagnosis of diseases.[72, 73] For example, in the United Kingdom (UK), different national SSS, utilising data from a variety of healthcare settings (a telehealth triage system, general practice and emergency departments) have been established to track infectious diseases and other public health hazards across England.[74, 75] These SSS monitor daily patterns of the

studied syndromes—such as flu-like illnesses and gastroenteritis. However, AEFI have not yet been included in the list of studied syndromes.

As inverstigators, we believe that syndromic surveillance that is based on non-specific health data or proxy measures could have the ability to augment early detection of vaccine safety problems. Therefore, assessing the utility of different healthcare datasets for syndromic surveillance of AEFI in the context of multimodal surveillance systems is crucial.

### 1.5 Thesis aims

The overarching aim of this thesis was to assess the potential novel use of syndromic healthcare data (specific and non-specific for AEFI) collected at different levels of healthcare provision to complement existing AEFI signal detection systems in Victoria, Australia.

The specific objectives were to:

1. summarise literature regarding the use of electronic healthcare data for AEFI signal detection, with emphasis on possible data sources and analysis approaches
2. examine the potential use of telephone helpline data to assist AEFI signal detection
3. assess the utility of post-vaccination GP consultations as a proxy measure of AEFI to assist AEFI signal detection
4. examine the validity of selected diagnosis codes to identify AEFI at the ED level.

# CHAPTER 2: SYSTEMATIC REVIEW

## Introduction

As outlined in Chapter 1, traditionally, the detection of AEFI has relied heavily on reported data (voluntary or solicited), which are collected mainly from health workers and people who get vaccinated or their caregivers. However, in recent years, post-licensure vaccine safety studies based on electronically available and routinely collected health data have been reported increasingly in the literature. Such data sources would allow population-based active AEFI surveillance to be conducted, especially to enhance the detection of rare AEFI. This chapter comprises a systematic review that summarised the literature on electronic healthcare data–based AEFI signal detection, with a particular focus on data sources, the methodological approach and statistical analysis techniques.

**Citation:** Mesfin YM, Cheng AC, Lawrie J, Buttery J. Use of routinely collected electronic healthcare data for post licensure vaccine safety signal detection: a systematic review. BMJ Glob Health 2019;4(4):e001065. DOI: 10.1136/bmjgh-2018-001065

BMJ Global Health

# Use of routinely collected electronic healthcare data for postlicensure vaccine safety signal detection: a systematic review

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**To cite:** Mesfin YM, Cheng A, Lawrie J, *et al*. Use of routinely collected electronic healthcare data for postlicensure vaccine safety signal detection: a systematic review. *BMJ Glob Health* 2019;**4**:e001065. doi:10.1136/bmjgh-2018-001065

**Handling editor** Seye Abimbola

Received 18 July 2018
Revised 13 October 2018
Accepted 29 December 2018



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## ABSTRACT

**Background** Concerns regarding adverse events following vaccination (AEFIs) are a key challenge for public confidence in vaccination. Robust postlicensure vaccine safety monitoring remains critical to detect adverse events, including those not identified in prelicensure studies, and to ensure public safety and public confidence in vaccination. We summarise the literature examined AEFI signal detection using electronic healthcare data, regarding data sources, methodological approach and statistical analysis techniques used.

**Methods** We performed a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Five databases (PubMed/Medline, EMBASE, CINAHL, the Cochrane Library and Web of Science) were searched for studies on AEFIs monitoring published up to 25 September 2017. Studies were appraised for methodological quality, and results were synthesised narratively.

**Result** We included 47 articles describing AEFI signal detection using electronic healthcare data. All studies involved linked diagnostic healthcare data, from the emergency department, inpatient and outpatient setting and immunisation records. Statistical analysis methodologies used included non-sequential analysis in 33 studies, group sequential analysis in two studies and 12 studies used continuous sequential analysis. Partially elapsed risk window and data accrual lags were the most cited barriers to monitor AEFIs in near real-time.

**Conclusion** Routinely collected electronic healthcare data are increasingly used to detect AEFI signals in near real-time. Further research is required to check the utility of non-coded complaints and encounters, such as telephone medical helpline calls, to enhance AEFI signal detection.

**Trial registration number** CRD42017072741

## Key questions

### What is already known?

- Adverse event(s) following immunisation (AEFI) signal detection has primarily relied on passive surveillance reporting.

### What are the new findings?

- AEFIs signal monitoring using population-based electronic health records (EHRs) is increasing, but has been primarily limited to diagnostic data from hospital settings.
- Continuous sequential (rapid cycle) analysis method allows AEFIs signal monitoring in near real-time.
- Data delays (data accrual lags) are the key challenges to perform near real-time AEFI monitoring using EHRs.

### What do the new findings imply?

- A complementary and efficient AEFI signal monitoring system is feasible using EHRs.
- Further research is required to evaluate the utility of syndromic data/proxy measures to enhance the timeliness of monitoring AEFIs.

## INTRODUCTION

Vaccination is one of the most effective public health interventions. Current immunisation programmes provide protection against up to 26 diseases and prevent an estimated 2–3 million deaths every year.[1 2] It is estimated that 1.5 million more deaths could be saved through further increasing vaccination coverage of existing vaccines.[3] However, this remarkable success has been challenged due to vaccine safety concerns and increasing vaccine hesitancy, largely due to fear of adverse event following immunisation (AEFIs). Notably, following the sharp reduction of incidence of vaccine-preventable diseases the public attention to AEFI has increased. This can result in loss of confidence in vaccination, a resultant drop in vaccine coverage and eventually lead to a re-emergence of controlled disease (figure 1).[4] Hence, timely detection of potentially causally related adverse events (AEs) and more rapidly refute spurious claims regarding AEs using real-world data is critical to maintain the community and providers confidence in vaccine programmes. Nevertheless, recent analysis of global AEFI reporting found that more than 36% of WHO

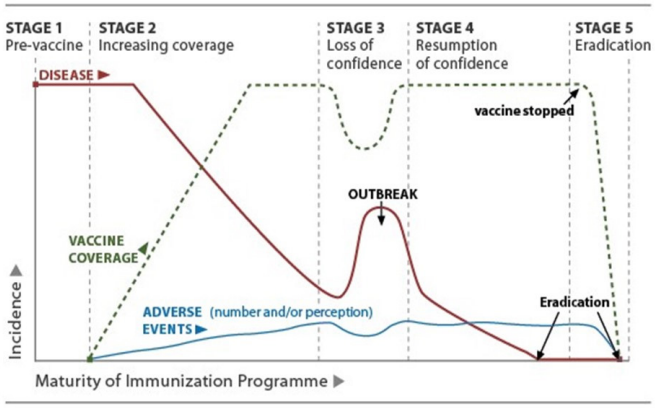


**Figure 1** Potential stage in the evolution of an immunisation programme, vaccine safety. Diagram adapted from Chen *et al*. The Vaccine Adverse Effect Reporting System (VAERS). *Vaccine* 1994:12(6):542–50.

member countries do not have a functional postlicensure safety monitoring system for vaccines.[5]

Postlicensure AEFIs monitoring is often classified into three stages: signal detection, signal refinement and signal confirmation. A vaccine safety signal is defined as 'reported information on a possible causal relationship between an adverse event and a vaccine, the relationship being unknown or incompletely documented previously'.[6] Generally, AEFI signal detection has been undertaken using passive surveillance or active surveillance system. Passive surveillance systems, the prevailing AEFI monitoring system, monitor reports of AEs that are spontaneously submitted by healthcare providers, vaccinated individuals/their caregivers or others. Its wide population coverage allows for detection of new and unanticipated AEs but has limitations of under-reporting and imprecise risk estimates due to lack of appropriate denominator data.[7] According to the 2015 Global Vaccine Safety Initiative meeting report, low passive AEFI reporting rates are a significant barrier to detect vaccine safety signal timely.[8] In contrast, active surveillance of AEFI involves proactively seeking information from healthcare providers, vaccinated individuals/their caregivers, or related datasets using well-designed study protocols. These surveillance systems provide more detail, less biased information and appropriate denominators. However, active surveillance systems are resource intensive and takes substantial time to achieve the required sample size to study rare AEs. Hence, their use in many settings are largely limited to investigate signals detected from the passive surveillance systems, literature review or possible prelicensure trial safety questions.[7 9 10]

Encouragingly, in recent years, new studies have shown that routinely collected electronic health records (EHRs) can be used as an alternative data source to monitor for AEFI signals in near real-time.[11 12] For example, in the USA, newly marketed vaccines are monitored for potential AEFIs weekly using the Vaccine Safety Datalink (VSD) collaboration between the US Centre for Disease Control and eight healthcare organisations. In the VSD, patient encounters and diagnoses made in an emergency department, outpatient clinic and hospital are linked with previous vaccine via patient-specific study identification numbers. Though the regular use of VSD is to investigate known AEFI signals identified from passive surveillance, published studies also show that VSD and other EHR detection systems are suitable for rapid detection of AEFIs signals.[13–15]

Considering the increasing availability of EHRs and the necessity of further improving the capacity of vaccine safety monitoring, particularly in low-income and middle-income countries, EHRs can offer an alternative data source to establish complementary active AEFI surveillance systems. By systematically summarising these literature, we intend to provide valuable information for countries considering establishing AEFI signal detection system based on EHRs. Therefore, we aimed to: (1) describe the features of postlicensure vaccine safety studies employing EHRs primarily for safety signal detection and (2) catalogue the nature of data sources, methodological approaches and analysis techniques applied

## METHODS

### Search strategy

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines,[16] as provided in online supplementary file 1. The protocol was registered at the international prospective register of systematic reviews (registration number CRD42017072741). We searched OVID Medline (1946 to September week 3 2017), OVID Embase (1974 to 2017 September 10), the Cochrane Library, Scopus and Web of Science. Comprehensive search terms for all databases were developed in consultation with a medical librarian to identify all potentially relevant studies. A combination of keywords and Medical Subject Headings (MeSH) were used in each database with appropriate adjustment. Final searches were performed on 25 September 2017. An example of the search strategy used in Ovid MEDLINE is shown in online supplementary file 1. In addition, bibliographies of relevant studies, conference papers/proceedings and grey literature databases, such as who.int and greylit.org, were searched to identify further important and unpublished studies.

### Studies selection criteria and screening

We included studies primarily focussing on AEFI signal detection using EHRs. Studies were included regardless of vaccine type, population group studied, study setting and methodology used. However, studies based on passive pharmacovigilance data or administrative (claim) data; studies conducted solely to test or verify the previously identified signals and feasibility studies or studies conducted to evaluate methodologies were excluded from the review. We also excluded non-English records and conference abstracts.

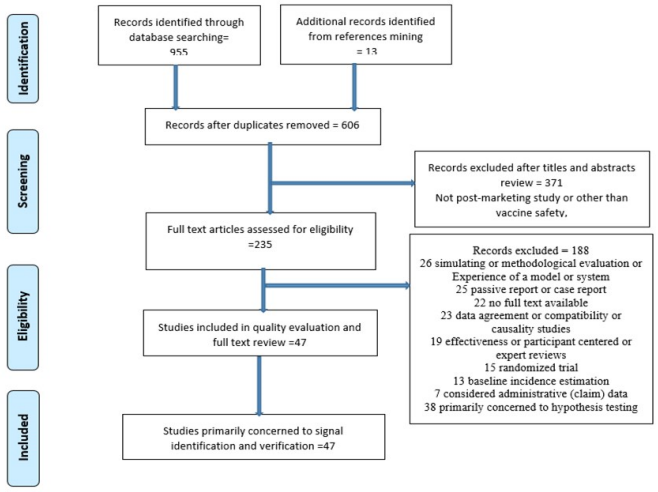


**Figure 2** Flow diagram shows stages of study selection and screening. Articles may have been excluded for more than one reasons.

Search results were downloaded and managed in EndNote X8. Articles were screened in three stages (titles alone, abstracts and then full-text review) based on the PRISMA flow of information (figure 2). At the initial stage, titles and abstracts were screened to remove duplicate records and studies clearly outside the scope of the review. Then, two reviewers conducted a full-text review to assess the eligibility based on the inclusions criteria. Study screening stages and the reasons for articles exclusion during full-text review are described in figure 2.

### Quality assessment and data extraction

We used a checklist adapted from the Food and Drug Authority (Best Practices for Conducting and Reporting Pharmaco-epidemiologic Safety Studies Using EHR).[17] Many of the critical appraisal tools extensively used to appraise observational studies, such as Ottawa-Newcastle tool and strengthening the reporting of observational studies in epidemiology (STROBE), are not suitable for evaluating pharmaco-epidemiological studies and public health surveillance as they are reasonably different from the standard epidemiological studies. The lead author (YMM) assessed risk of bias of all the included studies, and the second independent reviewer (TK) evaluated 25% of the studies randomly for verification. As there was no substantial risk of bias identified, we considered all appraised studies for the final review. The methodological quality and risk of bias assessment criteria were:

- Well defined research questions.
- Sample representativeness.
- Clear inclusion and exclusion criteria.
- Appropriateness of study design and comparison groups.
- Follow-up (risk interval) long enough for the events to occur.
- Appropriateness of data integration method, when relevant.
- Adjustment of confounders.
- Employed appropriate statistical analyses method.
- Used objective criteria to measure outcomes.

The lead author consistently extracted the required data using pretested data abstraction template. The following information were extracted across the included studies:

- Study author.
- Publication year.
- Study setting and period.
- Data source(s) and nature of the data (diagnostic vs prediagnostic).
- Study design(s) employed.
- Studied population.
- Vaccine(s) and AE(s) studied.
- Statistical analysis approaches and signal detection method used.
- Frequency of assessment.
- Method(s) of controlling confounders reported and challenges reported.
- Main findings (signal (s) identified or not).

### Data analysis

Key features of the studies are described quantitatively. Results from the selected studies are synthesised in a narrative analysis. The structure of the detailed review includes: vaccines monitored; AEs studied; study design(s) used; data analysis approach and signal detection method employed.

### Patient and public involvement statement

No patient data were consided in this study.

## RESULT

### Studies identified and characteristics

After removal of duplicate articles, we screened the titles and abstracts of 606 articles and excluded articles clearly out of the scope of this review. Then, we screened the remaining 235 full-text articles according to the exclusion criteria (figure 2). Studies could be excluded for more than one reason. Forty-seven articles, conducted between 2002 and 2017, were included in the final synthesis.[18–64] No studies were excluded based on quality or bias.

Almost all studies included in this review were conducted in the USA (n=45).[18–25 27–33 35–65] Two additional studies were conducted in the UK[26] and Taiwan.[34] A considerable number of studies (n=13, 28%) assessed the safety of vaccines administered to high-risk groups (pregnant women or elderly subjects). Fourteen (30%) studies assessed the AEFIs in near real-time (table 1).

### Vaccines studied

Multiple types of vaccines, including live, inactivated, monovalent and combined, were monitored after licensure for potential AEFI. Seasonal influenza vaccines (trivalent inactivated influenza vaccines (TIIV), live attenuated influenza vaccines, monovalent influenza vaccines and live attenuated monovalent influenza vaccines) were most frequently studied (n=17), followed by combined

**Table 1** Summary characteristics of selected studies

| Study characteristics | Number of studies |
|---|---|
| Data collection | |
| Retrospective | 37 |
| Prospective | 10 |
| Data source | |
| Immunisation record linked with: | |
| Outpatient, emergency department and inpatient data | 35 |
| Emergency department and Inpatient data | 8 |
| Outpatient and inpatient data | 3 |
| Outpatient (general practice) data | 1 |
| Study type | |
| Near real-time surveillance | 14 |
| Phase IV observation study | 33 |
| Study design | |
| Self-controlled study | |
| Self-controlled risk interval | 22 |
| Self-controlled case series | 4 |
| Cohort study | |
| Historical comparison (current vs historical design) | 20 |
| Concurrent/Parallel comparison group | 9 |
| Case-crossover study | 2 |
| Studied outcomes of interest | |
| Preselected adverse events | 35 |
| All medically attended events | 12 |
| Analysis method | |
| Non-sequential analysis | 33 |
| Group sequential analysis | 2 |
| Continuous sequential (rapid cycle) analysis | 12 |

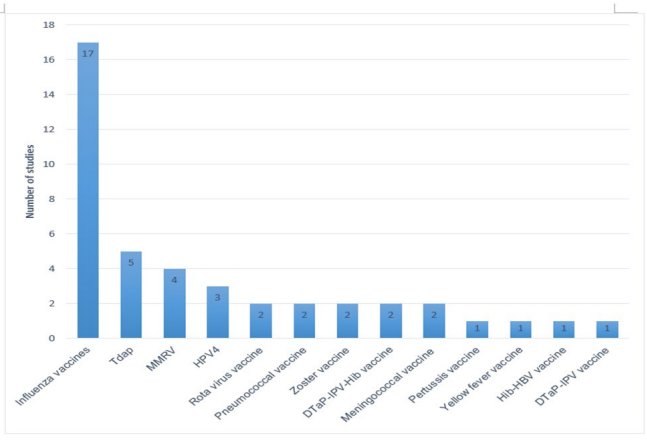


**Figure 3** Type of vaccines studied by the selected studies.

diphtheria-tetanus toxoid-acellular pertussis (Tdap) vaccines (n=5) (figure 3).

### AEFIs studied and data source

Most of the reviewed studies (n=35) studied preidentified AEs using a fixed postvaccination risk interval. AEs were selected based on the safety concerns from passive surveillance reports and prelicensure clinical trials. Frequently studied AEs were Guillain-Barré syndrome, febrile convulsions, seizures, anaphylaxis, meningitis/encephalitis and local reactions. Potential maternal and infant outcome (AEFIs), such as pre-eclampsia/eclampsia, maternal death, small for gestational age, preterm birth, stillbirth and neonatal death were also evaluated. Studied AEFIs were mainly identified using International Classification of Diseases (ICD) Clinical Modification codes as well as relevant ICD-9 or ICD-10 codes from electronic records (outpatient, inpatient and emergency department settings). In some studies, patients' charts/medical records were manually reviewed to verify the AEs.

In this review, 14 statistically elevated vaccine-AE pairs (signals) were detected, and 6 were confirmed. These were measles, mumps, rubella and varicella vaccine and seizure/febrile convulsion,[38 43] 2010–2011 TIIV and febrile seizure,[57] monovalent rotavirus vaccine and intussusception,[61] 2014–2015 TIIV and febrile seizures[48] and Tdap vaccine and chorioamnionitis.[41]

### Study designs employed

Self-controlled design was the most frequently used study design (n=22),[18–21 25 27 28 30–34 36 38 39 44–46 48 53–57 59 62 63] followed by cohort design with historical comparison (also called observed vs expected analysis) (n=20).[18 22–26 29 34 38 39 43 45 47–49 57 60 61 63 64] Self-controlled design can be self-controlled risk interval (SCRI) or self-controlled case series (SCCS). Cohort design with concurrent/parallel comparison group,[19 20 29 40–42 50–52] mostly to examine vaccines administered to pregnant women, and case-crossover study designs were also employed.[28 32] Of note, 18 studies (38.3%) employed more than one study design; of these, SCRI and current versus historical designs were often used together.[25 34 38 39 47 48 57 63]

### Statistical analysis and signal detection method

Two broad data analytic approaches, non-sequential analysis and sequential analysis, were employed to identify elevated risk of AEs associated with a given vaccine. In studies that employ a non-sequential analysis approach (n=33), statistical tests are performed after all the data are collected/accumulated. Detailed description of these studies and their analytic approaches are provided in online supplementary file 2. The sequential analysis approach allows repeated examination of data to check for AEFI increased occurrence. This was implemented in two different ways in the included studies: (i) as group sequential analysis (n=2), which involved a periodic statistical test and limited number of statistical tests over

time and (ii) as continuous sequential analyses (n=12), also called 'rapid cycle analysis', which involved a weekly statistical test until the end of the study period (table 2).

The choice of specific statistical tests was guided by the data analysis approach used. Standard analytic tests, such as logistic and Cox regression, were used to examine the data at the end of the study period (end-of-study analysis). A sequential hypothesis test statistic, the sequential probability ratio test (SPRT), was used to examine data for an elevated risk of AEFI continually over time. In particular, maximised sequential probability ratio test (MaxSPRT) was the most frequently applied sequential hypothesis test statistic.[22 24 29 34 39 43 47 48 57 61 62 64] It has different versions: Poisson MaxSPRT, Binomial MaxSPRT and Conditional MaxSPRT (table 2). Further, supplementary analyses were performed to verify the detected signals and instances of elevated risks. These included temporal scan statistics, to evaluate clustering of events after vaccination, and case-centred regression and logistic regression.[29 39 43 47–49 60 61 64]

### Confounder adjustment and potential challenges

Many different potential confounders were measured including age, gender, chronic conditions, site, seasonality, trend, concomitant vaccines and delay in the arrival of patient data. Generally, studies adjusted confounding variables in three ways: using data restriction, matching and stratification (alone or in combination). Strategies chosen were often design-based and included the following: (i) using a matched control design to adjust baseline confounders and seasonal trends; (ii) using self-controlled design, which automatically addresses time-invariant confounders and (iii) adjusting the expected rate calculated from historical data. Interestingly, during analysis, MaxSPRT inherently allows controlling bias due to repeated tests. In this review, the most cited challenges, particularly in the case of continuous sequential analysis, were uncertainty in estimating background rates, outcome misclassification, partially elapsed risk window and late-arriving data (data accrual lags).

## DISCUSSION

Routinely collected EHRs are increasingly used for the detection of AEFIs signal besides for testing hypothesis based on known signals. Evidence from this review suggests that electronic healthcare data have a significant potential to establish a near real-time AEFI surveillance systems. All the included studies used coded diagnostic medical data to get information about the studied AEs. Further, non-pharmacovigilance studies have also suggested that alternative non-coded medical information, such as telephone triage data and ambulance data, have potential for near real-time syndromic surveillance and rapidly detection of outbreak signal.[66 67]

A near real-time surveillance systems involves continuous checking (rapid cycle analysis (RCA)) of the EHRs for an elevated occurrence of AEs as the new data are added over the study period. It was first used to evaluate the safety of meningococcal conjugate vaccine using electronic healthcare data from the VSD in the USA,[14] though Davis *et al* established its feasibility by replicating the previously recognised rotavirus-intussusception signal.[68] Since then, we identified 12 studies that examined AEFI signal using RCA method.[14 22 24 29 39 43 47 48 57 61 62 64] The RCA method has been also used based on an alternative data sources other than EHRs. For example, in the UK, H1N1 vaccine was monitored using passive surveillance data,[69] and in Australia seasonal influenza vaccines have been monitored since 2015, based on data collected directly from consumers using SMS-messaging and email (AusVaxSafety).[70]

The near real-time AEFI surveillance systems use sequential analysis approach, primarily MaxSPRT, to continuously evaluate data for signals while adjusting bias due to multiple testing. MaxSPRT is an improved type of the classical SPRT, which uses a two-sided alternative hypothesis and a predefined relative risk (RR) value usually other than 1. MaxSPRT uses one-sided composite alternative hypothesis by defining the RR usually as >1 to declare statistically significant risk.[71] The key advantage of MaxSPRT over the classical SPRT is that it helps to minimise the risk of late detection of AEs due to an incorrect choice of RR and make it suitable for data monitoring more frequently.[14] Indications, advantages and weakness of both classical and MaxSPRT, including the three variants of MaxSPRT, are provided in table 3.[24 47]

As vaccines are often recommended for all persons in a given age group, traditional epidemiological cohort and case-control designs are usually not suitable to study vaccines AEs after licensure. The main reasons include an inadequate number of comparison groups (unvaccinated individuals), concern regarding comparability of the vaccinated to unvaccinated groups (selection bias), insufficient power and timeliness.[72] Rather, self-controlled design (SCRI and SCCS) and cohort design, with a historical comparison, are the preferred design choice in postlicensure vaccine safety studies (table 4). In self-controlled design, comparisons are made with individuals in two different periods, vaccination risk period and control period. The incidence of AEFI is compared between prespecified postvaccination risk period and control period (unexposed period).[73] Studies showed that including a prevaccination control period is essential to facilitate timely data analysis for vaccines administered in a short period, mostly in case of seasonal influenza vaccine. However, if there are clinical confounders that are a contraindication for vaccination (eg, allergic reaction) or indications for vaccination (eg, seizure disorder), a prevaccination control period is not recommended.[39 47 48 57 74 75]

**Table 2** Included studies implemented near real-time vaccine safety monitoring methods (sequential analysis)

| Study, Country | Data sources and period | Study design | Study subject | Vaccine studied | Adverse events studied | Analysis approach and signal detection method | Main finding |
|---|---|---|---|---|---|---|---|
| Yih, 2009 USA[64] | VSD (from August 2005 to May 2008) | ► Prospective active surveillance with observed vs expected analysis | 10–64 years of age | Tdap (new vaccine) | Encephalopathy-encephalitis-meningitis, paralytic syndromes, seizures, cranial nerve disorders (including Belly's palsy) and GBS. | ► Weekly sequential analysis, PMaxSPRT<br>► Supplementary analysis: end of surveillance analysis, temporal clustering and logistic regression analysis | No increased risks were identified for any of the outcomes over the course of 145 weeks surveillance |
| Klein, 2010 USA[43] | VSD (from January 2006 to October 2008) | ► Prospective active surveillance with observed vs expected analysis | Children age 12–23 months | MMRV | Seizures and fever | ► Weekly sequential analysis, PMaxSPRT<br>► Supplementary analysis: temporal clustering analysis, Poisson, logistic and case-centred regression analyses | Signal for seizure during days 7–10 was identified and confirmed, IRR=1.98 (1.43–2.73) |
| Huang, 2010 Taiwan[34] | (2009/2010 season) | ► Prospective active surveillance with SCRI and observed vs expected analysis | ≥6 months old age | H1N1 vaccine (LAMV and MIV) | Neurological, allergic and haematological AEs. | Weekly sequential analysis, BMaxSPRT and PMaxSPRT | No increased risks were identified for any of the outcomes over the course of 22 weeks follow-up |
| Belongia, 2010 USA[22] | VSD (May 2006 to May 2008) | ► Prospective active surveillance with observed vs expected analysis | Infant aged 4–48 weeks | Penta-Valente rota virus (new vaccine) | Intussusception and other (seizures, meningitis/encephalitis, myocarditis, Gram negative sepsis, gastrointestinal bleeding and Kawasaki syndrome) | ► Weekly sequential analysis, PMaxSPRT<br>► End of surveillance period analysis<br>► Single non-sequential analysis for gastrointestinal bleeding and Kawasaki syndrome | No increased risks were identified for any of the outcomes over the course of 164 weeks surveillance |
| Lee, 2011 USA[47] | VSD (November 2009 to April 2010) | ► Prospective active surveillance with SCRI and observed vs expected analysis | ≥6 months old age | H1N1 and seasonal influenza vaccine | 11 potential neurological, allergic and cardiac AEs. | ► Weekly sequential analysis, BMaxSPRT and PMaxSPRT<br>► Supplementary analysis: Temporal cluster analysis and Case-centred logistic regression | Signal was observed for Bell's palsy at week 20, but not confirmed after further analysis |

Continued

**Table 2** Continued

| Study, Country | Data sources and period | Study design | Study subject | Vaccine studied | Adverse events studied | Analysis approach and signal detection method | Main finding |
|---|---|---|---|---|---|---|---|
| Gee, 2011 USA[29] | VSD (August 2006 to October 2009) | ► observed vs expected and ► Cohort with concurrent comparison | 9–26-year-old female | Quadrivalent human papillomavirus vaccine (HPV4) | GBS), stroke, venous thromboembolism (VTE), appendicitis, seizures, syncope, allergic reactions, and anaphylaxis | ► Weekly sequential analysis, PMaxSPR and exact sequential analysis ► Supplementary analysis: Temporal cluster analysis and Case-centred and logistic regression analysis | Excess risk for appendicitis was identified but not confirmed |
| Tse, 2012 USA[57] | VSD (August 2010 to February 2011) | observed vs expected analysis and SCRI designs | Children ages 6–59 months | TIV | Febrile seizures in the 0–1 days following first dose TIV | Weekly analysis, both BMaxSPRT and PMaxSPRT | Excess risk for seizures identified and confirmed, IRR=2.4 (1.3–4.7) |
| Wise, 2012 USA[62] | Emerging Infections Programme (EIP) (October 2009 to May 2010) | ► Retrospective active surveillance with SCRI design | All individuals who received the vaccine | Influenza A (H1N1) monovalent vaccines | GBS during the 42 days following vaccination | ► Weekly sequential analysis, PMaxSPRT ► Sensitivity analysis ► Temporal cluster analysis | Excess risk for GBS was identified, not confirmed |
| Tseng, 2013 USA[60] | VSD (from April 2010 to January 2012) | ► Observed vs expected analysis | 1 month to 2 years | PCV13 Vaccine | Febrile seizures, encephalopathy, urticaria and angioneurotic oedema, asthma, anaphylaxis, thrombocytopenia, Kawasaki disease | ► Group sequential analysis (12 repeated tests were performed) | Excess risks for encephalopathy and Kawasaki disease identified but not confirmed |
| Nelson, 2013 USA[49] | VSD (September 2008 to January 2011) | ► Prospective active surveillance with observed vs expected analysis | children aged 6 weeks to 2 years | DTaP-IPV-Hib (combination) | MAF, seizure, meningitis/ encephalitis/myelitis, series no anaphylactic allergic reaction; not formally tested—anaphylaxis, GBS, invasive Hib disease, all hospitalisation | ► Group sequential testing, Poisson MaxSPRT (11 repeated tests were conducted) ► Sub group end-study-analysis | No increased risks were identified |
| Weintraub, 2014 USA[61] | VSD (April 2008 to March 2013) | ► Retrospective active surveillance with observed vs expected analysis | Infants ages of 4 and 34 weeks | Monovalent Rotavirus vaccine | Intussusception within 7 days following vaccination | ► Weekly sequential analysis, PMaxSPRT ► Temporal cluster analysis ► Exact logistic regression | Increased risk identified and confirmed, IRR=9.4 (1.4–103.8) |

Continued

**Table 2** Continued

| Study, Country | Data sources and period | Study design | Study subject | Vaccine studied | Adverse events studied | Analysis approach and signal detection method | Main finding |
|---|---|---|---|---|---|---|---|
| Kawai, 2014 USA[39] | VSD (September 2012 to February 2013) | ▶ Retrospective active surveillance with<br>▶ SCRI and observed vs expected analysis | 6 months to 17 years and 2–49 years | TIV, LAIV (first-dose vaccine) | Seizures, GBS, encephalitis and anaphylaxis | ▶ Weekly sequential analysis, BMaxSPRT and PMaxSPRT<br>▶ End of surveillance Logistic regression | No increased risks for any of the outcomes were identified |
| Daley, 2014 USA[24] | VSD (January 2009 to September 2012) | ▶ Prospective active surveillance<br>▶ Observed vs expected analysis | 4– 6 years old | DTaP-IPV combination | Meningitis/encephalitis, seizures, stroke, GBS, Stevens–Johnson syndrome and anaphylaxis | ▶ Weekly sequential analysis, PMaxSPRT and conditional MaxSPRT<br>▶ Posthoc analysis | No increased risks for any of the outcomes were identified |
| Li, 2016 USA[48] | VSD (June 2013 to April 2015) | ▶ Retrospective active surveillance with<br>▶ SCRI and observed vs expected analysis | ≥6 months old age | First dose of IIV3, IIV4 and LAIV4) | Acute disseminated encephalomyelitis, anaphylaxis, Bell's palsy, encephalitis, GBS, febrile seizures and transverse myelitis | ▶ Weekly sequential analysis using both BMaxSPRT and PMaxSPRT<br>▶ End of surveillance analysis after all the data have been collected | Excess risks for febrile seizure were identified and confirmed after vaccination of—IIV3: IRR=5.25 (1.57–1.75) and IIV4: IRR=12.3 (2.5–58.9) |

BMaxSPRT, binomial-based maximised sequential probability; CMaxSPRT, conditional maximised sequential probability; GBS, Guillain-Barré syndrome; IIV3, trivalent inactivated influenza vaccine; IIV4, quadrivalent inactivated influenza vaccine; IRR, incidence rate ratio; LAIV, live attenuated influenza vaccine; LAMIV, live attenuated monovalent influenza vaccine; MIV, monovalent influenza vaccine; MMRV, measles, mumps, rubella and varicella vaccine; PCV13, 13-valent pneumococcal vaccine; PMaxSPRT, Poisson-based maximised sequential probability test; TIV, trivalent influenza vaccine; VSD, vaccine safety data-link.

**Table 3** Sequential statistical approaches for postlicensure vaccine safety surveillance (description, indication and challenges)

| Statistical approaches | General description | Advantage/indication | Challenges/weakness |
|---|---|---|---|
| Group sequential analysis | ► Involves repeated (periodic) analyses overtime as data accumulate, at regular or irregular interval.<br>► Compares the test statistic to a prespecified signalling threshold, and stops if the observed test statistic is more extreme than the threshold | ► Commonly used in clinical trials<br>► More appropriate when data updates are less frequent<br>► Yield increased study power for a given sample size | ► Does not allow to capture the safety problems as soon as possible<br>► Very complex to compute<br>► Limited ability to control potential confounders |
| Continuous sequential analysis (rapid cycle analysis) | ► Allows examination of data frequently (as often as desired) over time.<br>► Surveillance starts as soon as uptake of the vaccine starts or delayed until a pre-set number of events occur | ► Allows to monitor the vaccine safety problems in real-time<br>► Suitable to identify true safety signals sooner. This method can signal after single AEs, if that event occurs sufficiently early.<br>► Require updated data in a real-time or in a continuous fashion | ► All data related to vaccinations and AEFIs may not be available timely for analysis (data accrual lags)<br>► The risk windows might be not fully elapsed for some AEFIs at the time of each analysis (partially elapsed window), particularly in case of influenza vaccine<br>► Inherently reduces statistical power |
| **Signal detection method/ statistical test** | | | |
| Binomial-based MaxSPRT | ► Based on the binomial distribution<br>► Events occurring among vaccine exposed individuals or time periods compared with the number of events among unexposed individuals to the studied vaccine/matched periods | ► Best fit for self-controlled designs<br>► More suitable when the AEs are relatively common<br>► Account bias due to multiple looks at a data | ► Limited ability to control potential confounders |
| Poisson-based MaxSPRT | ► Assumes a Poisson distribution<br>► Compare the observed number of events in a given preidentified risk period with a historical data or the scientific literature<br>► Does not depends on choice of RR, it uses a one-sided composite alternative hypothesis of RR>1 | ► More suitable when AEFIs are very rare<br>► Minimise the risk of late detection of AEFIs due to an incorrect choice of RR<br>► Adjust for multiple looks at a data | ► Relies on having accurate background rate of the outcomes for comparison<br>► Does not consider uncertainty in the estimation of expected rates, if the data are limited<br>► Limited ability to control potential confounders |
| Conditional-based MaxSPRT | Assumes a Poisson process for the cumulative person-time to observe a number of AEFIs | ► Accounts for uncertainty in historical data<br>► Adjust for multiple looks at a data | ► Assumes constant event rates are in historical and surveillance data<br>► Limited ability to control potential confounders |

AE, adverse event; AEFI, adverse events following immunisation; MaxSPRT, maximised sequential probability ratio test; RR, relative risk.

A cohort study design with a historical comparison is used frequently for detecting AEFI signals. This design compares the observed incidence of AEFI in the risk period after vaccination of the studied vaccine(s) against the expected incidence of AEFI projected based on the historical data.[22] It helps to improve the timeliness of detecting the AEFI signal because only data for the risk window is collected rather than waiting for data for

**Table 4** Commonly used study designs in postlicensure vaccine safety monitoring (study population, comparison group, indication, strength and weakness)

| Study design | Population | Comparison groups | Strength and preference | Weakness |
|---|---|---|---|---|
| **Cohort study design** | | | | |
| Cohort study with historical comparison group, also called current vs historical design | Individual vaccinated with the vaccine of interest | Historical incidence rate of AEFIs calculated from historical data on individuals that have not been exposed to the vaccine of interest<br>vs<br>Incidence of AEFIs in the prespecified risk period/window following vaccination | ► It has greater statistical power to detect rare AEFIs signal earlier<br>► It is less affected by data lags as it only collects for the risk window, rather than both for risk and comparison windows | ► Highly dependent on accurate estimation of background incidence rates of the AEFIs for comparison<br>► It may be subjected to difference in confounders between current and historical vacinees, seasonality and secular trends in AEFIs, diagnostic or coding criteria |
| Cohort study with concurrent/ parallel comparison group (matched or not) | Individual vaccinated with the vaccine of interest | Incidence of AEFIs in the prespecified risk period/window following vaccination<br>vs<br>Incidence of AEFIs among individuals without the vaccine of interest or totally non vaccinated individuals | ► Reduce the likelihood of false or missed signals due to secular trends in disease, diagnostic patterns or coding criteria | ► Difficult to get adequate number of unvaccinated control group, in case of studying routinely administered vaccines<br>► May be subjected to bias due to difference in characteristics of vaccinated and unvaccinated groups<br>► For a rare AE, it may not provide the earliest possible signal |
| **Self-controlled design** | | | | |
| SCRI | Vaccinated cases | ► Within subject comparison<br>► Incidence of AEs in the predefined risk period following vaccinations<br>vs<br>Incidence of AEFIs in the predefined control/non risk period | ► Automatically control time-invariant confounders that vary between individual, such as sex, socioeconomic status<br>► Less prone to misclassification of exposure, vaccinated cases are considered to collect information<br>► Compare the risk of AEFIs in the short control interval where time variables (such as age) have minimal effect in the study period. | ► Has less statistical power due to fewer events occurring in the shorter control interval<br>► Less suitable to capture subacute or chronic AEFIs for example, autoimmune disease<br>► Confounded by indication<br>► It is not free from bias due to time-varying confounders for example, Age and seasonality<br>► Selecting a risk interval that is too wide or too short may bias the risk estimate relative to the true risk window.<br>► Sensitive to indication bias |

Continued

**Table 4** Continued

| Study design | Population | Comparison groups | Strength and preference | Weakness |
|---|---|---|---|---|
| SCCS | Primarily vaccinated persons, but unvaccinated persons and experienced the AEs can be considered | ▲ Within subject comparison<br>▲ Incidence of AEFIs in the predefined risk period following vaccinations<br>vs<br>Incidence of AEFIs in the control period (time period before or after vaccination) | ▲ Inherently control time-invariant confounders<br>▲ Can be advantageous when identification of a vaccinated group is challenging and the outcome is rare | ▲ Less suitable to capture subacute or chronic AEFIs<br>▲ More susceptible to bias because of time-varying confounders, as the observation period is often longer than SCRI<br>▲ Problem with defining risk interval (selecting a risk interval that is too wide or too short may bias the risk estimate relative to the true risk window).<br>▲ Sensitive to indication bias |
| Case-crossover design | All individuals who are vaccinated and cases | Subjects serve as their own matched controls with defined by prior time periods in the same subject | ▲ Preferred method for studying risk of acute AEFIs<br>▲ Robust to time-invariant confounders by making within-person comparisons | ▲ Does not address confounders that vary over time<br>▲ Susceptible to exposure trend bias for example, due to change in policy for a vaccine<br>▲ Sensitive to indication bias |

AE, adverse event; AEFI, adverse event following immunisation; SCCS, self-controlled case series; SCRI, self-controlled risk interval.

the comparison window.[48] However, studies showed that accurate baseline risk estimation is a very challenging task, and it may introduce bias if the historical population are considerably different from the studied population. Nevertheless, this problem can be minimised through simultaneous use of the self-controlled design as they have complementary strengths (table 4).[14 48]

The essential requirement to conduct a near real-time AEFI surveillance based on EHRs is the availability of timely data. Both data accrual lag and partially elapsed risk window, the risk windows might not be fully elapsed for some AEs at the time of each analysis, can deter performing RCA.[74 76] Data accrual lag in EHRs can occur due to several reasons and the level of delay may vary depending on the outcomes studied. A study from UK showed that up to 30 days or more are required to completely record AEFI diagnoses at general practice level.[77] Two studies were included in this review,[39 48] and methodological evaluation studies suggested that various design-based measures can be taken for adjusting partially elapsed risk window and data accrual lags. These include: (i) calculating the expected counts of AEFIs comparable to the elapsed risk window length; (ii) restricting comparison periods proportional to the elapsed risk period or (iii) AEFIs occurring in later weeks in the risk window can be ignored if the matching weeks in the control period have not elapsed.[48 71 78–80]

## CONCLUSION

The utility of routinely collected EHRs for AEFI monitoring globally has been demonstrated, with most published experience drawn from US literature. In addition, the advancement of statistical analysis techniques and RCA provide a significant potential to detect AEFI signal in near real-time.

To date, AEFI monitoring based on EHRs use is limited to diagnostic medical information. Potential incorporation of other electronic health information, including non-coded complaints and encounters, offers further opportunities to improve AEFI real-time surveillance systems to help maintain safe immunisation programmes and maximise confidence in those programmes.

**Acknowledgements** The Australian Government through the International Postgraduate Research Scholarship funds YMM for his PhD study tuition fee. The authors are grateful to Ms Lorena Romero, a Senior Medical Librarian at the Ian Potter Library, Alfred Hospital, Melbourne for providing a feedback on the pilot search strategy for the review. We thank Mr. Kelmu T Kibret for his help in evaluating the methodological quality of studies considered in this review

**Contributors** YMM conceived the original research idea with guidance from JB. All authors contributed to the design of the study. YMM searched and screened the studies, extracted the data and wrote the initial drafts of the paper. JB, AC and JL revised the article critically. All authors contributed to and approved the final manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** The authors are happy to provide further data up on request.



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78. Li L, Kulldorff M. A conditional maximized sequential probability ratio test for pharmacovigilance. *Stat Med* 2010;29:284–95.
79. Nelson JC, Cook AJ, Yu O, *et al*. Methods for observational post-licensure medical product safety surveillance. *Stat Methods Med Res* 2015;24:177–93.
80. Nelson JC, Cook AJ, Yu O, *et al*. Challenges in the design and analysis of sequentially monitored postmarket safety surveillance evaluations using electronic observational health care data. *Pharmacoepidemiol Drug Saf* 2012;21:62–71.

Supplementary file 1: Medline search strategy

| # | Searches | Results |
|---|---|---|
| 1 | vaccin*.mp. | 316284 |
| 2 | exp Vaccines/ | 213087 |
| 3 | exp Vaccination/ | 76739 |
| 4 | immuni*.mp. | 383683 |
| 5 | immunization/ or immunization, secondary/ | 56023 |
| 6 | 1 or 2 or 3 or 4 or 5 | 592017 |
| 7 | exp Product Surveillance, Postmarketing/ | 13688 |
| 8 | surveillance.mp. | 174562 |
| 9 | safety.mp. | 406979 |
| 10 | adverse events following immunization.mp. | 247 |
| 11 | 7 or 8 or 9 or 10 | 575855 |
| 12 | (vaccin* adj5 safety).mp. | 6273 |
| 13 | (immuni* adj5 safety).mp. | 614 |
| 14 | (vaccin* adj5 monitor*).mp. | 1976 |
| 15 | (immuni* adj5 monitor*).mp. | 811 |
| 16 | 12 or 13 or 14 or 15 | 9025 |
| 17 | 6 and 11 | 33637 |
| 18 | 16 and 17 | 7241 |
| 19 | Electronic Health Records/ | 13786 |
| 20 | health record*.mp. | 20148 |
| 21 | medical record*.mp. | 156867 |
| 22 | datalink.mp. | 722 |
| 23 | General Practice data.mp. | 117 |
| 24 | outpatient data.mp. | 180 |
| 25 | admission data.mp. | 793 |
| 26 | emergency department data.mp. | 196 |
| 27 | 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 | 172102 |
| 28 | 18 and 27 | 282 |

Supplementary file 2: detailed description of selected studies employed non- sequential analysis

Supplementary file 2: detailed description of selected studies employed non- sequential analysis

| First author, year published | Setting and study period | Study design | Data source | Sample size | Study subjects | Vaccine studied | Adverse evets studied | Study purpose | Analyses method | Main finding |
|---|---|---|---|---|---|---|---|---|---|---|
| Baxter, 2016 | USA, September 2005 - October 2006 | Retrospective cohort with historical comparison and | Outpatient clinic, ED visits and inpatient data linked to immunization data | 124,139 Tdap5 | 11 through 64 years old | Tdap5, new vaccine | All health outcomes up to 6 months following vaccination were captured and reviewed | Signal identification and verification | -Cox regression - Temporal cluster analysis | No increased risks were identified for any of the outcomes |
| Baxter, 2012 | USA July 2006 through November 2007 | Retrospective, SCRI design | Inpatient and ED visits linked with immunization data | 29,010 individuals | 60 years of age or older | Zoster vaccine (ZostavaxTM) , new vaccine | -All clinical events led to hospitalization or ED visits | Signal identification and verification | -Cox regression - Temporal cluster analysis | No increased risks were identified for any of the outcomes |
| Baxter, 2012 | USA, October 2003 to March 2008 | Retrospective cohort with concurrent comparison groups and SCRI designs | Inpatient and ED visits linked with immunization data | 43,702 LAIV recipients | children aged 5–17 years | Ann Arbor strain live attenuated influenza vaccine | All medically attended adverse events | Signal identification and verification | Cox regression - Temporal cluster analysis | No increased risks were identified for any of the outcomes |
| Baxter, 2012 | USA, October 2003 - March 2008 | Retrospective cohort with concurrent comparison groups and SCRI designs | Outpatient visits, ED visits and inpatient data linked to immunization data | 21,340 subjects | adults 18–49 years of age | Ann Arbor strain live attenuated influenza vaccine | All medically attended events Within 42 days of vaccination | Signal identification and verification | Cox regression - Temporal cluster analysis | No increased risks were identified for any of the outcomes |
| Chao, 2012 | USA, August 2006 – March 2008 | Retrospective cohort study with current vs. historical design | Outpatient visits, ED visits and inpatient data linked to immunization data | 189 629 women who received at least 1 dose of HPV4 | Women in the age range of 9–26 years | Quadrivalent human papillomavirus vaccine (HPV4) , new vaccine | Potential new-onset and 16 pre-specified autoimmune conditions | Signal identification and verification | Non-sequential analysis, but not clearly stated | No safety signal was found |
| Davis, 2004 | USA, between 1 July 1997 and 31 | Retrospective cohort study with both current vs. | Outpatient visits, ED visits and inpatient data | 27,802 doses of COMVAX | All children 6 weeks to 36 months | COMVAX Combination vaccine, new | Adverse events resulting in medical utilization (hospitalizations, | Signal identification and | Exact binomial method | No safety signal was found |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | December 2000 | historical and Risk interval cohort) | linked to immunization data | | | | ED visits and outpatient clinic visits | verificatio n | | |
| Donegan, 2014 | UK, from 1 October 2012 to 31 March 2013 | Prospective cohort study with current vs. historical, and Risk interval designs | Primary care general practice databases (CPRD) | 20 074 pregnant women | Pregnant women who received any vaccine containing pertussis | Pertussis vaccine | Pre-specified events primarily stillbirth, but maternal and neonatal outcomes such as pre-eclampsia, eclampsia and low birth weight were included | Signal identificat ion | Cox proportional hazard and Poisson regression | No safety signal was found |
| Duffy, 2017 | USA, from 2008 to 2011 | Retrospective cohort study with the self-controlled risk interval design | Outpatient visits, ED visits and inpatient data linked to immunization data (VSD) | 12,354 LAIV | 2 through 49 years old persons with asthma | Live attenuated influenza vaccine (LAIV) | Medically attended respiratory events in the 14 days after LAIV | Signal identificat ion and evaluation | Poisson regression | No safety signal was found |
| France, 2004 | USA, January 1, 1993, through December 31, 1999 | Retrospective, case-crossover design | Outpatient visits, ED visits and inpatient data linked to immunization (VSD) | 251600 children and 438167 vaccine dose | individual's younger than 18 years | Influenza vaccine (TIV) | All medically attended event | Signal identificat ion and verificatio n | Conditional logistic regression | No safety signal was found |
| Glanz, 2011 | USA, between October 1, 2002, and March 31, 2006 | Retrospective cohort study with self-controlled case series design | ED visits and inpatient data linked to immunization (VSD) | 66 283 children aged 24 to 59 months | Children aged 24 to 59 months who received at least 1 TIV dose | trivalent inactivated influenza vaccine (TIV) | Pre-specified medically attended events in the 0-42 days' risk windows. | Signal identificat ion and verificatio n | Conditional Poisson regression | Signal for GIT symptoms (IRR, 1.18; 1.10-1.25), GIT disorders (7.70; 1.11-53.52), and fever (1.71; 1.64-1.80) are detected |
| Greene, 2012 | USA, between August 2009 and April 2010 | Retrospective study, self-controlled risk interval design | Outpatient visits, ED visits and inpatient data linked to immunization record (VSD) | 1.48 million doses (MIV) and 1.72 million doses (TIV) | All age groups | MIV and seasonal TIV | GBS within 1–42 days following vaccination. | Signal identificat ion and verificatio n | Poisson regression, Temporal and Case-centred analysis | No statistically elevated risk of GBS observed |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Hambidge, 2006 | USA, between January 1, 1991, and May 31, 2003 | Retrospective study with self-control risk interval, case-crossover and SCCS designs | Outpatient clinic, ED and inpatient data linked to immunization record (VSD) | 45 356 children received 69 359 influenza vaccinations doses | All children 6 to 23 months old who received TIV | Trivalent inactivated Influenza Vaccine (TIV) | Medically Attended Events 0-42 days after vaccination. | Signal identification and verification | -Conditional Poisson and logistic regression | No safety signal was found |
| Hanson, 2016 | USA, From October 1, 2008 through July 31, 2010 | Retrospective study with self-control risk interval and concurrent cohort designs | Outpatient clinic, ED and inpatient data linked to immunization record (KPNC) | 14,042 infants who received at least one dose | All 2-month-old infants | DTaP-IPV/Hib vaccine administered routinely as part of clinical care | All ED and hospital visits and selected outpatient outcomes during days 0–30 post-vaccination | Signal identification and verification | Non-sequential analysis, not clearly stated | No safety signal was found |
| Jackson, 2006 | USA, January 1996 through November 2002 | Retrospective study with Risk-interval design | Outpatient clinic, ED and inpatient data linked to immunization record (VSD) | 316,995 adults received least one first dose of a PPV | Persons >= 50 years old | 3rd dose of pneumococcal polysaccharide vaccine (PPV) | An injection site reaction within two weeks following vaccination. | Signal identification and verification | Fisher's exact test, logistic regression | No safety signal was found |
| Jackson, 2009 | USA, December 31,2004 to 2006 | Retrospective cohort study | Outpatient clinic an ED data linked to immunization record (VSD) | 128,297 Td, Tdap, and MCV4 vaccinations | Adolescents and young adults (9 to 26 years old) | Td, Tdap, and MCV4 vaccinations Concomitant or sequential administration | Medically attended local reactions within six days following the vaccination | Signal identification and verification | Poisson regression | No safety signal was found |
| Kharbanda, 2013 | USA, from June 1, 2002, to July 31, 2009 | Retrospective cohort compare who did and did not receive TIV | Outpatient clinic, ED and inpatient data linked to immunization record (VSD) | 74,292 vaccinated And 144,597 unvaccinated | All pregnant females aged 14–49 years | Trivalent inactivated influenza vaccine | All potential adverse obstetric events were identified | signal identification and verification | Poisson regression | No safety signal was found |
| Kharbanda, 2016 | USA, between January 1, 2007 and November 15, 2013 | Retrospective cohort with matched concurrent comparisons | Outpatient clinic, ED and inpatient data linked to immunization record (VSD) | 53,885 vaccinated and 109,253 matched unvaccinated | Pregnant women | Combined tetanus toxoid, reduced diphtheria toxoid, acellular pertussis | Medically attended acute adverse events within 3 days of vaccination AND medically attended neurologic events | Signal identification and refinement | Poisson regression | No safety signal was found |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | vaccine (Tdap) | within 0–42 days following vaccination | | | |
| Jacobsen, 2009 | USA, February 2006–June 2007 | Retrospective, self-controlled risk interval and current vs. historical | Outpatient clinic, ED and inpatient data linked to immunization record (KPSC) | 31,298 children | Children ages 12–60 months | MMRV, new combination vaccine | Pre-defined outcome, febrile convulsion during the 30 days' post-vaccination | Signal detection and refinement | Cox regression, Poisson regression | Febrile convulsion in days 5–12 following vaccination (RR = 2.20, 95% CI = 1.04, 4.65) |
| Klein, 2012 | USA, August 2006 and March 2008. | retrospective, observational cohort study (risk interval design) | Kaiser Permanente in California | 189 629 females (346 972 HPV4 Doses) | all females who received at least 1 dose of HPV4 | Quadrivalent human papillomavirus vaccine (HPV4), new vaccine | Emergency Department visits and hospitalizations grouped into predefined diagnostic categories from days 1 to 60 days | Signal detection and refinement | Conditional logistic regression | No safety signal was found |
| Klein, 2012 | USA, from January 2000 - October 2008 | Retrospective cohort with historical comparison | VSD | 86 750 for MMRV and 67 438 for MMR + V | children aged 48 to 83 months | MMRV and MMR + V | Febrile seizure during the 42 days after. | Signal detection and refinement | Poisson regressions | No safety signal for febrile seizure was found |
| Klein, 2015 | USA, from January 2000 - June 2012 | Retrospective study with self-controlled risk interval design | 8 VSD sites | 123 200 MMRV and 584 987 MMR + V doses | children were aged 12 to 23 months | Comparing MMRV with MMR + V, | Anaphylaxis, ataxia, arthritis, meningitis/ encephalitis, acute disseminated encephalomyelitis, Kawasaki disease, seizure, and fever | Signal detection and refinement | Exact binomial tests, logistic regression | No safety signal was found |
| Nordin, 2014 | USA, between June 1, 2002, and July 31, 2009 | Retrospective matched cohort study and | Outpatient clinic, ED and inpatient data linked to immunization record (VSD | 92 440 unvaccinated and 57 649 vaccinated. | Pregnant women, those aged 14-49 years | Trivalent inactivated influenza vaccine (TIIV) | Preterm and small for gestational age births | Signal detection and evaluation | Conditional logistic regression | No increased signal was found |
| Nordin, 2014 | USA<br><br>2008–2009 and2009–2010 seasons, | Retrospective, multisite matched observational cohort study | Outpatient clinic, ED and inpatient data linked to immunization record (VSD | 9349 women receiving MIV and 17,491 unvaccinated | Pregnant women | Monovalent H1N1 inactivated influenza (MIV) | Pre specified medically attended adverse events within 42 days of vaccination | Signal detection | Poisson regression | No increased signal detected |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sukumaran, 2015 | USA, betweenJanuary1,2007, and November 15, 2013 | Retrospective cohort | Outpatient clinic, ED and inpatient data linked to immunization record (VSD) | 29 155 pregnant women | women aged 14 through 49 years who received Tdap vaccine during pregnancy | tetanus, diphtheria, and acellular pertussis (Tdap) vaccine | Acute adverse events (fever, allergy, and local reactions) and adverse birth outcomes (small for gestational age, preterm delivery, and low birth weight | Signal detection and evaluation | log-binomial regression | No increased risk observed |
| Sukumaran, 2015 | USA, between January1,2007, and November 15, 2013 | Retrospective cohort study | Outpatient clinic, ED and inpatient data linked to immunization record (VSD) | 36,844 pregnant women | Pregnant women aged 14–49 years | Concomitant and sequential administration of Tdap and influenza vaccines | Medically attended acute events (fever, any acute reaction) and adverse birth outcomes (preterm delivery, low birth weight, small for gestational age | Signal detection | log-binomial regression | No increased risk observed |
| Tartof, 2017 | USA, between September 2011 and September 2014 | Retrospective observational safety study | Outpatient clinic, ED and inpatient data linked to immunization record (KPSC) | 387 vaccinated children | Children 2–10 years | Quadrivalent meningococcal conjugate vaccine (MenACWY-CRM) new vaccine | 26 Pre-specified events of interests AND serious medically attended events up to 1 year after vaccination | Signal detection | Poisson distribution, descriptive in nature, no statistical tests were performed | The data did not suggest safety concerns |
| Tseng, 2012 | USA. from1January2007to31December2008 | Case-centred design and self-controlled case series design | Outpatient clinic, ED and inpatient data linked to immunization record (VSD) | 193 083 adults aged 50 and older | All adults age >=50 years who received a zoster vaccine | Zoster vaccine | Pre-specified adverse events (Stroke, Cerebrovascular diseases, Cardiovascular diseases, Meningitis, encephalitis and encephalopathy etc) | Signal identification and evaluative | Binomial logistic regression, conditional Poisson regression and stratified analysis by age | The risk of allergic reaction was significantly increased within 1–7 days of vaccination (RR = 2.32, 1.85–2.91) |
| Tseng, 2017 | USA, during September 30, 2011 to June 30, 2013 | Cohort study with self-controlled case-series design | Outpatient clinic, ED and inpatient data linked to immunization record (KPSC) | 48 899 vaccinated individuals | Aged 11 to 21 years , new vaccine | Quadrivalent meningococcal conjugate vaccine (MenACWYCRM) | Twenty-six pre-specified events of interest including neurologic, rheumatologic and hematologic, disease 1 year after vaccination | Signal identification and evaluative | Conditional Poisson regression adjusted for seasonality | Increased risk of Bell's palsy identified but not confirmed |
| Jackson, 2002 | USA, January, 1997, and | Retrospective cohort | Outpatient clinic, ED and inpatient data linked to | 76 133 doses of DTaP | Children less than7 years of age who | Diphtheria-tetanus toxoids-acellular | Pre-specified outcome (injection site reactions, seizures and allergic responses within 7 | Signal identification | Descriptive, proportions were compared | - |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | December, 2000 | | immunization record Group Health Cooperative, Seattle | | received one or more doses of DTaP vaccine | pertussis (DTaP) | days of DTaP vaccination and febrile episodes within 3 days | | with the chi square test with Yates correction | |
| Kharbanda, 2014 | USA, between January 1, 2010, and November 15, 2012 | Retrospective cohort study | Outpatient clinic and inpatient data linked to immunization record (KPNC and KPSCN) | 26 000 women received Tdap compared to 97 265 not received | All pregnant women (singleton) | Maternal Tdap vaccination during pregnancy | Chorioamnionitis and hypertensive disorders of pregnancy preterm and small for-gestational-age (SGA) births | Signal identification AND evaluation | non sequential, one-time analysis logistic and Poisson regression | Marginal but statistically significant increased risk of chorioamnionitis diagnosis was observed (adjusted RR, 1.19; 95%CI, 1.13-1.26). |
| Nordin, 2013 | USA, 1 June 2002 through 31 July 2009 | Retrospective cohort study with matched concurrent comparison | Outpatient clinic, ED and inpatient data linked to immunization record (VSD) | 75,906 vaccinated and 147,992 unvaccinated | Pregnant women | Trivalent inactivated influenza vaccine | medically attended events occurring within 42 days of receiving the vaccine, | Signal identification and evaluation | Poison regression, matched by age, site, and pregnancy start date | No signal identified |
| Nordin, 2013 | USA, VSD cohort from 1991 -2006 and DoD cohort from 1999 -2007 | Retrospective cohort study with matched concurrent comparison and risk-interval designs | VSD and US Department of Defence (DoD) | 47,159 doses from VSD and 1.12 million doses from DoD | All yellow fever-vaccine-exposed individuals | Yellow fever vaccine | -Allergic and local reactions<br>-Visceral events and neurologic events | Signal identification and evaluation | Conditional logistic Regression and Poisson regression. (Matched by age-, site-, and gender-matched unexposed subjects | No signal identified |

*COMVAX® (Haemophilus b conjugate vaccine (meningococcal protein conjugate) and hepatitis B vaccine (recombinant));* gastrointestinal tract (GIT); CPRD - *Clinical Practice Research Datalink;* KPSC- Kaiser Permanente Southern California health care program; KPNC Kaiser Permanente Northern California health care program

# CHAPTER 3: RESEARCH METHODS

## 3.1 Chapter overview

Following the systematic review, Chapter 3 briefly describes the data sources, study design and statistical analyses that were used to answer the three further primary research aims that comprise this thesis.

## 3.2 Data source

Routine health data collected from three distinct healthcare settings were used, specifically from a telephone helpline service, GPs and EDs. These health data are potentially representative of the health behaviours of the population and the severity spectrum of possible AEFI. Notably, such data are not collected for research purposes, and it is important to acknowledge potential limitations, including data incompleteness. Retrospective data recorded in the respective healthcare settings between 2008 and 2017 were considered for analyses.

### 3.2.1 Telephone helpline data

Considering technology's advancement, even prior to the COVID-19 pandemic, primary healthcare services are being delivered increasingly through telephone and web-based services as an alternative to traditional face-to-face consultations.[68, 69] This is especially important to reach those living in rural and remote areas. Telephone helpline services have been in operation in Australia since 2008, with calls managed by registered nurses.[69] This service is publicly funded and covers all jurisdictions in Australia under a variety of contracts with Medibank Health Solutions, a private health insurance and health solutions provider. In Victoria, the telephone helpline service is provided through NURSE-ON-CALL (NOC), in Queensland through 13Health and in other jurisdictions, this service is delivered through Healthdirect Australia.[69, 76] The telephone helpline is available 24 hours a day and seven days a week, and

registered nurses manage calls. The nurses use computerised patient guidelines (algorithms) to assess patients' health conditions and to provide health advice or information regarding further actions.[69, 76, 77] The three basic steps nurses follow while providing telephone helpline services are outlined in Figure 3.1.

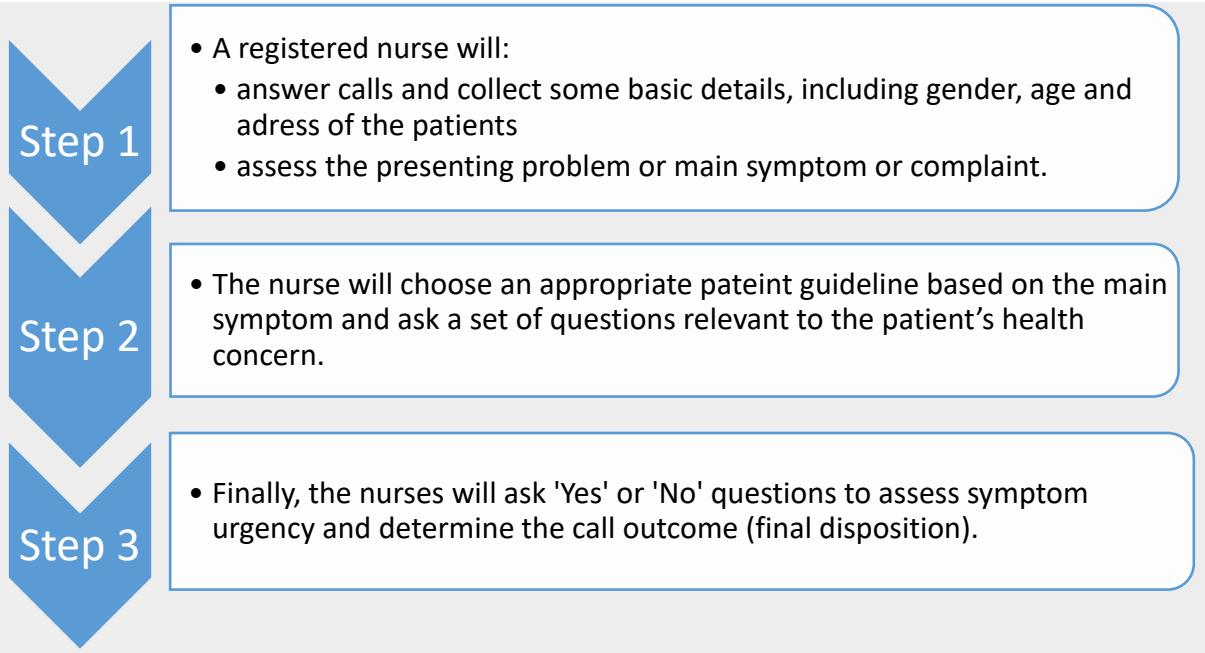


Figure 3.1. Basic steps nurses follow to respond to or manage patients' health concerns via telephone, Victoria, Australia[76]

NOC nurses can choose to select from more than 300 patient guidelines in the system. Based on entered information, the system will recommend guidelines that are relevant to patients' health concern based on their chief complaints or main symptoms for the nurses to select. For example, for a patient or caregiver inquiring about breathing difficulties, the nurse might choose one of the guidelines titled 'Breathing problems', 'Wheezing or asthma' or 'Colds and Flu' depending on the exact nature of the query and symptoms. Similarly, nurses would consult the patient guideline titled 'immunisation reactions infant child adult' to manage a patient enquiring about an AEFI. Finally, the nurses would ask 'Yes' or 'No' questions to assess symptom urgency and to determine a call outcome (final disposition).The final disposition generally falls into one of four outcomes: continue self-care at home; see a doctor within 72

hours; attend an ED immediately, or; be transferred immediately to the ambulance service if the condition is quite serious.

All telephone helpline calls are recoded routinely for quality control and research purposes. We requested NOC data that had been collected between 2009 and 2017 and that comprised three important data fields: patients' demographic information; patient guideline title, which is a proxy of the presenting problem or main symptom; and the final disposition, which shows the severity level of the health concern.

### 3.2.2 General practice data

Primary healthcare is the frontline of Australian's healthcare system and services are delivered predominantly through accredited general practices (GPs). Different health professionals—including practice nurses and midwives, but predominantly general practitioners—work in the GPs.[78] General practitioners are the first point of contact for most Australians seeking medical attention, specifically for non-emergency and preventative medical care. More than 87.8% of the population in Australia see a general practitioner at least once each year.[78, 79] In 2018, there were about 30,066 general practitioners nationwide providing primary healthcare services in over 6,300 accredited GPs. [80] [79] The following non-emergency and preventive medical care are provided at GPs:

- diagnosing and treating disease, pain and other conditions
- administering vaccinations
- providing mental health advice
- providing family planning advice
- providing wound care
- prescribing medication
- referring patients to specialists for secondary care when necessary.

Health professionals working at most general practices routinely record all consultations on their computer (hereafter reffered to as GP data), primarily for improving the services they provide (high-quality and safe care). GP data comprise a broad range of information, such as patients' socio-demographic data, diagnoses, prescriptions and immunisation history.[81, 82] In recent years, different academic institutions and commercial enterprises have been involved in extracting and storing electronic GP data for research purposes. Outcome Health is one of the commercial enterprises that works closely with GPs in Australia. Essentially, Outcome Health installs a clinical intelligence software (Population Level Analysis and Reporting [POLAR]) on general practitioners' computers to extract information from the practices' clinical software. Clinics may choose from a number of commercial providers of clinical software, with POLAR extracting from four of the most common systems.[83] POLAR has several uses: it helps general practitioners visualise and monitor key practice priorities and identify patient trends; it maps uncoded free text in the diagnosis fields into Systematised Nomenclature of Medicine (SNOMED) terminology and chronic disease groups; and it extracts de-identified data from the participating practices' computers and sends them to the Outcome Health POLAR data warehouse.[83] POLAR is a service that Outcome Health provides under contract to participating Primary Health Networks (PHNs) to enable their reporting to both federal authorities and practices within their region. The AURORA research database allows access to specific deidentified data from POLAR for projets that have received ethical approval and have been approved by the POLAR research council.

At the time of writing, the AURORA database was receiving de-identified electronic medical records from more than 1,000 practices across Australia.[84] However, while the study was being conducted, the database contained electronic medical records extracted from 300 practices located in two PHNs within south-east and eastern Melbourne, Victoria.

Table 3.1. List of variables extracted from the AURORA database and their description

| Variable | Description |
|---|---|
| Patient ID | A unique patient identifier |
| Age | Patient age during GP visit |
| Gender | Gender with which the patient considers or desires to be associated |
| Consultation date | When the patient had a GP consultation |
| Diagnosis date | When the patient received the diagnosis |
| Diagnosis | Mapped to SNOMED code from free text |
| Immunisation type | The type of immunisation given to a patient (e.g., influenza) |
| Immunisation date | The date when the immunisation was given to the patient |
| Immunisation age | The age of the patient when the immunisation was given |
| Immunisation group | The type of vaccine administered (e.g., Fluvax is within influenza vaccine) |

### 3.2.3 Emergency department data

Monash Health ED data were used to evaluate the validity of selected ICD-10 codes to identify anaphylaxis following immunisation (AFI). Preselected ICD-10-CM codes were used to identify possible EDs diagnoses of anaphylaxis following immunisation/vaccination as the same codes are used by the ICD-10-Australian Modification codebook. Monash Health's ED dataset comprised ED visits from five hospitals in south-east Melbourne: Monash Medical Centre, Dandenong Hospital, Casey Hospital, Moorabbin Hospital and Monash Children Hospital. Annually, more than 150,000 individuals visit Monash Health's emergency sites.[85]

### 3.2.4 Surveillance of Adverse Events Following Vaccination in the Community dataset

As stated in Section 1.3.1, suspected AEFI in Victoria are encouraged to be reported spontaneously to SAEFVIC, and after further assessment, all reports are forwarded to the

TGA.[46] SAEFVIC, established in 2007, encourages the community to report all possible AEFI except those that are common, minor or expected. All AEFI reported to SAEFVIC, irrespective of severity, are recorded into the SAEFVIC database. SAEFVIC provides not only clinical support for children and adults with AEFI but also education regarding vaccine safety that aims to improve AEFI reporting and maintain consumers' confidence in vaccination services.[46, 86] A study conducted by Clothier et al. demonstrated that the volume of AEFI reports submitted to SAEFVIC tripled between 2007 and 2014.[87] All AEFI that had been reported to SAEFVIC between 2009 and 2017 were used in this research to examine temporal patterns correlated with AEFI-related calls to NOC. De-identified data aggregated by week, year, gender and age group were obtained.

### 3.2.5 The 2010 and 2015 historical AEFI signals in Australia

In this thesis only the 2010 febrile convulsions and the 2015 allergic reactions following seasonal influenza vaccination were considered as historical AEFI signals for comparison as there was no vaccine safety signal detected between 2008 and 2017 in Australia by other existing surveillance modalities.

#### *Fever and febrile convulsions in young children*

In 2010, the annual influenza vaccination began on 8 March 2010 with four TIV vaccine brand types: Fluvax®, Fluvax Junior® (both CSL Biotherapies, Parkville, Australia), Vaxigrip® (Sanofi Pasteur, Lyon, France) and Influvac® (Solvay Pharmaceuticals, Pymble, Australia). On 23 April, use of TIV in children under five years of age was suspended across Australia due to increased rates of fever and febrile convulsions post-vaccination.[49] This event was initially noted in Western Australia following a spike in young children with fever and febrile convulsion visiting EDs after receiving the TIV. The TGA was notified of the event on 13 April. Later, the TGA received reports of febrile convulsions related to TIV from all

jurisdictions except the Northern Territory.[49] A subsequent investigation using epidemiological studies confirmed that the increase in frequency of fever and febrile convulsions in children aged under five years—associated particularly with the Fluvax and Fluvax Junior brands of TIV—was significantly higher than what would be expected based on the 2008 and 2009 records.[88] Unfortunately, as outlined in Section 1.3.1, the incident had not been detected by the existing state-based or national PSS at the time.

***Increased rates of allergic AEFI***

In 2015, TGA was alerted to a possible increase in allergy-related AEFI following the administration of the 2015 TIV vaccines by Victoria's SAEFVIC.[89] After further investigation TGA concluded the signal did appear real in Victoria but could not be detected in other juridictions. As the allergy-related AEFI involved a less severe illness spectrum in a predominantly adult age group, it did not justify a change to the advice for the immunisation program.[89, 90] The annual influenza vaccination was started on 20 April 2015 with both TIVs and quadrivalent influenza vaccines.[91]

### 3.3 Adverse events following immunisation syndrome

Pre-diagnostic or diagnostic data based–AEFI syndromes tailored to each data source were created (see Table 3.2).

Table 3.2. Data sources, studied syndromes and syndrome definitions

| Data source | Syndrome | Syndrome definition |
|---|---|---|
| NOC dataset | AEFI-related call | Any helpline call that is managed based on the patient guideline titled 'immunisation reactions infant child adult' |
| GP dataset | Post-vaccination GP consultation rate | A GP consultation for any reason within one week of receiving the seasonal influenza vaccination* |

| | | |
|---|---|---|
| Monash Health ED dataset | Anaphylaxis following vaccination | An ED diagnoses coded with ICD-10 codes of T80.5, T80.6, T88.1, T88.6, and T78.2 |
| SAEFVIC dataset | AEFI-related report | Any possible AEFI reported to SAEFVIC by the community |

*Note. T80.5 = anaphylactic reactions due to serum, which includes vaccines; T80.6 = other serum reaction, not anaphylaxis; T88.1 = other complication following immunisation not elsewhere classified; T88.6 = anaphylactic reaction or shock because of adverse effect of correct medicinal substance properly administered; T78.2 = anaphylactic reaction/allergic reaction unspecified. * GP consultation on same day of vaccination was excluded due to uncertainty whether it was truly a separate subsequent consultation*

### 3.4 Statistical analyses

In this thesis, several statistical techniques appropriate for the study designs were used. A systematic review, validation analysis and time-series (temporal pattern) analysis, including a signal detection analysis, were performed. The validation analysis used positive predictive values to estimate the accuracy of selected ICD-10 diagnosis codes in predicting anaphylaxis due to vaccination (Chapter 6). Examining the temporal pattern and detecting statistical aberrations (signals) in the studied syndromic indicators, AEFI-related telephone calls or rates of post-vaccination GP consultations, were the sole focus of Chapters 4 and 5. Nationwide datasets were unable to be obtained until the end of candidature; therefore, the analyses were restricted to evaluating the temporal patterns without integrating the spatial distribution. Two statistical signal detection algorithms were utilised to examine the time series for possible temporal signals. These were the Farrington surveillance algorithm[92] and the log likelihood ratio (LLR) cumulative sum (CUSUM) chart.[93]

#### 3.4.1 The Farrington surveillance algorithm

The Farrington surveillance algorithm is a statistical algorithm that has been used routinely by public health institutions—especially in Europe—for early detection of outbreaks of infectious diseases.[56] The Farrington algorithm was first introduced in 1996,[94] and its improved version,

known as the Farrington Flexible algorithm, was introduced in 2012.[95] Generally, this algorithm compares observed events against expected events to identify significant changes in weekly counts of time-series data. The Farrington algorithm follows three basic steps:

1. The expected number of cases for each time point (μt) in the surveillance period was estimated using baseline data from a pre-determined baseline period. The algorithm used a negative binomial regression and Poisson generalised linear model to compute the expected number of cases for each time point. It considered and adjusted for seasonality, trend and any trailing effects of past outbreaks. For example, to adjust for the effect of seasonal variation on expected values calculation, the algorithm considered counts observed in comparable weeks in the past years. To illustrate this, consider 't' as the current week of year 'h', 'b' as the number of past years to be considered and 'w' as the number of comparable weeks on either side of 't' from previous years. Thus, the expected number of cases was calculated using baseline counts only from weeks $(t - w)$ to $(t + w)$ of years $(h - b)$ to $(h - 1)$. Details of the algorithm and the method of adjusting the effect of trend and past outbreak(s) while calculating expected values are outlined in existing literature.[94, 95]
2. An upper bound, which is a threshold ($U_t$), of the expected value for each time point was calculated based on the estimated mean and its variance. The algorithm used a 2/3-power transformation to make the distribution approximately symmetric, which also stabilised positive rates. The threshold was calculated on the 2/3-power scale and then translated back to the original scale, yielding a threshold for the expected value. The threshold was defined as an upper bound of a one-sided $(1 - \alpha) \times 100\%$ CI of the predicted value, where α was a type I error.

3. The observed number of cases at each time point ($Y_t$) was compared to the upper bound of expected number of cases for the corresponding time point. Thus, an alarm (signal) would be declared at a time point where $Y_t > U_t$.

The original Farrington algorithm[94] was used in this analysis to monitor the weekly count time series of AEFI calls made to the NOC. The expected number of AEFI calls at each week was estimated based on historical data using w = 3 and b = 2. Thus, for a given surveillance week ($x$) in a given surveillance year ($y$), the baseline AEFI calls were calculated from weeks [$x - 3$, $x + 3$] in years [$y - 2$ and $y - 1$]. For example, the expected number of AEFI calls for week 10 of 2013 was estimated using baseline AEFI calls from weeks 7, 8, 9, 11, 12 and 13 of 2011 and 2012. A type I error (α) of 0.001 was considered so that the upper bound of the 99% CI of the expected value was the threshold above which signals were raised.

### 3.4.2 The cumulative sum chart

CUSUM charts are a statistical process control method used for monitoring accumulated data over time and are widely used in the manufacturing industry for quality control.[96, 97] After being developed further, CUSUM charts have come to be used in healthcare settings and in public health surveillance.[93, 98, 99] Unlike the Farrington algorithm, CUSUM charts allow the detection of small sustained shifts of cumulative event rates over time.[96] Both the Observed minus Expected (O–E) CUSUM and LLR CUSUM charts were used. Data were aggregated by week, and the chart statistic was the proportion of vaccinated individuals who visited a GP within a one-week period post-vaccination (post-vaccination GP consultation rate). The one-sided CUSUM chart was used to detect the increased rate of post-vaccination GP consultation; it works as follows:

1. The O–E CUSUM chart displayed accumulated residuals over time. That is, the initial value was zero, and the difference between the observed and expected numbers of post-

vaccination GP presentations was added to the total at each time point. The expected number was estimated from baseline data. Mathematically, it can be illustrated as:

$$Ct = Ct - 1 + (Ot - Et)$$

where $C_t$ is the cumulative sum of residuals at time 't', and $O_t$ and $E_t$ are the observed and expected numbers of post-vaccination GP consultations at time 't', respectively. The method was purely visual and did not offer thresholds or statistical tests.

2. The LLR CUSUM chart was a probability-based data monitoring approach that sequentially assessed whether the observed post-vaccination GP consultation rate was more consistent with a baseline rate than with a pre-determined alternative rate. Similar to the O–E CUSUM chart, the LLR CUSUM chart involved plotting accumulated data (*Ct*) over time (*t*), but the mathematical form was quite different. The test statistic was the LLR, which compared two likelihood models (the null hypothesis [Model 1] against the alternative hypothesis [Model 2]).

**Model 1** claimed that the post-vaccination GP consultation rate in the observed data was equal to the baseline rate estimated from historical data.

**Model 2** claimed that the post-vaccination GP consultation rate in the observed data was different from the baseline rate—either greater than or equal to a predetermined alternative rate based on the effected size—odds ratio (OR) the researchers wanted to detect during the surveillance period.

Hence,

$$\text{Likelihood ratio} = \frac{\text{odds of GP representation under the Model 2}}{\text{odds of GP representation under the Model 1}}$$

Suppose that after 't' weeks there was a total of 'k1' patients who had visited the GP post-vaccination and a total of 'k2' patients who had not visited the GP post-vaccination. Then the LLR of this data (which adds over time) would be:

$$LLR(t) = k1(t)log(OR)/(1 - po + ORpo)) + k2(t)log(1/(1 - po + ORPo))$$

where $Po$ is the baseline post-vaccination GP consultation rate, and $OR$ is the odds ratio that corresponds to the minimum unacceptable post-vaccination GP consultation rate (threshold) the chart should detect.

The LLR value was expected to oscillate close to zero if the observed rate of post-vaccination GP consultations at each time point was comparable to the baseline rate. For example, the LLR of zero corresponded to the likelihood ratio of one, which meant that the observed data supported the null hypothesis model more than the alternative hypothesis model (no difference between the observed GP representation rate and the baseline reference rate). Similarly, the LLR of one corresponded to the likelihood ratio of 2.2, which demonstrated that the likelihood of the observed data was approximately double under the alternative model compared to the null hypothesis model. Thus, a higher LLR value meant that the observed data were more likely to support the alternative hypothesis or that the observed rate was considerably higher than the baseline reference rate. However, the LLR value needed to exceed a pre-specified threshold (critical limit) to determine that a change in the rate of post-vaccination GP consultations from the baseline rate was unacceptably high.

Last, the timeliness and sensitivity of the datasets—GP data and NOC data—in detecting the known AEFI signals that had occurred in 2010 and 2015 were evaluated.[15, 90] In this study, sensitivity was defined as the identification of an unusual temporal pattern (aberration) in the syndromic indicators, the weekly number of AFEI-related calls or rate of post-vaccination GP consultations, coinciding with the two known AEFI signals with influenza vaccines in 2010

and 2015. Timeliness referred to how early the known AEFI signals could be detected using the syndromic indicators from the respective dataset.

### 3.5 Statistical software

Data were imported, cleaned and analysed using Stata/IC 15.1 (Statacorp, Texas), except analyses involving the use of signal detection algorithms. The R package surveillance was used to examine the temporal signal of AEFI calls. Additionally, Microsoft Excel 2016 (Microsoft Corp., Redmond, Washington) was used to calculate the O–E CUSUM chart and LLR CUSUM in examining the signal of GP representation rates.

### 3.6 Ethics

Approval for this project was obtained from the Monash Health Human Research Ethics Committee (HREC/18/MonH/345), and data access approval was obtained from the respective data custodians: Monash Health, the Outcome Health POLAR research council and NOC.

# CHAPTER 4: TELEPHONE HELPLINE DATA USE FOR SYNDROMIC SURVEILLANCE OF ADVERSE EVENTS FOLLOWING IMMUNISATION

## Introduction

As the systemic review in Chapter 2 demonstrated, healthcare data–based post-licensure vaccine safety studies rely predominantly on coded diagnostic information to identify health outcomes possibly related to vaccination. However, primary healthcare services are now actively delivered via telephone (telehealth) and online. Data generated from routine telephone consultations are used increasingly to monitor public health problems such as influenza-like illnesses; however, no published studies that examined the utility of telephone helpline data to monitor AEFI were found in the literature during the writing of this thesis. Hence, Chapter 4 presents a retrospective analysis of telephone helpline data in Victoria, Australia that were recorded between 2008 and 2017. Chapter 4 also presents evidence that telephone helpline data are a timely and representative data source to complement existing AEFI surveillance systems.

**Citation:** Mesfin YM, Cheng AC, Enticott J, Lawrie J, Buttery J. Use of telephone helpline data for syndromic surveillance of adverse events following immunization in Australia: a retrospective study, 2009 to 2017. Vaccine. 2020;38(34):5525–31

Vaccine 38 (2020) 5525–5531

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Use of telephone helpline data for syndromic surveillance of adverse events following immunization in Australia: A retrospective study, 2009 to 2017

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ARTICLE INFO

*Article history:*
Received 12 February 2020
Received in revised form 25 May 2020
Accepted 27 May 2020
Available online 24 June 2020

*Keywords:*
Adverse events following immunization
Safety signal detection
Syndromic surveillance
Telephone helpline data

ABSTRACT

*Background:* The increasing availability of electronic healthcare data offers an opportunity to enhance adverse events following immunisation (AEFI) signal monitoring in near real-time.
*Aim:* To evaluate the potential use of telephone helpline data to augment the existing AEFI surveillance system in Victoria, Australia.
*Methods:* Anonymised telephone helpline call data were extracted between 2009 and 2017. For comparison, we included AEFI reports to the Victorian enhanced passive surveillance system, SAEFVIC-"Surveillance of Adverse Events Following Vaccination In the Community". The temporal pattern cross-correlation coefficient at different time lags was estimated as a measure of timeliness evaluation. Historically known AEFI signals in 2010 and 2015 were examined using the Farrington statistical signal detection algorithm.
*Result:* During the study period, overall, the telephone helpline centre received 2,005,226 calls. Of these, 0.68% (13,719) were AEFI-related. In the same period, SAEFVIC received 10,367 AEFI related reports. Cross-correlation analysis, generally, showed that the two datasets were moderately correlated (r = 0.4) at a negative lag of 1 week. For individual years, the cross-correlation coefficient was highest (r = 0.66) in 2010 with the telephone helpline data leading by 2 weeks. Our analysis indicated the 2010 reported incidence of febrile convulsions and the 2015 reported increased allergic-related reactions following seasonal influenza vaccination three weeks and one week earlier respectively.
*Conclusion:* Telephone helpline data was able to detect an increased rate of AEFI earlier than the enhanced passive AEFI surveillance system. This dataset offers a valuable and near real-time component of an integrated AEFI early signal detection system in Australia.


## 1. Introduction

Post-licensure vaccine safety monitoring (PVSM) is an essential requirement in vaccination programs and crucial to ensure the safety of persons receiving vaccines and to maintain public confidence [1]. In most countries, passive (spontaneous) reporting of adverse events following immunization (AEFI) forms the backbone of PVSM. This approach relies primarily on AEFI notification by healthcare workers and consumers. The importance of passive AEFI surveillance is indispensable, particularly to detect unexpected and rare AEFI signals that require further investigation. Passive surveillance, however, has important limitations including underreporting and incomplete data, which are significant barriers to the timely detection of potential vaccine safety issues [2,3]. This is most concerning in the case of rapid implementation of vaccines with a catch-up program, such as annual seasonal influenza vaccines. In some developed countries, innovative active AEFI surveillance systems are in place to ensure early detection of potential AEFIs. These systems use either data reported directly from persons receiving the vaccines [3,4] or routinely collected healthcare data [5].

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https://doi.org/10.1016/j.vaccine.2020.05.078
0264-410X/

In the United States (US), newly licensed vaccines are monitored in near real-time using the Vaccine Safety Datalink (VSD), a network of linked healthcare databases. In the VSD, patients' vaccination information from vaccine registries is linked with their medical diagnoses at the outpatient clinic, inpatient and emergency department (ED) settings [6]. This approach allows population-level active surveillance of AEFI. However, less severe AEFI from persons who do not seek medical care at the ED, outpatient clinic or hospital settings are unlikely to be captured. Similarly, Australia has established a near real-time active AEFI surveillance system "AusVaxSafety" using data collected directly from persons receiving the vaccines (or their parents/carer). The data are solicited via automated short message or e-mail messages within three days of vaccination [4]. However, AusVaxSafety relies on an active response from each person.

Alternatively, syndromic surveillance based on pre-diagnostic healthcare data has been increasingly used for enhancing early detection of public health problems, such as influenza and gastroenteritis [7–10]. Telephone-based health services, also referred to as "telephone helpline" or "telephone triage", are considered an emerging data source for syndromic surveillance of potential public health events [7–9]. Key advantages of telephone helpline data are timeliness and the ability to ascertain healthcare information for individuals who do not attend ED or outpatient facilities. In the United Kingdom, phone calls to the National Health Service (111) are monitored daily to track influenza and norovirus [11], although this service does not currently include a category for AEFI. Globally, we could find no published research that evaluated the use of telephone helpline services as a source of surveillance data for AEFI surveillance.

In Australia, telephone helpline services have been in operation since 2008, where a registered nurse provides health advice and information to callers over the phone. This publicly funded telephone helpline covers all jurisdictions in Australia under a variety of contracts by Medibank Health Solutions (a private provider of health insurance and health solutions) and receives funding from several sources including the Australian Government. In Victoria, this service is provided through the State government funded Nurse-On-Call (NOC) system. This study aimed to evaluate the potential validity and timeliness of NOC telephone helpline data for near real-time syndromic surveillance of AEFI signals.

## 2. Methods

### 2.1. Study design and data source

We conducted a retrospective study utilizing de-identified data from the NOC database, from February 1, 2009 to December 31, 2017. NOC provides 24 h/seven-day a week telephone-based healthcare advice and information to the residents of Victoria, Australia. First, the nurse answers a call and collects demographic information, including address of the patients, and asks the main reason of call (symptom/chief complaint). Then, the nurses will choose guideline(s) that is/are relevant to the patient's health concern based on the main symptom. For example, for a patient inquiring about breathing difficulties the nurse might choose the guideline titled "Breathing problems" or "Wheezing or asthma" or "Colds and Flu", depending on the exact nature of the query and symptoms. Similarly, for a patient inquiring about an AEFI, the nurses will choose the guideline titled "immunisation reactions infant child adult". Finally, the nurses will ask "Yes/No" questions to assess urgency and thereby, to determine call outcome (final disposition). The final disposition generally falls into one of the five categories: (1) activate emergency phone number (000)/transfer to ambulance services; (2) attend ED immediately; (3) see a doctor: either immediately or within 4–72 h; (4) self-care advice; or (5) see an allied health provider (e.g. dentist, midwife or pharmacist) [12].

### 2.2. Classifying telephone helpline call as "AEFI-related call"

To designate a telephone helpline call as AEFI-related call, the nurse needs to consult the patient guideline titled "immunization reactions infant child adult" to manage the caller's health concern. We defined "AEFI-related call" as any NOC helpline call that is managed using the patient guideline titled "immunisation reactions infant child adult", which is a proxy of the presenting problem/main symptom. For each call, we obtained the following NOC data fields: age, date and time, patient guideline title, and final disposition (shows the severity level of the health concern).

### 2.3. Reference data

We used the Victorian enhanced passive surveillance system dataset, Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC), as reference data to evaluate the inherent timeliness of the telephone helpline dataset. SAEFVIC includes all AEFI reports made by health professionals, consumers or industry**.** SAEFVIC was established in 2007 aiming to improve reporting of AEFI, detect and validate AEFI signals, and support consumer confidence in vaccination [13]. Of note, improved visualization and analysis of SAEFVIC data have been recently demonstrated to improve signal detection capacity compared with historical safety event detection [14].

### 2.4. Data analysis

The primary outcome measure was the weekly number of AEFI-related calls made to the NOC. Descriptive analyses were undertaken, including a plot of the time series to examine the temporal pattern of AEFI calls. AEFI call and SAEFVIC data were analysed by age category in years ($\leq$4; 5–18; 19–64, and; $\geq$65 years) and year. Descriptive analyses were performed using Stata software version 15 (College Station, TX: StataCorp LLC) and possible temporal AEFI call signals were examined using the R package Surveillance, in particular using the Farrington surveillance algorithm [15].

The Farrington surveillance algorithm is a widely used automated statistical algorithm to examine time series of counts data for possible outbreaks of health events [16]. This algorithm uses a Poisson generalised linear model to calculate the expected count of AEFI calls for the current week based on historical data. Weeks were designated as surveillance weeks 1–52 for each calendar year. A signal was declared if the examined week's observed AEFI calls exceeded the upper bound (99% level) of the expected AEFI calls (threshold) for that week. The Farrington algorithm takes into account seasonality and trend in calculating the expected value. To account for seasonality, the expected value calculation is based on comparable periods in past years. Two key parameters in estimating a baseline are the number of years from which the baseline is calculated ($b$) and the number of weeks from each year that the form the baseline ($w$). Thus, for a given week $x$ in a given year $y$, the baseline is calculated from weeks $[x-w, x+w]$ in years $[y-1, y-2 \cdots y-b]$.

### 2.5. Timeliness assessment

We used two approaches to assess the timeliness of NOC data:

1. We compared the NOC data against the reference data, SAEFVIC. A cross-correlation function (CCF) between the time series of AEFI-related calls to the NOC and time series of AEFI-related report to the SAEFVIC at different time lags (using 1-week time steps) was calculated. If the two datasets are in temporal alignment, the maximum value of the CCF will occur at a time lag of zero weeks. Similarly, if the cross-correlation value is highest at a negative time lag, then a change in the volume of AEFI calls to the NOC service precedes a change in the volume of AEFI reports to SAEFVIC. Before computing the cross-correlation, we tested for the time series stationarity using the Dickey-Fuller test.
2. We also compared spikes in the time series of NOC data with the actual historical signal detection date of past known signals, reported febrile convulsions in 2010 [17] and reported allergic-related reactions in 2015 following seasonal influenza vaccines [18].

The 2010 vaccine safety event was due to a seasonal influenza vaccine brand (Fluvax™, and Fluvax Junior™, CSL Ltd) with an increased rate of reported fever and febrile convulsions. AEFI surveillance systems at the time did not detect a signal, with the first signal query by West Australian emergency departments 6 weeks following vaccine release. [19] Subsequently, improved visualisation and analysis of SAEFVIC data from that period using the proportional reporting ratio (PRR) has been demonstrated to detect the 2010 signal within two weeks of vaccine release [14]. The 2015 safety event was due to an increased rate of reported allergic events in adults following seasonal influenza vaccine from multiple brands, with signal detection initially raised by SAEFVIC nurses, and confirmed using PRR [18].

### 2.6. Validity assessment

NOC helpline data validity was evaluated based its potential of indicating the known past AEFI signals (sensitivity), and correctly identifying signal-free seasons from 2010 to 2017 inclusive (specificity). Sensitivity is calculated considering the two past known AEFI signals mentioned above as true positive signals. Similarly, specificity is calculated based on the assumption that no AEFI signal was detected in Victoria/Australia between 2010 and 2017 other than the 2010 and 2015 signals. Hence, we considered six AEFI signal negative seasons as denominator.

**Ethical approval:** Monash Health Human Research Ethics Committee (HREC/18/MonH/345) approved this study.

## 3. Results

### 3.1. Descriptive epidemiology

In total, during the study period, 2,005,226 telephone calls were made to the NOC helpline. Of these, 13,719 (0.68%) calls were categorized as AEFI-related calls. Children aged under five accounted for 75.42% of AEFI-related calls. Among non-AEFI-related calls, adults 19–64 years comprised nearly half of the calls (49.4%). The most AEFI-related calls were made in 2010, comprising 13.6% of all AEFI-related calls (Table 1). Regarding AEFI-related call dispositions, 52.5% received self-care advice, 38.8% were advised to see a doctor within 72 h and 7.5% linked to the ambulance service straightaway or advised to attend the ED immediately (Table 2).

During the same period (2009–2017), SAEFVIC received 10,912 spontaneous AEFI-related reports.

### 3.2. Timeliness assessment

A. NOC helpline time series peaks comparison

**Table 1**
Characteristics of all calls and AEFI calls to the NOC helpline from February 1, 2009 to December 31, 2017.

| | Non-AEFI calls N (%) | AEFI calls N (%) | % AEFI calls of all NOC calls |
|---|---|---|---|
| Total | 1,991,507 (1 0 0) | 13,719 (1 0 0) | 0.68 |
| *Gender* | | | |
| Male | 768,613 (38.5) | 6,460(47.1) | 0.83 |
| Female | 1,222,475 (61.3) | 7,257(52.8) | 0.59 |
| Unknown | 419 (0.02) | 2(0.01) | 0.48 |
| *Age (years)* | | | |
| ≤4 | 540,335 (27.1) | 10,347(75.3) | 1.88 |
| 5–18 | 270,782 (13.6) | 988(7.2) | 0.36 |
| 19–64 | 983,906 (49.4) | 1,811(13.2) | 0.18 |
| ≥65 | 196,484 (9.9) | 573(4.3) | 0.29 |
| *Year* | | | |
| 2009 | 185,365 (9.3) | 1,627(11.8) | 0.87 |
| 2010 | 202,464 (10.2) | 1,870(13.6) | 0.92 |
| 2011 | 191,745 (9.6) | 1,507(10.9) | 0.78 |
| 2012 | 205,583 (10.3) | 1,399(10.2) | 0.68 |
| 2013 | 218,481 (10.9) | 1,354(9.8) | 0.62 |
| 2014 | 213,493 (10.7) | 1,358(9.9) | 0.63 |
| 2015 | 228,753 (11.5) | 1,302(9.5) | 0.57 |
| 2016 | 269,354 (13.5) | 1,514(11.0) | 0.59 |
| 2017 | 276,269 (13.8) | 1,788(13.0) | 0.64 |

Visual inspection of the weekly time series graph (Fig. 1) showed that the 2010 spike dominates the whole chart. For all ages, there were drastic increases in AEFI calls in 2010 from week 11 to week 16, peaking on week 16 with 93 AEFI calls. For children aged 0–4 years, a similar pattern was observed, where the highest number of AEFI calls was recorded in week 16 (56 calls). This increase in AEFI calls to the NOC helpline coincided with the increase in febrile convulsions following influenza vaccination in 2010. Conversely, the early season AEFI calls increases in 2015 were not markedly evident compared to other seasons.

B. NOC helpline vs. SAEFVIC data

The time series from the two datasets appeared to be stationary, suggesting the statistical properties of the process generating the time series do not change over time, with no trend detected (Dickey Fuller test, p value < 0.001). From 2009 to 2012, the weekly volume of AEFI calls to the NOC helpline (mean = 32; 95% CI, 30.0–33.4) were significantly higher than the weekly AEFI reports received by SAEFVIC (mean = 19.2; 95% CI, 17.6–20.8). Conversely, from 2013 to 2017, the weekly average AEFI calls (mean = 28.1) and AEFI reports (mean = 26.9) were comparable (Fig. 2a). Further, the 2010 spike in the NOC data appeared ahead of the SAEFIC data (Fig. 2b).

Overall, cross-correlation analysis showed that changes in the helpline data tended to precede changes in the SAEFVIC data by 1 week on average: r = 0.41 for all age and r = 0.19 for 0–4 years group. However, the cross-correlation coefficient noticeably varied between individual years (Table 2). For all age groups, the maximum cross-correlation occurred in 2010 (r = 0.66) and in 2015 (r = 0.63) at a negative lag of 2 weeks and 1 week respectively. For the 0–4 years group, the maximum cross-correlation was seen in 2010 (r = 0.52) at a negative lag of 1 week (see Table 3).

### 3.3. Validity assessment

Considering all ages, the Farrington algorithm showed that the weekly observed count of AEFI in 2010 exceeded the upper bound of expected count for six consecutive weeks (week 11–16) (Fig. 3a). Additional AEFI signals were detected in 2011, 2014, 2015 and 2017. Except in 2017, all the above-mentioned signals were detected between 14 March and 23 May, coincident with the

**Table 2**
AEFI-related calls outcome by age group, 2009–2017, Victoria, Australia.

| Age group (years) | Final call outcome/disposition | | | | Total |
|---|---|---|---|---|---|
| | Advised to attend ED immediately/transferred to ambulance service, N (%) | Advised to see doctors within 72 h, N (%) | Given self-care advice, N (%) | Other | |
| 0–4 | 938 (9.07) | 3525 (34.07) | 5746 (55.53) | 138 (1.33) | 10,347 (100) |
| 5–18 | 83 (8.4) | 469 (47.47) | 423 (42.81) | 13 (1.32) | 988 (100) |
| 19–64 | 7 (0.39) | 987 (54.5) | 817 (45.11) | 0 (0.0) | 1811 (100) |
| ≥65 | 2 (0.35) | 347 (60.56) | 224 (39.09) | 0 (0.0) | 573 (100) |

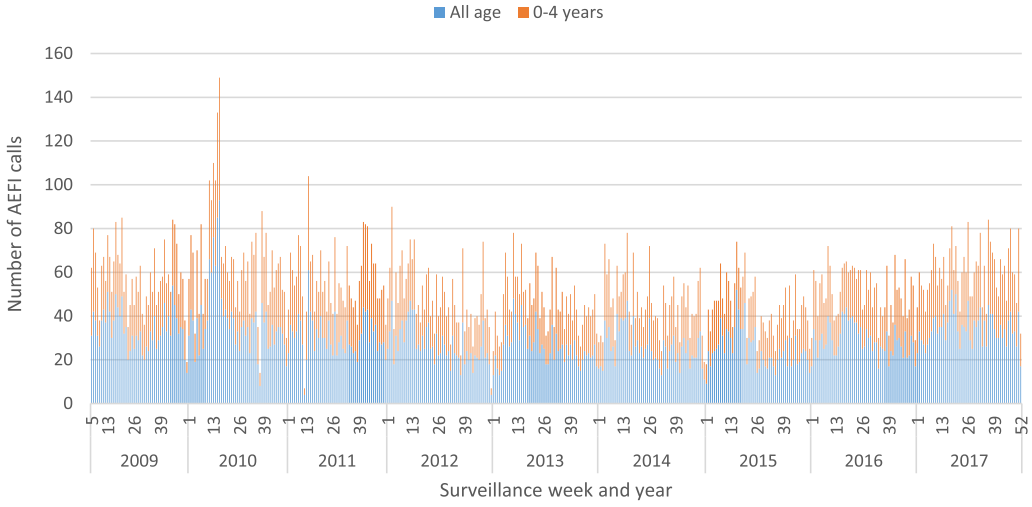


**Fig. 1.** Weekly number of AEFI calls to NOC helpline by age group in Victoria, Australia, from 1 February 2009 to 31 December 2017.

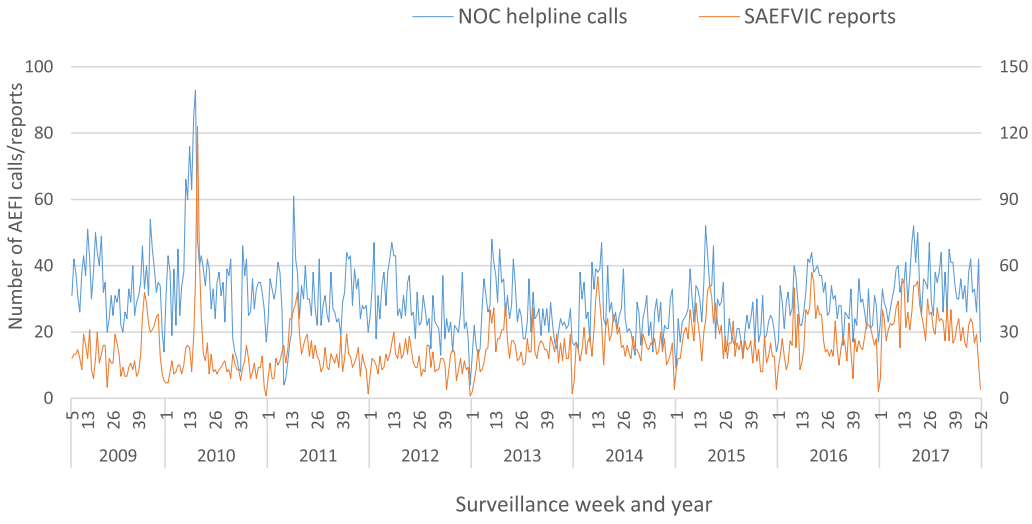


**Fig. 2a.** Weekly number of NOC AEFI calls and SAEFVIC AEFI reports in all age group, Victoria, Australia, from 1 February 2009 to 31 December 2017.

annual influenza vaccination period in Australia. When data are restricted to children aged under five, AEFI signals were detected in consecutive weeks only in 2010 (week 14–16) and 2017 (week 36–38) (Fig. 3b). The sensitivity of NOC helpline data to indicate past known AEFI signals was 100% (2/2) for all ages and (1/1) 0–4 years group. The specificity, to identify AEFI signal-free seasons correctly, was 50% (3/6) for all ages and 71.4% (5/7) considering data only for children aged 0–4 years.

## 4. Discussion

This study demonstrates that the telephone helpline data is a potentially timely and valid data source to augment the current AEFI surveillance system. Cross-correlation analysis showed that the increase in helpline AEFI-related calls occurred 1 to 4 weeks earlier than spontaneous AEFI reports submitted to SAEFVIC. Additionally, 52.5% of the AEFI-related calls were likely to relate

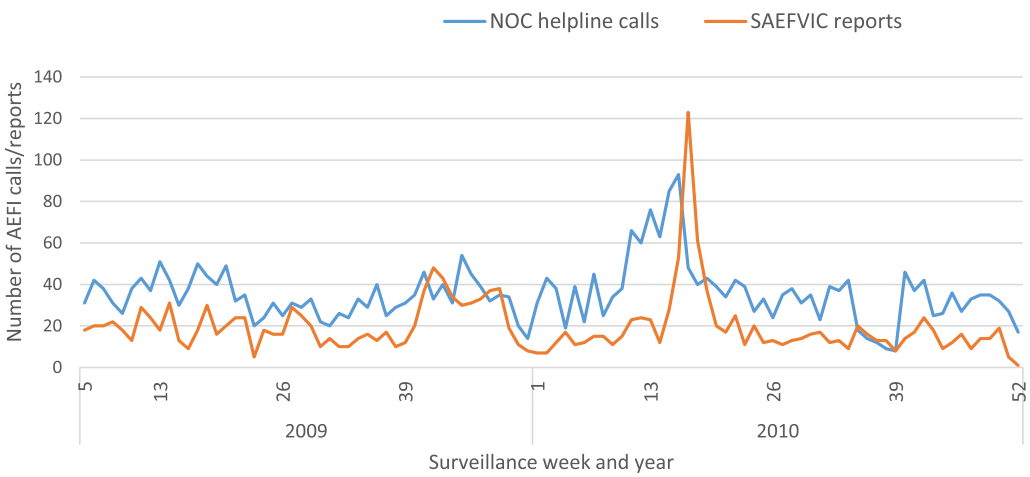


**Fig. 2b.** Weekly number of NOC AEFI calls and SAEFVIC AEFI reports in all age group, Victoria, Australia, from 1 February 2009 to 31 December 2011.

**Table 3**
Time lag in weeks at maximum correlation between NOC data and SAEFVIC data stratified by age and year. Correlation is shown in parentheses (maximum possible correlation is 0.66).

| Year | All age | 0–4 years |
|---|---|---|
| 2009 | −1 (0.46) | 0 (0.21) |
| 2010 | −2 (0.66) | −1 (0.52) |
| 2011 | −4 (0.49) | 0 (0.35) |
| 2012 | 0 (0.38) | −2 (0.16) |
| 2013 | 0 (0.52) | 0 (0.25) |
| 2014 | 0 (0.48) | 0 (0.33) |
| 2015 | −1 (0.63) | 0 (0.23) |
| 2016 | 0 (0.64) | 0 (0.33) |
| 2017 | 0 (0.41) | +1 (0.26) |
| 2009–2017 | −1 (0.41) | −1 (0.20) |

to non-severe AEFIs, with callers advised to manage the symptoms by themselves. Hence, helpline data could provide valuable information about less severe AEFI not requiring medical attendance. This may prove valuable for unexpected increased rates of known acute AEFI, such as local reactogenicity or fever, which may not be commonly reported to spontaneous reporting systems.

The NOC helpline data indicated the two past AEFI signals. In addition, the 2010 AEFI signal first flagged within 2 weeks of influenza vaccination commencing, and 4 weeks earlier than the alert raised at that time (Fig. 4). The Australian regulatory authority, Therapeutic Goods Administration (TGA) was notified about the apparent increase in febrile convulsions on 13 April 2010, primarily from West Australia emergency department settings. Ten days later, on 23 April, use of trivalent influenza vaccine in children aged 0–5 years was suspended across Australia [19,20]. Of note, in a recent reanalysis of 2010 spontaneous reporting to SAEFVIC using disproportionality analyses now routinely employed prospectively, the proportional reporting ratio (PRR), detected an AEFI signal on March 28 [14], confirming a signal using a different data source and method.

Similarly, the helpline data indicated AEFI signals at week 16 and 20 in 2015. Increased allergic-related reactions following seasonal influenza vaccination, predominantly in adults, was alerted to TGA primarily from SAEFVIC on week 18 (3rd May 2015) [18]. Unlike 2010, the two signals in 2015 were not sequential and might be weak, but the NOC helpline data indicated the incident at least one week earlier than the SAEFVIC data, and could be used

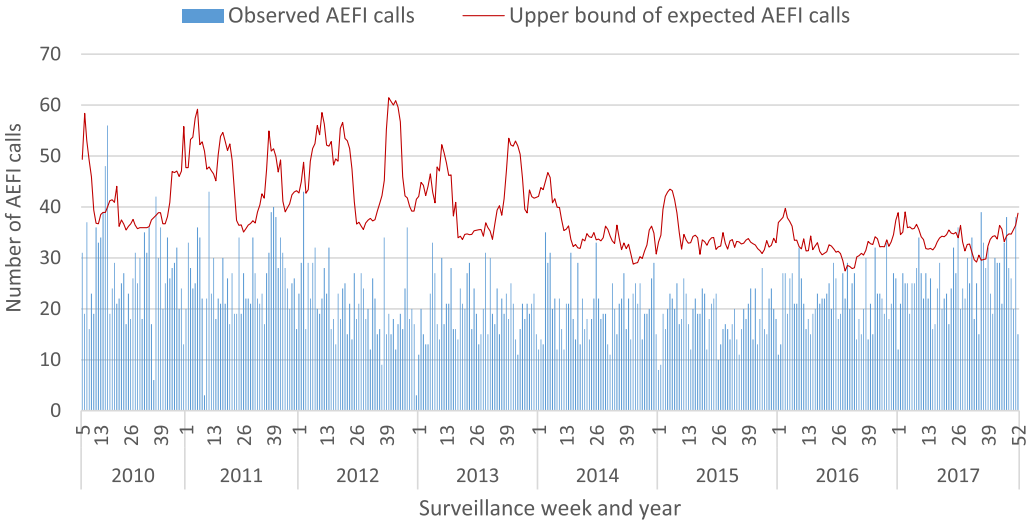


**Fig. 3a.** Weekly number of NOC AEFI calls for children aged 0–4 in Victoria, Australia. (a and b): test period (week 5/2010 to week 52/2017). Baseline period- 2 years of historical data immediately before the test period, except for 2010 which used 1 year. Each blue bar represents weekly observed AEFI calls and the red line represents the 99% upper bound of expected AEFI calls (threshold) calculated by the algorithm. Weekly signal is declared where the observed number of AEFI counts exceeds the upper bound. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

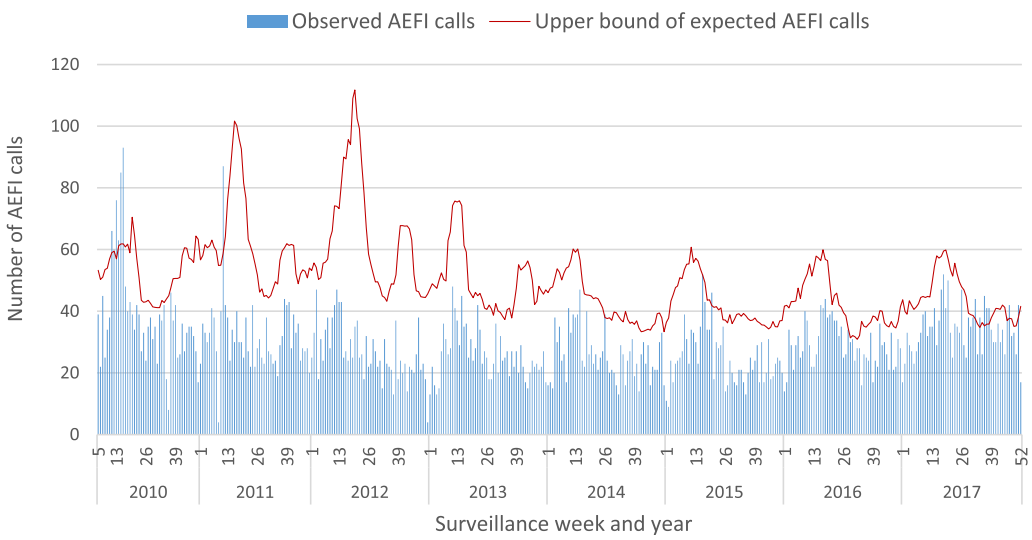


**Fig. 3b.** Weekly number of NOC AEFI calls for all age groups in Victoria, Australia. (a and b): test period (week 5/2010 to week 52/2017). Baseline period- 2 years of historical data immediately before the test period, except for 2010 which used 1 year. Each blue bar represents weekly observed AEFI calls and the red line represents the 99% upper bound of expected AEFI calls (threshold) calculated by the algorithm. Weekly signal is declared where the observed number of AEFI counts exceeds the upper bound. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

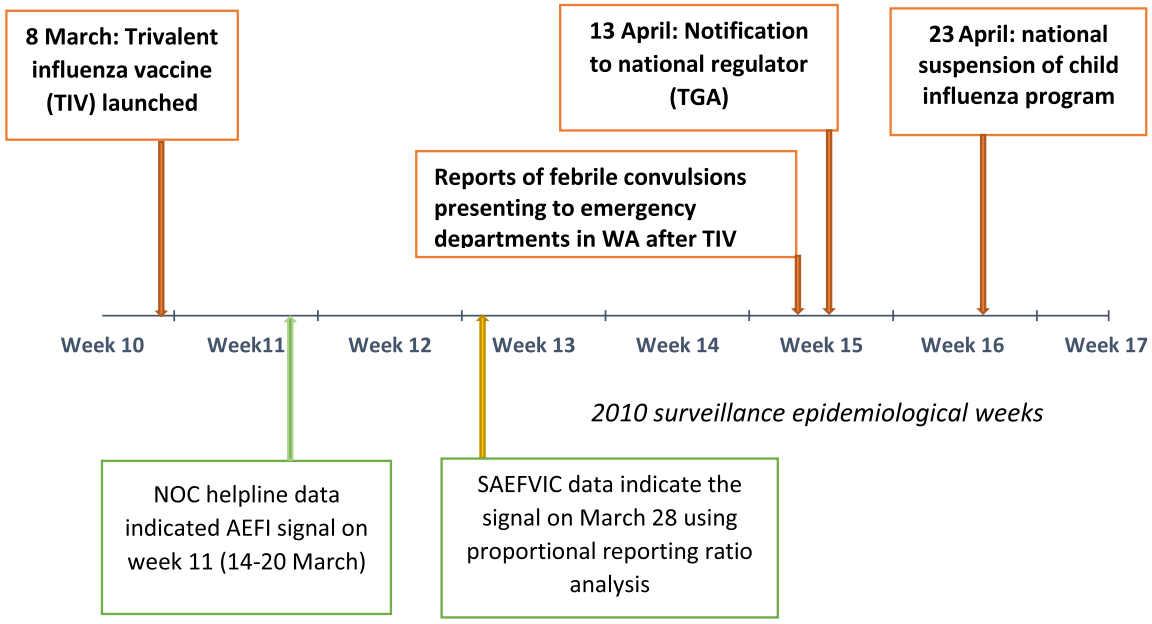


**Fig. 4.** Timeline of 2010 AEFI signal detection, week 10 starts on 07 March and week 17 ends on 01 May.

also for signal verification. Fortunately, after further investigation by the TGA, the clinical severity of the allergic reactions was not sufficient to require regulatory action and did not lead to withdrawal of the vaccines from the market.

We correctly identified three of the six seasons without an AEFI signal, which made the specificity 50%. False positive AEFI signals were detected in 2011, 2014 and 2017. Increasing the signal requirement to at least two consecutive weeks would potentially eliminate the 2011 and 2014 signals. However, several signals were detected in 2017 and this could be partially explained by higher proportion of under five years received influenza vaccination after August compared to the previous years, presumably due to belated vaccination of young children in response to a well-publicised high rate of influenza infections [21]. This could affect the expected and observed AEFI calls calculation of the algorithm. Another reason might be an increase in AEFI reporting rate following the introduction of meningococcal ACWY conjugate vaccine into the national immunisation program. According to the TGA annual report, there was a 12% increase in the overall AEFI reporting rate in 2017 compared to the previous year (2016) [22]. Of note, our study used helpline data from a single jurisdiction; it is likely that incorporating national helpline data could further improve timeliness and specificity.

To our knowledge, no published study has examined the utility of telephone helpline data for AEFI surveillance. An unpublished study by Hartley and colleagues (data not shown) evaluated the potential of Healthdirect helpline data, the telephone helpline services used in all Australian jurisdictions except Victoria and Queensland, for conducting syndromic surveillance of six different syndromes including AEFI. This study also identified an apparent

increase of AEFI-related calls to the Healthdirect helpline in 2010. However, the authors did not compare Healthdirect helpline data with other data such as SAEFVIC or ED visits. Other non-vaccine studies, conducted in Canada and Australia, also showed telephone triage data signals at least one week before ED data [7,23]. In Europe, the UK has established telephone helpline-based syndromic surveillance to monitor influenza and norovirus, also called "remote heath advice" syndromic surveillance [11]. However, this system does not currently collect data on AEFI (personal communication Nick Andrews, HPA, 21 December 2019).

There are potential limitations in utilising telephone helpline data. We considered the AEFI-related calls count as the outcome variable. Only callers' main complaint or reason for calling the helpline was included. Callers who had an AEFI as a secondary concern were not captured in our AEFI data, thus some underreporting is likely. In addition, key information about the patient's main complaint, such as the specific vaccines administered and reactions experienced were not available. The utility of telephone health advice datasets for syndromic surveillance would be improved by the addition of a free text field for symptoms. Such a field may improve specificity, with natural language processing techniques enabling automated analysis in rear real-time. Any community behaviour change regarding use of the telephone helpline would also affect our primary outcome. Additionally, the NOC dataset may not consistently capture the type of vaccine administered for each call; however, administration datasets such as the Australian Immunisation Register and spontaneous reporting data can be used to inform probable vaccines of interest in the relevant age group. For nurses to assign a call as an AEFI-related call, callers need to report a vaccination, which is more likely for AEFI with rapid onsets.

## 5. Conclusion

Telephone helpline data is a timely and representative data source that shows promise for near real-time syndromic surveillance of AEFI signals. Syndromic AEFI surveillance using routinely collected helpline data can provide a very low cost and unique complementary system of tracking post-licensure vaccine safety, but results need to be interpreted in conjunction with other surveillance data. Syndromic surveillance shows potential promise as a sensitive and cost-effective adjunct within an integrated vaccine safety surveillance system.

## 6. Financial support

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

We would like to thank Barbara Whyte and Karen Smith (Ambulance Victoria) and Roland Jauernig (Victorian Department of Health and Human Services) for access to NOC helpline data. Nick Andrews kindly reviewed the manuscript and provided comments. This research was supported by an Australian Government Research Training Program (RTP) Scholarship.

## Author contribution

Mesfin YM, Buttery J and Cheng A conceived the study concept and design. Mesfin YM and Lawrie J did the statistical analysis. Mesfin YM wrote the manuscript. All authors provided critical revisions on the draft and approved the submitted draft.

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# CHAPTER 5: USE OF PRIMARY HEALTHCARE DATA FOR SYNDROMIC SURVEILLANCE OF AEFI

## Introduction

Chapter 5 comprises a retrospective study that was conducted to examine whether healthcare visits were common after vaccination using the syndrome 'post-vaccination healthcare attendance rate', which is defined as individuals presenting to a healthcare service within one week of receiving a vaccination regardless of the reasons. The aggregated GP visits in one week following the influenza vaccination between 2008 and 2017 were analysed; the data were obtained from more than 300 GPs in Victoria, Australia. The study demonstrated unusual rises in post-vaccination GP consultations that temporarily corresponded with the known AEFI signals in 2010 and 2015. Therefore, the syndrome 'post-vaccination healthcare attendance rate' can potentially offer a sensitive proxy to indicate the unusual increases in healthcare visits due to AEFI.

Mesfin YM, Cheng AC, Enticott J, Lawrie J, Buttery J. Post vaccination healthcare attendance rate as a proxy-measure for syndromic surveillance of adverse events following immunisation: A validation study using CUSUM chart. Published online in Australian & New Zealand Journal of Public Health.

# Post-vaccination healthcare attendance rate as a proxy measure for syndromic surveillance of adverse events following immunisation

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## Abstract

**Objective**: This study explored whether all-cause healthcare attendance rate post-vaccination could detect the two historical influenza safety episodes occurring in 2010 and 2015 using a large de-identified general practitioner (GP) consultations dataset.

**Methods**: A retrospective observational cohort study was conducted using GP consultation data routinely collected from 2008 to 2017 in Victoria, Australia. Post-vaccination GP consultation rates were monitored, over a 22-week surveillance period each year that aligned with each year's influenza vaccination season, using the Observed minus Expected (O-E) and the Log-Likelihood Ratio (LLR) CUSUM charts. Days 1–7 post-vaccination were considered as the risk period. The LLR CUSUM was designed to detect both a 50% and two-fold rise in the odds of the baseline post-vaccination GP consultation rates.

**Results**: Over the 10-year study period, more than 1.5 million seasonal influenza vaccines doses were administered to 295,091 persons. Overall, 1.29% had a GP consultation within one week of vaccination, but 98.53% of the consultations occurred in days 1–3 post-vaccination. The LLR CUSUM chart detected significant increases in the weekly rates of post-vaccination GP consultation in 2010 in children aged under ten years and in 2015 in adults aged 19–64 years. These increases were aligned by week, but one week earlier and by age category, with the historical adverse events following immunisation (AEFI) signals occurring in 2010 and 2015. However, in the absence of historical AEFI signals, increased rates of post-vaccination GP consultations were identified in three of the eight influenza vaccination years.

**Conclusion**: The crude post-vaccination healthcare attendance rate has the potential to offer a sensitive proxy to monitor vaccine safety signal.

**Implications for public health**: Vaccine safety monitoring using syndromic indicator has the potential to augment the existing surveillance systems as part of an integrated vaccine safety monitoring approach.

**Key words**: vaccine safety signal detection, post-vaccination healthcare attendance, syndromic surveillance, vaccine safety

Public and healthcare worker perceptions of vaccine safety are crucial drivers of vaccine hesitancy, which is defined as a reluctance or refusal to vaccinate despite the availability of vaccines.[1] Vaccine hesitancy has been identified by the World Health Organization (WHO) as one of the 10 threats to global health.[2,3] Post-licensure vaccine safety surveillance remains the cornerstone for the detection of adverse events following immunisation (AEFI).[4] While most AEFI are mild and self-limiting, early detection of increased rates of known AEFI or AEFI not detected during clinical trials are critical to maintain trust in immunisation programs and minimise vaccine hesitancy.[5,6]

While spontaneous (passive) surveillance systems are the mainstay of post-licensure safety monitoring, these systems rely on voluntary reporting of AEFI by the community, mainly healthcare workers and vaccine recipients or their caregivers. Notably, because of the wider population coverage, surveillance systems can detect rare or long-term AE signals. A vaccine safety signal, as defined by the WHO, is "reported information on a possible causal relationship between an adverse event and a vaccine, the relationship being unknown or incompletely documented previously. The information can arise from one or multiple sources".[7] However, while recent innovations in data visualisation and automated disproportionality analyses show promise,[8] passive surveillance systems are limited by underreporting and a lack of timely vaccine administration denominator data for early vaccine safety signal detection.[9,10]

Near real-time active surveillance systems have been established in the US and Australia to facilitate early detection and verification of vaccine safety signals.[11,12] In the US, since 2005, all newly licensed vaccines have been monitored in near real-time using the VSD, a distributed network of clinical information databases from 10 healthcare organisations. In this approach, a set of pre-selected AEFI is monitored by analysing data weekly using the rapid cycle analysis method.[13] However, any medical condition that is a potential vaccine safety concern, but is not included in the pre-selected conditions, may go undetected. An alternative approach used in Australia is the participant-centred near real-time active

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Submitted: April 2020; Revision requested: May 2020; Accepted: September 2020

The authors have stated they have no conflict of interest.



*Aust NZ J Public Health.* 2021; Online; doi: 10.1111/1753-6405.13052

AEFI surveillance system 'AusVaxSafety', which has operated since 2014. Information is actively solicited from vaccine recipients (or their caregivers) via an SMS or email in the days following vaccination. Essentially, selected immunisation clinics across Australia (at the time of writing, >300 sentinel sites, predominantly GPs) send an automated SMS or email to individuals who have been vaccinated at their clinic asking whether they experienced any adverse event within three days of vaccination (a 'Yes' or 'No' question). If an individual's answer is 'Yes', the vaccine recipient or their caregiver receives a link to a web-based survey asking for more information regarding the adverse events.[11,14] Until 2020, the scope of AusVaxSafety had been limited to specific vaccines (i.e. influenza vaccine, pertussis vaccine and zoster vaccine), and it had relied on an active response from each person.

Some studies have shown that vaccine safety signals could be tracked using proxy measures, such as post-vaccination medical attendance rates.[15,16] The 2010 vaccine safety episode in Australia involving increased rates of post-vaccination fever and febrile convulsions in children was found to be due to one widely used brand of seasonal influenza vaccine (CSL products Fluvax™ and Fluvax Junior™).[17] An analysis of the Medicare Benefits Schedule claims data in Australia demonstrated that the number of people who visited a general practitioner (GP) after receiving the seasonal influenza vaccination in 2010 had increased.[15] Emergency department (ED) analyses conducted in Canada[18] and the UK[16] also reported considerably high numbers of ED presentations in the days following vaccination. Further, the AusVaxSafety system uses the self-reported 'medical attendance rate within three days after vaccination' as a surrogate measure of severe AEFI.[11,19] Notably, in communicable disease surveillance, syndromic surveillance using proxy measures has become widely used as an essential tool to provide an early warning of increased disease activity, such as influenza-like illnesses and gastroenteritis.[20,21]

## Objective

The objective of this study was to examine whether a large de-identified GP dataset, available in near real-time, could detect in a timely manner an increase in the all-cause GP consultation rate after vaccination using historical Australian historical influenza vaccine safety signals. These were the 2010 febrile seizures and the 2015 allergy-related reactions following influenza vaccination.[17,22]

## Methods

### Study design and data source

A retrospective observational cohort study was conducted using GP consultation data extracted from the Outcome Health's GP dataset, Population Level Analysis and Reporting (POLAR GP) Data Space (Aurora). The Aurora dataset, a subset of POLAR GP, comprises de-identified electronic medical records (including patient information such as demographics, clinical, immunisation history and prescriptions) extracted from Australian general practices who have consented for de-identified data to be used for approved research studies.[23,24] In 2020, more than 1,000 general practices in New South Wales and Victoria contribute data to the Aurora, serving a population of approximately three million people.[24,25] At the time this study was conducted, 300 general practices located within Victoria contributed data to Aurora.

### Study participants

All people (aged 6 months and older) who had received seasonal influenza vaccination and been registered in the Aurora dataset between 2008 and 2017 were included in the analysis. Of note, practices and individuals who opted out of sharing their data for research activities were not included in the analysis. Approval was obtained from the Monash Health Human Research Ethics Committee (HREC/18/MonH/345) and data access approval was obtained from the Outcome Health POLAR research council.

### Outcomes

The primary outcome measure was the post-vaccination GP consultation rate, a proxy measure of AEFI instances. Days 1–7 following vaccination were considered the risk period. Day 0 (the day of vaccination) was excluded from the risk period because of the difficulty of differentiating between individuals' GP consultations to receive a vaccination and consultations for other reasons on the same day. The post-vaccination risk period was constructed using the recorded date of vaccination and the GP consultation date after vaccination. The post-vaccination GP consultation rate was calculated using the number of individuals who had received the influenza vaccine from all participating practices as the denominator and the number of individuals who had received the influenza vaccine and revisited the practice during days 1–7 post-vaccination for any reason as the numerator.

Each calendar year was categorised by epidemiological weeks. The surveillance period was the first 22 weeks from each year's influenza vaccination period, aligned with each year's vaccination commencement date. Specifically, the surveillance period was between 5 March and 5 August for the vaccination years between 2008 and 2014, inclusive, and between 2 April and 2 September for the vaccination years between 2015 and 2017, inclusive.

### Exposure

Influenza vaccines can change from year to year as new strains of influenza virus appear. The seasonal influenza vaccines available with respect to age group for each of the study years under observation has been provided in Supplementary Table 1.

### Data analysis

The validity of the syndrome 'post-vaccination GP consultation rate' was evaluated based on its ability to detect the two historical AEFI signals: febrile convulsions in 2010[17] and allergy-related reactions in 2015.[22] Cumulative rates of all-cause post-vaccination GP consultations per week per 100 vaccine doses, by age group and vaccination year, were calculated. The temporal pattern of the post-vaccination GP consultation rates was examined on a weekly basis using two Cumulative SUM (CUSUM) charts, the Observed minus Expected (O–E) and one-sided log-likelihood ratio (LLR) CUSUM.

The CUSUM chart is a sequential data monitoring method that allows the detection of sustained shifts of cumulative event rates over time.[26,27] The O–E CUSUM chart was used in this study to plot the difference between the observed and expected post-vaccination GP consultation rate at each week across the surveillance period, and to visualise the general pattern of the post-vaccination GP consultation rate. Essentially, the chart is expected to oscillate around the horizontal line at zero if the weekly-observed post-vaccination GP consultation rate is consistent with the expected (baseline) rate. Conversely, the LLR CUSUM chart was used to

determine if the observed post-vaccination GP consultation rates had significantly changed from the expected rates, to identify statistical signals. Essentially, the LLR CUSUM compared two likelihood models: the baseline model, which claimed that the observed post-vaccination GP consultation rate was consistent with the expected rate, and the alternative model, which claimed that the observed rate was different from the expected rate, being either greater than or equal to a predetermined maximum acceptable rate (stated as an alternative odds ratio [$OR_A$]). The expected post-vaccination GP consultation rate for each studied vaccination year was estimated based on the average of the two preceding vaccination years, using data from years 2008–2016. Of note, post-vaccination GP consultation rates from 2010 and 2015 were excluded while calculating the expected rates, as there were confirmed vaccine safety episodes in those years.

In this study, the LLR CUSUM chart was designed to detect a 50% increase ($OR_A$=1.5) or a two-fold increase ($OR_A$=2) of the odds of the baseline post-vaccination GP consultation rate. Suppose that after 't' weeks there was a total of 'k1' patients who had visited the GP post-vaccination and a total of 'k2' patients who had not visited the GP post-vaccination. Then the LLR of this data (which adds over time) is:

$$LLR(t)=k1(t)\log(OR)/(1-po+ORpo))+k2(t)\log(1/(1-po+ORPo))$$

where *Po* is the baseline post-vaccination GP consultation rate, and  is the odds ratio that corresponds to the minimum unacceptable post-vaccination GP consultation rate (threshold) that the chart should detect. The LLR CUSUM chart limit was placed at '+1' to declare a weekly signal that corresponded to the likelihood of the data being approximately twice as likely under the alternative model compared to the baseline model.

All analyses were categorised by age group (6 months – 9 years, 10–18 years, 19–64 years and ≥65 years) and vaccination year. Data analyses were undertaken using Stata 15 (Statacorp, Texas) and Microsoft Excel 2016 (Redmond, CA).

## Result

### *Influenza vaccination*

During the study period, there were 1,576,545 records of seasonal influenza vaccinations in the Aurora dataset that were administered to 295,091 persons. Of these records, 916,335 (58.12%) influenza vaccine doses were given to females and 932,159 (59.13%) doses were given to individuals aged ≥65 years. The median age of vaccinated individuals was 68 years (range: 6 months – 109 years, and interquartile range=24 years). Generally, the number of administered influenza vaccine doses increased over the study period, except for a slight decrease in 2011 and 2012 (Supplementary Table 2).

### *General practice consultations following vaccination*

During the 10-year study period, there were 20,272 (1.29%) GP consultations in the one-week post-vaccination period. Of these consultations, 98.53% occurred on days 1–3 post-vaccination. Post-vaccination GP consultation rates ranged from 1.10% in 2008 to 1.64% in 2017 and were comparable between females and males. However, the post-vaccination GP consultation rates were significantly higher in individuals aged 19–64 and ≥65 years ($p< 0.001$); see Supplementary Figure 1. Additionally, the post-vaccination GP consultation rate was increased significantly over the 10-year study period (*p*-value for trend <0.001).

### *Weekly cumulative post-vaccination general practice consultation rate*

*A: 2010 influenza vaccine safety episodes*

The end of surveillance period post-vaccination GP consultation rate in children aged 6 months – 9 years for 2010 was 0.84%, higher than the same periods in 2008 and 2009 combined (0.56%), although not statistically significant (IRR=1.50, 95%CI [0.95–2.37]); see Supplementary Table 3. The O–E CUSUM chart (Figure 1a) illustrates that the weekly post-vaccination GP consultation rate for children aged 6 months – 9 years across the surveillance period (weeks 10–32, inclusive) was higher than the baseline rate (i.e. the rates of 2008 and 2009 combined); see Figure 1a. Furthermore, the LLR CUSUM chart detected a 50% increase (ORA = 1.5) of post-vaccination GP representation rate from the baseline rate in all weeks of the surveillance period except weeks 10, 11 and 12, with the observed weekly rates leading to signals ranging from 0.80% to 1.06%. Alternatively, considering an $OR_A$ of 2, the LLR CUSUM also indicated statistical signals for six consecutive weeks (weeks 13–18, inclusive). The weekly post-vaccination GP consultation rates leading to signals were 0.99%, 1.06%, 0.94%, 0.96%, 0.89% and 0.89%, respectively (see Figure 1b). The end of surveillance period rate was also higher for individuals 19–64 years (IRR=1.13, 95%CI [1.02–1.25]); however, the LLR CUSUM chart did not show a statistical signal in either scenario.

*B. 2015 influenza vaccine safety episode*

Generally, the 2015 end of surveillance period post-vaccination GP consultation rates were higher across all age groups – except in the 10–18 years group – compared to the baseline rates that were estimated from the 2013 and 2014 seasons combined. The observed post-vaccination GP consultation rates for the age categories of 6 months – 9 years, 10–18 years, 19–64 years and ≥65 years were 0.61%, 0.61%, 1.53% and 1.39%, respectively, and the baseline rates for the respective age categories were 0.58%, 0.64%, 1.23% and 1.27%. The unadjusted IRR showed that rates were significantly higher for the age categories of 19–64 years (IRR=1.29, 95%CI [1.21–1.38]) and ≥65 years (IRR=1.11, 95%CI [1.05–1.17]); see Supplementary Table 2.

The O–E CUSUM chart also showed that the weekly rates of period post-vaccination GP consultation were higher across all age groups – except in the 10–18 years group (Figure 2a). However, the LLR CUSUM chart demonstrated a 50% increase of post-vaccination GP consultation rates only for individuals aged 19–64 years, with rates ranging from 1.53% to 1.74%, from week 16 to 35 of the surveillance period. Conversely, unlike the 2010 rates, the LLR CUSUM chart did not show a signal across all age categories considering an $OR_A$ of 2 (Figure 2b).

For vaccination years 2011–14, inclusive, and 2016, the weekly cumulative LLR CUSUM chart did not show any statistical signal except in 2012 for the age group of 6 months – 9 years. In 2012, signals were detected from week 18 to 31 considering an $OR_A$ of 1.5. Compared to 2014 and 2016 combined, signals were also detected in 2017 in children aged 6 months – 9 years and 10–18 years considering both $OR_A$ of 1.5 and 2 (Table 1).

## Discussion

Using aggregated GP consultation data and post-vaccination GP consultation rate as a proxy measure for AEFI surveillance, the two historical AEFI signals in Australia following seasonal influenza vaccination were detected.

These were the fever and febrile seizure signal in 2010 and allergy-related AEFIs signal in 2015. Hence, the post-vaccination medical attendance rate could be a timely and sensitive proxy measure to monitor AEFI signals, particularly in the context of multimodal signal detection systems. As 98.53% of the representations occurred on days 1–3 post-vaccination, such a system would be timely and suitable to detect early-onset AEFI. However, in the absence of historical AEFI signals, statistically significant increases in post-vaccination GP consultation rates were also detected in three of the eight signal-free vaccination years.

Post-vaccination GP consultation rates varied considerably across age groups and surveillance years. Generally, the rate was lower in children <19 years than it was in adults. The AusVaxSafety active SMS-based AEFI surveillance system reported comparable findings for children aged <5, where between 0.7% and 1.1% of children sought medical attendance within three days of receiving the influenza vaccine in 2015, 2017 and 2019.[11,19,28] In contrast to this study's findings, these studies also reported low medical attendance rates (<0.5%) in individuals aged 19 years and older. The observed higher post-vaccination GP consultation rates in this study may be due to a number of potential reasons. Solicited response rates regarding medical attendance may be age dependant, and potentially occurring at a higher rate regarding children. This study also considered a longer post-vaccination risk period (days 1–7 rather than the first three days for AusVaxSafety). Additionally, adults and the elderly are more likely to visit GPs often due to healthcare issues other than AEFI, such as appointments for management of multiple medical problems, and these may also require multiple visits clustered over a short time period.

The weekly LLR CUSUM chart detected the 2010 event one week earlier than it had been detected at the time. Western Australian authorities notified the TGA on 13 April 2010 following an apparent increase in children with fever, vomiting and febrile convulsions visiting EDs soon after receiving the trivalent influenza vaccine.[29] Other studies, using different data sources and data analysis

**Figure 1a: Age-specific O–E CUSUM chart of weekly cumulative all-cause post-vaccination GP consultation rate: The 2010 vaccination season compared to the 2008 and 2009 seasons combined.**

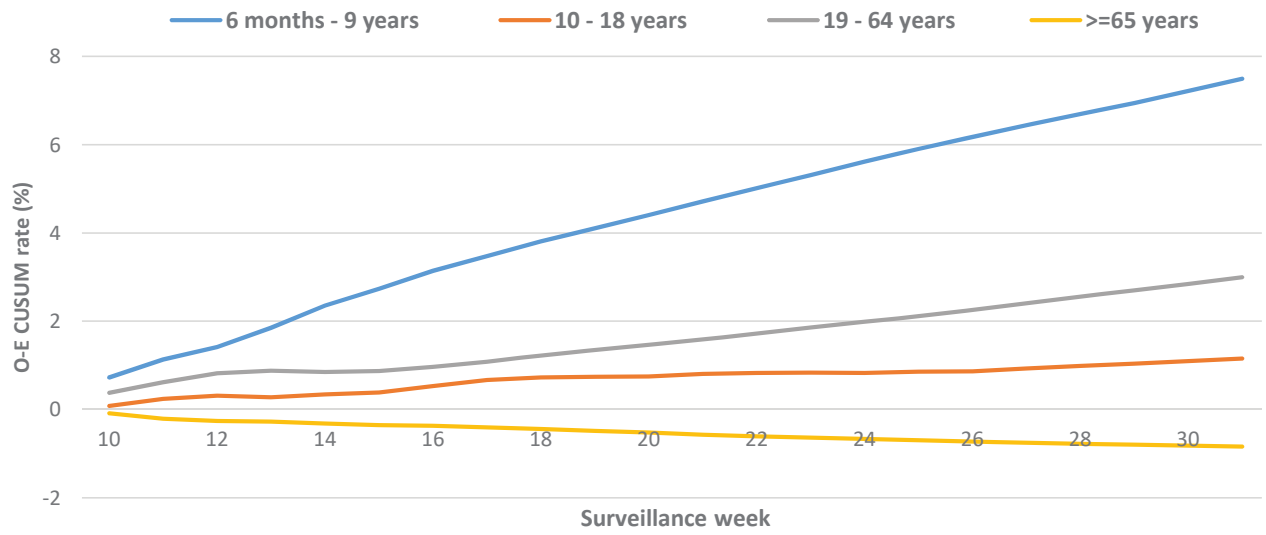
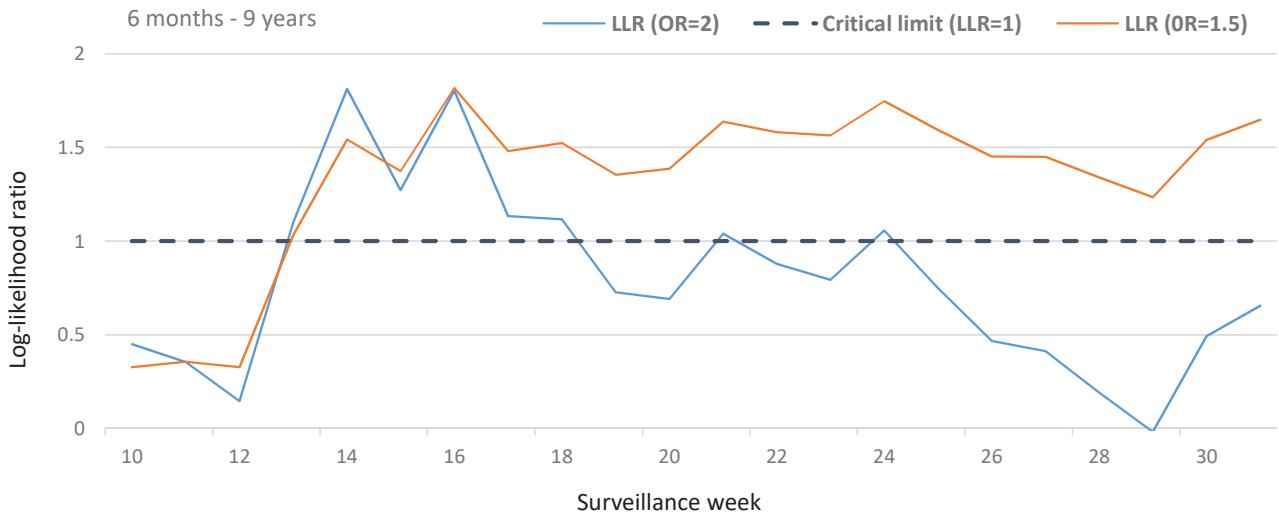



**Figure 1b: Cumulative LLR CUSUM chart of all-cause post-vaccination GP consultation rate for children aged 6 months – 9 years: The 2010 influenza vaccination season.**



approaches, also demonstrated that the event could have been detected earlier. Specifically, a recent study demonstrated that a signal could have been identified on 28 March by re-analysing the SAEFVIC data using a disproportionality analysis algorithm (proportional reporting ratio).[8] In addition, our previous study that used a weekly analysis of AEFI-related telephone helpline calls in Victoria, Australia, detected the event within two weeks of the influenza vaccination season commencing (Figure 3).[30]

Regarding the 2015 signal, SAEFVIC detected increased allergy-related AEFI following the seasonal influenza vaccination – predominantly in adults – two weeks after the program had started. This signal was confirmed using proportional reporting rate analyses at the time and re-confirmed at the end of the season. This signal was reported to the TGA, which conducted similar analyses and did not detect signals in jurisdictions other than Victoria. As the clinical severity of the allergic events was low, with no increase in severe events such as anaphylaxis, no regulatory action was needed, unlike the 2010 event.[22] The weekly LLR CUSUM did not show a two-fold increase in the odds of the baseline post-vaccination GP consultation rate over the 22-week surveillance period in 2015; however, there was at least a 50% increase in the 19–64 years group starting from week 11. The SAEFVIC proportional reporting rate[8] and telephone helpline call data analyses[30] indicated the signal 11 and 7 days before 3 May 2015, respectively.

Syndromic surveillance systems face a tension between detecting signals corresponding to significant events in the context of 'background noise'.[31] In this study, in the absence of historical AEFI clusters having occurred, the weekly LLR CUSUM chart demonstrated additional signals in 2012 (6 months – 9 years) and 2017 (6 months – 9 years and 10–18 years). Similar to other statistical tests, the LLR CUSUM chart can lead to false-positive signals, particularly due to an incorrect choice of a maximum acceptable 'baseline threshold' event rate. To help differentiate real signals from 'noise' in the post-vaccination GP consultation data, considering the following may be of value: duration of signal in weeks (whether signal occurring successively or not); data analysis

**Figure 2a. Age-specific O–E CUSUM chart of weekly cumulative all-cause post-vaccination GP consultation rate: The 2015 vaccination season compared to the 2013 and 2014 seasons combined.**

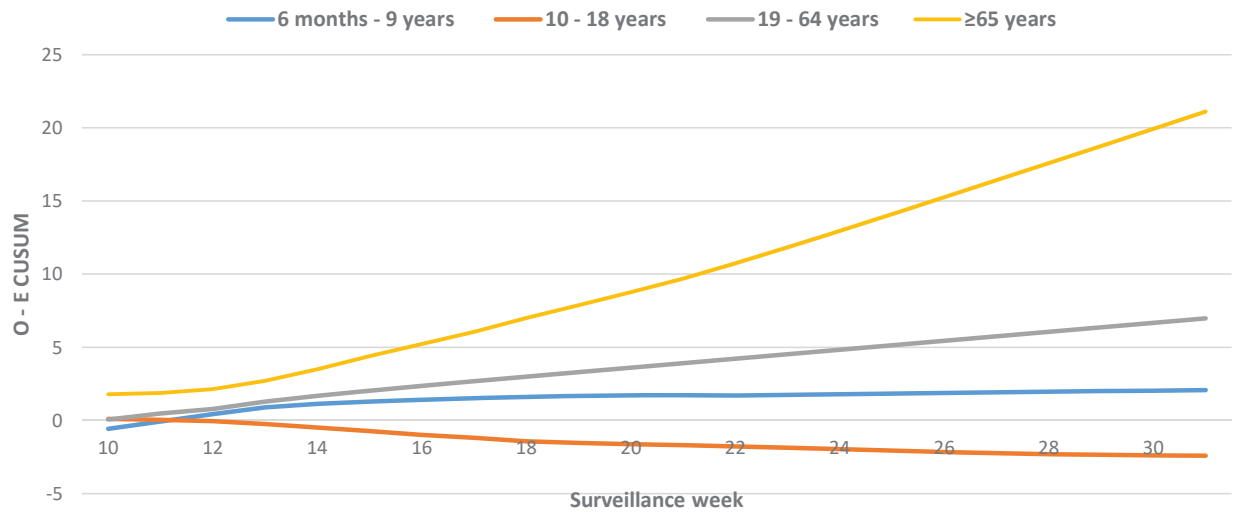
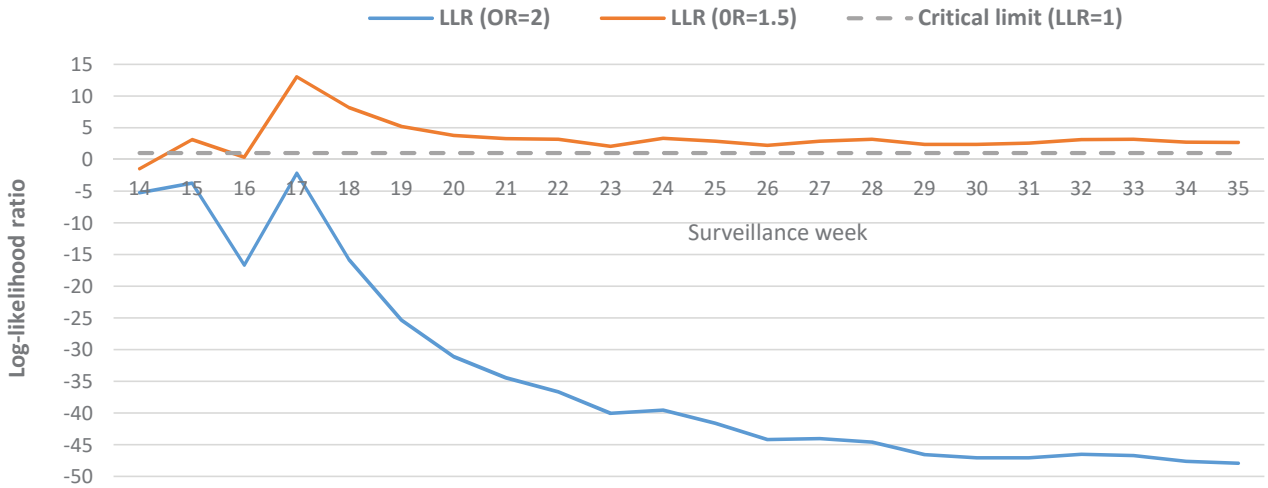



**Figure 2b. Cumulative weekly LLR CUSUM chart of all-cause post-vaccination GP consultation rate for adults aged 19–64 years, 2015 (influenza vaccination commenced in April, week 14).**



by vaccine brand; and whether other existing AEFI surveillance systems have indicated similar safety concerns.

### *Strengths and limitations*

This study is one of the few that has attempted to examine the utility of syndromic AEFI surveillance using post-vaccination healthcare attendance as a proxy measure of AEFIs with the aim of augmenting existing AEFI signal detection systems. However, this study only examined routine GP consultations after the influenza vaccination. In Australia, healthcare advice can also be accessed from funded telephone helpline services, after-hours GP services and hospital EDs, all of which may have a potential to augment AEFI monitoring. Additionally, this study employed an LLR CUSUM signal detection algorithm based on an observed vs. expected analysis. This algorithm works best when the time series of the outcome measures (post-vaccination GP consultation rate) is stationary over time. However, in this study, the post-vaccination GP consultation rate increased over the study period, specifically in adults and the elderly (Supplementary Figure 1). This may be due to the increasing prevalence of complex chronic diseases, which may necessitate repeat attendances, as noted previously. A similar trend has been observed in analyses of post-vaccination GP consultation rate in adolescents following the HPV vaccine in the UK (Andrews N, Public Health England March 2020, personal communication). Last, to evaluate the applicability of these findings, further research in a prospective setting is required using multi-jurisdiction GP consultation data and alternate analysis methods, such as temporal–spatial analysis. Since this study was performed, near real-time available GP datasets have increased more than four times in size and are more nationally representative,[24] offering increased sensitivity and generalisability.

**Table 1: Summary of post-vaccination GP consultation rate signals detected based on the LLR CUSUM chart.**

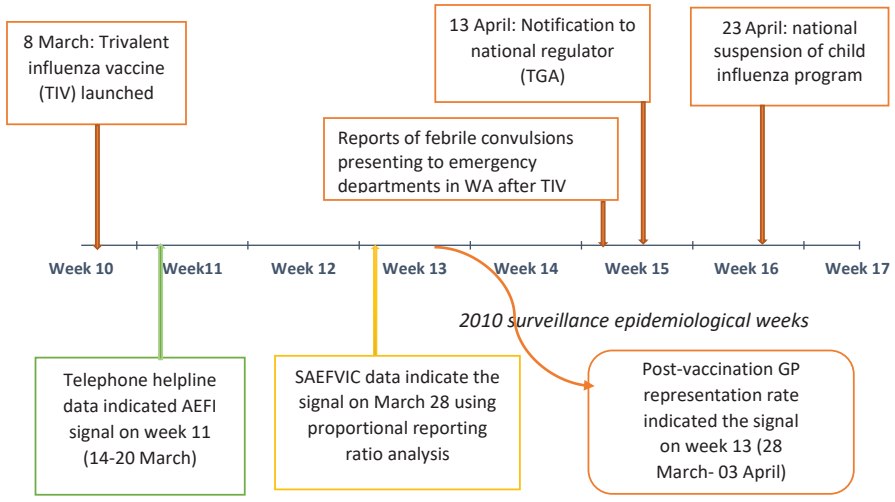
| Examined vs Baseline influenza vaccination year | Age category | Acceptable post-vaccination GP consultation rate | Post-vaccination GP consultation rate signal duration in weeks | Historical AEFI signal (yes/no) |
|---|---|---|---|---|
| 2010 vs 2008 and 2009 combined | 6 months–9 years | ORA of 2 | weeks 13–18 | Yes, on week 15 |
| | | ORA of 1.5 | weeks 14–31 | |
| 2012 vs 2009 and 2011 combined | 6 months–9 years | ORA of 2 | weeks 14–31 | No |
| | | ORA of 1.5 | weeks 18–31 | |
| 2015 vs 2013 and 2014 combined | 19–64 years | ORA of 1.5 | weeks 16–35 | Yes, on week 18 |
| 2016 vs 2013 and 2014 combined | 10–18 years | ORA of 1.5 | weeks 15–19 | No |
| 2017 vs 2014 and 2016 combined | 6 months–9 years | ORA of 2 | Weeks 18–31 | No |
| | | ORA of 1.5 | Weeks 18–31 | |
| | 10–18 years | ORA of 2 | Weeks 22–31 | No |
| | | ORA of 1.5 | Weeks 18–31 | |

*Notes:*

*For the GP data examined annually between 2008 and 2017 (over ten years), this method using either the ORA=1.5 or 2 criteria, was able to identify all the two historical AEFI signals occurred in Australia in 2010 and 2015. This method however also indicated additional signals in three of eight vaccination years without a historical AEFI signal.*

*ORA –alternative odds ratio; ORA=2 refers a two-fold increase in the odds of baseline rate; ORA=1.5 refers a 50% increase in the odds of baseline rate; signal was declared if the LLR≥1 (corresponding*

**Figure 3: Timeline of 2010 AEFI signal detection using different data sources (week 10 began on 7 March and week 17 ended on 1 May), adapted from previous publication.[30]**




## Conclusion

Healthcare attendance rate after vaccination can be a sensitive proxy measure of AEFI signal monitoring, but use should be in the context of multiple and integrated AEFI surveillance systems, as it is less specific. Crucially, the de-identified dataset used for the retrospective analysis is potentially available in near real-time, updating daily.

## Acknowledgements

This research was supported by an Australian Government Research Training Program (RTP) Scholarship. The authors would like to thank Outcome Health for providing data.

***Funding:*** This research did not receive a specific grant from funding agencies in the public, commercial or not-for-profit sectors.

***Ethical approval***: Approval for this project was obtained from the Monash Health Human Research Ethics Committee and data access approval was obtained from the Outcome Health POLAR research council

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## Supporting Information

Additional supporting information may be found in the online version of this article:

**Supplementary Figure 1**: End of surveillance period all cause post-vaccination GP consultation rate on day 1-7 after vaccination by year and age groups.

**Supplementary Table 1**: Seasonal influenza vaccines available for use in Australia from 2010–2017.

**Supplementary Table 2**: Seasonal influenza vaccines doses administered and demographic characteristics of vaccinated individuals, 2008–2017.

**Supplementary Table 3**: End of season incidence rate ratios (IRR) of GP representation by age group on days 1–7 following influenza vaccination, 2008–2017.

Supplementary Table 1: Seasonal influenza vaccines available for use in Australia from 2010 – 2017.

| Year | Vaccine name | Age group | Sponsor |
|---|---|---|---|
| 2010 | | | |
| Trivalent vaccines | Fluvax | | CSL |
| | Fluvax JR | | |
| | Influvac | | Solvay/Abbott |
| | Vaxigrip | | Sanofi-Pasteur |
| | Intanza | | |
| 2011 | | | |
| Trivalent vaccines | Fluvax | 5 years + | CSL |
| | Influvac | 6 months + | Abbott |
| | Vaxigrip | 6 months + | Sanofi Pasteur |
| | Intanza | 18-59 years | Sanofi Pasteur |
| | Fluarix | 6 months + | GSK |
| | Agrippal | 6 months + | Novartis |
| 2012 | | | |
| Trivalent vaccines | Influvac | 6 months + | Abbott Australasia |
| | Fluarix | 6 months + | GlaxoSmithKline |
| | Agrippal | 6 months + | Novartis Vaccines and Diagnostics - |
| | Vaxigrip | 6 months + | Sanofi-Pasteur |
| | Fluvax | 5 years + | bioCSL |
| 2013 | | | |
| Trivalent vaccines | Influvac | 6 months + | Abbott Australasia |
| | Fluarix | 6 months + | GlaxoSmithKline |
| | Agrippal | 6 months + | Novartis Vaccines and Diagnostics - |
| | Vaxigrip | 6 months + | Sanofi-Pasteur |
| | Fluvax | 5 years + | bioCSL |
| 2014 | | | |
| Trivalent vaccines | Influvac | 6 months + | Abbott Australasia |
| | Fluarix | 6 months + | GlaxoSmithKline |

| | | | |
|---|---|---|---|
| | Agrippal | 6 months + | Novartis Vaccines and Diagnostics - |
| | Vaxigrip | 6 months + | Sanofi-Pasteur |
| | Fluvax | 5 years + | bioCSL |
| 2015 | | | |
| Trivalent vaccines | Influvac | 6 months and over | BGP Products |
| | Fluarix | 6 months and over | GlaxoSmithKline |
| | Agrippal | 6 months and over | Novartis Vaccines and Diagnostics |
| | Vaxigrip Junior | 6 to 35 months | Sanofi-Pasteur |
| | Vaxigrip* | 6 months and over | |
| | Fluvax** | 5 years and over** | bioCSL |
| Quadrivalent vaccines | Fluarix Tetra | 3 years and over | GlaxoSmithKline |
| | FluQuadri Junior | 6-35 months | Sanofi-Pasteur |
| | FluQuadri | 3 years and over | |
| 2016 | | | |
| Quadrivalent vaccines | FluQuadri Junior | 6-35 months (<3 years) | Sanofi-Pasteur |
| | FluQuadri | 3 years and over | |
| | Fluarix Tetra | 3 years and over | GlaxoSmithKline |
| Trivalent vaccines | Influvac | 6 months and over | BGP Products |
| | Fluarix | 6 months and over | GlaxoSmithKline |
| | Fluvax | 5 years and over | Seqirus (formerly bioCSL) |
| 2017 | | | |
| Quadrivalent vaccines | Fluarix Tetra | 3 years and over | GlaxoSmithKline |
| | FluQuadri Junior | 6-35 months (<3 years) | Sanofi-Aventis |
| | FluQuadri | 3 years and over | |
| | Afluria Quad | 18 years and over | Seqirus |

Supplementary Table 2: Seasonal influenza vaccine doses administered and demographic characteristics of vaccinated individuals, 2008 – 2017.

| **Characteristics** | **Vaccinations N (%)** | **GP representations (%)** |
|---|---|---|
| Total | 1 576 545 (100) | 20 272 (1.29) |
| Gender | | |
| Female | 916 335 (58.12) | 11 565 (1.23) |
| Male | 657 093 (41.68) | 8564 (1.3) |
| Other | 3117 (0.20) | 143 (4.9) |
| Age group (years) | | |
| 6 months – 9 years | 41 249 (2.62) | 297 (0.72) |
| 10 - 18 | 51 259 (3.35) | 393 (0.77) |
| 19 - 64 | 551 878 (35.01) | 7268 (1.32) |
| ≥ 65 years | 932 159 (59.13) | 12 314 (1.32) |
| Year | | |
| 2008 | 119 683 (7.59) | 1319 (1.10) |
| 2009 | 132 780 (8.42) | 1596 (1.20) |
| 2010 | 147 469 (9.35) | 1749 (1.20) |
| 2011 | 139 008 (8.82) | 1787 (1.29) |
| 2012 | 139 970 (8.88) | 1604 (1.15) |
| 2013 | 162 366 (10.30) | 1954 (1.20) |
| 2014 | 166 749 (10.58) | 2042 (1.22) |
| 2015 | 184 610 (11.71) | 2578 (1.40) |
| 2016 | 192 179 (12.19) | 2501 (1.35) |
| 2017 | 191 731 (12.16) | 3142 (1.64) |

Supplementary Table 3. End of season incidence rate ratios (IRR) of GP representation by age group on days 1-7 following influenza vaccination, 2008-2017.

| Comparison | Age groups (years) | IRR (95% CI) |
|---|---|---|
| 2010 vs 2008 and 2009 combined | 0 - 9 | 1.50 (0.95 -2.37) |
| | 10-18 | 1.06 (0.69 -1.64) |
| | 19-64 | **1.13 (1.02 – 1.25)** |
| | >= 65 | 0.97 (0.90 - 1.05) |
| 2011 vs 2008 and 2009 combined | 0 - 9 | 0.92 (0.48 - 1.64) |
| | 10-18 | 0. 84 (0.52 - 1.34) |
| | 19-64 | 1.04 (0.94 - 1.15) |
| | ≥65 | 1.08 (1.00 - 1.16) |
| 2012 vs 2010 and 2011 combined | 0 - 9 | 1.05 (0.55 - 1.86) |
| | 10-18 | 0.91 (0.56 - 1.42) |
| | 19-64 | 0.83 (0.75 – 0.922) |
| | ≥65 | 1.00 (0.93 – 1.06) |
| 2013 vs 2011 and 2012 combined | 0 - 9 | 0.87 (0.56 - 1.31) |
| | 10 - 18 | 1.05 (0.73 - 1.48) |
| | 19 - 64 | 1.04 (0.96 – 1.14) |
| | ≥65 | 1.01 (0.94 - 1.08) |
| 2014 vs 2012 and 2013 combined | 0 - 9 | 0.66 (0.39 – 1.07) |
| | 10 - 18 | 0.71 (0.46 – 1.05) |
| | 19 - 64 | 1.06 (0.98 – 1.15) |
| | ≥65 | 1.03 (0.97 – 1.09) |
| 2015 vs 2013 and 2014 combined | 0 - 9 | 0.87 (0.57 - 1.29) |
| | 10 - 18 | 0.88 (0.61 - 1.25) |

| | | |
|---|---|---|
| | 19 - 64 | **1.29 (1.21 - 1.38)** |
| | ≥65 | **1.11 (1.05 - 1.17)** |
| 2016 vs 2013 and 2014 combined | 0 - 9 | 1.02 (0.63 - 1.64) |
| | 10 - 18 | **1.56 (1.08 – 2.25)** |
| | 19 - 64 | 0.88 (0.81 - 0.96) |
| | ≥65 | 1.00 (0.94 – 1.07) |
| 2017 vs 2014 and 2016 combined | 0 - 9 | **1.75 (1.21-2.53)** |
| | 10 - 18 | **1.49 (1.09-2.03)** |
| | 19 - 64 | **1.24 (1.15-1.33)** |
| | ≥65 | **1.19 (1.12-1.26)** |

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# CHAPTER 6: USE OF EMERGENCY DEPARTMENT DATA FOR SYNDROMIC SURVEILLANCE OF ADVERSE EVENT FOLLOWING IMMUNISATION

## Introduction

Healthcare data routinely collected at the EDs are often used for vaccine safety reseach, mainly to conduct epidemiological studies for the assessment of safety signals, by linking vaccination information with pre-specified medical outcomes (health conditions of interst) at the ED setting. Often, medical outcomes are identified from the ED electronic records using International Classification of Disease (ICD) codes. While not specific and all-inclusive, there are few ICD-10 codes that are assigned for AEFI-related diagnoses, such as allergy-related AEFI. Therefore, this chapter presents a study that examined the valididty of selected ICD-10 codes to predict anaphylaxis due to vaccination using ED data.

**Citation:** Mesfin YM, Cheng AC, Tran AH, Buttery J. Positive predictive value of ICD-10 codes to detect anaphylaxis due to vaccination: A validation study. Pharmacoepidemiology and Drug Safety. 2019 Oct;28(10):1353-60.

Received: 22 May 2019 | Revised: 15 July 2019 | Accepted: 15 July 2019

DOI: 10.1002/pds.4877



ORIGINAL REPORT

WILEY

# Positive predictive value of ICD-10 codes to detect anaphylaxis due to vaccination: A validation study

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## Abstract

**Purpose:** To validate the use of selected International Classification of Disease Codes 10th revision (ICD-10) to predict (positive predictive value) anaphylaxis due to vaccination using emergency department (ED) data.

**Methods:** We conducted a retrospective study using ED encounter data from a large tertiary-care teaching hospital, Monash Medical Centre, Melbourne, Australia. We searched all ED encounters potentially due to anaphylaxis after vaccination, between 1 January 2010 and 31 December 2018, using ICD-10-CM codes T80.5, T80.6, T88.1, T88.6, and T78.2. Health records of potential cases were examined to determine if they met the Brighton Collaboration (BC) criteria for anaphylaxis. We calculated the PPV to evaluate the accuracy of the selected ICD-10-CM codes in predicting anaphylaxis due to vaccination.

**Results:** Of the 69 health records identified and reviewed, 29 (42.2%) met the criteria for anaphylaxis regardless of the cause, and 24.6% (17/69) of records were confirmed as anaphylaxis triggered by vaccination (low positive predictive value). However, of the 23 records identified using ICD-10-CM code T80.5, 22 were classified as anaphylaxis cases regardless of the cause, and 12 were anaphylaxis due to vaccination cases giving PPV of 95.7% and 52.2%, respectively.

**Conclusions:** Given that there is no specific ICD-10-CM code for anaphylaxis due to vaccination, ICD-10-CM code T80.5 may be suitable to monitor anaphylaxis due to vaccination in the ED setting. The current study was conducted at a single centre and needs to be confirmed by future multicentre studies.

KEYWORDS

anaphylaxis, International Classification of Disease Codes, pharmacoepidemiology, vaccination, validation

## 1 | INTRODUCTION

Common vaccine adverse events are typically detected during prelicensure clinical trials prior to approval for general public use.[1] However, rare adverse events may either go undetected during clinical trials because of insufficient sample size or because the adverse events only occur in subpopulations that were not included in the trials. Adverse events following immunisation (AEFI) may cause health burdens on the vaccinated individuals and also negatively influence public confidence in vaccination, leading to vaccine hesitancy.[2] Thus, safety monitoring for vaccines continues after licensure to identify rare and unexpected AEFIs and changes in frequency of known ones.

In most countries, including Australia, passive surveillance of AEFI is considered the principal approach for monitoring the safety of vaccines after licensure, whereby health care providers, patients/caregivers, and

  

any concerned body voluntarily report AEFI.[3,4] Passive AEFI surveillance, however, has well-known limitations including under-reporting and data incompleteness.[3] Conversely, active surveillance of AEFI using routinely collected health care data has offered an opportunity to track vaccines safety in near real time.[5] Active AEFI surveillance studies often use linked data; exposure information (vaccination) from vaccination registry are linked with prespecified outcomes of interest identified from electronic records using computerised International Classification of Diseases (ICD) diagnosis codes.[6] Moreover, studies also suggest that vaccine safety signals can be tracked using proxy measures of AEFI occurrences, such as postvaccination health care utilisation/medical attendance rate.[7,8]

The ICD-10-CM (10th revision, clinical modification) contains diagnostic codes assigned for AEFI-related diagnoses, such as T80.5 (anaphylaxis due to serum/vaccine). However, anaphylaxis due to other serum products is also coded under T80.5. Other AEFI-related ICD-10-CM codes include T80.6 (other serum/vaccine reaction, not anaphylaxis), T88.1 (other complication following immunisation not elsewhere classified), and T88.0 (infection following immunisation).[9] Anaphylaxis is a potentially life-threatening severe allergic reaction and very rare event. All vaccines have the potential to trigger anaphylaxis, with risk estimates ranging from 1 to 10 per one million dose distributed, depending on the vaccine studied.[10-12] Vaccine safety studies most often use an ICD code to identify anaphylaxis from electronic health care record databases. However, there is scarcity of studies on the accuracy of AEFI-related ICD-CM codes, particularly on anaphylaxis due to vaccination. One study evaluated the accuracy of ICD-9 codes of anaphylaxis associated with medication and biologics of interest in general and reported positive predictive values (PPVs) ranging from 45.8% to 69%.[13] This study aimed to evaluate the PPV of selected ICD-10-CM codes to identify anaphylaxis following vaccination using an emergency department (ED) dataset for which codes are potentially available in real time.

**Key Points**

- Vaccine safety studies most often use diagnostic codes to identify potential adverse events following immunisation from electronic health records.
- Anaphylaxis is a potentially life-threatening severe allergic reaction and rarely occurs following immunisation.
- ICD-10 code T80.5 achieved a moderate positive predictive value to identify anaphylaxis following immunisation (AFI).
- Although coding is not an accurate indication of diagnoses, T80.5 can be used for tracking AFI in the emergency department setting.

## 2 | METHODS

### 2.1 | Data source and study population

We conducted a retrospective study using ED records at Monash Health, incorporating three ED sites in South-Eastern Melbourne, Australia. Monash Health is the largest health network in Melbourne, Australia, handling more than 206 000 emergency presentations each year. Monash Health includes Monash Children's Hospital, one of the largest children's hospitals in Australia with more than 65 000 annual ED presentations.[14] All ED encounters with preselected ICD-10-CM codes between 1 July 2010 and 30 June 2018 were searched to identify possible hospital visits for anaphylaxis due to vaccination. We primarily considered ICD-10-CM code T80.5 to identify anaphylactic reactions due to serum, which includes vaccines. To capture other possible cases of anaphylaxis due to vaccination, we additionally selected two nonspecific codes: T80.6 (other serum reaction, not anaphylaxis) and T88.1 (other complication following immunisation not elsewhere classified). Moreover, we surveyed a random sample of health records coded with T88.6 (anaphylactic reaction or shock because of adverse effect of correct medicinal substance properly administered) and T78.2 (anaphylactic reaction/allergic reaction unspecified) to check for incorrectly diagnosed or coded anaphylaxis because of serum products including vaccines. We included all health records coded with T80.5, T80.6, or T88.1 for chart review.

### 2.2 | Record validation

Two reviewers independently reviewed the selected medical records and extracted the following information: patient age, gender, ED visiting date, chief presenting complaints, history of vaccination, exposure other than vaccination, vaccination date and time, type of vaccine administered, signs and symptoms, and onset (suddenness) of the symptom and signs. Collated information were then categorised into the three levels of anaphylaxis diagnostic certainty based on the Brighton Collaboration (BC) case definition (Tables 1 and 2).[11] For records where the two reviewers disagreed, medical records were rechecked, and a final determination was made through discussion.

### 2.3 | Statistical analysis

Our study outcome was the PPV of an anaphylaxis due to vaccination diagnosis, defined as the proportion of ED encounters with diagnosis code of T80.5, T80.6, or T88.1 who had levels 1, 2, or 3 anaphylaxis based on BC case definition. We summarised data using descriptive statistics and determined the PPV with 95% confidence intervals (CIs). The PPV was calculated for individual ICD-10-CM codes and combinations of codes. In addition, PPVs were estimated according to age group, gender, calendar period, and principal presenting problem. We calculated the Cohen's kappa score, which measured the level of agreement between reviewers in categorising records into BC case definition levels of diagnostic certainty. Analyses were

**TABLE 1** Brighton Collaboration case definition of anaphylaxis

| |
|---|
| For all levels of diagnostic certainty: |
| Anaphylaxis is a clinical syndrome characterised by<br>• sudden onset AND<br>• rapid progression of signs and symptoms AND<br>• multiple (≥2) organ systems |
| Level 1 of diagnostic certainty<br>• ≥1 major dermatological AND<br>• ≥1 major cardiovascular AND/OR ≥ 1 major respiratory criterion |
| Level 2 of diagnostic certainty<br>• ≥ 1 major cardiovascular AND ≥ 1 major respiratory criterion<br>OR<br>• ≥1 major cardiovascular OR respiratory criterion AND<br>• ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems)<br>• (≥1 major dermatologic) AND (≥1 minor cardiovascular AND/OR minor respiratory criterion |
| Level 3 of diagnostic certainty<br>• ≥1 minor cardiovascular OR respiratory criterion AND<br>• ≥1 minor criterion from each of ≥2 different systems/categories |

**TABLE 2** Major and minor criteria used in the case definition of anaphylaxis: Brighton Collaboration criteria

| Syndrome | Major Criteria | Minor Criteria |
|---|---|---|
| Dermatological or mucosal | • Generalised urticaria (hives) or generalised erythema<br>• Angioedema, [a] localised, or generalised<br>• Generalised pruritus with skin rash | • Generalised pruritus without skin rash<br>• Generalised prickle sensation<br>• Localised injection site urticarial |
| Cardiovascular (major) | • Measured hypotension<br>• Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following:<br>• Tachycardia<br>• Capillary refill time > 3 s<br>• Reduced central pulse volume<br>• Decreased level of consciousness or loss of consciousness | • Red and itchy eyes<br>• Reduced peripheral circulation as indicated by the combination of at least 2 of<br>• Tachycardia and<br>• A capillary refill time > 3 s without hypotension<br>• A decreased level of consciousness |
| Respiratory | • Bilateral wheeze (bronchospasm)<br>• Stridor<br>• Upper airway swelling (lip, tongue, throat, uvula, or larynx)<br>• Respiratory distress—2 or more of the following:<br>• Tachypnoea<br>• Increased use of accessory respiratory muscles (sternocleidomastoid, intercostal etc)<br>• Recession<br>• Cyanosis<br>• Grunting | • Persistent dry cough<br>• Hoarse voice<br>• Difficulty breathing without wheeze or stridor<br>• Sensation of throat closure<br>• Sneezing, rhinorrhea |
| Gastrointestinal | | • Diarrhoea<br>• Abdominal pain<br>• Nausea<br>• Vomiting |

[a]Not hereditary angioedema.

conducted using STATA/IC version 15.1 (StataCorp LLC, College Station, TX, USA).

## 3 | RESULTS

Of the 249 895 ED encounters during the study period, we identified 76 ED visits with the ICD-10 diagnosis codes of T80.5, T80.6, and T88.1. Seven records (9.2%) were excluded because of either missing records or lack of adequate information in the records (particularly progression of signs and symptoms) leading to uncertainty of the patient's diagnosis. In addition, we screened 167 records coded with T78.2 and T88.6 but did not identify any potential anaphylaxis cases due to serum/vaccination/immunisation. The remaining 69 patient records (90.8%) were considered for further analyses (Figure 1); 57.9 % were male, 53.6% were aged 0 to 10 years, and 63.8% of the patients had a documented vaccination history (Table 3). The levels of agreement (Cohen's kappa score) between reviewers to categorise the identified records as anaphylaxis case or not were substantial; 0.64 for T88.1 code, 0.68 for T80.5 code, and 0.78 for T80.6 code.

### 3.1 | Confirmed anaphylaxis diagnosis

On the basis of chart review, we confirmed 29 cases of anaphylaxis; 17 (58.6%) anaphylaxis cases were triggered by vaccination, and 12 cases were associated with other causes. All cases were classified as BC case definition level 1 (37.9%) or 2 (62.1%), with none being categorised as level 3. Other causes triggering anaphylaxis include desensitising immunotherapy (n = 6), cortisone injections/antibiotics (n = 3), and bee sting (n = 2). For one case, it was unclear what triggered anaphylaxis because the patient had received vaccination and cat exposure simultaneously. The onset of symptoms among cases was within 30 minutes (13 cases), between 30 minutes and 2 hours (11 cases), and 2 to 24 hours (5 cases). Eighteen patients (62.1%) presented to the ED with the chief complaint of anaphylactic reaction, six (20.7%) with allergic reaction, and the

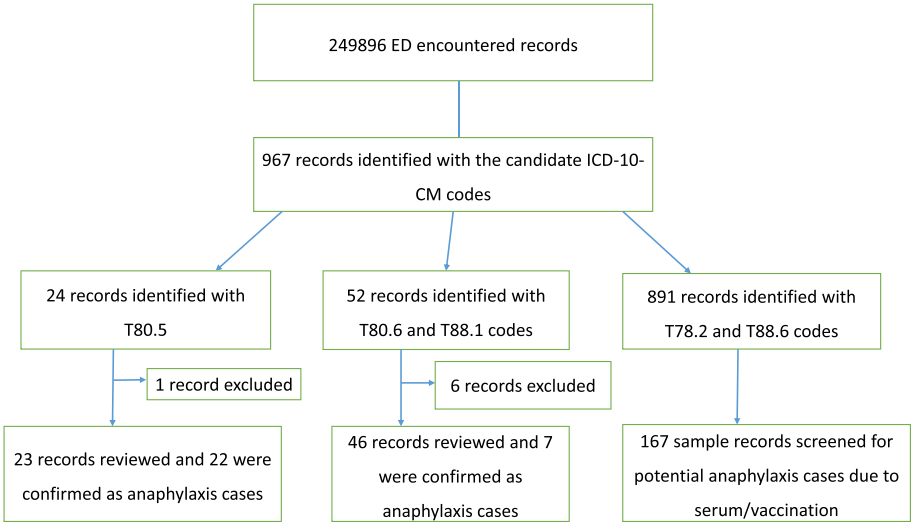


**FIGURE 1** ICD-10-CM coding algorithm to identify emergency department visits for anaphylaxis due to vaccination. Records were excluded because of either missing records or lack of adequate information in the records [Colour figure can be viewed at wileyonlinelibrary.com]

**TABLE 3** Demographic and diagnostic characteristics of the 69 patients identified for review in the ED dataset, 2010 to 2018

| Characteristic | Number of Charts Reviewed | Anaphylaxis Case Level of Certainty | | |
|---|---|---|---|---|
| | | Level 1, n (%) | Level 2, n (%) | Not anaphylaxis case, n (%) |
| Total | 69 | 11 (15.9) | 18 (26.1) | 40 (58.0) |
| Gender | | | | |
| Female | 29 | 7 (24.1) | 6 (20.7) | 16 (55.2) |
| Male | 40 | 4 (10.0) | 12 (30.0) | 24 (60.0) |
| Age group (years) | | | | |
| 0 to 10 | 37 | 4 (10.8) | 3 (8.1) | 30 (81.0) |
| 11 to 19 | 11 | 2 (18.2) | 5 (45.5) | 4 (36.3) |
| 20 to 64 | 19 | 5 (26.3) | 9 (47.4) | 5 (26.3) |
| ≥65 | 2 | 0 | 1 (50) | 1 (50) |
| ICD-10-CM codes | | | | |
| T80.5 | 23 | 7 (30.4) | 15 (65.2) | 1 (4.4) |
| T80.6 | 26 | 3 (11.5) | 2 (7.7) | 21 (80.8) |
| T88.1 | 20 | 1 (5.0) | 1 (5.0) | 18 (90.0) |
| Vaccination received | | | | |
| Yes | 44 | 7 (15.9) | 11 (25.0) | 26 (59.1) |
| No/Not documented | 25 | 4 (16.0) | 7 (28.0) | 14 (56.0) |
| Chief presenting complaints | | | | |
| Anaphylactic reaction | 19 | 6 (31.6) | 12 (63.2) | 1 (5.3) |
| Allergic reaction | 11 | 3 (27.3) | 3 (27.3) | 5 (45.4) |
| Others | 39 | 2 (5.1) | 3 (7.7) | 34 (87.2) |

remaining five patients presented due to rash/urticaria, collapse, or distress post-immunisation. Characteristics of the confirmed anaphylaxis cases are summarised in Table 3.

The overall PPV considering codes T80.5, T80.6, and T88.1 was 42% (29/69, 95% CI, 30.2-54.5). However, the overall PPV could be 38.2% (29/76) when considering the number of records that were

found with the code-based algorithm search as the denominator, while assuming the excluded seven records as non-anaphylaxis cases. The PPVs were highest for code T80.5 (22/23, 95.6%) and for patients presenting to the ED with a chief complaint of anaphylactic reaction (18/19, 94.7%). Based on age group, PPVs were higher in older children and non-elderly adults with 63.6% (7/11) in the 11 to 19 and 73.7% (14/19) in the 20 to 64 age category (Table 4).

There were eight misclassified cases out of the 69 patients identified using the code-based algorithm: one false positive case and seven false negative cases. Out of the 23 anaphylactic cases identified using code T80.5, one case was classified as not true anaphylaxis case by human review (no major dermatological or respiratory signs and symptoms, only two major cardiovascular signs [hypotension and loss of consciousness]) of the patient medical record. Five true anaphylaxis cases, based on the BC case definition, were identified out of the 26 records using code T80.6. The original diagnoses for those five patients were urticaria (two cases), reaction to vaccine (two cases), and febrile illness for one case. Out of the 20 records identified using code T88.1, two anaphylaxis cases were incorrectly diagnosed as seizure postvaccination.

### 3.2 | Anaphylaxis cases triggered by vaccination/immunisation

Of the confirmed anaphylaxis cases, 58.6% (17/29) occurred after the patients received vaccinations. The type of vaccines administered were seasonal influenza vaccine, human papillomavirus (HPV) vaccine, diphtheria-tetanus-pertussis (DTaP) vaccine, meningococcal vaccine, pneumococcal polysaccharide vaccine (PPV23), and other vaccines routinely administered at 2, 4, 6, 12, and 18 months and 4 years in the Australian National Immunisation programme.[15] Details of vaccines administered, other exposures triggered anaphylactic reaction, chief presenting complaints, and primary diagnosis are presented in Supporting Information.

The PPVs to identify anaphylaxis following vaccination were 24.6% (95% CI, 15.1-36.5) and 52.2% (95% CI, 30.6-73.2) considering all the three codes and T80.5 alone, respectively. Based upon subgroup analysis, PPV was relatively high for the 11 to 19 age group (54.5%; 95% CI, 23.4-83.3) and for patients who presented to the ED with convulsion or distress or altered consciousness (80.0%; 95% CI, 28.4-99.5). More than two-thirds (70.6%) of ED visits because of anaphylaxis following vaccinations presented with chief presenting

**TABLE 4** Positive predictive value for each ICD-10 code, study period, and subgroup of patients

| Characteristics | Number of Charts Reviewed (n) | Anaphylaxis Confirmed Regardless of Cause (n) | PPV (95% CI) | Anaphylaxis after Vaccination (n) | PPV (95% CI) |
|---|---|---|---|---|---|
| ICD 10 codes | | | | | |
| T80.5 | 23 | 22 | 95.6 (78.1-99.9) | 12 | 52.2 (30.6-73.2) |
| T80.6 | 26 | 5 | 19.2 (6.6-39.4) | 3 | 11.5 (2.4-30.2) |
| T88.1 | 20 | 2 | 10 (1.2-31.7) | 2 | 10.0 (1.2-31.6) |
| All codes | 69 | 29 | 42 (34.2-54.5) | 17 | 24.6 (15.1-36.5) |
| Gender | | | | | |
| Male | 40 | 16 | 40.0 (24.9-56.7) | 8 | 20.0 (9.1-35.6) |
| Female | 29 | 13 | 44.8 (26.4-64.3) | 9 | 31.0 (15.3-50.8) |
| Age groups (y) | | | | | |
| 0-10 | 37 | 7 | 18.9 (7.9-35.2) | 5 | 13.5 (4.5-28.8) |
| 11-19 | 11 | 7 | 63.6 (30.8-89.1) | 6 | 54.5 (23.4-83.3) |
| 20-64 | 19 | 14 | 73.7 (48.8-90.9) | 6 | 31.6 (12.6-56.6) |
| 65 and older | 2 | 1 | 50.0 (12.6-56.7) | 0 | - |
| Chief presenting complaints | | | | | |
| Anaphylactic reaction | 19 | 18 | 94.7 (73.9-99.9) | 8 | 42.1 (20.3-66.5) |
| Allergic reaction | 11 | 6 | 54.5 (23.4-83.3) | 4 | 34.4 (10.9-69.2) |
| Convulsion/distress | 5 | 4 | 80.0 (28.4-99.5) | 4 | 80.0 (28.4-99.5) |
| Others | 34 | 1 | 2.9 (0.7-15.3) | 1 | 2.9 (0.7-15.3) |
| Study period | | | | | |
| 2010-2014 | 28 | 9 | 32.1 (15.9-52.4) | 7 | 25.0 (10.7-44.9) |
| 2015-2018 | 41 | 20 | 48.8 (32.9-64.9) | 10 | 24.4 (12.4-40.3) |

*Note*. T80.5—anaphylactic reaction due to serum/vaccine; T88.1—other complication following immunisation not elsewhere classified; T80.6—other serum reaction, not anaphylaxis.

Abbreviations: CI, confidence interval; PPV, positive predictive value.

problems of either anaphylactic reaction/shock or allergic reaction. There was a substantial increment in the number of confirmed anaphylaxis following vaccination in 2017 ($P$ value < .0001) (Figure 2). The PPV of individual ICD-10-CM codes and based on subgroup analysis is presented in Table 4.

## 4 | DISCUSSION

Our medical chart review found that ICD-10-CM code T80.5 was most predictive for anaphylaxis due to vaccination or other serum products (95.7%; 95% CI, 78.1-99.9) and was higher than estimates reported in prior studies.[13,16] However, T80.5 resulted in a modest PPV to detect anaphylaxis only due to vaccination/immunisation (52.2%; 95% CI, 30.6-73.2). An additional seven cases of anaphylaxis were identified by reviewing 46 medical records identified using nonspecific codes (T80.6 and T88.1), but the PPVs considering all the three codes were below average: 43.9% for anaphylaxis due to vaccination or other serum products and 25.8% for anaphylaxis only due to vaccination. The absence of a diagnostic code specific to anaphylaxis due to vaccination may have affected the result of this study. Moreover, under-diagnosis of anaphylaxis due to vaccination and incomplete recording of patient's vaccination history may also affect the PPV of the algorithm because of misclassification of codes.

We did not identify any previous studies that evaluated the accuracy of ICD codes to identify anaphylaxis due to vaccination. However, some have reported on the accuracy of anaphylaxis specific or nonspecific ICD codes in predicting episodes of true anaphylaxis. A study evaluated the accuracy of ICD-9 codes to identify anaphylaxis associated with medication and biologics of interest reported a PPV of 69.0% (95% CI, 58-78.7)[13]. This study validated ICD-9 codes of 99.5 (other anaphylactic shocks) and 999.4 (anaphylactic shock due to serum) using ED and inpatient medical records. A higher PPV (88.4%) of predicting anaphylaxis case was reported by another study using anaphylaxis specific ICD-10 codes in the ED setting: T78.1 (anaphylactic reaction due to food), T78.1 (anaphylactic reaction due to peanut), and T78.2 (anaphylactic reaction due to shellfish).[16] Both of the aforementioned studies used different gold standards to confirm anaphylaxis case: the clinical criteria for diagnosing anaphylaxis developed during the second symposium on the definition and management of anaphylaxis [17] and the World Allergy Organisation (WAO) anaphylaxis clinical diagnosis criteria, respectively.

We did not evaluate the sensitivity and specificity of the algorithm, but we evaluated patients with codes suggestive of anaphylaxis. The difference in PPVs by principal presenting problems may be an important key to improve the accuracy of the algorithm through combination of chief presenting complaints and the ICD-10-CM codes. Over two-thirds (70.6%) of confirmed anaphylaxis after vaccination patients presented to the ED with chief complaints of anaphylactic reaction, allergic reaction, or distress/altered consciousness. Given that anaphylaxis after vaccination is under-diagnosed/missed-diagnosed and a very rare event, adding non-anaphylactic codes such as T80.6 and T88.1 may have utility in vaccine safety syndromic surveillance. In this study, patients verified as postvaccination anaphylaxis but originally coded as non-anaphylaxis cases were coded under T88.1 (10.5 %) and T80.6 (11.5%). Our findings demonstrate that considering anaphylaxis-specific secondary diagnosis code or associated diagnosis codes other than anaphylaxis can improve the identification of true anaphylaxis cases.[18] Typically, electronic health record surveillance involves a trade-off between sensitivity and PPV, with no set "acceptable PPV" threshold defined, and likely to vary depending upon the condition surveyed.[19] Given the rarity and severity of anaphylaxis postvaccination, a lower PPV may be acceptable.

We observed an increase in anaphylaxis following vaccination presentations to the ED from 2010 to 2017. Nearly half (47%) of all the anaphylaxis presentations were seen in 2017 and 2018. While we used data from a single health network, a state-wide report from the Safer Care Victoria anaphylaxis clinical care standard in 2019 also showed that anaphylaxis presentations to Victorian public hospital EDs, from 2012/13 to 2016/17, grew by 30%.[20]

### 4.1 | Limitations

The generalisability of our findings to broader syndromic surveillance of anaphylaxis following vaccination over time is limited by its small sample size, with the included population from a single hospital

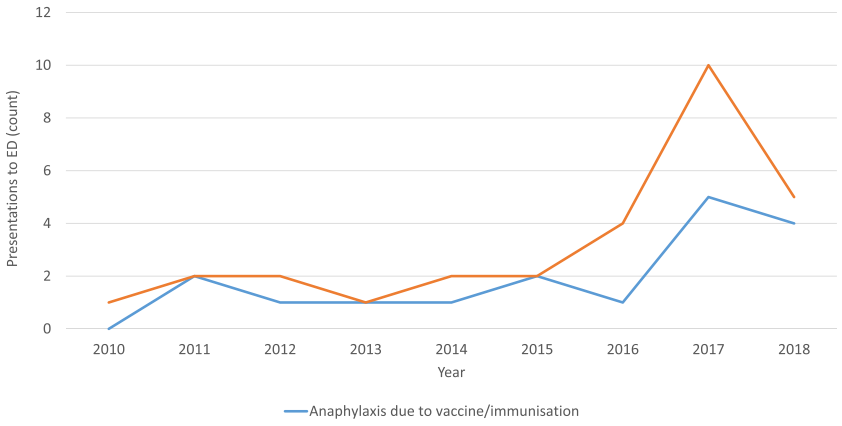


**FIGURE 2** Annual number of anaphylaxis presentations to the Monash Health emergency department between 2010 and 2018 [Colour figure can be viewed at wileyonlinelibrary.com]

network, albeit the largest in Victoria incorporating three separate EDs. We only considered medical records from the ED setting, and medical records were identified solely using primary diagnosis code. Discharge ICD codes were not considered in this study as they are not available in real time in our health system and cannot yet inform potential near-real-time surveillance. The use of a variety of ICD codes have been assessed for their accuracy in vaccine safety research across institutions and health-care level (inpatient, ED, outpatient). Significant variation in accuracy was found between different codes and also between health-care levels.[21] While inpatient coding related health-care funding may introduce bias in inpatient coding, ED coding is not affected by potential funding bias in our setting. This study assessed PPVs and could not evaluate sensitivity and specificity. Medical record reviewers were not blinded to the study objective. Seven of the 76 ED presentations (9.2%) examined had missing records or insufficient clinical information to assign a diagnosis or BC level, limiting full assessment of coding accuracy.

## 5 | CONCLUSION

The overall PPV of the algorithm to identify anaphylaxis due to vaccination/immunisation in the ED dataset was low. However, the PPV was improved using ICD-10-CM code of T80.5 alone. Given that there is no specific ICD-10-CM diagnosis code for anaphylaxis due to vaccination, ICD-10-CM code T80.5 may be suitable to monitor anaphylaxis due to vaccination in the ED setting. Validation of the utility of monitoring T80.5 in vaccine safety signal detection should to be confirmed in future multicentre studies.

### 5.1 | Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available as they contain sensitive information, but aggregated data are available from the corresponding author on reasonable request.

### FUNDING INFORMATION

This research did not receive specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

### ETHICS STATEMENT

This study was part of the project "Near real-time automated vaccine safety signal detection using routinely collected health care data: Potential for continuous active surveillance" approved by the Monash Health Human Research Ethics Committee (HREC) (HREC/18/MonH/345) on 05 May 2018.

### AUTHORS CONTRIBUTION

Y.M.M. made substantial contribution to the conception/design of the manuscript, data analyses, and drafting the paper with guidance from J.B. and A.C.C. A.H.L.T. made substantial contribution to the medical records review and data analyses. All authors critically revised the paper and approved the final manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Mesfin YM, Cheng AC, Tran AHL, Buttery J. Positive predictive value of ICD-10 codes to detect anaphylaxis due to vaccination: A validation study. *Pharmacoepidemiol Drug Saf*. 2019;28:1353–1360. https://doi.org/10.1002/pds.4877

# CHAPTER 7: CONCLUSIONS AND FUTURE DIRECTIONS

This thesis evaluated the potential use of the near real-time analysis of syndromic healthcare data (aggregated and de-identified) to augment the early detection of vaccine safety signals. Chapter 7 summarises the main findings, discusses the main strengths and limitations of the thesis and highlights the implications for further research and practise.

## 7.1 Summary of the main findings

Published research findings demonstrated that electronically available healthcare data offered an alternative data source to enhance the capacity of post-licensure vaccine safety monitoring, particularly to conduct epidemiological studies to evaluate vaccine safety signals. A systematic review was performed to summarise the literature regarding the use of routinely collected healthcare data for vaccine safety signal detection. The review demonstrated that ongoing active AEFI surveillance based on linked electronic health records, by linking immunisation records with computerised health outcomes from different healthcare settings, has proven useful for early detection of vaccine safety signals. However, the studied possible AEFI were pre-selected and identified primarily using diagnostic codes. This approach is not routinely performed outside the US.

Establishing large, individual-level linked database can be impractical in some settings, particularly in low-income and middle-income countries, because it requires significant resources and expertise. Conversely, for some countries like Australia, establishing the system is attainable but might not be feasible for routine use and timely identification of vaccine safety signals due to privacy laws and delayed data access.[100] However, in recent years, de-identified and aggregated health data collected across different levels of healthcare provision have been made increasingly available for research purposes. Fortunately, some of these datasets comprise both vaccination and health outcome information, while others contain only health

outcomes (medical diagnoses) or health outcomes in relation to vaccination. Therefore, during my doctoral candidature, I assessed the potential use of near real-time analyses of de-identified and aggregated routine healthcare data collected during telephone helpline consultations, GP consultations and ED attendances to complement existing AEFI signal monitoring systems. All datasets used were potentially capable of near- real-time availability.

First, telephone helpline data were evaluated for syndromic AEFI signal monitoring. Considering that these days many healthcare services are actively delivered via telephone, data generated from telephone helpline consultations are considered useful for disease surveillance.[101] To the researchers' knowledge, this is the first study to evaluate the use of telephone helpline data for AEFI surveillance. This study demonstrated that on average, 0.68% of all telephone helpline calls were AEFI-related, which—although a small fraction of total calls—represents a significant number. Additionally, 7.5% of AEFI-related calls were categorised as serious enough to seek immediate ED attendance. The weekly time-series analysis demonstrated that AEFI-related calls were considerably higher in 2010 and 2015 than in other years in the study period. Further, the temporal signal detection algorithm indicated that the two historical AEFI signals occurred in 2010 and 2015 could have been detected two to four weeks earlier by using telephone helpline data. Overall, the findings suggest that telephone helpline data are a timely and representative data source that can potentially detect AEFI signals promptly if integrated with existing AEFI surveillance systems.

Second, considering that more than 85% of the Australian population visits a GP at least once a year, and vaccination is mainly provided through GPs in Australia, the study in Chapter 5 was conducted to examine the utility of a large GP consultation dataset for syndromic surveillance of AEFI. Notably, the GP datasets comprise information regarding both exposure (vaccines administered) and health outcomes (medical diagnoses). A syndrome called 'post-vaccination GP consultation rate' was created using the date of vaccination (day 0) and the date

of GP encounters following vaccination. This syndrome is a proxy measure of AEFI occurrence as it assumes that the reason for a variable proportion of GP visits in one week (days 1–7) after vaccination is AEFI, with non–AEFI related visits within one week of vaccination remaining relatively constant over time. This study demonstrated that over a 10-year period, the rate of GP consultations within one week of patients receiving the influenza vaccination was 1.29% on average. The rate varied across age groups and was significantly higher in adults and the elderly. The majority (98.53%) of GP consultations occurred in the first three days post-vaccination. The weekly time-series analyses using CUSUM chart demonstrated that the rates of post-vaccination GP consultation were significantly higher in children aged under 10 years in March and April of 2010 compared to the expected rate, estimated from 2008 and 2009 combined. These increases occurred two weeks earlier than the spikes of febrile seizure following the 2010 influenza vaccination. Overall, this study highlighted that near real-time monitoring of proxy measures of AEFI, such as the rate of healthcare attendance after vaccination, can potentially flag unusual occurences of AEFI timely. For primary analysis, days 1-7 was considered as risk period despite 98.53% of GP consultations occurred in the first three days post-vaccination. Hence, further work following my doctoral work with other vaccines in the same dataset will explore optimal post-vaccination representation windows for each vaccine and age groups. In adition, as the dataset included the brand of vaccine administered, further analyses can explore whether one particular brand has a higher risk, in the context in which more than one brand is used for the same indication. Moverover, since the time when this study was performed, the POLAR–GP dataset has increased in size and are more nationally representative, offering increased sensitivity and generalisability.

Last, I explored whether ED data were suitable for syndromic AEFI surveillance. Vaccine safety studies based on ED data have often been performed by linking vaccination information from vaccine registries with medical diagnoses identified using diagnostic codes. In the ICD-

10 code list, there is no specific section (code block) allocated for medical diagnoses associated with vaccines adverse event. Further, some AEFI-related medical diagnoses were coded together with other medical diagnoses despite specific codes are allocted. For example, in practice, anaphylaxis due to vaccination and anaphylaxis due to other serum products were coded under T80.5 (anaphylactic reaction due to serum) though the allocated specific codes are T80.52 and T80.59 respectively. Therefore, the utility of discharge diagnoses–based ED data for AEFI surveillance is likely to be limited to only a few vaccine specific adverse events or to non specific ICD-10 codes. Hence, a validation study was conducted to evaluate the accuracy of selected ICD-10 codes to predict anaphylaxis due to vaccination. The study demonstrated that ICD-10 code T80.5 (anaphylaxis due to serum or vaccine) has a moderate positive predictive value (52.2%) to identify analphylaxis due to vaccination. Considering that anaphylaxis is a reportable disease in Australia, ICD-10 T80.5 may be suitable to track anaphylaxis following vaccination in the ED settings. This may be especially useful during rapid implementations and catch-up programs, including possible COVID-19 vaccines. Besides, ED data could have utility to monitor other potential AEFI, such as febrile seizures, or acute flaccid paralysis, but needs futher research.

Altogether, the findings presented in this thesis have highlighted that near real-time monitoring of AEFI syndromes (categorised symptoms and diagnoses or proxy indicators) using health data routinely generated from telephone helpline consultations, and GP encounters have utility to advance the early detection of vaccine safety issues. However, AEFI signals detected from syndromic surveillance must be interpreted in conjunction with existing national or jurisdiction-based AEFI signal monitoring systems.

### 7.2 Strengths

The main strength of the thesis was that it analysed health data generated from three different levels of healthcare provision, with each independent data source providing a different level of AEFI severity. To the researchers' knowledge, no national AEFI surveillance system in developed and developing countries incorporates telephone helpline data. Table 7.1 summarises the strengths of both the telephone helpline dataset and the GP consultation dataset based on the attributes of the public health surveillance system: data quality, timeliness, sensitivity and representativeness.

Table 7.1. Evaluation of telephone data and GP data based on the attributes of the public health surveillance system

| **Attribute** | **Telephone helpline data (NOC dataset)** | **GP consultation data (POLAR–GP dataset)** |
|---|---|---|
| Data quality | The data fields required to perform syndromic AEFI surveillance are consistently recorded in the dataset and include:<br>• the date and time of the call<br>• the patient's age, gender and postcode<br>• the chief complaint recorded in a free-text field<br>• the title of the patient guideline used<br>• the call outcome. | Both vaccination and medical diagnosis information are well-recoded in the dataset and include:<br>• the date of vaccination and the type of vaccine administered<br>• the patient's age, gender and postcode<br>• the date of the GP encounter following vaccination<br>• the medical diagnosis recorded in a free-text field or coded with SNOMED code. |
| Timeliness | Data are routinely recorded and updated daily. | Data are routinely recorded, extracted, and updated daily. |
| Sensitivity | Results demonstrated that telephone helpline data have the ability to indicate the unusual | The dataset has the ability to indicate an unusual increase in GP visits related to AEFI. |

| | | |
|---|---|---|
| | occurrence of vaccine safety concerns. | |
| Representativeness | The telephone helpline service is accessible to all those living in Victoria, Australia. Similar datasets are available nationally. | At the time of writing, more than 1,000 GPs were contributing data to the POLAR–GP database across south-eastern Australia (Victoria, New South Wales and Australian Capital Territory Australia. |

### 7.3 Limitations

The limitations of this thesis arose primarily from the nature of the data used, as they were not collected for research purposes. The limitations of each study were discussed explicitly in the discussion sections of Chapters 4, 5 and 6. This section discusses the limitations of the thesis as a whole with a view to improving the utility of syndromic AEFI surveillance.

First, as nationwide datasets were unable to be obtained, the temporal pattern analysis of the AEFI syndromes was the focus of study. However, examining the spatial distribution (clustering) of syndromes is key to maximising the validity and specificity of a syndromic surveillance system.[102] Considering that the 2010 febrile convulsion signal had been first detected in Western Australia, spatial analysis would have likely shown variation in AEFI-related telephone call volumes or rates of post-vaccination GP consultation across the jurisdictions. Therefore, further studies using nationwide data are important to refine how syndromic AEFI surveillance can better complement existing AEFI signal detection systems.

The second limitation of this thesis was related to the signal detection algorithms used. The Farrington surveillance algorithm and the LLR CUSUM chart were used to identify statistical signals (unexpected increase) of the studied syndromes. Even though both algorithms are used widely for monitring healthcare outcomes and public health problems in non-pharmacovigilance studies, as outlined in Chapter 3, the researchers are unaware of whether published studies that validate using these algorithms for vaccine safety studies exist. Both

algorithms rely on the O–E analyses and work best when using long historical baseline data while estimating the expected values of the syndromes. Studies demonstrated that statistical algorithms based on long historical baseline data (at least three to five years of data) perform better in terms of sensitivity and timeliness of signals detection.[103, 104] However, for the studies included in this thesis only two years of historical (baseline) data were considered while estimated the expected values as temporal trend of the syndroms was noticed over the study period. This could have affected the specificity of the algorithms because additional signals of AEFI syndromes were detected in the absence of historical AEFI signals.

Third, the AEFI syndromes studied in this thesis were not specific enough to either identify the exact adverse reactions occurred or discover which vaccines were administered to the patients. As outlined in Chapters 3 and 4, the nurses would label a call as AEFI-related based on the caller's main complaint or symptom, and they would refer to the patient guideline 'immunisation reactions infant child adult' to assess the caller's health concern comprehensively. AEFI-related calls from the telephone helpline dataset were aggregated based on the patient guideline 'immunisation reactions infant child adult'. However, this patient guideline title did not contain the specific vaccine reaction or the type of vaccine administered to the caller. Such information might be captured in the free-text field along with the initial reason for calling, as described by the caller. Conversely, 'post-vaccination GP consultation rate' was used as a proxy measure of AEFI, which was a syndrome created based on the vaccination date and the date of the GP encounter following vaccination. Because this syndrome includes GP visits within one week of vaccination regardless of the reason, the syndrome is not specific to vaccine reactions and can be affected by factors that influence the healthcare-seeking behaviour of the population, such as the COVID-19 pandemic. Notably, the GP dataset contained the reason for the visit in free text or coded diagnoses. Further analyses can be conducted to identify the specific vaccine reaction by using natural language processing

techniques for free-text analysis to identify diagnoses while maintaining privacy. It is worth noting, that the datasets used complement each other, for example a potential AEFI signal noted in the NOC dataset can be explored rapidly by examining the likely vaccines implicated from the GP adminitration data for that particular age group.

Last, the two known AEFI signals associated with the seasonal influenza vaccine in 2010 and 2015 were considered as comparator as they were the only confirmed safety signals in Australia from 2008 to 2017. However, both the NOC helpline analysis and the GP data analysis identified additional signals. Despite they lablled as "false positive signals", these signals might be real safety concerns not identified by existed AEFI surveillance systems at the time. Hence, future work needs to be done to answer questions like how to explore safety signals identified in one system and not others, and how to balance sensitivity and specificity of different surveillance systems in an integrated AEFI surveilance approach. Besides, only the influenza vaccine was considered as exposure to create the proxy measure of AEFI: post-vaccination GP consultation rate. Seasonal influenza vaccines are given to a large number of people in a short period. The findings in this thesis may be directly applicable to new vaccines with rapid implementation or for catch-up programs although in the case of new vaccines one or more control vaccines would need to be selected for a "control representation rate'. However, further studies are important to validate whether these findings are applicable to routine vaccines administered under the National Immunisation Program.

### 7.4 Personal development

During the course of my PhD, my knowledge of and skill in performing epidemiological research using large health datasets greatly improved. When I began my PhD, my understanding of vaccine safety research was quite basic. The systematic review I conducted allowed me to learn the specific method and data analysis approach used to perform post-

licensure vaccine safety monitoring. Additionally, I developed coding skills in Stata with which I performed large dataset cleaning, management and analysis. Further, my PhD experience enhanced my writing skills greatly. The feedback I received on my written documents from my supervisors and journal reviewers enabled me to improve my writing and the way in which I communicate my work. Finally, apart from the work of my PhD, I had the opportunity to develop my teaching skills: I tutored first-year undergraduate students taking Population Health and Biostatistics courses.

### 7.5 Implications and future directions

As there is a continuing growth of vaccines introduced into the market, such as for COVID-19, and public confidence in vaccination is increasingly challenged by safety concerns, the need for a robust AEFI monitoring system that can quickly and accurately identify any vaccine safety concern is more critical than ever. The findings of this thesis suggest that existing AEFI signal detection systems can be complemented by syndromic surveillance of routinely collected, de-identified and non-linked health data. The telephone helpline detection methodology has already been utilised by the Victorian Department of Health and Human Services to examine a contemporaneous possible AEFI signals in 2020. Further, the emergency department code validation and GP representation rate methodologies have been key methodological proposals incorporated into a national active vaccine safety tender currently under assessment (Health/20-21/PH20/1278). The work reported in this thesis provides a basis from which future studies in other countries with similar datasets can explore the possibilities of developing syndromic AEFI surveillance systems. Future studies must explore opportunities to enhance the validity and specificity of syndromic AEFI surveillance by including data from the free-text of the reason for the call or GP visit. Usng natural language processing techniques, record level free-text could be analysed without compromising the anonymity of the vaccinee.To sum up, findings included in the thesis have shown that AEFI signal detection

using syndromic surveillance holds promise for improving overall vacine safety monitoring system.

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## Appendix: Ethics Approval

**REVISED LETTER**

23 May 2018

Prof Jim Buttery
Department of Paediatrics, level 5
Monash Children's Hospital
Clayton VIC 3168

Dear Researcher,

**Study title: Near real-time automated vaccine safety signal detection using routinely collected healthcare data: Potential for continuous active surveillance**

**NMA HREC Reference Number: HREC/18/MonH/345**
**Monash Health Ref: RES-18-0000-232A**

The Monash Health HREC reviewed the above application at the meeting held on 03 May 2018. In addition, the HREC is satisfied that the responses to our correspondence of 07 May 2018 have been sufficiently addressed.

The HREC approved the above application on the basis of the information provided in the application form, protocol and supporting documentation.

This reviewing HREC is accredited by the Consultative Council for Clinical Trial Research under the single ethical review system.

**Approval**

The HREC approval is from 21 May 2018.

Approval is given in accordance with the research conforming to the *National Health and Medical Research Council Act 1992* and the *National Statement on Ethical Conduct in Human Research (2007)*. The HREC has ethically approved this research according to the Memorandum of Understanding between the Consultative Council and the participating organisations conducting the research.

Approval is given for this research project to be conducted at the following sites and campuses:

- Monash Health
- Royal Children's Hospital
- Barwon Health
- POLAR GP
- Outcome Health
- HealthDirect

You must comply with the following conditions:

The Chief Principal Investigator is required to notify the Manager, Human Research Ethics Committees, Monash Health of:

1. Any change in protocol and the reason for that change together with an indication of ethical implications (if any)

2. Suspected Unexpected Serious Adverse Reactions (SUSARs) involving a Monash Health participant or a participant at site that Monash Health has provided HREC Review.
3. Serious Adverse Events (SAEs) that occur with a Monash Health participant or with a participant from a site that Monash Health has provided HREC review that are considered by the Investigator as being definitely related, probably related, possibly related and unknown.
4. Any unforeseen events that might affect continued ethical acceptability of the project.
5. Any expiry of the insurance coverage provided in respect of sponsored trials.
6. Discontinuation of the project before the expected date of completion, giving reasons.
7. Any change in personnel involved in the research project including any study member resigning from Monash Health &/or the study team.

At the conclusion of the project or every twelve months if the project continues, the Principal Investigator is required to complete and forward an annual progress report to the Committee.

Reminders to submit annual progress report forms will be forwarded to the researcher.

The Coordinating Principal Investigator is responsible for notifying Principal Investigators. The Coordinating Principal Investigator and Principal Investigators should forward a copy of this letter to their site's Research Governance Officer.

**Approved documents**

Documents reviewed and approved at the meeting were:

| *Document* | *Version* | *Date* |
|---|---|---|
| Human Research Ethics Application | *AU/1/4EB5319* | *18 April 2018* |
| Victorian Specific Module | | *18 April 2018* |
| Protocol | *2* | *14 May 2018* |

**Site-Specific Assessment (SSA)**

SSA authorisation is required at all sites participating in the study. SSA must be authorised at a site before the research project can commence.

The completed Site-Specific Assessment Form and a copy of this ethics approval letter must be submitted to the Research Governance Officer for authorisation by the Chief Executive or delegate. This applies to each site participating in the research.

If you should have any queries about your project please contact Deborah Dell or Julie Gephart by email deborah.dell@monashhealth.org /julie.gephart@monashhealth.org

The HREC wishes you and your colleagues every success in your research.

Yours sincerely

D. Dell

**DEBORAH DELL**
Manager, Human Research Ethics Committee

Cc: Mr Yonatan Moges Mesfin

**Checklist: Post-ethics approval requirements that must be met before a research project can commence at a study site.**

**Please ensure that as a PI (including the CPI) the following are completed at each study site.**

| **Requirements** | **Yes/No/NA** |
|---|---|
| **Ethics approval notification**<br>The PI must send a copy to the RGO at that study site. | N/A |
| **HREC Review Only Indemnity**<br>The PI must forward a copy of the signed HREC Review Only Indemnity to the RGO at that study site. | N/A |
| **CTN Acknowledgement for Commercially Sponsored Studies**<br>The PI must forward a copy of the CTN Acknowledgement to Research Support Services. | N/A |
| **CTN Lodgement for Collaborative Group/Investigator Driven Studies**<br>The PI or nominated delegate is requested to make an appointment with the Monash Health Research Support Services contact for the study deborah.dell@monashhealth.org or michael.kios@monashhealth.org so that the lodgment may be completed by both the investigator and Research Support Services. The banking details for payment to the TGA will need to be brought along to this appointment, in order to finalise notification to the TGA. The fee for lodging a CTN is $335. | N/A |
| **SSA authorisation notification**<br>The PI must forward the SSA form and attached documents (e.g. CTRA) to the RGO so the authority approving the conduct of the trial, at that site, can complete and sign. | N/A |
| **Radiation**<br>If applicable, the RGO must contact the Medical Physicist so that the study may be notified to the Radiation Risk Section of the Department of Health and Human Services. | N/A |
| **Other Commonwealth statutory requirements**<br>Ensure compliance with the following e.g. Office of the Gene Technology Regulator, NHMRC Licensing Committee, NHMRC Cellular Therapies Advisory Committee. | N/A |