Evolution and Opportunities: Vaccine Pharmacovigilance in Australia

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Authorship attribution statement

Chapter 1 of this thesis is published as *Phillips A, Patel C, Pillsbury A, Brotherton J, Macartney K. Safety of human papillomavirus vaccines: an updated review. Drug Safety. 2017; 41 (4): 329–346*.

I was the first author. I worked with the institute librarian to develop the search strategy, and reviewed and selected the abstracts. I conducted the review of the included manuscripts for surveillance systems, observational studies and case reports. I drafted the manuscript and revised it with input from co-authors and peer reviewers.

Chapter 2 of this thesis is published as *Phillips A, Hickie M, Totterdell J, Brotherton J, Dey A, Hill R, Snelling T, Macartney K. Adverse events following HPV vaccination: 11 years of surveillance in Australia. Vaccine. 2020; 38 (38): 6038–6046*.

I was the first and corresponding author. I designed the study in collaboration with the co-authors. I worked with James Totterdell (biostatistician) to analyse the data on rates, which I collated, presented and interpreted; I worked with Megan Hickie and Richard Hill to interpret additional descriptive information from the Therapeutic Goods Administration. I drafted the manuscript and revised it with input from co-authors and peer reviewers.

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I was the first and corresponding author. I designed the study with input from co-authors.
I conducted analysis of participant demographics and rates with support from Catherine Glover.
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I was co-first author and corresponding author. I designed the study protocol which was amended following review and input from co-authors. I contributed to planning and interpretation of the analysis, which was conducted by James Totterdell. I drafted the manuscript and revised it with input from co-authors and peer reviewers.

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I am the first and corresponding author for this submission. I conceived the study along with Kristine Macartney. I designed the protocol and amended it following feedback from the other authors. I conducted the interviews and analysed the data; Samantha Carlson also analysed the first three interviews so that a codebook could be developed. I completed the data analysis and sought feedback from the co-authors. I drafted the manuscript and made the required amendments after review by all authors.

STUDENT

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Signature

Anastasia Phillips Date 10/6/21

SUPERVISOR

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Signature

Kristine Macartney Date: 4 June 2021

Statement of originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Signature

Anastasia Phillips Date 31/MAY/2021

Thesis abbreviations

AEFI	Adverse event following immunisation
AEFI-CAN	Adverse Events Following Immunisation Clinical Assessment Network
AEMS	Adverse event management system
AESI	Adverse event of special interest
CEM	Cohort event monitoring
COVID-19	Coronavirus disease 2019
CPRD	Clinical Practice Research Datalink
HPV	Human papillomavirus
NCIRS	National Centre for Immunisation Research and Surveillance
NIP	National Immunisation Program
NPS	National Prescribing Service
PAEDS	Paediatric Active Enhanced Disease Surveillance
SCCS	Self-controlled case series
TGA	Therapeutic Goods Administration
UK	United Kingdom
US	United States of America
VAERS	Vaccine Adverse Events Reporting System
VSD	Vaccine Safety Datalink
WHO	World Health Organization
ZVL	Live attenuated herpes zoster vaccine

Abstract

Immunisation has an immense impact on preventing morbidity and mortality worldwide. However, among healthcare providers, governments and the public, there is low tolerance for risk associated with vaccines, given they are used in large, healthy populations to prevent rather than treat disease. Although vaccines used in Australia have an excellent safety profile, and are registered and recommended only after they have been shown to be safe and effective in large, pre-licensure clinical trials, rare, late and population-specific adverse events following immunisation (AEFI) may occur. While the temporal occurrence of an event after a vaccine does not confirm a causal relationship with vaccination, post-marketing safety surveillance (also known as vaccine pharmacovigilance) is essential to ensure the ongoing favourable benefit–risk profile of each vaccine, as both a registered product and in the program setting. Robust vaccine pharmacovigilance is also necessary to maintain confidence in the safety of vaccines, so that immunisation coverage remains high and is not impacted by vaccine hesitancy.

Vaccine pharmacovigilance is traditionally undertaken through spontaneous (or passive) reporting systems, including in Australia. While valuable for signal identification, such systems are widely recognised to be limited by underreporting, stimulated or variable reporting, and inconsistent data quality. Additional modalities, including active surveillance, are required to fully characterise the safety profile of vaccines within populations and sub-populations. Further, signals may be detected through spontaneous reporting systems that require confirmation and investigation, including through methodologically robust comparisons between vaccinated and unvaccinated populations. As surveillance and data analytic technology evolve, the development of more tailored solutions is possible.

Australia's vaccine safety journey has evolved considerably over the past decade. Australian investigations into safety issues related to human papillomavirus (HPV) and rotavirus vaccines between 2007 and 2010 contributed to global evidence supporting a positive benefit–risk profile. However, in 2010, a significant safety issue was identified in Australia after febrile seizures in children were associated with one brand of influenza vaccine, leading to a program suspension. This prompted the modification and development of Australian vaccine pharmacovigilance systems. Now, in 2021, both passive and active surveillance systems are routinely used to monitor vaccine safety in Australia, and specific studies continue to be conducted as required. However, additional pharmacovigilance opportunities exist. Methods that utilise large, and ideally linked, electronic healthcare databases have not developed to the extent that has occurred in some other comparable countries. There has been no published review or overview of the entirety of Australia's safety systems since 2013, and it remains unclear whether systems have evolved sufficiently to robustly monitor vaccine performance in the current era. In particular, introduction of global, population-wide COVID-19

immunisation programs using novel vaccines is presenting unprecedented challenges in terms of both pharmacovigilance and public confidence.

This thesis hypothesises that multi-faceted and adaptive vaccine pharmacovigilance methods, implemented strategically, are necessary to monitor vaccine safety in Australia and to inform ongoing benefit–risk assessment for vaccines and immunisation programs. Further, this thesis proposes that Australia can contribute to an international body of evidence through strengthening its own pharmacovigilance systems, thereby supporting immunisation programs globally.

Anchored in the analysis of two vaccines that have presented vaccine safety challenges (HPV vaccine and live attenuated herpes zoster vaccine [ZVL]), this thesis assesses the value and limitations of Australia's current vaccine pharmacovigilance system through analysis of cumulative data from multiple sources. The exploration begins in Chapter 1 with a review of HPV vaccine safety, drawing on data from across the globe gathered via different pharmacovigilance modalities, and highlighting the unjustified loss of confidence that may result from assumptions based on insufficient evidence. The following three chapters present published papers that explore the safety profile of these two vaccines using either longstanding or emerging Australian pharmacovigilance modalities. Chapter 2 continues the focus on HPV vaccine in a detailed analysis of the Australian spontaneous reporting system over 11 years, including 2 years of enhanced surveillance data. The study confirms the validity of using spontaneous surveillance (particularly when enhanced) and the absence of any unexpected safety signals; simultaneously this chapter also describes inherent system limitations and the challenge of relying on this type of data in isolation.

The third chapter presents an analysis of Australia's active surveillance system (AusVaxSafety-Active), which was developed to supplement the spontaneous reporting system following the events of 2010. While the AusVaxSafety system was initially designed to monitor short-term reactogenicity (including fever) after influenza vaccine in children, using automated parent surveys, it has progressively expanded, and this study explores its utility for a live vaccine (ZVL) in older adults. The analysis confirms the validity and adaptability of AusVaxSafety-Active for profiling reactogenicity in near-real time, including in older adults, but highlights its limitation in monitoring rare, later onset AEFI. To address this limitation, systematic approaches to interrogate population-level databases are required. Chapter 4 explores such an approach to examining the safety of ZVL using the self-controlled case series methodology within a novel primary care (general practice) data source never previously used for vaccine pharmacovigilance in Australia. No safety signals were identified. While the study validates this methodology, it highlights the limitations of using primary care data in isolation, as this does not enable complete ascertainment of serious or hospitalised AEFI.

In the final chapter, a qualitative study is presented which aims to understand the perceptions of key stakeholders on the progress of Australia's vaccine pharmacovigilance system since the unexpected events

of 2010, and its readiness to monitor COVID-19 vaccine safety. Based on input from expert informants, this study identifies significant innovation within Australia's suite of vaccine safety modalities. However, it also identifies the need for system integration, and the clear requirement for access to large, population-level databases (including those based on linked data) in which to conduct active surveillance and test safety signals using robust epidemiological methods. This study has been submitted for publication.

The thesis concludes by confirming that multi-faceted and adaptive vaccine pharmacovigilance methods must be strategically implemented as immunisation programs evolve, including expansion of programs to protect people across the lifespan and to enable global recovery from the COVID-19 pandemic. Australia has the opportunity to strengthen country-level systems and enhance its global contribution to vaccine pharmacovigilance. The thesis concludes with the following recommendations:

1. Develop nationally coordinated and systematic approaches for population-level active surveillance within a strategic framework that facilitates streamlined access to large, linked patient cohorts; analysis using robust epidemiological methods; and rapid adaptation to new pharmacovigilance challenges.
2. Better integrate Australia's suite of pharmacovigilance resources to create a multi-faceted and adaptive system that can rapidly respond, in a coordinated manner, to vaccine safety challenges under real-world conditions.
3. Vaccine pharmacovigilance should be focused, purposive and informed by clear governance structures that value and drive innovation, with representation from both government and public health organisations, and benchmarking through a regular monitoring and evaluation framework.
4. Peak national organisations should leverage opportunities to contribute to an international body of evidence in vaccine pharmacovigilance as part of a global community.
5. Ensure that the healthcare community and the public contribute to vaccine pharmacovigilance and are well informed about the risk of vaccines in relation to their benefit.

Contents

Introduction

Immunisation is widely cited as one of the most successful public health interventions in history, preventing around 2 million child deaths each year, with many more deaths potentially preventable if vaccines were fully utilised in underreached populations, and with expansion of coverage to adolescents and adults. (1-4) Modern vaccines generally have an excellent safety profile (5); in Australia and globally, they are registered and recommended for use only once they are shown to be safe and effective in clinical trials with many thousands of participants. However, as with all medicines, adverse events can occur following vaccination – either causally or in a temporal context.

Given that immunisation programs may be delivered to millions of individuals, ongoing pharmacovigilance is essential in the post-marketing phase to detect, assess and respond to rare and later-onset adverse events, which clinical trials are not powered to detect. (5, 6) Further, there is a need to identify any safety issues in sub-populations who may not have been included in clinical trials. (5, 6) Unlike other medicines, vaccines are largely administered to healthy populations, including children and adolescents; consequently, and rationally, there is a low tolerance for risk. (7) As post-marketing data emerge, the benefit–risk balance of vaccines at the individual and population levels must be systematically reviewed, considering both the profile of the vaccine as a registered product and the impact on the immunisation program more broadly. (8)

An adverse event following immunisation (AEFI) is 'any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine; the adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease'. (5, p.10) Pharmacovigilance mechanisms must be robust and agile enough to rapidly investigate reported associations, assess causality, determine whether the benefit–risk profile remains favourable in different contexts, and provide data for effective communication. (5, 9) The science and outputs of vaccine pharmacovigilance are inexorably linked to vaccine confidence, which is influenced by perception of risk, temporal associations between vaccines and medical events (the assumption of '*post hoc ergo propter hoc*'), and trust in the companies that produce vaccines and agencies, including Governments, that promote vaccination. (10) Vaccine hesitancy was considered by the World Health Organization (WHO) as one of the top 10 threats to global health in 2019 (11), with reduced confidence in immunisation programs and reduced coverage linked to outbreaks of vaccine-preventable disease globally (7), including in Australia. (12) The WHO's Immunisation Agenda 2030 articulates the risks to public health associated with stalled or regressing immunisation programs, and the potential for complacency to undermine successes. (4)

In 2021, there is concern that vaccine hesitancy could threaten recovery from the COVID-19 pandemic. (13) Within a few months of program implementation globally, several safety signals have required urgent review

to assess association, causation, and the benefit–risk balance of COVID-19 vaccines. (14-16) The emergence of a new rare but serious AEFI, most commonly referred to as thrombosis with thrombocytopenia syndrome (TTS), that appears to have a plausible causal association with at least two of the adenovirus-vectored COVID-19 vaccines, is challenging vaccine pharmacovigilance systems and risk communication globally. (16, 17) Based on post-marketing surveillance data, the risk of TTS appears higher in younger adults; yet, the epidemiology of COVID-19 varies by country and by age and some countries do not have access to alternative vaccines. (18, 19) Because of these complexities, benefit–risk assessments in a number of settings, including Australia, have focused on clinical guidance for the immunisation program, or regulatory warnings, rather than withdrawal of registration or program cessation. (18, 20, 21) Such complexity underpins the need for systematic, purposive pharmacovigilance, clear communication of benefit and risk, and maintaining global linkages.

Mechanisms for vaccine pharmacovigilance

Vaccine pharmacovigilance systems (also called post-marketing safety surveillance systems) aim to identify and characterise AEFIs, including vaccine product-related reactions, vaccine quality defect-related reactions, immunisation error-related reactions (due to inappropriate handling, prescribing or administration), immunisation anxiety-related reactions, and coincidental events. (5) Pharmacovigilance systems must ensure the quality manufacture and administration of vaccines, and the safe delivery of vaccines in the context of the immunisation program. Their key function is to identify potential safety signals, confirm the validity of those signals, and investigate whether the identified AEFI is causally related to vaccination, by using epidemiological data and assessing evidence of a biologically plausible mechanism. (9, 22) A prompt response is essential to minimise harm associated with either the vaccine or the impact on vaccine confidence. (5, 22)

As for any disease surveillance system, vaccine pharmacovigilance systems can be passive, active or enhanced. Passive (or spontaneous) reporting systems are established in some, but not all, countries globally and have been progressively improved over decades; examples include the Vaccine Adverse Events Reporting System (VAERS) in the United States (US), and the Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card system in the United Kingdom (UK). (23, 24) The WHO recommends that all countries have an effective passive surveillance system that can monitor and respond to AEFI, including for COVID-19 vaccines. (5, 25) Such systems rely on reports from healthcare providers, pharmaceutical companies and the public; spontaneous reporting systems can also be enhanced to target specific vaccine safety concerns. (26) The main value of spontaneous reporting is in the early detection of an unexpected and serious safety signal, which may then generate a hypothesis and further investigation. Signals may be detected following reports of serious cases or adverse events of special interest (AESIs), and through analysis

of patterns and trends over time. Ideally, AEFI rates should be derived where data on doses administered or distributed by age group or other demographic parameters are available. In addition, analyses can be conducted to assess disproportional reporting of selected AEFIs for one vaccine compared to others. (5, 23)

However, spontaneous reporting systems have numerous inherent limitations. Such systems rely on reporting by clinicians or the public; underreporting and data inconsistency are common. (27) Conversely, reporting of specific medical events may be stimulated in response to information circulated within healthcare provider communities or via the media. (23) Further, spontaneous surveillance systems only identify the number of events in individuals who have been vaccinated; accurate data on vaccine coverage is not always available so it may not be possible to calculate rates. Further, there are no data on such events in unvaccinated populations, or on the number of vaccinated individuals who do not experience the event of interest. Consequently, the existence and size of any risk cannot be formally quantified (Figure 1). This means that any hypothesis generated from spontaneous reporting systems must almost always be confirmed through other methods. (5, 23)

Figure 1 Representative 2 x 2 table for epidemiological analysis of causality of adverse events following immunisation

		Adverse event	
		Yes	No
Vaccinated	Yes	a	b
	No	c	d

Rate in vaccinated = a/a+b

Rate in unvaccinated = c/c+d

Shaded cell represents where some information can be obtained from spontaneous reporting systems; however, this is inherently incomplete.

Source: Adapted from Chen, Glanz and Vellozzi, Box 26.1, Chapter 26 of 'Pharmacoepidemiology') (28)

Active surveillance is an important additional modality that enables the systematic collection of AEFIs. It can be conducted by ascertainment of cases of specific AESI, for example, at sentinel surveillance sites (known as event-based monitoring) or through active follow-up of a vaccinated cohort for any AEFI (cohort event monitoring, CEM). (5, 25) For example, sentinel active surveillance in hospitals is used widely for infectious diseases and has been used specifically for AEFI in some settings internationally, for example, in Canada's Immunization Monitoring Program ACTive (IMPACT). (29) Hospital-based surveillance has the benefit of data accuracy (particularly for complex syndromes) and can be expanded to monitor specific AESI; however, it is resource intensive and so may be limited by the number of participating sites. (29)

CEM may be less resource intensive, particularly if using digital ('eHealth') and mobile ('mhealth') approaches; methods of follow-up include diary cards, telephone surveys, or surveys delivered via short message service (SMS; text message) or web-based methods. (25) CEM based on these methods may be powered to characterise the risk profile of a vaccine rather than identifying rare events, and may be limited by response rates. (5, 30) However, a cohort of individuals can also be actively monitored within large, linked healthcare databases such as the Vaccine Safety Datalink (VSD) in the US, which monitors selected vaccines in near-real time through rapid cycle analysis to identify signals within a cohort from nine large healthcare organisations. (31)

To comprehensively investigate vaccine safety signals and test hypotheses, epidemiological studies are generally required. (5, 23, 25) These may use a variety of methods, including cohort, standard case control, case-centred and self-controlled case series approaches. (32) Internationally, such studies are often performed within large linked healthcare databases, including the VSD and others such as the UK Clinical Practice Research Datalink (CPRD), which includes primary and secondary care data, and routine data collections in Europe. (33-35) These studies have, over time, either demonstrated no link between hypothesised vaccine–event associations (31, 33, 36) or quantified the risk associated with some vaccine-attributable adverse events. (37-39)

Overview and history of vaccine pharmacovigilance in Australia

Most vaccines in Australia are delivered free under the National Immunisation Program (NIP) and recorded on the national Australian Immunisation Register which has captured data on all childhood immunisations since 1996 (to age 7 years) and vaccines given to people of all ages since 2016. (40, 41) Australia has maintained high coverage for childhood vaccines over many years and has one of the most comprehensive publicly funded immunisation programs by global standards. The NIP is underpinned by access to Australia's longstanding universal healthcare system, known as Medicare. (42)

Australia's spontaneous reporting system has been operated by the national medicines regulator, the Therapeutic Goods Administration (TGA), for decades (Table 1). The TGA is the statutory authority responsible for assessing the safety, quality and effectiveness of vaccines and other medicines for registration in Australia, and for monitoring the safety of all vaccines approved for use. (43) Reports are managed within the Adverse Events Management System (AEMS) database, and formal annual reports of AEFI rates in Australia have been published each year since 2001 as part of a collaboration between the TGA and the National Centre for Immunisation Research and Surveillance (NCIRS). (44, 45)

Like similar systems internationally, providers, consumers and pharmaceutical companies can report AEFI. Somewhat uniquely, reporting is also a statutory obligation for healthcare providers in most (five of eight)

jurisdictions (Australian states and territories), and mostly occurs via jurisdictional vaccine safety surveillance systems before being collated nationally by the TGA in the AEMS. (46) Even in the context of legislative requirements, AEFI reporting still relies mostly on clinicians with an index of suspicion (27), but the statutory framework allows jurisdictions to conduct local public health follow-up of reported events. Jurisdictional surveillance mechanisms vary but include reporting via local public health units and centralised systems with links to state-based AEFI clinics (47, 48); clinical assessment and review occurs locally to varying degrees.

In Australia, the spontaneous reporting system has performed well as the routine pharmacovigilance mechanism in some circumstances; in others, its limitations have been highlighted. In 2007, a safety signal for anaphylaxis following human papillomavirus (HPV) vaccine was identified through spontaneous reporting in one state. The TGA, together with state and territory authorities (who deliver the NIP in partnership with the Australian Government) investigated the reports, including through review by an expert panel. (49, 50) Subsequently, additional, enhanced passive surveillance activities were used when the HPV vaccination program was extended to males in 2013. (26) To expand pharmacovigilance for HPV, as well as other vaccines, a clinical network was formalised (the Adverse Events Following Immunisation Clinical Assessment Network [AEFI-CAN]), which now connects specialist immunisation clinics and clinicians across Australia (Table 1). (51)

However, in 2010, a major safety incident occurred in Australia when an unexpected increase in fever and associated febrile convulsions in young children following seasonal influenza vaccination was seen with one vaccine brand. This very high profile issue led to temporary suspension of seasonal influenza vaccination programs for children under 5 years of age (52, 53), and long-term impacts on influenza vaccine confidence and coverage for this age group. (54, 55) While the signal was identified through the spontaneous reporting system, a Government-commissioned national review (53) identified concerns with the surveillance process, particularly around timeliness of reporting and response. These concerns were echoed by others, who highlighted the inherent limitations of spontaneous reporting, delays in data transmission and signal detection, and the need for complementary active surveillance systems. (52)

Following these events, some researchers, clinicians and public health practitioners embarked on efforts to monitor reports of fever following childhood influenza vaccine, leading to development of two regional active electronic CEM systems (SmartVax in Western Australia and Vaxtracker in New South Wales). These systems were subsequently brought under the umbrella of a national Australian Government-funded system called AusVaxSafety-Active (Table 1). (56-58) This system collects solicited AEFI reports, via SMS or online surveys, from vaccinated persons (or their caregivers) across several hundred immunisation provider sites across Australia. It has been expanded to include all vaccines, with special focus on new vaccines and

program changes. (58) A simulation study has shown that if it was in place at the time, AusVaxSafety-Active is likely to have identified the 2010 safety signal within 3 weeks of vaccine distribution. (59)

Australia also has an active, prospective sentinel hospital-based surveillance system (the Paediatric Active Enhanced Disease Surveillance [PAEDS] network) (29, 60), similar to the IMPACT system in Canada (Table 1). Between 2007 and 2010, the PAEDS system investigated the risk of intussusception following introduction of rotavirus vaccines (37), a potential concern based on experience with a previous vaccine in the US. (61) PAEDS data also contributed toward a national self-controlled case series analysis of verified hospitalised cases of intussusception. (62) The use of these mechanisms to investigate one specific AESI allowed Australian authorities to review the vaccine from both a regulatory and program perspective, to implement a parent communication strategy that the overall benefit–risk balance of rotavirus vaccines continued to be positive, and to contribute to the evolving global knowledge base. (37, 62, 63) Coverage for rotavirus vaccine is now over 90% in Australia. (41)

Emergency department surveillance is also undertaken in some states. (64) Finally, ad hoc specialised studies, including using large linked databases, have been conducted by research groups in Australia; some proof-of-concept studies have been necessarily limited in scope, and access to data is often not timely. (65, 66)

Table 1 Summary of national vaccine pharmacovigilance systems in Australia

System	TGA AEMS	PAEDS (60)	AusVaxSafety-Active (58)	AEFI-CAN
Commenced	**Pre-2000**	**2007**	**2014[a]**	**2014[b]**
Description	Spontaneous reporting Enhanced surveillance for specific vaccines (26)	Sentinel hospital-based active surveillance system; select paediatric-specific AESI	Cohort event monitoring system (active surveillance)	Network of vaccine specialist clinics and staff (51)
Data collection	Consumer, provider and pharmaceutical company reporting Submitted mostly via state and territory surveillance programs	Specialist nurses screen hospital admission, ED records and lab data in 8 tertiary, paediatric hospitals to identify selected AESI[c]	Solicited AEFI reports via SMS surveys from 375+ immunisation provider settings[d]	Specialised immunisation clinics in most states and territories
Review and analysis	Local follow-up in some states Coded using standardised MedDRA® terms Clinical review of AESI and serious AEFI Signal detection (PRR and other methods) (67)	Case review Epidemiological analysis	Analysis of AEFI and medical attendance rates (proxy for serious AEFI) Signal detection (FIR CUSUM and Bayesian analyses) (59) Case follow-up by states and territories	Clinical review Selected AEFI entered into database Analyses as required
Response and communication	Monthly teleconferences with stakeholders Annual AEFI reports (44) Searchable Database of Adverse Event Notifications (DAEN) (68) Safety advisories (69) and provider letters Regulatory action	Annual reports Reporting to spontaneous reporting system	Website reports (58) Reports to stakeholders Vaccine-specific reports and publications (70, 71)	Regular teleconferences with members and TGA Specific publications
Governance	TGA (manages) ACV (independent advice) (72) Investigation and causality assessment panels (as required)	National collaboration led by NCIRS Reference Group	AusVaxSafety consortium led by NCIRS Expert Leadership Group and Advisory Committee	AusVaxSafety consortium led by NCIRS

ACV – Advisory Committee on Vaccines; AEFI – adverse event following immunisation; AEFI-CAN – Adverse Events Following Immunisation – Clinical Assessment Network; AEMS – Adverse Events Management System; AESI – adverse event of special interest; ED – emergency department; FIR CUSUM – fast initial response cumulative summation; MedDRA – Medical Dictionary for Regulatory Activities; NCIRS – National Centre for Immunisation Research and Surveillance; PAEDS – Paediatric Active Enhanced Disease Surveillance; PIMS-TS – paediatric inflammatory multisystem syndrome temporally associated with SARS-COV-2; PRR – provisional reporting ratio; SANE – serious adverse neurological events; SMS – short message service; TGA – Therapeutic Goods Administration.

[a] Active participant-based surveillance (cohort event monitoring) began in 2014, with the name 'AusVaxSafety' adopted in 2016.

[b] Clinician network meetings formalised and network secretariat established.

[c] Includes intussusception, febrile seizures, SANE, COVID-19 and PIMS-TS.

[d] Sites include primary care, hospitals, schools, pharmacies, community clinics and Aboriginal Medical Services.

Hypotheses and thesis guide

The central hypothesis of this thesis is that multi-faceted and adaptive vaccine pharmacovigilance methods are necessary to monitor vaccine safety in real-world conditions in Australia and to inform ongoing benefit–risk assessment for vaccines and immunisation programs. It is proposed that while multi-modal methods should be complementary, a strategic approach to the implementation and conduct of such systems is needed. Further, this thesis proposes that, in an interconnected world where vaccine safety concerns anywhere can lead to global program disruption, Australia can contribute to an international body of evidence through strengthening its own pharmacovigilance systems. Quality data from countries like Australia, based on robust scientific methods and presented in a timely manner, can support immunisation programs globally. Conversely, robust and timely country-level pharmacovigilance can protect Australia from the potentially damaging impact of safety concerns identified elsewhere, whether real or perceived, through evaluation and benefit–risk assessment for the local context.

The thesis examines the evolution of Australian vaccine pharmacovigilance mechanisms since 2010, focusing on vaccines that have been the subject of specific safety concerns over the past 11 years, and considers the value and limitations of each system and method. The conception of this thesis and the work herein predated the COVID-19 pandemic by 4 years; however, importantly, during 2020 and early 2021, the final chapters of this thesis sought to explore whether Australian systems have evolved sufficiently to robustly monitor the safety of the COVID-19 immunisation program.

The first four chapters of this thesis present published papers with an introduction and implications section to contextualise the work. Chapter 1 uses the example of HPV vaccine to examine approaches to vaccine pharmacovigilance. HPV vaccine, the first vaccine that aims to prevent cancer, has been impacted globally by case reports of complex or poorly defined disease syndromes, and parental concerns about safety. (73) This paper demonstrates the importance of evidence-based review to collate, assess and interpret the body of evidence on vaccine safety. It also describes the impact of program decisions made on the basis of limited evidence, and the value of robust vaccine pharmacovigilance mechanisms in resolving safety concerns.

Chapter 2 continues with the example of HPV vaccine pharmacovigilance, examining data from Australia's longstanding spontaneous reporting system over 11 years. This chapter documents the role and value of spontaneous reporting systems with a focus on one vaccine over time; it highlights the potential to identify and respond to safety signals, particularly through the use of enhanced passive surveillance. However, the inherent limitations of reliance on spontaneous reporting systems are also highlighted, particularly in relation to drawing robust conclusions about the risk of rare autoimmune and neurological conditions without a valid comparison to event rates in an unvaccinated population.

Chapter 3 describes Australia's novel, active, CEM system (AusVaxSafety-Active), using the example of live attenuated herpes zoster vaccine. This chapter highlights the value of active CEM for rapid data accumulation and for monitoring short-term reactogenicity, via mhealth, in the older target population for this vaccine. However, the limitations of Australia's CEM system in assessing the risk of later-onset AEFI are identified. This chapter provides evidence that while active surveillance can add significant value, it cannot be relied upon alone; access to data on longer-term health outcomes is needed. Further, while CEM can generate useful signals, comparison to an unvaccinated population is required to assess risk.

Chapter 4 presents an exploratory analysis of a novel primary care data source – the National Prescribing Service's (NPS's) MedicineInsight program, which extracts data from general practice software systems. Analysis of MedicineInsight data has been proposed as a mechanism to understand later-onset AEFI and capture information about AEFI in relation to underlying medical conditions. The study uses the self-controlled case series method, in which vaccinated individuals effectively act as their own controls, enabling estimation of risk. While the approach was able to identify expected AEFI, limitations of this primary care data were identified, particularly a lack of data on serious events resulting in emergency department attendance or hospitalisation. Exploratory analyses such as this are an essential element of moving towards a diverse and robust suite of vaccine pharmacovigilance mechanisms in Australia.

Finally, Chapter 5 presents a qualitative examination of Australia's vaccine pharmacovigilance systems over the past 10 years, bookended by the issue of febrile seizures following influenza vaccine in 2010 and COVID-19 immunisation program planning in 2020. Effective implementation of COVID-19 immunisation programs is essential to enable the world to exit the pandemic. With the use of novel vaccines under emergency authorisation, and in the face of heightened vaccine hesitancy, governments and other organisations globally have introduced additional layers of vaccine pharmacovigilance. (74, 75) Expert participants in this study highlighted the value of systems introduced in Australia since the events of 2010. However, they also emphasised the ongoing need for population-level active surveillance, including through systematic analysis of data within large linked databases, and the need for a strategic, integrated approach to pharmacovigilance for both the COVID-19 immunisation program and the whole NIP. A modified version of the content in this chapter (including some introductory content from the broader thesis) has been submitted for publication.

The thesis concludes by confirming that multi-faceted and adaptive vaccine pharmacovigilance methods are indeed required as immunisation programs expand to additional populations and diseases, including COVID-19. While Australian systems are evolving and are complementary, a strategic approach to implementation is required to ensure a robust and efficient response to safety signals, including both the assessment and communication of benefit and risk. Further, within Australia's suite of pharmacovigilance

resources, capacity to access population-level linked health data is lacking and must be further developed to enable the timely identification and evaluation of safety signals, including those that are rare or late onset, using appropriate epidemiological methods. This development is urgently required if Australia is to provide a valuable contribution to global vaccine pharmacovigilance and safeguard our own programs, both for COVID-19 vaccines and future immunisation programs.

Chapter 1: Global pharmacovigilance methodology – strengths and impediments, the example of human papillomavirus vaccine

1.1 Introduction

The key purpose of vaccine pharmacovigilance is to provide evidence to both regulatory and public-health agencies about the ongoing benefit–risk profile of vaccines. (7) As with all elements of clinical and public health practice, the highest quality scientific evidence should support decision-making. Case series and case studies are generally considered the lowest level of evidence. (6) For vaccines, hypotheses generated from both spontaneous reporting systems and case reports/series must be tested using approaches that can estimate risk; further, both epidemiological and mechanistic evidence are required to confirm an association. (5, 6, 9, 22)

Globally, implementation of immunisation programs for HPV vaccines has been impacted by reduced public confidence following published case reports, spontaneous reporting system data used out of context, and media attention on specific syndromes. For example, there was significant decline in vaccination coverage in Denmark, and other Scandinavian countries, following negative publicity and increased reporting of suspected adverse events following HPV vaccine from the Danish medicines regulator in 2013. (76) At the same time, in Japan, a cluster of AEFIs reported in the media led the government to suspend its proactive recommendation for the vaccine; coverage fell substantially from over 70% to less than 1%. (77) In Ireland, studies indicate that parental concern about long-term vaccine side effects and chronic illness, along with uncertainty about benefit, have been barriers to vaccination. (78)

Pharmacovigilance methods that produce population-level estimates of risk, including cohort studies using large study populations that may be drawn from linked databases, provide the most robust estimates of risk that can be considered in regulatory and programmatic decision-making and communication. Although randomised controlled trials are traditionally considered the highest level of evidence, the value of observational studies is well established for pharmacoepidemiology, including for vaccines. The limited sample size and lack of external validity of clinical trials impacts their value in assessing the risk of rare or later-onset AEFI; well-designed epidemiological studies are essential for vaccine pharmacovigilance in the real world. (6)

Internationally, several countries routinely conduct robust epidemiological studies within large populations for the purposes of vaccine pharmacovigilance. In the case of HPV vaccine, a potential signal for venous thromboembolism arose through early spontaneous surveillance in the US;

subsequent analysis of linked healthcare records within the US Vaccine Safety Datalink (VSD) using a self-controlled case series method did not find an increased risk. (79) Similarly, population-level analysis using linked data from Scandinavia has not identified an increased risk for various adverse events of special interest (AESIs) reported in association with human papillomavirus (HPV) vaccine in less robust studies (33, 80); such systems previously provided high-level evidence against the link between measles-mumps-rubella (MMR) vaccine and autism. (81)

The following review article describes the global evidence base for HPV vaccine safety, and the value of robust epidemiological studies using population-level data to examine associations and make a statistical determination of risk. It articulates the impact resulting from assumptions made on the basis of insufficient evidence. This study filled an important gap in collating all recent published evidence, building on a previous (2013) review of safety undertaken by some members of the authorship team. (82) In the 4 years between the first and second reviews, a very large number of new studies (109; see Appendix A) on HPV vaccine safety were identified, including 23 case reports or case series, some of which had significantly impacted vaccine confidence and coverage in several countries globally.

1.2 Publication 1: Phillips A, Patel C, Pillsbury A, Brotherton J, Macartney K. Safety of human papillomavirus vaccines: an updated review. Drug Safety. 2017; 41 (4): 329–346.

See also supplementary material in Appendix A.

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REVIEW ARTICLE

Safety of Human Papillomavirus Vaccines: An Updated Review

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Abstract Human papillomavirus (HPV) vaccines are now included in immunisation programmes in 71 countries. Unfortunately, uptake has been impacted in some countries by reduced confidence in the safety of the HPV vaccine. In 2013, we published an extensive review demonstrating a reassuring safety profile for bivalent (2vHPV) and quadrivalent (4vHPV) vaccines. A nonavalent (9vHPV) vaccine is now available and HPV immunisation programmes have been extended to males in 11 countries. The aim of this updated narrative review was to examine the evidence on HPV vaccine safety, focusing on the 9vHPV vaccine, special populations and adverse events of special interest (AESI). The previous searches were replicated to identify studies to August 2016, including additional search terms for AESI. We identified 109 studies, including 15 population-based studies in over 2.5 million vaccinated individuals across six countries. All vaccines demonstrated an acceptable safety profile; injection-site reactions were slightly more common for 9vHPV vaccine than for 4vHPV vaccine. There was no consistent evidence of an increased risk of any AESI, including demyelinating syndromes or neurological conditions such as complex regional pain or postural orthostatic tachycardia syndromes. The risk–benefit profile for HPV vaccines remains highly favourable.

Key Points

There is a large volume of evidence on the safety of the human papillomavirus (HPV) vaccine.

Our review has identified robust scientific evidence that supports the safety of the HPV vaccine.

Communication regarding vaccine safety should be based on comprehensive review of the body of quality scientific evidence, as assumptions based on insufficient evidence may lead to unjustified loss of confidence in vaccine safety.

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1 Introduction

Infection with human papillomavirus (HPV) is extremely common [1, 2]; persistent infection with an oncogenic type is necessary for the development of cervical cancer and is associated with a significant proportion of anogenital and oropharyngeal cancers [3, 4]. The virus is responsible for around 5% of the global cancer burden [5] and evidence of HPV vaccination effectiveness for the prevention of infection and high-grade cervical disease (pre-cancerous changes) has now been demonstrated [6]. Declines in

cervical cancer among vaccinated young women are expected to be seen within the next decade [6].

As with all vaccines, HPV vaccine safety was evaluated in large pre-licensure clinical trials and is monitored in post-marketing surveillance systems worldwide. However, reported adverse events (AEs) following HPV vaccine have been the subject of several high-profile case reports and have generated considerable media interest. Although case reports of AEs are frequently published after receipt of a new vaccine and imply a temporal association with vaccination, this does not infer a cause and effect relationship. Attribution of causality requires sound epidemiological data demonstrating evidence for causality at the population level, with supporting evidence of biological plausibility [7].

As at May 2017, the HPV vaccine was included in national immunisation programmes for females in 71 countries and for males in 11 countries [8]. In some jurisdictions, including Japan, Denmark and Ireland, reduced public confidence in HPV vaccine safety has led to declines in uptake, withdrawal of, or failure to implement, HPV immunisation programmes [9]. While safety concerns have been well-managed in many countries [10], they have been one barrier to providing equitable protection against HPV-related cancer globally [6].

In 2013, we published a review of 103 HPV safety studies [11] that demonstrated an excellent safety profile of the two available vaccines, bivalent vaccine (2vHPV vaccine, GlaxoSmithKline Biologicals, Belgium), containing virus-like particles for oncogenic HPV types 16 and 18, and quadrivalent vaccine (4vHPV vaccine, Merck and Co., USA), containing virus-like particles for types 16 and 18 plus two additional types, 6 and 11. In late 2014, a nonavalent HPV vaccine (9vHPV vaccine, Merck and Co., USA) containing virus-like particles for the 4vHPV vaccine types and five additional oncogenic types (HPV31/33/45/52/58) was licensed in the USA and is now registered in Europe, Canada and Australia, among other countries [6]. All three HPV vaccines contain adjuvants to enhance the immune response (proprietary aluminium hydroxyphosphate sulphate system for 4vHPV and 9vHPV vaccines, and AS04 containing an aluminium salt and monophosphoryl lipid A for 2vHPV vaccine).

The purpose of our updated review is to provide an extended assessment of the body of evidence on HPV vaccine safety in the context of the expanded use in new populations (including males) and the introduction of the 9vHPV vaccine. The reduction in confidence in HPV vaccine safety currently being experienced in certain countries in a limited number of regions also underpins the need for this independent review. Other aims were to compare the safety of the 9vHPV vaccine with the 2vHPV and 4vHPV vaccines, to assess differences in AEs between males and females, and to identify any evidence for AEs of special interest (AESI) related to the HPV vaccine in any population, including in persons with pre-existing medical conditions.

2 Methods

The search strategy used in our initial review was replicated [11] and enhanced. To update the searches previously conducted on 10 May 2012, a search update was conducted on 9 August 2016 in OVID MEDLINE and on 11 August 2016 in OVID EMBASE. Search terms included HPV vaccine (including 9vHPV vaccine), safety and post-licensure data, including both database-controlled vocabulary terms and commonly used free-text terms. In addition, search terms for specific AESI [namely Guillain-Barré syndrome (GBS), postural orthostatic tachycardia syndrome (POTS), premature ovarian insufficiency (POI), autoimmune disease (AID), acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS) and complex regional pain syndrome (CRPS)] were included. There was no language restriction; however, only articles in the English language were reviewed. Conference abstracts were excluded. The reference lists of key documents were hand-searched to identify additional studies, and immunisation guidelines and position statements were also reviewed. Data presented here do not include studies cited in our original review [11] but build on that earlier evidence summary.

Data were extracted on all relevant safety outcomes of interest, including the frequency and/or incidence of injection-site reactions (ISRs), systemic AEs, serious AEs (SAEs), medically significant conditions (MSCs), AESI [as listed in the previous paragraph plus allergy and anaphylaxis, venous thromboembolism (VTE) and syncope] and mortality following HPV vaccination. MSCs were defined within the studies as conditions prompting emergency department or physician visits that were not related to common diseases or routine visits for physical examinations, and included SAEs not related to common diseases. Clinical trial outcomes were reported based on terms used in the published studies, which did vary across studies. Pregnancy outcomes in women who received HPV vaccination shortly before or after conception were also noted.

All types of study designs in peer-reviewed publications were examined if they contained original data. Data were tabulated by study design (see Electronic Supplementary Material) [clinical trials, post-marketing data from spontaneous reporting systems (SRS), population-based observational studies and case reports/series] and each safety outcome was assessed in all study types. Data are presented as appropriate to the study design. Clinical trial data generally provide the

proportion of AEs experienced in vaccine recipients and controls, with tests for significance presented where these were conducted by study investigators. Analyses based on SRS data include rates based on denominator dose data (either doses administered or doses distributed depending on available data), observed versus expected analyses, proportional reporting ratios (PRRs) for signal detection or case counts. Results from population-based observational studies are generally presented as estimates of risk between a study cohort and comparator (or self-comparator). Case series and case reports present clinical data on an individual (or individuals) with no epidemiological analysis.

This was a narrative review without formal quality assessment. We provide interpretation of study results in the context of the wider body of evidence, with a focus on higher levels of evidence [12] (Fig. 1); that is, well-designed and conducted population-based epidemiological studies and clinical trials. Evidence was also considered in relation to findings from our earlier review [11]. Clinical trials generally provide robust data, often including large numbers of participants, randomised to either the active vaccine or a control as a comparator. However, they may not have sufficient power to detect rare events or sufficient follow-up time to detect differences in chronic conditions, and trial participants may not be representative of the general population due to criteria for participation [13]. Post-licensure surveillance, such as SRS and near real-time monitoring, provides data for signal detection and hypothesis generation [14–17] for rare or unexpected events in large, diverse populations. However, SRS data must be interpreted with caution due to inherent limitations, including data quality and completeness, biased reporting and, most importantly, inability to determine causality. When SRS reports are taken out of context or analysed inappropriately, erroneous conclusions will be generated about the risk of AEs and about cause and effect [17]. Ecological data are also reported for some AEs, and provide evidence of correlation but not causation. Epidemiologic evidence from well-conducted observational studies of populations provides the best evidence for

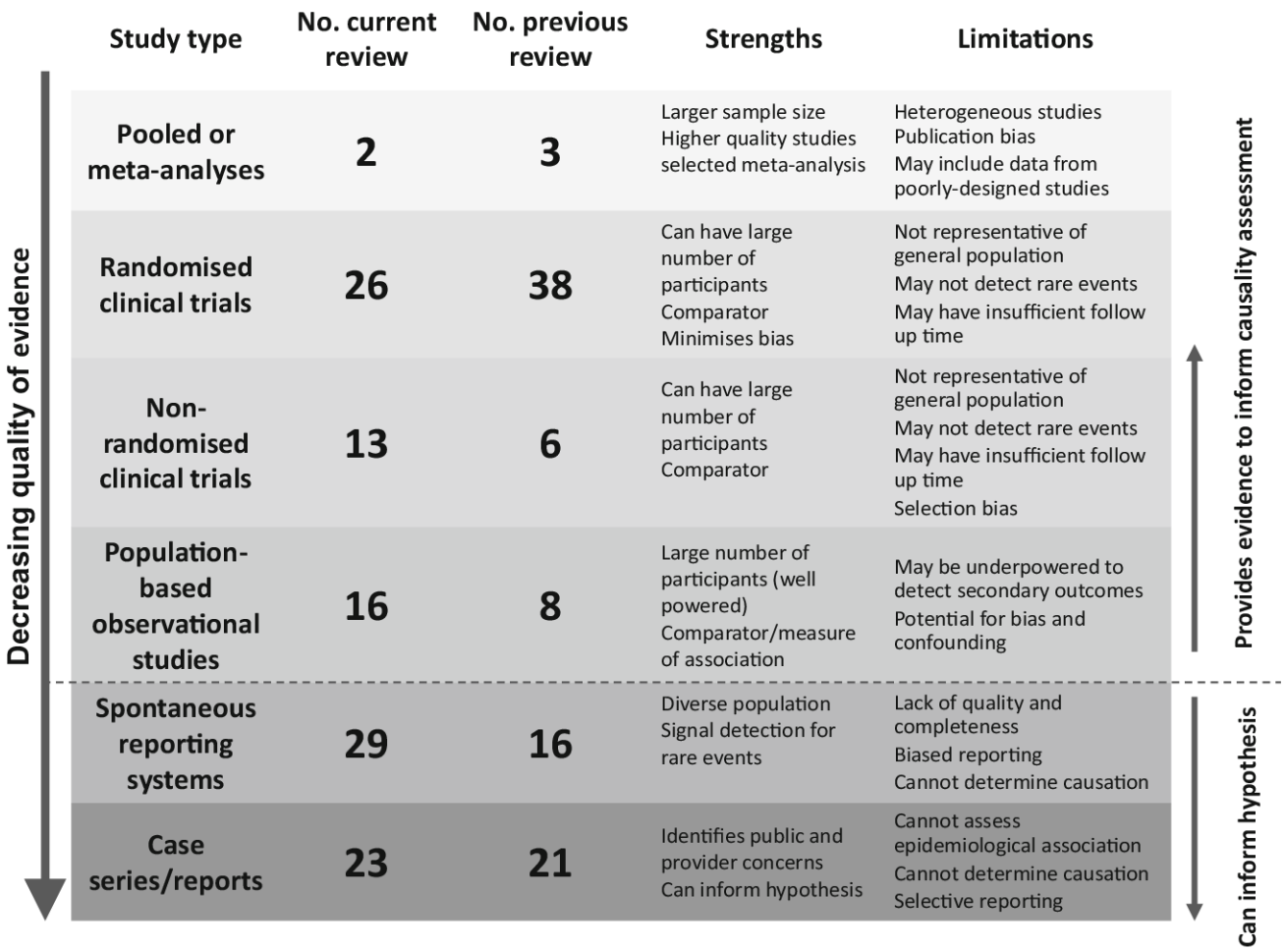

Fig. 1 Number of studies examined in current and previous [11] reviews by level of evidence. Adapted from National Health and Medical Research Council (NHMRC) evidence hierarchy [157] and GRADE [150]

assessment of the risk of AEs, which can be coupled with an assessment of potential biologic plausibility ('mechanistic evidence') to examine hypotheses identified from passive surveillance [18]. As for our previous review, our aim was to examine public and provider AE concerns, some of which have been raised by individual case reports or small studies. Importantly, while such published studies are referenced in this review, they can rarely be used to imply a cause and effect relationship between the vaccine and an AE [18].

3 Results

3.1 Body of Evidence

We identified 109 studies (Fig. 1). Forty-one publications reported on a total of 81 clinical trials. Twenty-nine studies of surveillance systems were examined (including one pregnancy registry), along with 23 case reports or case series and 16 population-based studies (several using multiple methods of analysis) across six countries.

3.2 Overall Safety Profile

3.2.1 Bivalent (2vHPV) and Quadrivalent (4vHPV) Vaccines

We previously determined that ISRs (such as pain and swelling) were among the most common AEs reported following 2vHPV and 4vHPV vaccine administration [11]. In recent clinical trials, both 2vHPV [19–24] and 4vHPV vaccines [25–27] also showed higher rates of ISRs than control (see Electronic Supplementary Material 1), with absolute rates ranging from 21.9 to 85% in vaccine recipients. In SRS data (see Electronic Supplementary Material 2), ISRs were reported at rates varying from 2.29 to 35.3 per 100,000 doses (distributed or administered), depending on reporting systems [28–31], and were among the most commonly reported AEs. Trials comparing 2vHPV and 4vHPV vaccines reported higher rates of injection-site pain and swelling with 2vHPV vaccine (see Electronic Supplementary Material 1) [32–35].

In 2vHPV vaccine clinical trials, systemic AEs were similar or slightly higher in the vaccine than in the control groups (see Electronic Supplementary Material 1) [19, 20, 36], in keeping with previous findings [11]. In the pooled analysis of 42 clinical studies in 33,339 girls and women [36], unsolicited AE rates within 30 days were similar between HPV (30.8%) and control groups (29.7%), as were MSCs (9.6 vs. 10.4%) (see Electronic Supplementary Material 1). As in our previous review, systemic AEs did not differ significantly between vaccine and placebo groups in 4vHPV clinical trials (see Electronic Supplementary Material 1) [25–27]. Trials comparing the 2vHPV and 4vHPV vaccines report similar rates of systemic AEs (see Electronic Supplementary Material 1) [32, 33].

For both the 2vHPV [30] and 4vHPV vaccine [28, 31], fever, headache, nausea and dizziness were the most frequently reported systemic AEs from SRSs (see Electronic Supplementary Material 2), similar to our previous findings [11]. The rate of any reported AE in SRSs is variable (from 19.2 per 100,000 doses distributed in Canada based on a restricted cohort and strict case definitions [29] to 37.2 per 100,000 doses distributed in the USA [37], 34.8 per 100,000 doses administered in Australia [28], 100 per 100,000 administered in the UK [38] and 149.5 per 100,000 distributed in Slovenia [31], where reporting is mandatory). In most of these countries, the 4vHPV vaccine was used exclusively or for the vast majority of doses, while the 2vHPV vaccine was used in the UK.

No increased risk of SAEs has been reported among vaccine as compared with control recipients in clinical trials of the 2vHPV [19, 21–23, 36] or 4vHPV vaccine [25–27] (see Electronic Supplementary Material 1), in keeping with our previous findings [11]. In two follow-on reports from a head-to-head 2vHPV and 4vHPV vaccine comparator study, SAEs and MSCs occurred at similar rates with each vaccine over a 48- to 60-month period of follow-up (see Electronic Supplementary Material 1) [39, 40]. The definition of SAEs is variable within SRSs, but rates were generally low (see Electronic Supplementary Material 2), e.g. 2.5 per 100,000 for 4vHPV in Australia from 2007 to 2014 [28], with emergency department visits reported at 4.6 per 100,000 in a single year of enhanced surveillance in 2013 [41]. In Slovenia, where reporting is mandatory, SAEs were identified at a higher rate of 8.4 per 100,000 (five in 59,520 doses distributed over 2009–2013), but no permanent sequelae were reported [31]. SAEs accounted for 7.5% of 4vHPV events in Canada [29] and 31% of AE reports for the 2vHPV vaccine in the UK, where specific alert terms are considered serious and the majority of serious reports were reported as "psychogenic in nature (due to the injection process and not due to the vaccine per se)" [38].

The relative risk (RR) of death in the 30-day window following any vaccination was examined in the US Vaccine Safety Datalink (VSD) study from 2005 to 2011, which used a case-centred method in females aged 9–26 years administered 1,355,535 doses of HPV vaccine (see Electronic Supplementary Material 3) [42]. The rate of death in HPV recipients was significantly lower than expected for this age group and there was no vaccine-attributable increase in risk to 30 days [RR1.28;95% confidence interval (CI) 0.44–3.68] (excluding external causes

such as homicide, suicide and accident). No deaths were causally associated with HPV vaccine. This is consistent with our previous findings that there was no increased risk of death in clinical trials and no causally related deaths identified in SRSs [11]. There was no relationship between deaths and the 4vHPV vaccine in a large observational study cited in our original review [43]. In a recent pooled analysis of 42 clinical trials, deaths were rare and balanced between groups [36]. In two recent trials, one reported an equivalent proportion of deaths between vaccine and control groups (0.2%) [19] and the other reported 14 deaths in 2881 vaccinated and three deaths in 2871 control participants, with no clustering in cause of death, no temporal relationship between vaccination and death, and no causal link with vaccination identified [20]. No deaths identified from SRSs were causally linked to HPV vaccination (see Electronic Supplementary Material 2) [29, 30].

3.2.2 9vHPV Vaccine

Data from clinical trials reported a similar safety profile for the 9vHPV vaccine as for 4vHPV (see Electronic Supplementary Material 1). Overall ISRs (including severe ISRs) were slightly more frequent with the 9vHPV vaccine [44–46], which is likely related to the greater amount of adjuvant (500 vs. 225 μg of aluminium). For example, in a multicentre trial of more than 14,000 females aged 16–26 years, ISRs and severe ISRs were reported in 90.7 versus 84.9% and 4.3 versus 2.6% in 9vHPV and 4vHPV vaccine recipients, respectively [44]. Frequencies of systemic AEs were similar between groups [44, 46] with headache the most common (11.4–14.6% of participants receiving 9vHPV vaccine and 11.3–13.7% among 4vHPV vaccine recipients). In a trial of 900 adolescent girls and women previously vaccinated with three doses of 4vHPV, randomised to receive a three-dose course of 9vHPV vaccine or placebo, AE rates, particularly ISRs, were higher in the 9vHPV vaccine group but similar to those in other 9vHPV vaccine trials [47]. Two trials examining concomitant vaccine administration (with diphtheria–tetanus–pertussis and inactivated poliomyelitis vaccine [48] or diphtheria–tetanus–pertussis and quadrivalent meningococcal conjugate vaccine [49]) demonstrated similar AE rates with concomitant vaccination compared with 9vHPV vaccine alone, although injection-site swelling at the 9vHPV vaccination site was significantly more frequent with concomitant administration. In the former study [48], swelling occurred in 13% of concomitant vaccine recipients compared with 8.2% of 9vHPV vaccine recipients ($p = 0.011$); in the latter [49], swelling occurred in 14.4% of the concomitant administration group and 9.4% of the 9vHPV vaccine-only group ($p = 0.07$).

In a combined analysis of seven clinical trials including 15,776 9vHPV vaccine recipients, SAEs occurred in 2.3% [45]. No vaccine-related SAEs were reported when the 9vHPV vaccine was administered concomitantly with other vaccines [48, 49]. The 9vHPV vaccine has recently been introduced into national and state vaccination programmes, including in the USA and parts of Canada from 2015 and New Zealand from 2017. SRS data have not yet been published, but no safety signals have been reported to date. There was no imbalance in deaths in clinical trials [44–46] and routine surveillance through population-level data is ongoing.

3.3 Adverse Events of Special Interest

3.3.1 Syncope

Our previous review highlighted syncope from SRSs at a rate of 8–10 per 100,000 doses [11], although analysis of VSD data did not demonstrate an increased risk following the 4vHPV vaccine compared with other adolescent vaccines (RR 0.86) [11, 50]. Syncope on the day of vaccination was associated with HPV vaccine in a large observational study cited in our previous review [43]. Recent SRS data [28, 30, 31, 51, 52] shows variable reporting rates for syncope (see Electronic Supplementary Material 2). During enhanced surveillance in Australia in 2013 [41], syncope was found to be more common in younger females and males (12–13 years) than in older males (14–15 years). Whilst syncope itself is relatively benign, its occurrence following vaccination mandates that prevention and management protocols be in place as these prevent syncope-related injury.

3.3.2 Allergy and Anaphylaxis

We previously reported SRS data showing similar HPV vaccine-related anaphylaxis rates as for other vaccines (1–10 cases per million doses) [11]. The rate of anaphylaxis reported from the VSD at that time was 1.7 per million doses [50]. Recent SRS data provide anaphylaxis rates in Australia [28] and Canada [29] (0.31 and 0.30 per 100,000, respectively) and anaphylaxis or anaphylactoid reaction rates in the UK [38] (1 per 100,000) that are consistent with our earlier analysis (see Electronic Supplementary Material 2). In Germany, active surveillance based on paediatrician reporting cards combined with passive reporting in a capture–recapture analysis reported an anaphylaxis rate of 0.223 per 100,000 doses (see Electronic Supplementary Material 2) [53]. HPV vaccines are contraindicated in those with hypersensitivity following a previous dose, or to the vaccine components [54].

3.3.3 Venous Thromboembolism

Our [11] and another HPV safety review included an early report from the US Vaccine Adverse Event Reporting System (VAERS) [55], which detected a potential safety signal for vaccine-associated VTE, but noted that near-real-time monitoring of the HPV vaccine did not find a significantly increased risk among girls [50]. Recent SRS-based studies (see Electronic Supplementary Material 2) have not found any safety signal for VTE, and several population-based studies have found no increased risk (see Electronic Supplementary Material 3). This includes data from two self-controlled studies from the USA that found no significant increase in risk in any post-vaccination window [56, 57]. Both studies accounted for contraceptive use as a risk factor and conducted a medical review. A Canadian national registers study observed three cases of VTE among 195,270 girls within 42 days of HPV vaccination; all three had other conditions known to be associated with VTE [58]. Two large European studies also found no increased VTE risk: one in 296,826 4vHPV vaccine recipients [RR 0.86 (95% CI 0.55–1.36) within 90 days] [59] and a second in 500,345 females within 42 days [adjusted incidence rate ratio (IRR) 0.80; 95% CI 0.55–1.16] [60].

3.3.4 New-Onset Autoimmune Disease

3.3.4.1 Overview of Previous Data and Clinical Trials AIDs are described in clinical trial data as either potential immune-mediated disease (pIMD) (a condition that may include autoimmune and other inflammatory and/or neurological conditions) or a new-onset AID (NOAD) (a pIMD that is considered to be of new onset based on review of medical history) [22]. In our previous review [11], we reported data from 2vHPV vaccine trials [61–64], 4vHPV vaccine trials [65] and a pooled analysis of trials of vaccines containing ASO4 adjuvant (including the 2vHPV vaccine) [66] showing no difference in the frequency of NOADs between vaccine and control groups. Previously cited [11] large studies based on population data sources [67, 68] did not identify a safety signal for multiple (up to 16) pre-specified autoimmune conditions; one detected an elevated IRR for Hashimoto's thyroiditis which, after further investigation, did not suggest an association. The recent pooled analysis of 42 completed or ongoing clinical studies of the 2vHPV vaccine in females (33,339 vaccinated and 24,241 controls) found no difference in the onset of PIMDs [36], consistent with the findings of other 2vHPV vaccine studies, including in low-income ($n = 1$) and upper-middle-income ($n = 5$) countries (see Electronic Supplementary Material 1) [19–23, 69, 70]. Among 4vHPV vaccine studies reporting SAEs, including those with long-term follow-up, autoimmune events were not identified [71, 72] (see Electronic Supplementary Material 1) [73].

3.3.4.2 Neurological Autoimmune Conditions In our first review, we cited an analysis of US VAERS data that detected a possible increased risk of GBS following HPV vaccination [74]. However, this study was noted to have a number of significant limitations in the interpretation of data and assessment of the exposure period [75]. A risk was not identified in other VAERS analyses or subsequent large population-based studies [50, 68, 75]. At that time, well-conducted population-based studies had also not found any increased risk of MS or ADEM [68]. Similarly, well-conducted population-based studies examined for this current review have not consistently demonstrated any increased risk for demyelinating diseases following HPV vaccination (see Electronic Supplementary Material 3).

A large linkage study in Denmark and Sweden used both cohort and self-controlled case series analyses to examine the risk of demyelinating disease up to 2 years following vaccination among 3,983,824 females, 789,082 of whom were vaccinated [76]. In the cohort study, there was no increased risk of MS (IRR 0.90 [95% CI 0.70–1.15]) or other demyelinating diseases [including optic neuritis (ON), neuromyelitis optica, transverse myelitis (TM) and ADEM; IRR 1.00 (95%CI 0.80–1.26)]. There was also no increased risk in the self-controlled analysis [MS IRR 1.05 (95% CI 0.79–1.38); other demyelinating diseases IRR 1.14 (95% CI 0.88–1.47)] and no increased risk in any sensitivity analyses. Another linkage study in Denmark and Sweden [59] examined a cohort of 296,826 girls for 23 AIDs (see Electronic Supplementary Material 3) and found no significant increase in risk for 20 conditions including paralysis (although specific demyelinating conditions were not assessed).

Another large cohort study was conducted in France and had been published as a report at the time our search was conducted (see Electronic Supplementary Material 3) [77]; the peer-reviewed article has recently been published [78]. This study examined 842,120 vaccinated and 1,410,596 unvaccinated girls, identifying no increased risk for 12 of 14 AIDs and no increased risk for AID overall [hazard ratio (HR) 1.07 (95% CI 0.99–1.16)] (see Electronic Supplementary Material 3). An elevated HR of 4.00 (95% CI 1.84–8.69) was found for GBS, which was reported in 19 vaccinated and 21 unvaccinated girls. This association was most marked in the first 3 months following vaccination and remained consistent in sensitivity analyses. However, the risk windows assessed were long, which may introduce bias, and cases were identified through routinely coded hospitalisation data alone. There was no case validation performed to confirm the diagnoses. The World Health Organization's (WHO) Global Advisory Committee of the

Safety of Vaccines (GACSV) reviewed this report in 2015 [79] and noted the small risk of GBS in the 3 months after vaccination identified in the report had not been seen in smaller studies, and that additional, sufficiently powered studies would be needed to assess the magnitude of any risk (see Sect. 4 for further details).

Several case-control studies have also assessed the relationship between HPV vaccine and AIDs (see Electronic Supplementary Material 3). In France, a study in which 211 cases with incident AID were matched to 875 general practice controls [80] found no increased risk for AID [adjusted odds ratio (adjOR) 0.9 (95% CI 0.5–1.5)] and no significant increased risk for individual specific AIDs including MS [OR 0.3 (95% CI 0.1–0.9)] (although unlike the larger cohort studies cited earlier, the study had insufficient power to detect risk for individual diseases). No cases of GBS ($n = 15$) were exposed to the HPV vaccine. In the USA, a nested case-control study matched 92 females with AID, including cases of MS and other acquired CNS demyelinating syndromes (ADEM and clinically isolated syndromes including idiopathic TM and ON) to 459 controls [81], showing no significant increased risk up to 3 years after vaccination [OR 1.05 (95% CI 0.62–1.78)].

These large population-based cohort studies add value to rates identified from several reports of SRSs and trends identified from ecological studies (see Electronic Supplementary Material 2 and 3), where it is not possible to assess vaccine-attributable risk. An ecological study based on hospital admissions in Scotland following the introduction of a female HPV vaccination programme [82] reported that rates of demyelinating disease did not exceed expected incidence except in 2010–2011; MS alone did not exceed expected incidence (see Electronic Supplementary Material 3). Analyses of SRSs by external researchers accessing publically available online databases have produced variable rates for MS [83] and ADEM [84], while low rates of MS [30] and GBS [28] have been identified from other SRSs with no confirmed signal identified (see Electronic Supplementary Material 2) [85].

3.3.4.3 Other Autoimmune Conditions Other autoimmune conditions have been examined in the literature, including systemic lupus erythematosus (SLE), ON, inflammatory bowel disease (IBD), arthritis, including juvenile arthritis, and thyroiditis. The large linkage study in Denmark and Sweden [59] found no increased risk of SLE [RR 1.35 (95% CI 0.69–2.67)], ON [RR 0.67 (95% CI 0.27–1.64)], juvenile arthritis [RR 0.99 (95% CI 0.78–1.26)], idiopathic thrombocytopenic purpura (ITP) [RR 1.18 (95% CI 0.65–2.17)], coeliac disease [RR 1.11 (95% CI 0.90–1.36)], Crohn's disease [RR 0.85 (95% CI 0.62–1.17)], ulcerative colitis [RR 0.71 (95% CI 0.49–1.03)] or thyroiditis [RR 1.12 (95% CI 0.82–1.52) for Hashimoto's thyroiditis] (see Electronic Supplementary Material 3). The study did identify three conditions that had a significant rate ratio [Bechet's syndrome RR 3.37 (95% CI 1.05–10.80), Raynaud's disease RR 1.67 (95% CI 1.14–2.44) and type 1 diabetes mellitus (T1DM) [RR1.29 (95% CI 1.03–1.62)]. However, none of these conditions met the three predefined, required signal strengthening criteria [(i) analysis based on ≥ 20 cases; (ii) rate ratio of ≥ 3; and (iii) significant rate ratio in country specific analyses] to support an association. There was no consistent timing of disease onset after vaccination and no significant difference in risk within versus beyond 180 days following vaccination. Given the multiple ($n = 29$) comparisons made, these associations are likely to be due to chance [86].

The French cohort study report [77] identified no increased risk for AID overall [HR 1.07 (95% CI 0.99–1.16)], but reported an elevated HR for IBD [HR 1.18 (95% CI 1.01–1.38)]. Conversely, no link was identified in the linkage study from Denmark and Sweden (described in Sect. 3.3.4) [59]. The French cohort study had a number of limitations, including a relatively small population size that was likely inadequate to assess changes in multiple individual conditions over time [82].

The French case-control study [80] found no increased risk of any connective tissue disorders (SLE, rheumatoid arthritis or juvenile chronic arthritis) [OR 0.8 (95% CI 0.3–2.4)], ITP [OR1.0 (95% CI 0.4–2.6)], or T1DM [OR 1.2 (95% CI 0.4–3.6)] following HPV vaccination (see Electronic Supplementary Material 3). These findings are consistent with an ecological study demonstrating no increase in hospitalisations for SLE (see Electronic Supplementary Material 3) [87]. In an ecological study from Scotland [82], coeliac disease, T1DM and juvenile rheumatoid arthritis did not exceed the expected incidence following the introduction of HPV vaccine except in 2011, and the incidence of T1DM and coeliac disease also increased in boys who were not vaccinated (see Electronic Supplementary Material 3).

Autoimmune conditions, including SLE and ON, have been reported at very low rates in SRSs (see Electronic Supplementary Material 2) [30]. While one study purported to use a case-control design to examine publically available online VAERS data and described an increased odds ratios for six of eight autoimmune conditions following HPV vaccination (including SLE and arthritis) [88], this analysis was significantly flawed. The VAERS database only receives AE cases, so does not provide sufficiently unbiased data to design or test an association using case-control methodology and its use is limited to hypothesis generation [89]. In keeping with evidence presented in our first review [11, 68], data from the well-conducted, population-level

observational studies cited earlier do not support a causal association between AID and HPV vaccine, as hypothesised by case reports and case series, which are more susceptible to bias (see Electronic Supplementary Material 4) [90–93].

Case reports of primary ovarian insufficiency (POI) with variable and sometimes long intervals between HPV vaccination and onset, and without a biological mechanism and/or inadequate case definitions, have been construed to propose a link between vaccination and POI (see Electronic Supplementary Material 4) [94–96]. However, rates of POI are low in SRSs [97] (0.065 per million doses in the USA and 0.14 per million doses in Australia) (see Electronic Supplementary Material 2) with no consistent pattern with HPV vaccine [98], and ecological data do not identify any increase over expected levels (see Electronic Supplementary Material 3) [82].

There is no robust evidence to confirm the validity of the recently proposed autoimmune/inflammatory syndrome induced by adjuvants (ASIA). This term appears to cover an ill-defined, diverse range of conditions [99, 100] with non-specific criteria for diagnosis and lack of a biological mechanism [100] described in case series (see Electronic Supplementary Material 4) [101–103] and from SRS data (see Electronic Supplementary Material 2) [99]. There are currently no data to support the causation of this collection of symptoms by vaccine adjuvants [100]. Of note, patients receiving much larger doses (at least 100 times more) of adjuvant for allergen-specific immunotherapy have actually been shown to have a lower incidence of AID [104]. Reports of the presence of HPV *L1* gene DNA fragments in post-mortem specimens [105, 106], including claims of a link to autoimmune cerebral vasculitis, have been criticised by both the Centers for Disease Control and Prevention (CDC) (Clinical Immunization Safety Assessment working group) [107] and the WHO Global Advisory Committee on Vaccine Safety (GACVS) [108] due to substantial methodological concerns and lack of evidence to support conclusions.

3.3.5 Other Neurological and Complex Conditions

3.3.5.1 Seizure and Convulsion Our original review [11] cited the near real-time VSD study [50] in which there was no statistically significant increased risk of seizure in vaccine recipients. In the recent linkage study of 296,826 vaccinated girls in Demark and Sweden [59], there was a reduced risk of epilepsy reported within 180 days of vaccination [RR 0.66 (95% CI 0.54–0.80)] (see Electronic Supplementary Material 3). Surveillance systems have reported variable rates for seizure following HPV vaccine (noting that studies may have included seizure secondary to syncope), from 0.3 per 100,000 in Canada, where inclusion criteria for passive reporting are more stringent [29], and 1.36 per 100,000 [28] in Australia (4.2 per 100,000 with enhanced surveillance) [41] to 3.4 per 100,000 doses distributed in Slovenia, where a high rate results from mandatory reporting (see Electronic Supplementary Material 2) [31].

3.3.5.2 Nerve Palsies In the linkage study from Denmark and Sweden, there was a no association between Bell's palsy and HPV vaccination [RR 1.02 (95% CI 0.72–1.43)] (see Electronic Supplementary Material 3) [59]. Long-term follow-up [72] of one 4vHPV vaccine clinical trial cited in our initial review [109] reported one case of cranial nerve paralysis as an SAE. SRS data from VAERS identified seven cranial nerve palsies following the 4vHPV vaccine, which were in some cases part of a broader clinical syndrome [110], and VIIth cranial nerve paralysis was reported at a low rate of 0.066 per 100,000 doses of 2vHPV vaccine distributed by the GSK global safety database (see Electronic Supplementary Material 2) [30]. Ecological data based on Scottish hospital admissions demonstrated no increase in the rate of Bell's palsy pre- and post-introduction of HPV vaccination [82] and data linkage within the same study identified four vaccinated cases among 12 reported cases of Bell's palsy in females aged 12–13 years diagnosed in 2012–2014 (see Electronic Supplementary Material 3).

3.3.5.3 Complex Regional Pain Syndrome, Postural Orthostatic Tachycardia Syndrome and Chronic Fatigue Syndrome CRPS and POTS have been the subject of controversial reports regarding HPV vaccination. These conditions are described as having unclear, heterogenous aetiology and are diagnostically challenging, with onset difficult to determine. Although autonomic dysfunction may be seen in both conditions, they are clinically distinct, and symptoms overlap with other conditions such as chronic fatigue syndrome (CFS) and non-organic disorders [5, 79, 111]. CRPS describes chronic pain typically following (often minor) trauma or injury [15, 79]. POTS is a condition characterised by a substantial, sustained increase in heart rate when moving from lying to sitting, accompanied by symptoms of orthostatic intolerance [79]. Although POTS may be severe, it has a favourable long-term prognosis with appropriate management. Both conditions are well-recognised as occurring in adolescence and early adulthood, although with poorly defined epidemiology due to difficulty in diagnostic precision. Thus, the background incidence may be variable and is not well-described.

Reports of fatigue syndromes (which may overlap with CRPS and POTS) from the Medicines and Healthcare Regulatory Products Agency (MHRA) yellow card passive surveillance system were compared with background rates

from the Clinical Research Practice Datalink (CRPD), a large general practice-based dataset, with reports consistent with background rates even in sensitivity analyses allowing for low reporting [112]. The CRPD was also used to conduct ecological analyses, with no increase in the risk of fatigue syndromes between 2006 and 2007 (pre-HPV vaccination) and 2009–2011 (post-HPV vaccination) [IRR 0.094 (95% CI 0.78–1.14) for girls] (see Electronic Supplementary Material 3) [112]. In a self-controlled case series of 187 girls based on the same data source, there was no increased risk in the 1 year following vaccination compared with the remainder of the study period [IRR 1.07 (95% CI 0.57–2.00); $p = 0.84$] [112]. Based on UK yellow card reports for 2008–2012, observed rates of CRPS were below expected rates using two different published estimates of background incidence (see Electronic Supplementary Material 2) [38]. Ecological data from Scotland did not show an increase in POTS admissions between 2004 and 2014 (see Electronic Supplementary Material 3) [82].

These findings do not support the conclusions based on case reports of CRPS (along with other less well-defined conditions) from Japan (see Electronic Supplementary Material 4) [113], which led to withdrawal of the Government recommendation for HPV vaccination and have been determined by expert review to be unrelated to the vaccine [79]. Similarly, a case report of CRPS and fibromyalgia following HPV vaccine (see Electronic Supplementary Material 4) [114] has been criticised based on ill-defined clinical assessment [115]. POTS following HPV vaccine has been reported in two case series from Denmark (see Electronic Supplementary Material 4) [116, 117]. These reports have been criticised by the European Medicines Agency (EMA) due to the diversity of clinical features and potential syndromes included (see Sect. 4) [111]. In clinical trials, one case of neurocardiogenic syncope dysautonomia [118] and one case of somatoform autonomic dysfunction following the 2vHPV vaccine [19] were reported, along with one POTS case 4 years following vaccination in a 9vHPV vaccine trial that was independently deemed not related to vaccination [45].

The rate of CRPS reported to SRSs is low at 0.07% of VAERS reports [15], with 17 cases among 18,391 reports to the global GSK database [119], only five of which were confirmed to meet diagnostic criteria following independent review (see Electronic Supplementary Material 2). Including all 17 reported cases, the rate was 0.08 per 100,000 in the UK and 0.14 per 100,000 in Japan. The observed rate was less than the background rate in the USA and Netherlands but higher in the UK and Japan when unconfirmed or unlikely cases were included in the analysis. However, SRSs are subject to stimulated reporting following media coverage, and 35% of reports were received after a media report of an initial Japanese case.

3.3.5.4 Other Conditions A case-centred study in the USA found no significantly increased risk for sudden sensorineural hearing loss in the 28 days post-vaccination [OR 4.155 (95% CI 0.17–29.13)] [120]. There was no significant risk for migraine in a cohort study from the Netherlands [121] based on ecological data, cohort analysis or in a self-controlled design [RR 6.3 (95% CI 0.80–49.1)]. In the linkage study of 296,826 girls from Denmark and Sweden, there was a reduced risk of paralysis [RR 0.56 (95% CI 0.35–0.90)] in vaccinated girls, and no association with narcolepsy [RR 0.71 (95% CI 0.29–1.79)] [59] (see Electronic Supplementary Material 3).

3.4 Special Populations

3.4.1 Males

We previously reported that clinical trials of the 2vHPV and 4vHPV vaccine showed similar or lower incidence of AE in males than in females [11]. Recent studies of 4vHPV vaccine have included males [26, 122], with 42% of male participants reporting AEs (46.7% of which were ISRs) and no SAEs in one study (see Electronic Supplementary Material 1) [122]. For the 9vHPV vaccine, a multisite single-armed study of men and women [123] reported a lower proportion of AEs among men than women, including ISRs (67.2 vs. 84.1%) and systemic events (16.0 vs. 23.4%). A study of the 9vHPV vaccine among women (16–26 years), girls (9–15 years) and boys (9–15 years) reported a lower proportion of ISRs and systemic AEs among girls and boys than among women (see Electronic Supplementary Material 1) [124]. AEs were compared between males and females during a period of enhanced surveillance following the commencement of the 4vHPV immunisation programme for males in Australia in 2013 (see Electronic Supplementary Material 2) [41]. Overall, the rate of AEs was higher in younger females than younger males (12–13 years), and rates were notably lower among older males (aged 14–15 years) (see Electronic Supplementary Material 2). Rates of ISR and syncope were notably lower among males.

3.4.2 Pregnant Women

HPV vaccines are not recommended for use in pregnant women, but data from women vaccinated during pregnancy or who became pregnant shortly after vaccination are reported from clinical trials, post-marketing surveillance and clinical registries. We previously found no evidence of an association between congenital abnormalities or spontaneous abortion and receipt of vaccine, but data were limited [11].

A recent pooled analysis of 2vHPV vaccine clinical trials [36] reported no increased risk of spontaneous

abortion among 914 women vaccinated during pregnancy [15.3% among 465 HPV vaccine recipients and 11.1% among 449 controls, RR 1.37 (95% CI 0.94–2.01)]. Specific pregnancy outcomes were similar between groups, and this is consistent with other 2vHPV vaccine trials [20, 23]. In one 4vHPV vaccine trial, healthy live births and fetal loss were similar between vaccine and control groups; spontaneous abortion as the reason for fetal loss was reported at a higher rate in the vaccine group but it was noted that there were more high-risk women in the vaccine group [27]. A review of seven trials of 9vHPV vaccine found similar pregnancy outcomes among 9vHPV and 4vHPV vaccine recipients, with spontaneous abortion and congenital anomalies rates reported comparable to expected published prevalence rates and no AE related to a pregnancy being reported as vaccine-related [45].

Data from SRSs, registries and population-based studies have not demonstrated any increase in foetal loss above background rates, and do not report any concerning pattern in foetal loss or anomalies following HPV vaccination. VAERS reports between 2006 and 2013 [125] included 147 pregnancies, of which 70.1% reported no AE, and the spontaneous abortion rate (10.2%) was in keeping with the expected background rate (see Electronic Supplementary Material 2). Data from a pregnancy registry from the USA, France and Canada [126] reported rates of spontaneous abortion [6.7 per 100 (95% CI 5.5–8.2)] and foetal death [0.8 per 100 (95% CI 0.4–1.4)] in keeping with rates in the general population, and major birth defects [2.4 per 100 (95% CI 1.7–3.3)] did not show any pattern in type or timing to vaccination (see Electronic Supplementary Material 2). A UK cohort study [127] identified HPV-vaccinated women aged 15–25 years registered with the Clinical Practice Research Datalink (CRPD) and defined exposure based on the window between the last vaccine dose and first day of gestation. Overall, there was no increased risk of spontaneous abortion among the 207 women exposed to HPV vaccine during the risk window compared with the 632 unexposed women [HR 1.30 (95% CI 0.79–2.12)] (see Electronic Supplementary Material 3). In sensitivity analyses, the risk of spontaneous abortion following two doses within 4–5 weeks was 2.55 (95% CI 1.09–5.93) based on analysis of six exposed and 29 unexposed women. These findings provide reassuring information for counselling patients inadvertently vaccinated around the time of conception or in early pregnancy, but do not support a routine recommendation for HPV vaccination in pregnancy [126, 127].

3.4.3 Persons with Pre-Existing Autoimmune Disease

Clinical trials in populations with pre-existing autoimmune conditions have not identified any safety concerns (see Electronic Supplementary Material 5). Two studies of the 4vHPV vaccine in patients with SLE [128, 129] reported no difference in the likelihood of disease flares, with rates between vaccinated and unvaccinated patients of 0.22 and 0.20 per patient per year, respectively, in one study [128]. ISRs were mild and systemic events were rare in both groups [128]. In a study of the 2vHPV vaccine in patients with juvenile idiopathic arthritis, the frequency of local and systemic reactions did not differ between patients and healthy controls [130]. Among 37 patients with IBD receiving the 4vHPV vaccine, almost half reported soreness at the injection site while other local AEs were uncommon and systemic AEs were rare [131]. These studies are reassuring with regards to the safety of the HPV vaccine in patients with pre-existing AID, although sample sizes were small.

3.4.4 HIV-Infected Persons

Five clinical trials have examined the use of HPV vaccine in HIV-infected persons, of which two studies included HIV-negative control groups (see Electronic Supplementary Material 5). One 2vHPV vaccine study reported a similar incidence of local and systemic AEs in HIV-positive and HIV-negative vaccine recipients, with the most common AEs being injection-site pain and swelling and headache [132]. Similar results were found in a 4vHPV vaccine study in HIV-positive ($n = 46$) and HIV-negative subjects ($n = 46$), although injection-site pain was more frequent in HIV-positive recipients (32.6 vs. 18.8%) [133]. A head-to-head trial of the 2vHPV versus 4vHPV vaccine in HIV-positive patients reported that ISRs were more common in the 2vHPV vaccine group (91.1 vs. 69.6%; $p = 0.02$) [134], as has been reported in studies of non-HIV-infected individuals [32–35]. Across all five studies, very few SAEs ($n = 7$) were reported. Only one vaccine-related SAE was reported in a patient who experienced fatigue [135]; another study reported an allergic reaction and grade 3 fatigue but did not indicate if these events were vaccine related [136].

4 Discussion

4.1 Summary of Data from This and Our Earlier Review

We have reviewed 109 publications between May 2012 and August 2016 that present original data on potential adverse outcomes following HPV vaccination (using three registered vaccines) in diverse populations and locations, and in males and females as well as persons with pre-existing medical conditions, building on our earlier review.

With the aim of addressing all AESI and in the context of reduced confidence in HPV vaccine among some groups, our review examined all identified case reports, analyses of post-marketing surveillance data, ecological studies, clinical trials and population-level observational studies. However, our conclusions are based on critical consideration of the limitations and strengths of each study type, with findings based primarily on robust data from well-designed clinical trials and observational studies, particularly those in large populations. A number of the publications reviewed, notably among the case studies, cases series and some analyses of data from SRSs, contained critical flaws. These include major issues in case ascertainment and classification (e.g. inappropriately attributing a diverse array of individual symptoms to a syndromic illnesses), unsuitable analytic methods and/or misleading conclusions. Although case reports and series by their very nature can almost never provide evidence of a cause and effect relationship between a vaccine exposure and an adverse outcome, data from such reports, often by the same few authors, have been presented to provide evidence of harm, despite the volume of high-quality studies to the contrary. The WHO GACVS has repeatedly expressed concern that allegations based on poor-quality evidence have a damaging impact on vaccine coverage that "will result in real harm" [137].

In summary, and as previously recognised [11], ISRs were among the most common AEs following HPV vaccine administration and occurred more frequently following the 9vHPV vaccine, although they were usually mild and self-limiting overall. Systemic AEs occurred at similar rates following the 9vHPV vaccine compared with the 4vHPV vaccine. Consistent with findings from our earlier overview, no increased risk of SAEs was evident in this review. Rates of anaphylaxis were also in keeping with rates reported for other vaccines. Syncope, a known but manageable risk of adolescent vaccination [137, 138], continues to be reported, most commonly in younger females and males. It is now well-recognised that this is related to the population and setting for administration of HPV vaccine and that practical measures, including a 15-min observation period post-vaccination, should be taken to reduce the risk of syncopal seizure or falls following adolescent vaccination [137, 138].

To augment the previous review, this review examined additional outcomes in specific populations and found no consistent evidence for an increased risk of any AESI, including demyelinating syndromes, VTE, AID, or neurological conditions such as CRPS and POTS. No safety concerns were identified in specific populations, including males and those with underlying medical conditions.

4.2 Key Reviews, Independent Expert Analyses and Recent Publications

Our findings concur with that of the recent WHO position paper [8] and the most recent GACVS report [137]. The GACVS has met on seven occasions since 2007 to discuss the safety of the HPV vaccine and have assessed concerns related to anaphylaxis, syncope, mass psychogenic illness, AID including GBS and MS, VTE, CRPS and POTS [9, 137]. The GACVS "considers HPV vaccines to be extremely safe" [137], and reports have been consistently reassuring with no new AEs of concern identified in the 2017 report based on many large, high-quality studies and recent data [137].

In 2015, both the GACVS [79] and the EMA [111] reviewed the evidence for a causal association between the HPV vaccine and POTS and CRPS. The GACVS reported that it had "not found any safety issue that would alter its recommendations for the use of the vaccine". The EMA review, which included data from clinical trials, post-marketing surveillance and literature, in addition to expert review, found no support for a causal association between HPV vaccine and CRPS or POTS. The rate of CRPS and POTS in HPV vaccinated and unvaccinated groups in clinical trials did not differ; there was no suggestion of an increased occurrence of CRPS or POTS in relation to HPV vaccine in observed versus expected analysis; and no consistent pattern in timing following vaccination or in clinical features of reported CRPS or POTS cases. The majority of POTS cases in the EMA review arose from the single centre in Denmark [116, 117], and the overlap with CFS was noted. Both organisations emphasised the reassuring results from the analysis of fatigue syndromes in the UK [112]. Despite this robust assessment, reports of patients with a diverse range of symptoms have recently been published but do not provide epidemiological or mechanistic evidence of a causal association [139, 140]. The 2017 GACVS statement [137] reiterated that there was no new evidence for a causal association between HPV vaccine and POTS, CRPS, diverse symptoms or pain and motor dysfunction, or POI. Future population-based epidemiological studies examining the spectrum of conditions that include POTS and CRPS, using standardised case definitions, are required to ensure ongoing confidence.

The 2015 GACVS [79] review noted the small risk of GBS in the 3 months following vaccination identified in the French report [77] and, at that time, called for additional, well-powered studies to examine the risk. While several studies have found no cases of GBS in the post-vaccination risk period [80, 141], a large self-controlled case series has recently been published from the UK [142], along with several studies on AID more generally [141, 143, 144]. The UK study [142] assessed 100 young

females with GBS and showed no increase in risk of disease onset in the 3-month risk window following HPV vaccination [RR 1.04 (95% CI 0.47–2.28)], nor within 6 or 12 months following vaccination. The 2017 GACVS report [137] assessed this additional evidence, along with new VAERS data (based on 60 million doses distributed) and VSD data (based on 2.7 million doses administered), which found no association between HPV vaccine and GBS and concluded that a risk of >1 case per million vaccine doses could now be excluded. The original French cohort study was recently published [78], citing an adjusted HR of 3.78 (95% CI 1.79–7.98) at any time following vaccination, higher in the first 2 months, and consistent with analyses using the self-controlled case series method on the same data (based on 19 cases). This study used routine hospital coding and did not validate cases or diagnostic criteria; the authors stated the need for further studies to confirm the apparent increased risk of GBS. The recent UK study [142] uses clinician-validated cases and a robust case definition and is the largest study so far published. Along with additional evidence cited by the GACVS, these findings do not confirm a risk of GBS.

With respect to AID more generally, no recent studies have consistently identified an increased risk. A Swedish data-linkage study in a cohort of 70,265 females with pre-existing AID found no increased risk for new-onset AID following HPV vaccination (IRR 0.77 [95% CI 0.65–0.93]) [143]. A case-control study from France [141] assessed 478 cases matched to 1869 controls and found a negative association between HPV vaccination and AID overall [OR 0.58 (95% CI 0.41–0.83)], and no increased risk of individual diseases. A large cohort study based on the UK CRPD [144] examined vaccinated females compared with a historical female cohort (along with concurrent and historical male cohorts), with 65,000 subjects in each group. The analysis found no evidence of an increased overall risk of AID following 2vHPV vaccination. For three individual diseases with ten or more cases, there was no increased risk for Crohn's disease or T1DM. An elevated IRR for confirmed autoimmune thyroiditis of 3.75 (95% CI 1.25–11.31), which did not persist in analyses of confirmed and non-confirmed cases, and has not been shown in other studies [59], should be examined specifically in future studies.

Other evidence published since the search conducted for this review includes a linkage study [145] demonstrating no significant risk of adverse pregnancy outcomes following 4vHPV vaccination. A pilot analysis [146] using novel methodology to assess electronic health insurance data of more than 1.9 million recipients of 4vHPV in males and females only identified signals for known AEs, predominantly ISR. The 2017 GACVS report concluded that inadvertent HPV vaccine administration during pregnancy has not been shown to be associated with adverse outcomes. The GACSV report [137] also cited evidence from a systematic review of randomised controlled trials which showed no difference in the rates of selected SAEs between HPV vaccine and control participants. Currently, publicly available data indicates there have been 5403 notifications related to the 9vHPV vaccine, of which the vast majority (97.9%) of events were not serious, although no conclusions can yet be drawn from these data due to lack of completeness [147]. A detailed post-marketing safety analysis plan for the 9vHPV vaccine has been implemented in the USA [98].

Other authors have recently published reviews of 4vHPV vaccine safety. A systematic review of 4vHPV vaccine randomised clinical trials included 14 studies and concluded that the vaccine was safe and well-tolerated, with ISR and fever the main AEs and a low frequency of SAEs [148]. A narrative review from the CDC concluded that there were no confirmed safety signals identified for the 4vHPV vaccine apart from syncope, which is preventable [98]. Another narrative review of post-licensure surveillance data also noted that syncope, and possibly skin infections, were associated with vaccination and that SAEs, including AID, had not increased beyond background rates [149].

4.3 Important Considerations

As discussed in Sect. 2, randomised clinical trials are widely recognised as having a lower risk of bias, observational studies (including surveillance) are more susceptible to bias [150, 151], and case studies have the highest risk of bias [96]. In the case of vaccine safety, where long follow-up times are required and concerns exist that AEs could potentially be rare and population-specific, epidemiological data from well-conducted population-based observational studies is invaluable [18]. A focus on case reports, including those magnified through unbalanced accounts in traditional and social media [96, 152], has led to community and individual concern regarding the safety of HPV vaccine, which is far out of step with the body of the evidence available on its safety. For example, negative and inappropriate interpretation of information, including in widespread media coverage of reported AEs, has been associated with a substantial drop in vaccine uptake in Japan despite no safety signal having been recorded [153]. As a recent commentary noted, unfortunate individuals affected by rare or complex disorders have been encouraged to attribute harm to HPV vaccination, while real harm is conversely occurring through ongoing inability to achieve vaccine uptake that will prevent HPV-related disease in a country with low participation in cervical screening [153]. The GACVS [137] has also recently raised

concern about the focus on case reports and "unsubstantiated allegations" that have a negative impact and could result in significant harm through reduced coverage. Other authors have echoed this concern about potential loss of public confidence based on safety issues that have been discounted in well-conducted studies [98].

Large-scale immunisation programmes for adolescents are relatively new [154] and the baseline prevalence of new-onset AID is high among adolescent girls and young women, who are the target group for HPV vaccination [98, 138]. For example, the incidence of thyroiditis, IBD and SLE is reported at around 1–10 per 100,000 in adolescent females in the USA [154]. Development of an autoimmune or chronic disease is usually underscored by complex potential or unknown aetiological factors. In this context, vaccination may be identified as a possible precipitant of disease because of the memorable nature and relative infrequency of experiencing administration of a vaccine [154]. When population-based programmes commence, there will inevitably be a temporal association between vaccination and autoimmune conditions [154]. Only robust, scientifically sound studies can effectively establish an absence of risk. Parental concerns about vaccine safety has been identified as a significant barrier to vaccine uptake, with concerns about safety and adverse effects of adolescent vaccinations increasing from 4.5% in 2008 to 16.4% in 2010 in the USA [155]. Moreover, the recent unanticipated declines in HPV vaccine uptake in a number of countries, driven by unsubstantiated safety concerns, underpins the need to improve communication around HPV vaccine safety [156]. A rapid response to reported AEs and publicised concerns is required. There is a moral imperative to ensure that conclusions drawn from high-quality evidence can be communicated by physicians and public health authorities in a way that provides public confidence in the safety of the HPV vaccine.

5 Conclusions

The overwhelming conclusion from our analysis is that a large volume of scientifically robust evidence demonstrates the safety of HPV vaccines. Our review brings together this evidence, supporting the position of the GACVS, the EMA and other expert groups in finding no evidence of any safety issue that should impact the use of this vaccine in immunisation programmes worldwide. The new 9vHPV vaccine demonstrates a good safety profile from clinical trial data. As with the 2vHPV and 4vHPV vaccines, ongoing post-marketing surveillance, targeted population-level studies, a rapid response to concerns and effective communication are required to maintain or indeed improve upon public confidence in HPV immunisation programmes. The prevention of cervical cancer remains a priority [79] and HPV vaccination is highly effective. Strategies to ensure public, provider and political acceptance are critical [152].

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Compliance with Ethical Standards

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1.3 Implications of publication 1

This review collates the large volume of evidence on HPV vaccine safety, and highlights studies based on robust pharmacovigilance methods which have supported a better understanding of the safety of HPV vaccine. The findings are consistent with statements from both the European Medicines Agency and the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (83, 84); the study has been cited 68 times, including in the American Autonomic Society's valuable position statement on HPV vaccine and autonomic disorders. (85)

Of all vaccines used worldwide, HPV vaccine safety has been among the most prominent controversies (86), despite this and other reviews finding no increased risk of autoimmune disease, neurological conditions or other disorders of concern. (87, 88) This review included 23 case reports or case series; such studies cannot (with extremely rare exceptions) demonstrate causality (89), but these and other low-level evidence have triggered safety concerns. Vaccine pharmacovigilance requires the use of multiple modalities, as demonstrated by this review. The totality of post-marketing evidence, including case reports, spontaneous surveillance, active surveillance and observational studies, allows full exploration of safety issues and robust conclusions can be drawn. As demonstrated by population-based studies presented in this review, including studies using linked databases, adaptive methods that can rapidly investigate newly reported AESI at the population level are critical.

The impact on coverage of programmatic decisions based on lower levels of evidence has been ongoing in Japan, where an increase in cervical cancer among young women has been reported and it has been estimated that reduced vaccine coverage may result in around 5000 otherwise preventable deaths from cervical cancer. (77) In Denmark, there has been some recovery in vaccine uptake following a national immunisation campaign. (90) The WHO Global Advisory Committee on Vaccine Safety stated in 2017 that 'the ongoing unsubstantiated allegations have a demonstrable negative impact on vaccine coverage in a growing number of countries, and that this will result in real harm'. (84, p.400)

However, globally, some researchers and governments continue to place undue emphasis on case reports and other low-level evidence, even once higher-level studies and reviews have investigated reported signals and found no evidence of association or causality. Two commentary letters were published following this review which questioned the hierarchy of evidence presented and the accepted parameters of causality assessment. (91, 92) Appendix B of this thesis provides a response to these letters, and exemplifies the ongoing need for dialogue to reinforce the risk of assumptions based on temporally reported AEFI and the validity of multi-faceted, robust pharmacovigilance approaches in testing hypotheses based on these reports. (93)

Chapter 2: Spontaneous post-marketing surveillance – essential for signal detection and hypothesis generation

2.1 Introduction

In contrast to several other countries, coverage for human papillomavirus (HPV) vaccine in Australia has remained high at over 80% in females and 75% in males (in 2017). (94) The vaccine was developed by an Australian research team, and Australia was the second country globally to introduce the HPV vaccine and the first to introduce a fully funded national program for female adolescents in 2007, with catch-up to age 26 years. The female program was followed by a funded program for males from 2013. (95)

However, as in other countries, safety concerns have been raised in Australia which required investigation and resolution. Several signals were identified shortly following implementation of the HPV vaccine program, including seven presumptive cases of post-vaccination anaphylaxis reported to the spontaneous reporting system in one state, New South Wales (NSW). (49) Reports were first reviewed at the state level, before escalation to the Therapeutic Goods Administration (TGA). Based on classification against Brighton Collaboration case definitions, the estimated incidence rate was 2.6 per 100,000 doses, which was higher than for other school-based program vaccines. (49) The review led to communication with providers, updated product information and consent forms, and information on the TGA website. (49, 50) A subsequent study of anaphylaxis following childhood vaccines in a different Australian state (Victoria) estimated a lower rate following HPV vaccine of 0.32 per 100,000 doses. (96) Around the same time, a separate safety issue of psychogenic illness (mass syncope) was reported, initially from Victoria (97, 98); several cases were reviewed in the specialist adverse event following immunisation (AEFI) clinic that is linked to that state's spontaneous reporting system. (98) Syncope is recognised as an immunisation anxiety-related reaction. (5)

In these examples, state-based spontaneous reporting systems effectively identified and investigated vaccine safety issues, while simultaneously engaging with and escalating to the TGA. Conversely, early reports of rare neurological events (including demyelinating syndromes) were investigated directly by the TGA (50) following a published case series of five patients. (95, 99) Investigation included an expert panel review, which determined that the incidence of neurological syndromes reported did not exceed what would be expected to occur by chance. Information provided by the TGA online in response to these issues was transparent and described the potential

for coincidental association between vaccination and neurological events. (50) Following this series of safety events, and under a national vaccine safety plan, when HPV vaccination was expanded to males in 2013, the TGA implemented an enhanced passive surveillance program for adverse events of special interest [AESIs] (anaphylaxis, syncope, and conditions requiring emergency department or hospital presentation). (26) Conducted within the spontaneous reporting system, this was an example of adaptation to incorporate enhanced surveillance in response to a specific safety concern.

The study presented in this chapter analysed 11 years of longitudinal data from the national spontaneous reporting system, following administration of 9 million doses of quadrivalent HPV vaccine. It incorporates the enhanced surveillance period and focuses on AESIs targeted in that program (including anaphylaxis and syncope), along with AESIs that have triggered reduced confidence internationally, as identified in Chapter 1. The study presents age- and sex-specific rates of AEFIs and trends over time, along with detailed review of cases of specified AESIs.

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Adverse events following HPV vaccination: 11 years of surveillance in Australia

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ABSTRACT

Background: Australia was the first country to implement a fully funded vaccination program with quadrivalent human papillomavirus vaccine (4vHPV) in 2007, including males from 2013. We examined adverse events (AE) following vaccination with 4vHPV from 11 years of post-marketing data, focusing on a period of enhanced surveillance and adverse events of special interest (AESI).
Methods: AE following 4vHPV doses administered between April 2007 and December 2017 reported to Australia's national regulator, the Therapeutic Goods Administration, were examined; reports collected during enhanced surveillance in 2013 and 2014 were analyzed separately. Age and sex-specific rates, using denominator data from the national HPV vaccination register, were determined. Pre-specified AESI were identified using Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms and examined in detail.
Findings: Following nine million doses of 4vHPV vaccine administered in Australia, 4551 AE reports were identified. The crude reporting rate was 39.8 per 100 000 doses in the funded cohorts, excluding the enhanced surveillance period. The reported rate of syncope in 12 to 13-year-old males and females was 29.6 per 100 000 doses during enhanced surveillance and 7.1 per 100 000 doses during the remaining study period; rates of syncope were higher in younger compared to older adolescents. The rate of anaphylaxis (0.32 per 100 000 doses) was consistent with published rates. Other AESI including autoimmune disease, postural orthostatic tachycardia syndrome, primary ovarian insufficiency, Guillain-Barré syndrome, complex regional pain syndrome and venous thromboembolism, were reported at low rates and analysis did not reveal unexpected patterns that would suggest causal association.
Interpretation: AESI, apart from syncope, were reported rarely. The higher rate of syncope among younger adolescents highlights the need for management protocols to prevent syncope-related injury. Analysis of this large, longitudinal dataset in a country with high vaccine uptake, including a period of enhanced surveillance, affirms the safety profile of 4vHPV.

1. Introduction

Australia has a comprehensive, fully funded, national human papillomavirus (HPV) vaccination program with high coverage. A three-dose course of quadrivalent HPV vaccine (4vHPV) was introduced through the National Immunization Program (NIP) as a school-based program for 12 to 13-year-old females in 2007

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and males in 2013, with catch-up programs for other age groups [1].

HPV vaccination primarily aims to protect against cervical, anogenital and oropharyngeal cancers, and high-grade cervical lesions related to HPV infection [2]. Australia has been a world leader in demonstrating early program impacts, including declines in HPV prevalence, high grade cervical lesions and genital warts, as well as herd immunity effects, such as a decline in genital wart incidence in heterosexual males prior to the inclusion of males under the NIP [3]. Globally, HPV vaccine programs have been uniquely affected by concerns and issues related to vaccine safety that have negatively impacted upon vaccine uptake [4,5]. Although questions around safety have arisen in Australia, particularly in the early years of the program, relatively high uptake has been sustained with 80.2% three dose coverage among females and 75.9% among males in 2017, measured at 15 years of age [6].

HPV vaccine safety has been evaluated in pre-licensure clinical trials, post-marketing surveillance systems and observational studies worldwide [7,8]. While possible signals for an association of HPV vaccine with Guillain-Barré syndrome (GBS) [9,10] and venous thromboembolism (VTE) [11] were previously identified, these were excluded in subsequent observational studies [12–19]. Associations of HPV vaccine with other specific conditions and syndromes, including postural orthostatic tachycardia syndrome (POTS), chronic fatigue syndrome (which overlaps with POTS), complex regional pain syndrome (CRPS) and primary ovarian insufficiency (POI) have been the subject of case reports and media interest [7]. While observational studies and expert reviews have not supported causal associations [20–24] these continue to be proposed. Only syncope has been consistently associated with HPV vaccination [25] and is known to be associated with vaccination more generally [26]. While generally benign and categorized as an immunization anxiety-related reaction [27] (rather than related to vaccine constituents), syncope following vaccination carries the risk of harm from syncope-related injury.

The initial safety concerns which arose following the introduction of the HPV vaccination program for females in Australia included a potential signal for anaphylaxis [28] and a series of reports of demyelinating syndromes [29]. In Australia, spontaneous reports of adverse events (AE) following vaccination are made to the national regulator of vaccines and other therapeutic goods, the Therapeutic Goods Administration (TGA). A Gardasil Expert Panel, established by the TGA, found that the incidence of demyelinating disorders following HPV vaccination was no higher than expected by chance, and that the rate of anaphylaxis was similar to that for other vaccines [30]. A high rate of syncope [31] was reported as an early concern but later found to be consistent with expected rates [32].

Following these evaluations, and as one of the first countries to implement a fully funded male program, a period of enhanced surveillance was implemented prospectively under the vaccine safety plan for introduction of the male program. Specifically, school-based AE surveillance was strengthened during 2013 and 2014 by: a) ensuring school immunization nurses recorded data on all AE occurring at the time of, or shortly after, vaccination (typically notified in the first four hours while immunization teams were still onsite at schools); b) a focus on collecting data on four pre-specified significant acute AEs: 1) anaphylaxis; 2) loss of consciousness (including syncope); 3) generalized allergic reaction and; 4) any condition requiring emergency department presentation or hospitalization [33]. During this period there was also more frequent analysis and reporting of data, intended to closely monitor safety in the new cohort (males) and compare it with females.

Safety surveillance data is now available for a large cohort of Australian adolescents over 11 years, including five years of data for males. Over this period, 4vHPV accounted for 99.9% of doses. We analyzed AE following 4vHPV doses administered between April 2007 and December 2017, focusing on determining age and sex-specific reporting rates, analyzing the impact of enhanced surveillance, and examining adverse events of special interest (AESI).

2. Methods

2.1. Study population and surveillance system characteristics

Australia has a population of approximately 25 million with over nine million doses of HPV vaccine administered between 2007 and 2017, according to the National HPV Vaccination Program Register (NHVPR). The HPV vaccine eligible population changed over the study period (Table 1). The majority of doses were given through the school-based vaccination program (94% for males, 69% for females overall and 92% for females once early community catch-up programs ceased).

Anyone can report a suspected AE to the TGA, including immunization providers, consumers, parents and pharmaceutical companies (Australian sponsors). In most jurisdictions (comprising eight states and territories) with responsibility for administering school-based vaccination programs, AE reporting is a statutory obligation for healthcare providers and predominantly occurs via state and territory vaccine safety surveillance mechanisms [34]. Reporters are requested to provide patient identifiers including date of birth or age, details of the product involved and the suspected adverse event, including dates. The reporter is also able to provide contact details, if consent is provided, to enable communication to seek additional information, if required. Reports are coded by the TGA on initial receipt based on the information provided in the report, using the internationally recognized Medical Dictionary for Regulatory Activities (MedDRA®) standardized terms, including Preferred Terms [35]. AE reports are stored within the TGA's Adverse Events Management Systems (AEMS) database.

Australian sponsors are required to apply seriousness coding to ensure legislated requirements are met. Other reports are coded (typically on initial receipt) as 'serious' based on criteria similar to the World Health Organization definition [27] and available information, where any of the following outcomes are documented: death; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability; life-threatening; or congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of these outcomes (a medically important event or reaction) may also be considered as serious. The TGA identifies and reviews medically important cases, which are flagged for review by a TGA medical officer. Where there is insufficient information for a serious AE report to be assessed, the TGA requests follow up information from the reporter with assistance from the relevant state or territory health department, including medical record information where required; however, this may not always be obtained.

We analyzed AEs within the TGA AEMS database following 4vHPV vaccine doses administered between 1 April 2007 and 31

Table 1
Nationally funded quadrivalent human papillomavirus (4vHPV) vaccination cohorts in Australia, 2007 to 2017.

Program delivery type	Age group	Year of program delivery
Primary program		
Female	12 to 13-years	2007 to 2017
Male	12 to 13-years	2013 to 2017
Catch-up program		
Female	14 to 26-years	2007 to 2009
Male	14 to 15-years	2013 to 2014

December 2017 for females, and between 1 February 2013 and 31 December 2017 for males, and reported by March 2018, to allow for reporting lag. Reports following nonavalent (9vHPV) or bivalent (2vHPV) HPV vaccine were excluded. The nonavalent vaccine was not available until 1 January 2018 after which it was added to the NIP, replacing 4vHPV vaccine. The bivalent vaccine was not supplied under the NIP and thus only administered to a small number of women within primary care over the study period; where no vaccine type was specified, reports were included and presumed to be 4vHPV. Reports following vaccination during pregnancy were identified using methods described previously [36].

For reports that were missing vaccination date, the date of reaction onset was used (the median lag time between vaccination date and reaction onset date was 0 days in this cohort). Where the reaction onset date was missing, the vaccination date was replaced with the date the report was received minus 15 days (the median lag time from vaccination to report in this cohort). Vaccination date was only used to determine annual rates and changes in rates over time. For description of individual AESI, additional free text data and medical record information, where available, was used to review time between vaccination and reaction onset. Where multiple 4vHPV doses were recorded within one report, the date of latest vaccination was used.

This study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (reference LNR/18/SCHN/440).

2.2. Descriptive analysis

AE reports were described for males and females by age group, reporter type, concomitant vaccination and seriousness code. We identified the top 10 most commonly reported MedDRA Preferred Terms by sex. Crude AE reporting rates per 100 000 doses administered were calculated across the entire program with age and sex-specific adverse event rates calculated for the NIP cohorts (Table 1). Rates for females and males in the primary target cohort were analyzed separately during the enhanced surveillance period. Doses administered by vaccine type, age, sex and time period were obtained from the NHVPR.

2.3. Adverse events of special interest (AESI)

AESI were determined by review of the literature [7,8,26] and from recent analyses of the United States (US) Vaccine Adverse Events Reporting System (VAERS) [37]. The following conditions were selected: syncope, venous thromboembolism (VTE), anaphylaxis, autoimmune disease (AID), postural orthostatic tachycardia syndrome (POTS), complex regional pain syndrome (CRPS) and Guillain-Barré syndrome (GBS). To allow comparison with international data, MedDRA Preferred Terms were selected as described previously in VAERS analyses [37] (Appendix 1) with the exception of GBS, where the term 'chronic inflammatory demyelinating polyradiculoneuropathy' (CIDP) was added (CIPD is considered a chronic form of GBS) [38]. These MedDRA terms were used as a sensitive search for potentially relevant cases, which were then further reviewed to determine whether cases met published criteria for the specific condition, where information was available. Case details were obtained from the TGA for all AESI except syncope. TGA case details included those obtained during investigation of the AE, which may include follow up information from the reporting source, medical record information and findings of any relevant expert panel. Reports of anaphylaxis, but not other AESI, were routinely classified according to Brighton Collaboration criteria by the TGA based on available data. [39] Reports were described by dose number where documented; there was no information on whether individuals received subsequent doses.

Signal detection methods were not applied in this retrospective analysis; signal detection is undertaken continuously and prospectively by the TGA using the provisional reporting ratio (PRR) and other methods.

3. Results

For 4vHPV doses given between 1 April 2007 and 31 December 2017, the TGA received 4556 adverse event reports up to 31 March 2018. Five reports for males were excluded from the main analysis (three for males vaccinated prior to the 2013 NIP expansion and two for male infants whose mothers were vaccinated) leaving 4551 adverse event reports.

Most reports were for the primary NIP funded cohort (12 to 13-year-old males and females) and the most common reporters were the respective state and territory health departments, reflecting established pathways for reporting to the TGA (Table 2). The most commonly reported MedDRA Preferred Terms were similar among males and females with headache and syncope the most common (Table 3).

Most reports (92.2%) were not coded as serious by the TGA (Table 2). Of the 354 that were coded as serious all were assessed by the TGA as meeting at least one criterion of the WHO definition for a serious AE; most (n = 224) were coded as serious due to the criterion 'caused or prolonged hospitalization'. The proportion of reports coded as serious changed over the study period with the highest proportion for females in 2009 (13.9%) and 2017 (13.2%) and the lowest proportion during the enhanced surveillance period (3.9% for females and 2.7% for males) (data not shown). The top 10 preferred terms were similar when limiting to reports coded as serious; injection site reaction was not one of the top 10 preferred terms for reports coded as serious.

3.1. Adverse event reporting rates in target cohorts

Between 1 April 2007 and 31 December 2017, almost 9.4 million doses of 4vHPV vaccine were recorded by the NHVPR in Australia, with an overall AE reporting rate of 48.5 per 100 000 doses administered across all age groups and 3.8 reports per 100 000 doses coded as serious.

One-hundred and two reports had either missing age, sex or both and were not included in age- and sex- specific AE rates. Vaccination date was missing in five per cent of cases (n = 243) and was substituted with reaction onset date for calculation of annual rates.

Excluding the enhanced surveillance period (2013–2014), the reporting rate among primary and catch-up NIP cohorts (Table 1) was 39.8 per 100 000 doses, compared to 72.3 during enhanced surveillance, where AE reporting rates were higher overall as compared with other time periods. During this enhanced surveillance period, the rate was notably lower among older males (14 to 15 years) compared to younger (12 to 13 years) males and females (39.1 compared to 88.4 per 100 000 doses) (Fig. 1, Appendix 2). Following the conclusion of enhanced surveillance, reporting rates for females 12 to 13 years of age were maintained at slightly higher levels than before 2013.

3.2. Pregnancy reports

Thirteen of the 4556 reports (including 3221 females and two reports for infant males), were identified as occurring during or following pregnancy. Four of the 13 reports identified spontaneous abortion and one was a report of preterm labor.

There were four reports of vaccination in pregnancy that specified AE as being various infant congenital anomalies. Three of these

Table 2
Summary of adverse event reports to the Australian Therapeutic Goods Administration (TGA) for males and females following quadrivalent human papillomavirus vaccine (4vHPV) given to females (2007 to 2017) and males (2013 to 2017).

	Female n (%)	Male n (%)	Unknown n (%)	Total n (%)
Total reports	3221 (70.8)	1298 (28.5)	32 (0.7)	4551
Coded as serious	295 (9.2)	54 (4.2)	5 (15.6)	354 (7.8)
4vHPV only	2167 (67.3)	604 (46.5)	22 (68.8)	2793 (61.4)
Reporter type				
Health Professional	447 (13.9)	53 (4.1)	6 (18.8)	506 (11.1)
Patient/Consumer	180 (5.6)	38 (2.9)	2 (6.2)	220 (4.8)
Sponsor	106 (3.3)	1 (0.1)	8 (25.0)	115 (2.5)
State/Territory surveillance system	2488 (77.2)	1206 (92.9)	16 (50.0)	3710 (81.5)
Age group (years)				
Under 12 years	99 (3.1)	39 (3.0)	3 (9.4)	141 (3.1)
12–13 years	1740 (54.0)	960 (74.0)	7 (21.9)	2707 (59.5)
14–17 years	695 (21.6)	277 (21.3)	5 (15.6)	977 (21.5)
18 years and over	627 (19.5)	9 (0.7)	4 (12.5)	640 (14.1)
Unknown	60 (1.9)	13 (1.0)	13 (40.6)	86 (1.9)

Table 3
Top 10 Preferred Terms and as a percentage of all MedDRA Preferred Terms for adverse events following quadrivalent human papillomavirus vaccine (4vHPV) reported to the Australian Therapeutic Goods Administration (TGA) for females (2007 to 2017) and males (2013 to 2017)[a].

Females	n (%)	Males	n (%)
Headache	550 (6.5)	Syncope	362 (13.8)
Syncope	467 (5.5)	Headache	188 (7.2)
Nausea	460 (5.5)	Pyrexia	156 (6.0)
Dizziness	423 (5.0)	Nausea	133 (5.1)
Pyrexia	324 (3.8)	Injection site reaction	120 (4.6)
Injection site reaction	307 (3.6)	Dizziness	111 (4.2)
Vomiting	262 (3.1)	Vomiting	108 (4.1)
Rash	255 (3.0)	Pre-syncope	85 (3.2)
Urticaria	212 (2.5)	Rash	64 (2.4)
Malaise	210 (2.5)	Urticaria	62 (2.4)

[a] Note that total number of Preferred Terms will not equal total number of AE reports as there may be more than one Preferred Term per report

reports involved individuals who did not yet know they were pregnant when they received the vaccine, and the fourth report did not contain enough narrative detail to determine this information. There was one report of eczema in an infant following administration of 4vHPV to the infant's mother during pregnancy. Other medical conditions were noted among data contained in these reports. No adverse outcomes were reported for the remaining pregnancy reports.

3.3. Adverse events of special interest (AESI)

Of pre-defined AESI, syncope (as a composite measured defined by the MedDRA Preferred Terms 'syncope', 'syncope vasovagal' or 'loss of consciousness' (see Appendix 1)) was the most commonly reported (Table 4). One death was reported with the cause stated as being cervical cancer years following HPV vaccination as an adult; the information provided in the report (which was based on a press article) was insufficient to determine causality.

3.3.1. Syncope

Of 856 AE classified as syncope, 825 were coded with the MedDRA Preferred Term 'syncope'; 23 were coded as 'loss of consciousness'; and eight were coded with both preferred terms. Preferred Terms that may relate to seizures ('seizure', 'partial seizures', 'generalized tonic-clonic seizure', 'clonic convulsion', 'tonic convulsion' and/or 'tonic clonic movements') were also assigned in a subset of reports coded with 'loss of consciousness' (n = 15) and a small proportion of reports coded as 'syncope' (n = 23). There were 14 reports coded with both 'syncope' and injury (including Preferred Terms 'concussion', 'contusion' and 'head injury') of which 13 were on the same day as vaccination.

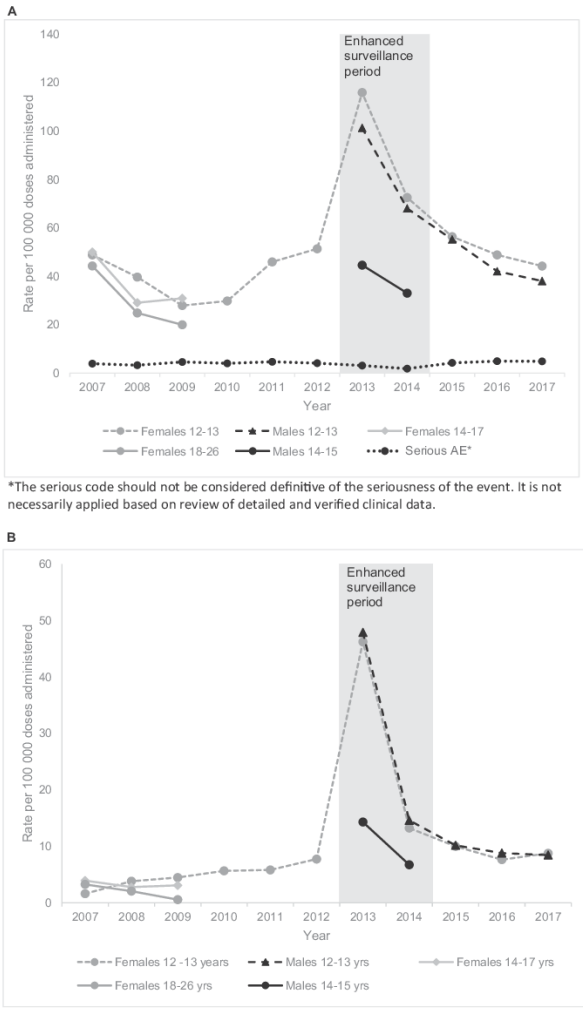

Fig. 1. Rates of adverse events following quadrivalent human papillomavirus vaccine (4vHPV) given to females (2007 to 2017) and males (2013 to 2017), reported by year; before, during and after an enhanced surveillance period (2013 to 2014). A: All adverse event reports including reports coded as serious based on preliminary review. B: Syncope (including MedDRA Preferred Terms 'syncope', 'syncope vasovagal' and 'loss of consciousness').

Table 4
Number and rate of potential adverse events of special interest (AESI) reported following quadrivalent human papillomavirus vaccine (4vHPV) in females (2007 to 2017) and males (2013 to 2017), in Australia.

AESI[a]	N[b]	Rate in overall surveillance period (enhanced surveillance period)[c]
Syncope	856	9.11 (23.8)
Anaphylaxis	30	0.32 (0.26)
Guillain-Barre syndrome	5	0.05
Postural orthostatic tachycardia syndrome	13	0.14
Autoimmune disease	13	0.14
Primary ovarian insufficiency	12	0.17[d]
Complex regional pain syndrome	4	0.04
Venous thromboembolism	3	0.03

[a] AESI were identified using grouped Preferred Terms as identified in Appendix 1
[b] Number of cases based on all those identified using prescribed search terms; not all cases are clinically confirmed, and causality is not assumed.
[c] Rate per 100 000 doses administered in overall surveillance period (2007–2017); rate during enhanced surveillance period (2013–2014) for AESI that are likely to occur on the day of vaccination (therefore responsive to enhanced surveillance methodology).
[d] Denominator includes female doses administered only (DA = 7,014,406).

Over half of syncope cases (n = 453) were reported during the enhanced surveillance period. During this period, the rate of reported syncope in the primary target cohort (12 to 13-year-old males and females) was 29.6 per 100 000 doses administered, over four fold higher than the rate during the remaining study period for this same age group (7.1 per 100 000 doses). The rate in 12 to 13-year-old males and females was around three times higher than the rate in 14 to 15-year-old males during the enhanced surveillance period (10.7 per 100 000 doses) (Fig. 1, Appendix 3). Rates decreased in 2014, following a peak in 2013 (from 47.1 to 13.9 per 100 000 doses in the primary target cohort). All reports followed dose 1, where dose number was documented (94.7%, n = 811).

3.3.2. Anaphylaxis

All 30 cases of anaphylaxis were coded using the MedDRA Preferred Term 'anaphylactic reaction' and all were confirmed by TGA coders to meet the Brighton Collaboration case definition. Of the 24 cases that had reaction onset date and vaccination date documented, all occurred on the day of vaccination; six reported concomitant administration of another vaccine (DTPa, Hepatitis B and/or influenza vaccines). The median age was 14 years; of the 28 cases where gender was reported, 26 were females.

Over one third of cases (n = 11) were reported in 2007. Low annual numbers were reported following 2007 (one to four cases per year), including during the enhanced surveillance period. The rate over the entire program was 0.32 per 100 000 doses administered and 0.26 per 100 000 doses during the enhanced surveillance period (Table 4). All reports followed dose 1, where dose number was documented (90%, n = 27).

3.3.3. Guillain-Barré syndrome (GBS)

Four cases were reported as GBS (three females and one male; median age 13 years) and one as CIDP. One of the four GBS cases was subsequently reclassified to CIDP. Three GBS cases were reported as confirmed based on nerve conduction studies; the fourth case, reviewed by the jurisdictional vaccine safety surveillance system, was determined to have met level 2 of diagnostic certainty using the Brighton Collaboration case definition. Two of the four GBS cases were reported to have had evidence of an antecedent illness (viral infection, mycoplasma infection) and one reported concomitant vaccination with DTPa vaccine.

3.3.4. Postural orthostatic tachycardia syndrome (POTS) and other postural dizziness

Of 13 cases identified using the MedDRA Preferred Terms 'postural orthostatic tachycardia syndrome', 'dizziness postural' or 'postural reflex impairment', most (n = 11) were in females. Six had been coded with the Preferred Term 'dizziness postural' of which five were self-limiting and occurred at the time of, or shortly after, vaccination; three had also received concomitant vaccination (hepatitis B, DTPa and/or influenza vaccine).

For the remaining seven cases coded with the MedDRA Preferred Term 'postural orthostatic tachycardia syndrome', all were reported from 2015 and there was insufficient information on symptoms, heart rate, blood pressure, investigations and/or duration of illness to establish a diagnosis of POTS according to published criteria [40]. Three cases were reported as being treated for orthostatic intolerance; two cases were reported to have also been diagnosed with chronic fatigue syndrome (CFS). Reaction onset dates were varied, but where documented, ranged from six months to over a year following vaccination.

3.3.5. Autoimmune disease (AID)

All 13 reports of AID were in females; the median age at vaccination was 15 years. Three had documented pre-existing AID and reported escalation in symptoms following 4vHPV vaccination. Of the remaining new onset cases, conditions reported included arthritis, systemic lupus erythematosus, dermatomyositis, autoimmune hemolytic anemia, ulcerative colitis, thyroiditis, diabetes mellitus, multiple sclerosis (coded with the preferred term 'autoimmune disorder'), and non-specific diagnoses. There was no pattern regarding time of onset following vaccination, which was reported in seven cases and varied from one week to three months. All reports followed dose 1, where dose number was documented (69%, n = 9).

3.3.6. Primary ovarian insufficiency (POI)

Of 12 reports identified using the MedDRA Preferred Terms 'premature menopause', 'ovarian disorder' and 'amenorrhea' (Appendix 1), three were published previously in an Australian case series [41]. Of the remaining cases, none had sufficient information to confirm a diagnosis and two had other generalized symptoms. Among the 12 cases, the median age at vaccination was 16 years; where documented, amenorrhea was reported to have occurred at variable times following vaccination.

3.3.7. Complex regional pain syndrome (CRPS)

The four reported cases of CRPS were all in females with a median age of 14 years and occurred in the individual's vaccinated arm. Three of the cases were also identified in a published case series and were reported to fulfill the diagnostic criteria for CRPS [42]. The remaining case had a history of injury to the hand prior to vaccination and was reported to have been diagnosed with CRPS by a pediatrician.

3.3.8. Venous thromboembolism (VTE)

The three reports of VTE were for deep vein thrombosis (DVT) in females with a median age of 19 years; two were documented to be taking the oral contraceptive pill and confirmed to have a thrombophilia. These DVTs were reported at variable times (five days to three months) following vaccination.

4. Discussion

This review of 11 years of post-marketing vaccine safety surveillance data from Australia's spontaneous adverse event reporting system has provided valuable information on HPV vaccine safety, as well as identified novel insights in relation to syncope during the two-year period of enhanced surveillance implemented when males were included in the vaccination program. While the overall adverse event reporting rate (48.5 per 100 000 doses administered) was slightly higher than the rate of reporting of AE following 4vHPV to the US VAERS (32.7 per 100 000 doses distributed) [37], this was impacted by higher reporting rates during the enhanced surveillance period. Excluding the enhanced surveillance period, the reporting rate (39.8 per 100 000 doses) among all funded primary and catch-up cohorts was similar to that of VAERS and is robust due to the use of denominator data obtained from the NHVPR on doses administered. In Australia in 2017, the number of 4vHPV AE reports in 7 to 17-year-olds (n = 277, 3 dose series) was similar to that recorded for other adolescent vaccines when taking into account scheduled doses (diphtheria-tetanus-pertussis containing vaccine [n = 173, single dose] and quadrivalent meningococcal vaccine [n = 83, single dose]), noting these vaccines are usually given concomitantly [43].

Reporting rates for 4vHPV were maintained at slightly higher levels following the enhanced surveillance period which likely reflects continued improvements in the reporting system and the commensurate increased awareness of and reporting of AE, as has been seen for other NIP vaccines over time [43]. While the increase in reporting during the enhanced surveillance period may suggest underreporting at other times, the higher proportion of reports that were non-serious during enhanced surveillance, as a result of instructions to nurses to report simple syncope, is reassuring.

Syncope was notable as the adverse event detected at an increased rate during the period of enhanced, nurse-led school-based surveillance. For the composite outcome of 'syncope' (including the MedDRA preferred terms 'syncope', 'syncope vasovagal' and 'loss of consciousness'), nearly half of all reported cases occurred during the two-year enhanced surveillance period, and the rate was over four times higher among both females and males in the primary target cohort during this time, as compared with the periods of routine surveillance. Inclusion of data from this enhanced surveillance period likely explains why the overall rate of syncope in this study was nearly double the rate reported by VAERS in 2018 using the same Preferred Terms [37].

Analysis of enhanced surveillance data also revealed that syncope was about three times as likely to occur in younger adolescents (aged 12 to 13 years) than in older males (14 to 15 years) as noted in a preliminary report by the TGA [33]. However, rates in 12 to 13 year old females were similar to that in males of the same age. Overall, this suggests an age-related relationship with this well-recognized immunization stress-related reaction, that has not previously been noted in population-level post marketing surveillance, to our knowledge.

This comprehensive data on syncope in both sexes of young adolescent vaccine recipients during the enhanced surveillance period allowed for a greater awareness of this condition among immunization program staff which ensured management protocols were in place to mitigate against syncope and prevent syncope-induced injury. The proportion of reports of syncope that were associated with a Preferred Term indicating injury was low in this study; similarly, the TGA review of the enhanced surveillance period identified very few syncopal episodes associated with injury or that had medical review, such that a decision was made not to request school-based reporting of simple syncopal events in the second year of enhanced surveillance [33]. Syncope following vaccination may be preventable but can create concern among vaccine recipients and/or carers and lead to negative perceptions of vaccination. It is important that immunization providers are aware of the frequency at which this can occur, particularly in younger adolescents, to avoid unduly negative outcomes [44].

The rate of anaphylaxis was higher in our study than the rate reported to VAERS (0.32 per 100 000 doses administered compared to 0.06 per 100 000 doses administered for VAERS) [37], but was similar to previously reported rates from Australia (0.32 per 100 000) [45], Canada (0.3 per 100 000) [46] and Europe (0.22 per 100 000) [47]. There was likely to be high awareness and reporting of anaphylaxis following initial signal investigation early in the HPV vaccination program in Australia. In this context, it was considered possible that there was a reduced threshold for using adrenaline and that syncope cases were more likely to meet the Brighton Collaboration criteria for anaphylaxis where anaphylaxis code was based on the treatment given. The reporting rate for anaphylaxis was not elevated during the enhanced surveillance period, during which it was a specified condition, further supporting our impression that anaphylaxis is rare after HPV vaccination, occurring in fewer than 1 in 300,000 young adolescent 4vHPV vaccine recipients.

We selected a number of other AESI to analyze in detail. Notably, while many reports were not confirmed to meet diagnostic criteria for the various conditions, reporting rates were nonetheless low, and comparable to rates using similar surveillance methods [37]. Spontaneous reporting systems like the AEMS have specific characteristics, including incomplete and selective reporting, that mean it is almost never possible to conclusively determine causality for an individual case based on available data. The absence of detailed clinical data, despite requests initiated by the TGA, made it difficult to assess a causal relationship to vaccination for the reports in this study. Importantly, these conditions occur at a background rate in the population, irrespective of vaccination, [48] although data on local and age-specific prevalence and incidence is often not available.

Only four cases of GBS, two of which had documented infection prior to disease onset, were reported during the entire 11-year surveillance period. The incidence of acute flaccid paralysis in Australia (of which GBS is the diagnosis in almost half of cases) has been estimated to be 0.8 per 100 000 children less than 15 years of age [49]. An early possible signal for GBS following HPV vaccine was identified and investigated in the United States [10] but was not confirmed in analyses of either VAERS [37] or the Vaccine Safety Datalink (VSD) [16,26]. While a cohort study in France suggested an elevated hazard ratio for GBS in vaccinated versus unvaccinated females [9], a UK self-controlled case series subsequently found no evidence of an increased risk in the 3 months following vaccination [12], and a Canadian study did not identify any increased risk of GBS-related hospitalization in HPV-target cohorts [14]. Evidence from our analysis is consistent with these studies in suggesting no increase in GBS in association with the introduction of HPV vaccination.

AE identified using search criteria that may suggest POTS (a syndrome of orthostatic intolerance associated with increase in heart rate in the absence of orthostatic hypotension and with light-headedness, palpitations and weakness [40]) were reported at a low rate in our study, similar to that from two analyses of US VAERS data (0.11 and 0.16 per 100 000 doses distributed, respectively) [37,50]. Although the prevalence of POTS in Australia is not well described, globally it is estimated to affect 0.2% of the population, supporting the observation of low rates in our cohort [40]. Many of the AE identified using our search strategy described simple postural dizziness on the day of vaccination; for

those reported as POTS specifically, it was not possible to establish a diagnosis of POTS according to published criteria in any case. Similarly, in a recent study based on VAERS data, only 29.5% (n = 29) of reports (using the preferred terms that we also used in our study) met POTS diagnostic criteria, and a pre-existing medical condition was documented in 20 cases, including five cases of CFS [50].

While some published reports have suggested an association between POTS and HPV vaccination [7], neither the World Health Organization's Global Advisory Committee on Vaccine Safety (GACVS) [51] nor the American Autonomic Society found evidence to support a causal association [52]. POTS is a heterogenous condition that is prevalent in the same population that receives HPV vaccine (adolescents and females) and symptoms can overlap with other syndromes that occur in adolescence, such as fatigue syndromes [52]; no association between HPV vaccination and increased risk of fatigue syndromes has been identified in epidemiological studies [20,22].

Most reports in our study were made after 2015 which may reflect the responsiveness of spontaneous reporting systems to media interest and public concern; clusters of non-specific symptoms attributed to POTS and CFS were reported in Denmark and increased following heightened media reporting in 2013 and 2015 [53]. Concern arising from causal attribution given to such temporal associations has led to declines in vaccine uptake in some countries [4,5], resulting in lost opportunities to prevent high grade cervical lesions [3], cervical and other cancers.

Of the other AESI examined, no vaccine safety signals were identified. Disease flare in individuals with pre-existing AID was reported in three cases; clinical trials did not identify any difference in the risk of disease flare between vaccinated and unvaccinated individuals with pre-existing AID [7]. New onset AID was reported rarely with no consistent pattern and variable syndromes reported; large, population-based studies have not demonstrated any increased risk of new-onset AID following 4vHPV [13,15]. The reported rate of POI was similarly low with lack of clinical and diagnostic data; a recent population-based epidemiological study found no significant risk of POI following 4vHPV (HR 0.30, 95% confidence interval 0.07 to 1.36) [24] and in 2017, the GACVS stated that there was no evidence for a causal association between HPV vaccine and POI [51]. The rate of complex regional pain syndrome was similar to that reported from the US (0.28 per million doses distributed) [37]. The rate of VTE in our study, based on just 3 cases, was comparable to the rate reported to VAERS [37]; recent evidence [15,17] has not supported any increased risk of VTE following the early safety signal identified in VAERS data [11].

While HPV vaccines are not recommended for use in pregnancy, data from spontaneous reporting systems as well as registries have not identified fetal loss or congenital anomalies above background rates or any concerning pattern of fetal loss following 4vHPV vaccine [7,36,54]; our study findings supports this conclusion. In 2017, the GACVS concluded that inadvertent administration of 4vHPV during pregnancy has not been shown to be associated with adverse outcomes [51].

A limitation of our study was interpretation of the seriousness code for reported AE which, while included for completeness, is primarily used as a guide for sponsor reporting. Although multiple attempts are made to obtain additional information from the reporter, coding may not be based on review of detailed and verified clinical data in every case and may not capture all medically important events [55]. These limitations should be considered in interpreting the code and it should not be considered definitive of the seriousness of the event. Identification of potential AESI was limited by the search terms selected, which may not have captured all potentially relevant cases. Review of individual AESI was limited by the case details obtained by the TGA during investigation; despite multiple attempts, sufficient detail is not always obtained. Our study is also subject to the inherent limitations of spontaneous reporting systems, including incomplete and selective reporting. While essential for signal detection and hypothesis generation (which is undertaken prospectively by the TGA and may lead to regulatory action), spontaneous reporting systems do not allow comparison to rates in unvaccinated populations; epidemiological studies are required to explore a potential association [56]. Comparison with AE rates for other adolescent vaccines, also delivered in schools under the NIP, was limited as vaccines are often given concomitantly with 4vHPV. The use of national vaccine registry data as a denominator for doses administered may slightly underestimate total doses due to under-notification from predominantly catch up vaccination delivered by primary care practices, which may have modestly inflated rate estimates.

5. Conclusion

Over an 11-year period, reporting rates of AE following 4vHPV administration in Australia were consistent with data from similar surveillance systems internationally and did not reveal any new or concerning safety issues. However, during a period of enhanced surveillance implemented to monitor introduction of the vaccine to adolescent males in addition to females, syncope was noted to occur at a higher rate in younger adolescents than previously observed. AESI, except for syncope, were reported rarely following 4vHPV and no new or concerning patterns were identified. This comprehensive analysis further contributes to the large body of existing data affirming the safe post-marketing profile of 4vHPV vaccine in both males and females and the value and characteristics of long-term spontaneous reporting systems in monitoring vaccine safety.

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Author contributions

All authors attest they meet the ICMJE criteria for authorship. AP, KM, TS, JB and AD contributed to the conception and design of the study; AD, RH and MH contributed to acquisition of data; AP, JT, RH and MH analyzed the data; all authors contributed to interpretation of data; AP drafted the manuscript; all authors revised the manuscript critically for important intellectual content and approved the final version.

Declaration of Competing Interest

Over three years ago, JB was an investigator on two investigator-initiated HPV epidemiological studies that received partial unrestricted grants to support HPV typing components (cervical cancer typing study from Seqirus Australia, recurrent respiratory papillomatosis study from Merck) but has never received any personal financial benefits. The other 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.06.039.

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Appendix 1: Preferred terms used to identify adverse events of special interest (AESI)

- **Syncope**: Syncope, syncope vasovagal, loss of consciousness
- **Anaphylaxis**: Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, anaphylactoid shock
- **Autoimmune disorders (AID)**: Antinuclear antibody positive, autoantibody positive, autoimmune disorder, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune thrombocytopenia, Bechet's syndrome, colitis ulcerative, dermatomyositis, mixed connective tissue disease, myasthenia gravis, polymyalgia rheumatica, Reiter's syndrome, rheumatoid arthritis, scleroderma, sicca syndrome, Sjogren's syndrome, systemic lupus erythematosus, polymyalgia rheumatica
- **Venous thromboembolism (VTE)**: Thrombosis, deep vein thrombosis, mesenteric vein thrombosis, cerebral venous thrombosis, cavernous sinus thrombosis, intracranial venous sinus thrombosis, pulmonary embolism, embolism venous, axillary vein thrombosis, venous thrombosis
- **Guillain-Barré syndrome (GBS)**: Guillain-Barré syndrome, Miller Fisher syndrome, demyelinating polyneuropathy, chronic inflammatory demyelinating polyradiculoneuropathy
- **Postural orthostatic tachycardia syndrome (POTS)**: Postural orthostatic tachycardia syndrome, dizziness postural, postural reflex impairment
- **Complex regional pain syndrome (CRPS)**: Complex regional pain syndrome, mononeuropathy multiplex
- **Primary ovarian insufficiency (POI)**: Premature menopause, ovarian disorder, amenorrhea

Appendix 2: Reported adverse event rates per 100,000 doses administered to females and males in Australia within funded primary and catch-up programs by specified surveillance periods

Year of vaccination		2007–2009	2010–2012	2013–2014 Enhanced surveillance period		2015–2017	
Program	**Age group**	**Female** Rate (n/DA)	**Female** Rate (n/DA)	**Female** Rate (n/DA)	**Male** Rate (n/DA)	**Female** Rate (n/DA)	**Male** Rate (n/DA)
Primary	12–13 years	37.0 (317/856,802)	42.7 (377/883,335)	93.1 (561/602,666)	83.8 (513/612,057)	49.7 (485/975,043)	44.8 (447/996,689)
Catch-up	14–15 years	NA	NA	NA	39.1 (230/588,958)	NA	NA
	14–17 years	41.0 (605/1,475,484)	NA	NA	NA	NA	NA
	18–26 years	30.5 (543/1,777,470)	NA	NA	NA	NA	NA

DA: doses administered; NA: not applicable as not funded program (small denominators)

Appendix 3: Reported rate of syncope[a] per 100,000 doses administered to females and males in Australia within funded primary and catch-up programs by specified surveillance periods

Year of vaccination		2007–2009	2010–2012	2013–2014 Enhanced surveillance period		2015–2017	
Program	**Age group**	**Female** Rate (n/DA)	**Female** Rate (n/DA)	**Female** Rate (n/DA)	**Male** Rate (n/DA)	**Female** Rate (n/DA)	**Male** Rate (n/DA)
Primary	12–13 years	3.7 (32/856,802)	6.5 (57/883,335)	28.9 (174/602,666)	30.4 (186/612,057)	8.72 (85/975,043)	9.13 (91/996,689)
Catch-up	14–15 years	NA	NA	NA	10.7 (63/588,958)	NA	NA
	14–17 years	3.5 (51/1,475,484)	NA	NA	NA	NA	NA
	18–26 years	2.2 (39/1,777,470)	NA	NA	NA	NA	NA

[a]Including the preferred terms 'syncope', 'syncope vasovagal' and 'loss of consciousness' (see Appendix 1)

DA: doses administered; NA: not applicable as not funded program (small denominators)

Appendix 4: Abbreviations used in this manuscript

Abbreviation	Term
AE	Adverse event
AEMS	Adverse Events Management Systems database
AESI	Adverse event of special interest
AID	Autoimmune disease
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CRPS	Complex regional pain syndrome
GBS	Guillain-Barré syndrome
HPV	Human papillomavirus
4vHPV	Quadrivalent human papillomavirus vaccine
MedDRA®	Medical Dictionary for Regulatory Activities
NHVPR	National HPV Vaccination Program Register
NIP	National Immunisation Program
POI	Primary ovarian insufficiency
POTS	Postural orthostatic tachycardia syndrome
TGA	Therapeutic Goods Administration
VTE	Venous thromboembolism

2.3 Implications of publication 2

The cumulative analysis in this study provides reassuring data on the benefit–risk profile of HPV vaccine and demonstrates the value of spontaneous reporting systems. Serious and immediate AEFI such as anaphylaxis are likely to be spontaneously reported, and the accumulation of large amounts of data over time can provide useful information. In the case of HPV vaccine in the Australian context, there is the advantage that a denominator of doses administered was available for the period of this study, which has not historically been possible for many adolescent or adult vaccines in either Australia or many other parts of the world. The longitudinal data provides valuable evidence that is consistent with data from the US Vaccine Adverse Events Reporting System (VAERS). (100) Analysis of data captured over an extended period can contribute to an international body of evidence and provide reassurance to countries who are planning vaccine introduction or managing safety concerns.

For this study, the enhanced surveillance period provided particularly useful information. The stability of the anaphylaxis rate during this period provides added reassurance that the reported rate approximates the true rate and remains acceptable over time. In contrast, enhanced surveillance proved to be sensitive to detection of a much higher rate of syncope than previously reported. While enhanced surveillance was considered to be quite resource intensive with respect to the reporting requirements for school immunisation teams, it provided important new data on differential patterns related to age and sex that can inform programs globally. This data, a version of which was released in preliminary format by the TGA (26), had implications for management of student vaccinations in school-based programs, where measures to prevent and monitor for syncope were adopted and reinforced. The enhanced surveillance program was implemented under the HPV vaccine safety plan; its effectiveness as an adaptive and strategically implemented pharmacovigilance methodology highlights the value of formal vaccine safety plans, which have not necessarily been developed for each new vaccine introduction or recommendation.

This study also did not identify any safety concern for specific AESIs, including neurological syndromes, which were reported rarely. The very low rate of reports was particularly reassuring given the longitudinal nature of the study; however, data from this spontaneous system in isolation are limited and cannot be used to estimate risk in vaccinated compared to unvaccinated populations. (23) Disproportionality analyses may be applied to spontaneous AEFI reports to determine the relative reporting of specific AESIs, with one vaccine compared to another. However, this may be difficult for adolescent vaccines; most are given concomitantly in the Australian school-based immunisation program, and comparison with vaccines delivered in younger or older age

groups may not be valid, given the increased incidence of certain conditions such as immunisation anxiety-related reactions, syncope and autoimmune disease in the adolescent population. (101)

Spontaneously reported data can add value when reported rates of specific AESIs are compared to the expected, population rate of such events. While this approach was considered and reported for neurological conditions by the Gardasil Expert Panel in 2008 (50), expected rates of specific AESIs are not readily available in Australia as part of a multi-faceted adaptive pharmacovigilance approach. In the UK, background rates calculated from linked data within the Clinical Practice Research Datalink (CPRD) have been used effectively as a comparator for spontaneous reports of fatigue syndromes following HPV vaccine. (36) The importance of comparing rates of AESIs to the rate at which specific medical events occur in the background, and within sub-populations, has been increasingly recognised as critical during implementation of COVID-19 immunisation programs, to enable initial assessment of a potential safety signal. (102) Once a signal is identified, as discussed in Chapter 1, epidemiological studies conducted in large, population-level databases are required to systematically assess the risk of such rare conditions.

Australia's spontaneous reporting framework is a complex and multi-stakeholder system, allowing data transmission to underpin signal detection at the national level, while also facilitating agile, local responses. It is interesting that the signals for anaphylaxis and psychogenic illness were identified through spontaneous reporting in two of Australia's largest states, prior to collation of AEFI reports nationally. (49, 98) This highlights the flexible and timely response that may result from localised surveillance; conversely it may suggest lack of timeliness in collation of such data at a national level. AusVaxSafety-Active was established following the influenza vaccine concerns in 2010, to complement the spontaneous reporting system and improve timely recognition of safety signals. (57) For HPV vaccine, AusVaxSafety-Active is used to ensure that short-term reactogenicity is closely monitored, particularly in the context of program changes to include the 9-valent vaccine and a two-dose schedule. (58) This platform is described in the following chapter, where its use for live attenuated herpes zoster vaccine is assessed.

Chapter 3: Cohort event monitoring – an adaptive approach valuable for short-term safety

3.1 Introduction

The development of the SmartVax and Vaxtracker platforms, combined under AusVaxSafety-Active since 2014, represents an important step towards expanding Australia's suite of vaccine pharmacovigilance modalities. AusVaxSafety-Active directly fills a gap, identified after the 2010 safety incident with influenza vaccine, for 'complementary active surveillance systems which can methodologically detect potential AEFI [adverse event following immunisation] signals'. (52, p.492) It has been retrospectively established that such active surveillance would have identified the safety signal for febrile seizures within 3 weeks of implementation of the 2010 seasonal influenza immunisation program. (59) AusVaxSafety-Active can be variously described as active, participant-centred surveillance or cohort event monitoring (CEM) and uses two digital platforms, SmartVax and Vaxtracker. Both platforms enrol individuals through their immunisation provider and actively solicit information using standardised surveys over specified time periods following vaccination. Medical attendance is used as a proxy measure for a potentially serious AEFI, and the system uses a variety of mechanisms to prompt for further medical follow-up and/or submission of an AEFI report via state- and territory-based spontaneous reporting systems if appropriate. (56-58)

Although developed with childhood influenza vaccine safety surveillance in mind, the system has now been expanded to include all National Immunisation Program (NIP) vaccines, with a focus on detailed reports for new vaccines and new vaccine recommendations. In 2021 the system underwent significant adaptations to also include COVID-19 vaccines under the national pharmacovigilance plan. A recent review of participant-centred active surveillance systems internationally identified 23 studies that were either time limited or focused on single vaccines; 10 were focused solely on influenza vaccine. (30) While some, including Canada's healthcare worker influenza surveillance system, have been adapted for other vaccines (103), data on the usefulness of ongoing CEM for vaccines other than influenza was required at the time the study presented in this chapter was conducted.

A number of AEFIs will have onset within the first days after vaccination and relate to expected immune stimulation by the antigen or vaccine adjuvant. However, some adverse events may have their onset in the weeks, rather than days, after vaccination, including those related to live vaccines, due to the mechanism of viral replication in the context of immunodeficiency (whether known or

unknown at the time of vaccination). (5) AEFI due to live attenuated vaccine virus replication (whether from varicella-zoster virus [VZV], measles virus, Bacillus Calmette-Guérin vaccine or other vaccine strains) have the potential to lead to life-threatening complications in immunocompromised hosts. (104)

Live attenuated herpes zoster vaccine (ZVL) was included on the NIP in 2016 for adults aged 70 years, with catch-up to 79 years of age, and was the first live vaccine to be included for adults; it is contraindicated in immunocompromised individuals. (104) Vaccine strain-associated disseminated disease has been reported up to 7 weeks following vaccination with ZVL in immunocompromised individuals (105); prior to implementation of the Australian program, one case report of fatal, disseminated, vaccine-strain VZV infection had been published. (106) Consequently, in devising active surveillance approaches for ZVL using the AusVaxSafety-Active system, we sought to not only better understand short-term reactogenicity in this new elderly cohort targeted for vaccination, but also to explore whether later patient surveys were feasible to identify potential AEFI associated with vaccine virus replication. Thus, for monitoring of ZVL AEFI through AusVaxSafety-Active, the survey period was extended to 24 days for the Vaxtracker platform to supplement the standard 3-day surveillance period.

The following paper presents an analysis of AusVaxSafety-Active data for ZVL over the first 2 years of the program, describing overall short-term AEFI rates from 17,458 SmartVax participants (who responded to the standard day-3 survey), including an assessment of the risk of AEFI by sex and concomitant vaccination. The analysis by concomitant vaccination demonstrates the value of adaptive pharmacovigilance under real-world conditions, given that these vaccine combinations may not be assessed in clinical trials, and that schedules vary by country. A smaller cohort of 346 Vaxtracker participants provided surveillance data at 16 and 24 days following vaccination; risk was assessed by sex, concomitant vaccination and underlying medical condition. The adaptation of AusVaxSafety's methodology to include an older cohort and a longer survey period represents another example of real-world pharmacovigilance with the potential to explore the safety of vaccination in individuals with underlying medical conditions (including possible immunocompromise) and further understand the benefit–risk balance of an immunisation program. This study assesses the value of such adaptation, providing data to determine whether it is strategic to introduce such approaches for future immunisation programs, including for COVID-19.

3.2 Publication 3: Phillips A, Glover C, Leeb A, Cashman P, Fathima P, Crawford N, Snelling TL, Durrheim D, Macartney K. Safety of live attenuated herpes zoster vaccine in Australian adults 70–79 years of age: an observational study using active surveillance. BMJ Open. 2021; 11 (3): e043880. Available from: https://bmjopen.bmj.com/content/11/3/e043880

BMJ Open

Safety of live attenuated herpes zoster vaccine in Australian adults 70–79 years of age: an observational study using active surveillance

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ABSTRACT

Objectives To assess the safety of live attenuated herpes zoster vaccine live (ZVL) through cumulative analysis of near real-time, participant-based active surveillance from Australia's AusVaxSafety system.

Design and setting ZVL was funded in Australia for adults aged 70 years from November 2016, with a time-limited catch up programme for those up to 79 years. This cohort study monitored safety in the first two programme years through active surveillance at 246 sentinel surveillance immunisation sites.

Participants Adults aged 70–79 years vaccinated with ZVL who responded to an opt-out survey sent via automated short message service (SMS) 3 days following vaccination (n=17 458) or contributed supplementary data through a separate, opt-in online survey at 16 and 24 days following vaccination (n=346).

Primary and secondary outcome measures Rates of overall and prespecified adverse events following immunisation (AEFI) by sex, concomitant vaccination and underlying medical condition. Signal detection methods (fast initial response cumulative summation and Bayesian updating analyses) were applied to reports of medical attendance.

Results The median age of participants was 72 years; 53% were female. The response rate following automated SMS was high (73% within 7 days of vaccination). Females were more likely than males to report any adverse event within 7 days of vaccination (RR 2.07, 95% CI 1.86 to 2.31); injection site reaction was the most commonly reported (2.3%, n=377). Concomitant vaccination was not associated with higher adverse event rates (RR 1.05, 95% CI 0.93 to 1.18). Rates of medical attendance were low (0.3%) with no safety signals identified. Supplementary opt-in survey data on later onset adverse events did not identify any difference in AEFI rates between those with and without underlying medical conditions.

Conclusions ZVL has a very good safety profile in the first week after vaccination in older adults. Active, participant-based surveillance in this primary care cohort is an effective method to monitor vaccine safety among older adults and will be used as a key component of COVID-19 vaccine safety surveillance in Australia.

Strengths and limitations of this study

- ► High participation rates among older adults in an active, short message service-based, near-real-time vaccine safety surveillance system.
- ► Participant data enabled analyses of adverse events reported up to 7 days post-vaccination by sex and concomitant vaccination.
- ► Near real-time monitoring and signal detection will be used as a key component of COVID-19 vaccine safety surveillance in Australia.
- ► Only a small study group with underlying medical conditions were followed out to 24 days post-vaccination, limiting our ability to capture any late-onset adverse events.

INTRODUCTION

Herpes zoster (HZ) is a painful rash associated with significant morbidity, including postherpetic neuralgia in approximately 20% of those with HZ.[1] Live attenuated herpes zoster vaccine live (ZVL; Zostavax) is recommended to prevent HZ infection in older adults.[2] In Australia, a single dose of ZVL has been funded under the National Immunisation Programme (NIP) since November 2016 for adults aged 70 years, with catch-up until October 2021 for those aged 71–79 years. This is the first time a live attenuated vaccine has been routinely used in older adults in Australia, with guidance providing detailed information on contraindications in those with severe immunocompromise.[3]

Prior to inclusion of ZVL in the Australian NIP, data on ZVL safety in immunocompetent adults were predominantly available from clinical trials.[4–7] These studies identified a risk of localised injection site reactions (ISR) (48% in vaccine recipients compared with 16% of placebo recipients in the Shingles Prevention Study)[7] and no evidence of

an increased risk of serious adverse events, hospitalisation or death.[2 4–9] Higher rates of ISR were reported when ZVL was administered concomitantly with influenza vaccine (42.9% compared with 35.4% within 5 days)[10] and pneumococcal polysaccharide vaccine (23vPPV) (43.8% compared with 35.9% within 5 days)[11]; the rate of systemic adverse events was similar. One vaccine-related death was reported during post-marketing use of ZVL in an immunocompromised individual in the UK, contraindicated to receive the vaccine.[12] Shortly after commencement of vaccination under the NIP, a death in a vaccine contraindicated individual was also reported from Australia.[13]

Passive (spontaneous) postmarketing surveillance is used routinely in Australia to monitor safety following the introduction of a new vaccine. While this is an important tool to identify rare or population-specific adverse events following immunisation (AEFI) and has the advantages of being relatively low cost and open to reporting from the whole population, it is limited by the potential for under-reporting and biased reporting, lack of contemporary vaccinated population denominator data and, for ZVL, is confounded by the higher prevalence of chronic disease in the older target population.[8 14] In addition, lack of denominators (vaccine doses administered) and fluctuations in reporting numbers over time hinder analysis of data and signal detection. The addition of active surveillance of AEFI is increasingly recognised as an important component of postmarketing safety monitoring and can be undertaken using a range of different approaches.[15]

AusVaxSafety is an Australian Government Department of Health funded system that undertakes regular monitoring of AEFI through collection of survey data from individuals following routinely administered vaccines at sentinel sites across Australia.[16] This active, participant-based surveillance system uses two monitoring platforms (SmartVax and Vaxtracker),[17–19] and near-real-time surveillance data are analysed using signal detection methods. To coincide with introduction of the funded programme, active safety surveillance for ZVL, including fortnightly to monthly detailed analysis and reporting, was conducted for 2 years through AusVaxSafety.[20] This was the first time AusVaxSafety had been used for a live vaccine in an older adult population; however, this cohort is also included in surveillance of influenza[16 21] and pneumococcal vaccine safety.[20]

We aimed to cumulatively analyse prospectively collected AusVaxSafety data to provide a detailed assessment of the rates of specific early-onset AEFI following administration of ZVL and any concomitant vaccines (particularly influenza and 23vPPV vaccines) in adults aged 70–79 years from November 2016 to November 2018. In a subset with underlying medical conditions, we aimed to identify both early and later onset AEFI through the Vaxtracker monitoring platform.

METHODS

Study design

This was an observational cohort study conducted in 246 Australian sentinel primary care surveillance sites. Data were collected prospectively through AusVaxSafety active surveillance with AEFI rates and signal detection data reported in near real time. This study assessed cumulative data for the entire surveillance period and summarised near-real-time signal detection analyses.

Data sources

AusVaxSafety undertakes regular monitoring through collection of data from patients attending sentinel, primary care immunisation surveillance sites (general practices and hospital-based clinics); the system has been described previously.[16 21 22] AusVaxSafety was originally established to monitor influenza vaccine safety and had therefore focused on automated, short-term AEFI monitoring. For ZVL, the SmartVax monitoring platform was the primary data collection tool, focusing on early-onset AEFI from November 2016 to November 2018. In addition, supplementary data were collected from a separate patient cohort using an opt-in, online survey administered via the Vaxtracker platform up to 24 days following vaccination. These data were collected to allow for identification of later-onset AEFI and underlying medical conditions in this additional cohort.

SmartVax is an opt-out programme using an automated tool that integrates with immunisation provider software. Patients are automatically enrolled by their clinic and receive a communication via short message service (SMS) 3 days after vaccination asking whether they experienced any 'reactions' to the vaccine/s administered (as SMS are not sent on weekends, some may be sent up to 5 days postvaccination). For those who respond 'yes' (ie, report an AEFI), a second SMS is sent seeking information on whether medical attention was sought and a simultaneous SMS links to an online survey requesting further details (online supplemental appendix 1). During the period of this study, Vaxtracker was an opt-in programme, employing an initial manual step which required patients to be explicitly consented and enrolled by clinic staff following vaccination.[19] For ZVL, Vaxtracker sent a welcome message 3 days after vaccination by SMS or email (according to participant preference), confirming enrolment and advising to expect the survey at a later date. An initial online survey link was then sent 16 days after vaccination; for those who responded, a final survey link was sent 24 days following vaccination (online supplemental appendix 1).

The SmartVax SMS/survey and Vaxtracker day 16 survey collected data on any post-vaccination adverse event or symptom and on medical attendance; the day 24 Vaxtracker survey asked participants if they experienced specific adverse events (a chickenpox-like rash or influenza-like symptoms) or if they had been hospitalised since vaccination for any reason, which could potentially indicate later-onset vaccine associated AEFI, in

particular, disseminated varicella zoster virus (VZV) infection (online supplemental appendix 1). For SmartVax, demographic information was automatically extracted from the practice management software. For Vaxtracker, demographic information (including Indigenous status and sex) was self-reported in the day 16 survey; age was collected at enrolment because the vaccine was restricted by age. Only Vaxtracker collected self-reported information on participants' underlying medical conditions. For both platforms, reports of medically attended events triggered clinical follow-up by immunisation providers and/or public health authorities in each respective state or territory.

Study population

The primary cohort was adults aged 70–79 years vaccinated with ZVL and enrolled via the Smartvax platform. Individuals were included in the primary, short-term AEFI analysis if they responded to the Smartvax SMS/survey within 7 days of the vaccination, in order to minimise the risk of recall bias. The supplementary cohort was adults aged 70–79 years vaccinated with ZVL enrolled via the Vaxtracker platform. Individuals were included in analysis of the initial Vaxtracker survey data if they responded within 7 days of receipt of the initial (day 16) survey. In order to explore the usefulness of the final (day 24) Vaxtracker survey, which was designed to assess later-onset AEFI, participants were included regardless of the timeliness of their response (online supplemental appendix 1).

Data analysis

Data from the two platforms were analysed separately due to the different reporting timeframes and data collection processes. The median age of respondents and non-respondents, and of those responding within and following the 7-day period, were examined for both cohorts; sex differences were examined in the primary cohort only as sex of non-respondents was unknown for the supplementary cohort.

Rates of overall and specific AEFI, including 95% CIs, were calculated by sex and receipt of concomitant vaccination; where sex was missing, individuals were still included in overall rates. Supplementary analysis of later-onset AEFI also examined rates by concomitant vaccination and self-reported underlying medical condition. Analyses were conducted using R v3.5.1.[23] Where medical attendance was documented, further information was obtained, where available, from the healthcare provider and/or public health authorities involved in follow-up.

Signal detection

During the active surveillance period, rates of participant-reported medical attendance were analysed using signal detection and descriptive methods. Results were reported fortnightly to all relevant health authorities and made available publicly at ausvaxsafety.org.au from November 2016 to November 2017, and then monthly to November 2018. Fast initial response cumulative summation (FIR CUSUM) control charts monitored log-likelihood ratios of medical attendance being at a maximum acceptable level vs an expected level. The maximum acceptable (3%) and expected (2%) medical attendance rates were based on AEFI data from clinical trials and post-marketing surveillance.[6 7 24] A safety signal was 'detected' if the log-likelihood ratios exceeded a predetermined threshold log-likelihood ratio. Using simulated vaccination data, the threshold log-likelihood ratio was selected such that there was ≥80% probability of signal generation within 3 weeks if the event rate was at the maximum acceptable level, and an overall ≤2% probability of (false) signal generation when the event rate was at the expected level.

Bayesian updating analyses were conducted for robust estimates of the 95% credible interval (calculated from the posterior beta distribution) for true cumulative medical attendance rates. Data from the literature were used to establish the mean of the beta distribution (initial prior probability) for medical attendance at the commencement of the surveillance period.[6 7 24] Priors were updated with each fortnight or month's observed data throughout the surveillance period.

During real-time enhanced surveillance, both analyses included all participants (not limited to those responding within 7 days). All data on signal detection presented here thus reflects the cumulative result of real-time analyses that were conducted during the active surveillance period.

Patient and public involvement

The AusVaxSafety data monitoring platforms were piloted and developed with feedback from users. The AusVaxSafety surveillance system Advisory Committee includes a consumer representative. Surveillance results are uploaded to the AusVaxSafety website, www.ausvaxsafety.org.au, and available to the public.

RESULTS

Participation

Between 1 November 2016 and 4 November 2018, 23 875 individuals who received ZVL were enrolled in SmartVax; 74% responded to the first SMS (n=17 675) (figure 1A). Those who did not respond were similar in age to those who did (median 74 vs 72 years). There was little difference in the proportion of females and males who responded (75% vs 73%, respectively). Of those who responded to the first SMS, 99% (n=17 458) responded within 7 days of vaccination and were considered participants for the remainder of the primary analysis of short-term AEFI (figure 1A). The median age (72 vs 73 years) and proportion of males and females was similar among those who responded within 7 days compared with those who took longer to respond.

Between 13 December 2016 and 10 May 2018, 554 individuals were enrolled and invited to respond to the Vaxtracker survey; 67% (n=370) responded to the initial

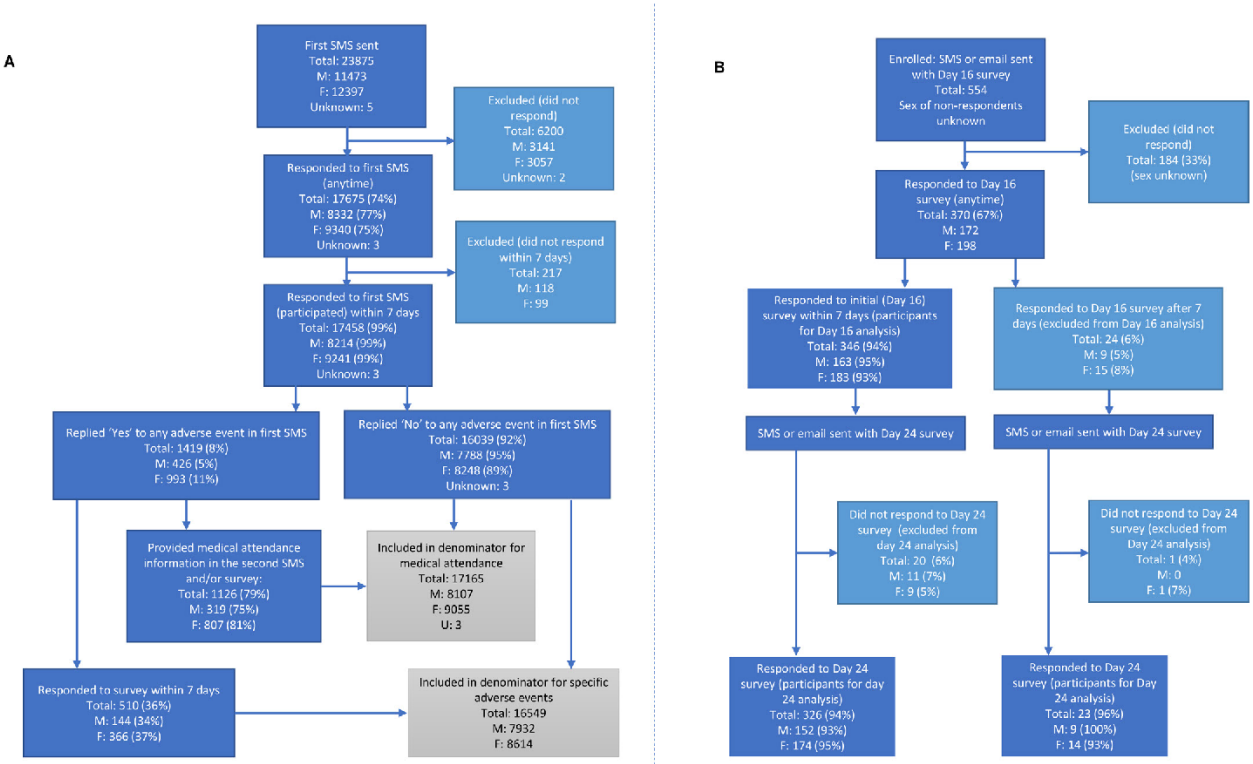

Figure 1 Number of individuals responding to and participating in sentinel, active participant-based surveillance platforms contributing to AusVaxSafety surveillance of live attenuated herpes zoster vaccine. (A) Short-term AEFI monitoring platform, SmartVax primary cohort (1 November 2016 to 4 November 2018). (B) Later-onset AEFI monitoring platform, Vaxtracker supplementary cohort (13 December 2016 to 10 May 2018). AEFI, adverse events following immunisation; SMS, short message service.

(day 16) survey. The age of those who responded was similar to the age of those that did not respond (median 73 vs 74 years). Of those who responded, 94% (n=346) responded within 7 days of receipt of the initial survey and were considered participants for the analysis of initial survey data (figure 1B). The median age (73 vs 75 years) and proportion of males and females was similar among those who responded within 7 days compared with those who responded later. Most participants in the initial survey also responded to final (day 24) survey (n=326, 94%); 23 individuals who responded to the initial survey after 7 days and responded to the final survey and were included in analysis of the final survey data (figure 1B).

Participant demographics

The median age of participants was 72 years and 47% were male; demographics were similar between participants using the two surveillance platforms (table 1). Concomitant vaccines were received slightly more frequently among participants in the primary cohort than in the supplementary cohort. Underlying medical conditions were reported by 41% of respondents in the supplementary cohort (table 1); the most common conditions were arthritis, diabetes, heart disease and respiratory disease.

Short-term AEFI (primary analysis)

Of the 17 458 participants, 8.1% reported any AEFI (n=1419); females were significantly more likely than males to report AEFI (table 2). Thirty-six per cent of those who reported an AEFI responded to the online survey and provided additional details (figure 1A); injection site reaction was the most commonly reported specific AEFI (2.3%, n=377) (table 2). Of participants who reported fever, 72.3% (60 of 83) reported the use of antipyretics or analgesics. Participants who had received one or more concomitant vaccine (22.9%) were no more likely to report any AEFI than if those who received ZVL alone; however, they were less likely to report a rash and more likely to report fever (table 2). Of those receiving only influenza vaccine concomitantly, 7.6% (n=230 of 3032) reported any AEFI, compared with 11.6% (n=57 of 492) of those receiving only 23vPPV with ZVL; 19.4% (n=28 of 144) of those who received both influenza and 23vPPV concomitantly (with no other vaccines) reported any AEFI.

Medical attendance within a week following vaccination was reported by 0.3% (n=49) of the participants who provided a response regarding medical attendance (figure 1 and table 2). Of those who provided more

Table 1 Demographic characteristics of AusVaxSafety participants who received live attenuated herpes zoster vaccine*

Variable	Category	Primary cohort (SmartVax) N=17 458†	Supplementary cohort (Vaxtracker) N=346	Overall N=17 804‡
Median age (IQR)		72 years (70–75)	73 years (71–76)	72 years (70–75)
Sex n (%)	Male	8214 (47.1)	163 (47.1)	8377 (47.1)
	Female	9241 (52.9)	183 (52.9)	9424 (52.9)
Indigenous status n (%)	Aboriginal	59 (0.4)	2 (0.6)	61 (0.4)
	Torres Strait Islander	8 (0.06)	0	8 (0.05)
	Both	5 (0.03)	0	5 (0.03)
	Total	72 (0.5)	2 (0.6)	74 (0.5)
Concomitant vaccination§ n (%)	At least one concomitant vaccine	3993 (22.9)	57 (16.5)	4050 (22.8)
	23vPPV	657 (3.8)	11 (3.2)	668 (3.8)
	Influenza vaccine	3218 (18.4)	45 (13.0)	3263 (18.3)
	Diphtheria/tetanus vaccine	235 (1.3)	3 (0.9)	238 (1.3)
Underlying medical condition n (%)	Yes	NA	143 (41.3)	NA
	No	NA	203 (58.7)	NA

*SmartVax participants responding to an opt-out SMS within 7 days of vaccination between November 2016 and November 2018; Vaxtracker participants responding to an opt-in survey via SMS or email within 7 days of survey receipt following vaccination between December 2016 and May 2018.
†Denominator 17 455 for sex which was missing in three reports; denominator 14 342 for Indigenous status, which was missing in 3116 reports.
‡Denominator 17 801 for sex which was missing in three reports; denominator 14 688 for indigenous status, which was missing in 3116 reports.
§Some participants received more than one concomitant vaccine.
NA, not available; SMS, short message service; 23vPPV, 23-valent pneumococcal vaccine.

detailed information (n=13), most attended a primary care provider (n=11) and two attended a hospital emergency department. Detailed data were provided by jurisdictions for seven of these reports. Three involved a reaction at the injection site, one of which also reported rash. One report described systemic symptoms including fever, headache, fatigue and weakness 8 hours following vaccination. One report was for hyperglycaemia in a known diabetic and one was an unrelated surgical admission. All were resolved or resolving on follow-up.

Table 2 Short-term AEFI reported by AusVaxSafety participants following live attenuated herpes zoster vaccine live (ZVL) by sex and concomitant vaccination

	Males n (%)	Females n (%)	RR (95% CI) (female vs male)	ZVL alone n (%)	ZVL+concomitant vaccine/s n (%)	RR (95% CI) (concomitant vs ZVL alone)
Any AEFI *	426 (5.2)	993 (10.7)	2.07 (1.86 to 2.31)	1082 (8.0%)	337 (8.4%)	1.05 (0.93 to 1.18)
Injection site reaction †	86 (1.1)	291 (3.4)	3.12 (2.45 to 3.96)	304 (2.4%)	73 (1.9%)	0.81 (0.63 to 1.05)
Fever †	23 (0.3)	60 (0.7)	2.40 (1.49 to 3.88)	56 (0.4%)	27 (0.7%)	1.63 (1.03 to 2.58)
Rash †	12 (0.2)	54 (0.6)	4.14 (2.22 to 7.74)	59 (0.5%)	7 (0.2%)	0.40 (0.18 to 0.88)
Medical attendance ‡	16 (0.2)	33 (0.4)	1.85 (1.02 to 3.35)	38 (0.3%)	11 (0.3%)	0.98 (0.50 to 1.91)

*Denominator includes SmartVax participants responding to an opt-out SMS within 7 days of vaccination (M=8214, F=9241, total: 17 458, sex missing in 3). ZVL alone was received by 13 465 participants and concomitant vaccine/s by 3993 participants.
†Denominator includes SmartVax participants who reported any AEFI within 7 days of vaccination and then also responded to a survey within 7 days of vaccination, and SmartVax participants who reported no AEFI within 7 days of vaccination (M: 7932, F: 8614, total: 16 549, sex missing in n=3). In this subset, ZVL alone was received by 12 778 participants and concomitant vaccines were received by 3771 participants.
‡Denominator includes SmartVax participants who reported any AEFI within 7 days of vaccination and then also provided medical attendance information within 7 days via SMS and/or the online survey, and SmartVax participants who or reported no AEFI within 7 days of vaccination (M=8107, F=9055, Total: 17 165, sex missing in 3). In this subset, ZVL alone was received by 13 246 participants and concomitant vaccines were received by 3919 participants.
AEFI, adverse events following immunisation; SMS, short message service.

Later-onset AEFI (supplementary analysis)

Of 346 participants providing supplementary data through the initial Vaxtracker survey, 15.0% (n=52) reported any AEFI and ISR was the most common specific event (6.6%, n=23). Females were no more likely than males to report an AEFI, apart from ISR (table 3), and concomitant vaccination was not associated with a change in reported AEFI. Those with a self-reported underlying medical condition (41.3%, n=143) were no more likely to report an adverse event than those without (table 3).

Medical attendance was reported by 1.7% of participants (n=6) in the initial survey; all six participants visited a primary care provider. These included three reports of influenza-like illness within 2 days of vaccination; one report also described leg pain. There were two reports of rash including one report of hives (timing after vaccination unknown) and one reported diagnosis of eczema at day 14. There was one report of ISR on the day of vaccination, which resolved.

Of those completing the final survey (n=349), 151 (43%) had an underlying medical condition. Those with a medical condition were no more likely to report influenza-like illness or chickenpox-like rash than those without (table 4). Of participants reporting influenza-like illness, most (84%) had received ZVL alone. Two participants reported hospitalisation for allergic reaction (one following a dental procedure and one following consumption of shellfish).

Cumulative event rates and signal detection

Overlay of bimonthly Bayesian analyses conducted during near real-time surveillance demonstrated increased precision of the rate estimates with data accumulation (figure 2); rates of participant-reported medical attendance remained below the prespecified maximum threshold rate. The FIR CUSUM control charts for the entire surveillance period found no evidence that the event rate for medical attendance was closer to the maximum threshold than the expected rate (figure 2).

DISCUSSION

Using this unique, active postmarketing vaccine safety surveillance programme in Australia, AusVaxSafety, we found ZVL to have a very good safety profile in the first week after vaccination in older adults. Participation rates among the primary cohort were high using an opt-out surveillance platform (SmartVax), which provided 98% of all data (n=17 458 participants). As most participants responded quickly, data was provided in near real-time, enabling AusVaxSafety to efficiently monitor the introduction of a new immunisation programme, including through signal detection methods. This active surveillance complemented existing passive surveillance and did not identify any safety signals for ZVL; however, the rare reports of vaccine associated death due to disseminated VZV infection with onset weeks after vaccination, in immunocompromised individuals, remains an issue

Table 3 Later-onset AEFI reported by AusVaxSafety participants following live attenuated herpes zoster vaccine live (ZVL) by sex, concomitant vaccination and underlying medical condition (initial survey)*

	Males n (%)	Females n (%)	RR (95% CI) (female vs male)	ZVL alone n (%)	ZVL +concomitant vaccine/s n (%)	RR (95% CI) (concomitant vs ZVL alone)	No medical condition n (%)	Medical condition n (%)	RR (95% CI) (medical condition vs no condition)
Any AEFI	19 (11.7)	33 (18.0)	1.55 (0.92 to 2.61)	46 (15.9)	6 (10.5)	0.66 (0.30 to 1.48)	28 (13.8)	24 (16.8)	1.22 (0.74 to 2.01)
Injection site reaction	6 (3.7)	17 (9.3)	2.52 (1.02 to 6.25)	19 (6.6)	4 (7.0)	1.07 (0.38 to 3.02)	13 (6.4)	10 (7.0)	1.09 (0.49 to 2.42)
Fever	2 (1.2)	6 (3.3)	2.67 (0.55 to 13.1)	8 (2.8)	0 (0.0)	NA	2 (1.0)	6 (4.2)	4.26 (0.87 to 20.8)
Rash	3 (1.8)	5 (2.7)	1.48 (0.36 to 6.12)	7 (2.4)	1 (1.8)	0.72 (0.09 to 5.77)	5 (2.5)	3 (2.1)	0.85 (0.21 to 3.51)
Medical attendance †	2 (1.2)	4 (2.2)	1.78 (0.33 to 9.60)	5 (1.7)	1 (1.8)	1.01 (0.12 to 8.52)	4 (2.0)	2 (1.4)‡	0.71 (0.13 to 3.82)

*Denominator includes Vaxtracker participants responding within 7 days to an initial opt-in survey by SMS or email sent 16 days following vaccination (M: 163, F: 183, total: 346). Of these, 57 had received a concomitant vaccine and 143 had an underlying medical condition.
†All those reporting medical attendance reported visiting a primary care provider.
‡One participant had arthritis and one had diabetes.
AEFI, adverse events following immunisation; NA, not available; SMS, short message service.

Table 4 Later-onset AEFI reported by AusVaxSafety participants following live attenuated herpes zoster vaccine by sex and underlying medical condition (final survey)*

	Males n (%)	Females n (%)	RR (95% CI) (females vs males)	No medical condition n (%)	Medical condition n (%)	RR (95% CI) (medical condition vs no condition)
Influenza-like Illness	10 (6.2)	22 (11.7)	1.88 (0.92 to 3.86)	17 (8.6)	15 (9.9)	1.16 (0.60 to 2.24)
Chickenpox-like rash	1 (0.6)	7 (3.7)	5.99 (0.75 to 48.2)	4 (2.0)	4 (2.6)	1.31 (0.33 to 5.16)
Hospitalisation †	1 (0.6)	1 (0.5)	0.86 (0.05 to 13.64)	2 (1.0)	0 (0.0)	NA

*Denominator includes Vaxtracker participants responding to a final opt-in survey by SMS or email sent 24 days following vaccination (M: 161, F: 188, total: 349). Of these, 151 had an underlying medical condition.
†Hospitalisation for allergic reaction (one following a dental procedure and one following consumption of shellfish).
AEFI, adverse events following immunisation; NA, not available; SMS, short message service.

of concern which is being closely examined.[25 26] Active vaccine safety surveillance with SMS-based technology in older adults has also been effective in monitoring influenza vaccine safety (response rate 69.6%)[21] and 23vPPV[20] and will be used for surveillance of COVID-19 vaccine safety in Australia. In the USA, a similar system (V-Safe) has been introduced to support safety monitoring for COVID-19 vaccine.[27]

Self-reported AEFI rates in our study were low and similar to those reported by AusVaxSafety following various inactivated influenza vaccines in adults over 65 years (4.8%–8.9%).[16 21] Rates of medical attendance (as a proxy for serious adverse events) were also low, consistent with other studies that have not identified an increased risk of serious adverse events following administration of ZVL.[8 28–30] ISR was the most commonly reported specific

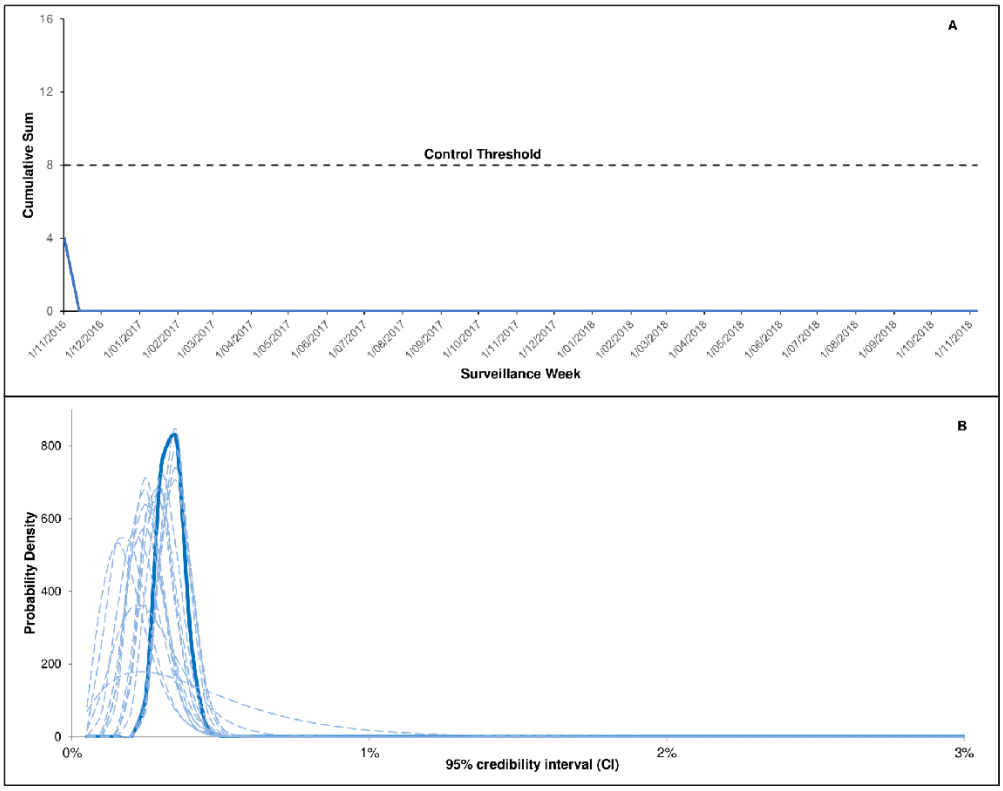

Figure 2 Cumulative signal detection analyses and cumulative event rates following live attenuated herpes zoster vaccine for respondents using the SmartVax platform (regardless of timeliness of response). (A) Fast initial response cumulative sum (FIR CUSUM) safety signal detection chart for medical attendance following live attenuated herpes zoster vaccine during the surveillance period (FIR CUSUM tracks the relative log-likelihood ratio of the event rate being at the maximum acceptable rate (set at 3%) vs expected rate (set at 2%) given the accumulated data). (B) Overlayed bimonthly Bayesian analyses showing the probability density curve of medical attendance (dotted lines indicate bimonthly posterior density curves throughout the surveillance period; Solid line is the final posterior density curve). FIR CUSUM, fast initial response cumulative summation.

AEFI in our study, which has also been observed via passive surveillance in Australia, the USA and globally.[2 8 25] A recent Australian study using a large general practice dataset similarly demonstrated an increased risk of ISR following vaccination with ZVL using the self-controlled case series method.[29] Our study did not identify an increased risk of ISR with concomitant vaccination, consistent with the findings of a more recent randomised controlled trial comparing ZVL administered alone or concomitantly with quadrivalent influenza vaccine.[31] While AusVaxSafety has previously demonstrated significantly higher rates of AEFI for individuals receiving 23vPPV concomitantly with influenza vaccine, this has not been shown for ZVL administered with influenza vaccine, compared with influenza vaccine alone.[21] Interestingly, AEFI were reported more commonly by females than males, as has been observed in other vaccine safety surveillance in Australia (for various inactivated influenza vaccines using AusVaxSafety data: 8.7% of women reported AEFI vs 5.8% of men)[21 32] and internationally.[33] Biological differences in immune function[34] and behavioural differences that may have influenced reporting rates are potential factors underpinning these observed differences.[33]

This study included supplementary analysis of longer-term data in a small group of participants, in view of the potential for late-onset AEFI. Rates of AEFI were higher over the longer follow-up period (15% from the initial survey, sent at day 16, compared with 8.1% in the first week for any AEFI), which may relate to the potential to capture more AEFI over a longer time period, and to the intrinsic differences in the way in which participant responses were solicited via this opt-in survey. Despite this, our analysis did not signal any vaccine safety concerns; the rate of medical attendance (1.7%) which, based on patient descriptors, sometimes included routine attendance for unrelated matters, was similar to the rate of serious adverse events reported in clinical trials (1.4% in the Shingles Prevention Study).[7] Similarly, no increased risk of late-onset (up to 42 days postvaccination) AEFI, including cardiovascular and cerebrovascular events, was demonstrated in two large studies of older adults using data from the sites participating in the US Vaccine Safety Datalink project,[28 30] or in a self-controlled case series analysis of Australian general practice data from 150 054 older adults.[29]

Use of ZVL in immunocompromised patients has been associated with vaccine strain disseminated VZV disease occurring up to 7 weeks following ZVL vaccination,[8 12 13] with fatal outcomes reported in immunocompromised individuals from the UK[12] and Australia,[12 13] including a case reported shortly after programme commencement[13] and two additional individuals following completion of this study.[26] Australian guidance provides detailed information on contraindications in immunocompromised patients.[3] In our study, those with underlying medical conditions were no more likely to report an AEFI or medical attendance than those without, and there was no increased risk of any of the AEFI prespecified in the final survey. Similarly, a recent prospective cohort study of 1500 patients in Japan did not identify an increased risk of AEFI following ZVL among those with underlying conditions such as malignancy, diabetes mellitus, autoimmune diseases and renal diseases,[35] and an analysis of UK primary care data identified only two cases of VZV disease among 1742 individuals who were inadvertently vaccinated while immunosuppressed; neither were hospitalised.[36]

Recorded coverage of ZVL in Australia was 33.9% in 70-year-old adults from commencement of the NIP programme in November 2016 until 31 March 2018 (noting that underreporting is likely given that only 489 605 of 1 370 395 doses distributed were recorded as being administered).[25] The recombinant VZV vaccine is registered in Australia but not currently available; in future, this vaccine may provide an alternative option for immunocompromised individuals.[37]

This study has a number of limitations. The supplementary cohort was small and our assessment of later-onset AEFI was likely limited by the potential for recall bias; larger studies are required to assess the risk of later-onset AEFI, including in individuals with underlying medical conditions. The opt-out approach for the primary cohort resulted in a high initial response to the SMS on the presence of absence of AEFI (74%) but a lower response to the more detailed survey (36%). A similar trend has been observed through active surveillance for other vaccines, including influenza and 23vPPV vaccination in older adults.[20] While survey completion rates were higher using an opt-in approach for the supplementary cohort, consistent with previous studies,[38] this is more resource intensive and difficult to implement for a large cohort. In use of this methodology for COVID-19 vaccine safety surveillance, AusVaxSafety has now combined the initial SMS contact and detailed survey into one message with the aim of increasing response rates to all study questions; data will also be collected several weeks following vaccination for COVID-19. As for all observed AEFI, a causal relationship between the reported events and vaccination cannot be assumed; AEFI event rates reported here are comparable to those reported for ZVL and other vaccines in post-marketing surveillance of this age group.[16 21 29]

CONCLUSION

AusVaxSafety's active, participant-based surveillance system contributed timely safety data, particularly on short-term AEFI, following implementation of a funded ZVL programme in an older Australian population, confirming the known low risk of ISR, and with no safety signals identified. This system is an efficient, automated addition to Australia's established passive vaccine safety surveillance. However, limitations remain in utilising individual reporting systems alone; the ability to routinely link this vaccine safety surveillance data (both active and passive AEFI reports), denominator data from the Australian Immunisation Register,[39] and data sources that

include medical presentations for adverse events, such as primary care data, hospitalisation and mortality data would further assist the assessment of serious or late-onset AEFI.[29] With the implementation of COVID-19 immunisation programmes, targeted at older adults and people with underlying medical conditions that may increase the risk of AEFI, expansion of effective real-world vaccine safety surveillance systems, particularly those that can detect rare, novel, or late onset AEFI, is paramount and is already occurring in Australia.

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Contributors AP, CG, TLS, NC and KM made substantial contributions to the conception or design of the manuscript. AP and CG were responsible for drafting the manuscript and conducting all data analyses, with the exception of signal detection analyses, which were performed by PF. TLS and PF were responsible for the conceptualisation and execution of the weekly safety signal detection analyses. AL, as codeveloper of the SmartVax system, served as the system operator and advisor regarding SmartVax data. PC and DD served as system operator and advisors regarding Vaxtracker data. PC, AL, TLS, DD and KM were integral to the design and development of the AusVaxSafety vaccine safety surveillance system and served as key vaccine safety experts. All authors made substantial contributions to the interpretation of data for the work and revised the manuscript critically for important intellectual content. All authors had final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix 1: Surveillance questionnaires

Short-term AEFI (SmartVax)

First SMS: 'We would like to know if there were any reactions to the vax. Please reply with 'Y' for Yes, 'N' for No or 'Stop' to opt out.

Second SMS: Thanks for responding. Could you please complete a 2 min survey by following [link]

As a result of the vaccination reaction, did you visit a doctor, medical centre, after hours service or hospital emergency dept? Please answer Y or N only.

Survey:

Initial question	Options	Follow up questions
Did you experience any of the following symptoms following your vaccination? Tick all that apply.	Fever/temperature	Time to onset Duration Highest temp
	Swelling or redness at injection site	Time to onset Duration Which side
	Pain at injection site	Time to onset Duration Which side
	Tired/fatigue	Time to onset Duration
	Irritable	Time to onset Duration
	Sleep pattern change	Time to onset Duration
	Rash	Time to onset Duration
	Headache	Time to onset Duration
	Vomiting	Time to onset Duration
	Diarrhoea	Time to onset Duration
	Convulsions/seizures	Time to onset Duration
	Rigors (shaking or shivering with high temp)	Time to onset Duration

	Non-responsiveness/loss of consciousness	Time to onset Duration
	Other	Time to onset Duration Specify other
Was there any anti-fever or anti-pain medication taken (for example, Panadol or Nurofen) as a result of your reaction?	Yes No	
As a result of your reaction, did you phone any of the following for medical advice (leave blank if none)?	Doctor/Medical centre Healthdirect Other	
As a result of your reaction, did you visit, or were you visited by, any of the following (leave blank if none)?	GP/Medical centre After hours/locum ED	
Have these symptoms resolved?	Yes No Unsure	
If you would like to discuss your reaction with a healthcare professional, please call your medical centre on [number]. Thank you for taking the time to answer these questions.		

Longer-term AEFI (Vaxtracker)

Initial survey (sent at day 16): Welcome to the Zostavax Vaxtracker Survey. We would like to ask you about symptoms you may have had in the sixteen days following your vaccination date [date]. Your calendar or diary may be useful in answering these questions. Please complete the questions below for yourself and press the button at the bottom to submit the survey.

Initial question	**Options**
What is your gender?	Male Female
What is your date of birth?	
What is your postcode of residence?	
Do you identify as Aboriginal or Torres Strait Islander?	Aboriginal Torres Strait Islander Both Neither

In the last twelve months, were you treated for the following medical conditions?		Cancer Diabetes Arthritis Heart Disease Respiratory Disease Dialysis Blood/Immune Disease
Initial question	**Options**	**Follow up question**
In the 16 days since vaccination, did you experience any kind of symptoms?	Yes/No	
Redness and/or swelling at injection site?	Yes/No	What date did this symptom begin? Have you fully recovered from this symptom? What date did you recover?
Pain at the injection site?	Yes/No	What date did this symptom begin? Have you fully recovered from this symptom? What date did you recover?
Itching at the injection site?	Yes/No	What date did this symptom begin? Have you fully recovered from this symptom? What date did you recover?
Fever?	Yes/No	What was the highest temperature (if known)? What date did this symptom begin? Have you fully recovered from this symptom? What date did you recover?
Rash?	Yes/No	Where was the rash? *At injection site/ Elsewhere* Did you also have Flu-like symptoms? What date did this symptom begin? Have you fully recovered from this symptom? What date did you recover?
Headache	Yes/No	Was it *new headache/ aggravated headache* What date did this symptom begin?

		Have you fully recovered from this symptom? What date did you recover?
Fatigue	Yes/No	Was it *new fatigue/aggravated fatigue* What date did this symptom begin? Have you fully recovered from this symptom? What date did you recover?
Arm/Leg Pain?	Yes/No	Was it *new pain/aggravated pain* What date did this symptom begin? Have you fully recovered from this symptom? What date did you recover?
Other symptoms?	Yes/No	Would you like to add a description?
Did you seek medical attention for any of the symptoms?	Yes/No	We may contact you to assess the symptoms you have reported. Please let us know the best contact details to use.

Final survey (sent at day 24): Welcome to the Final Zostavax Vaxtracker Survey. Please complete the questions below for yourself and press the button at the bottom to submit the survey.

Initial question	Options	Follow up question
Since the vaccination, have you had the following symptoms?	Chicken Pox like rash Flu like symptoms	
Have you been admitted to hospital in the last 24 days?	Yes/No	What was the admission date? What was the diagnosis?
We may contact you to assess the reactions you have reported. Please let us know the best contact details to use.		

3.3 Implications of publication 3

This paper provides reassuring data on the short-term safety profile of ZVL using a novel approach not reported from any other setting. No new safety signals were identified; ISR was the most commonly reported AEFI. There was no increased risk of ISR with concomitant vaccination, which differed from prior experience of influenza vaccine given concomitantly with pneumococcal polysaccharide vaccine. (71)

The study also demonstrates the benefit of this CEM system in providing regular data to enable ongoing signal detection analyses during program implementation. In particular, this study validates the use of such methodology in an older cohort. The response rate (73%) using this novel mhealth approach was similar to that reported for children under 5 years (70%, January to July 2020; C. Glover, National Centre for Immunisation Research and Surveillance, personal communication, 11 May 2021) and for influenza vaccines across all age groups (71.8%) (107), and higher than that reported for adolescents (57.3%, January to July 2020; C. Glover, personal communication).

This study considered a supplementary cohort with follow-up at 16 and 24 days post vaccination, providing useful information to assess later-onset AEFI. However, the supplementary cohort was small, limiting conclusions that could be made about risk. Further, the usefulness of participant-centred surveys in collecting reliable information at a time distant from vaccination is likely to be impacted by recall bias and the potential for increased reporting of unrelated medical events. Reports of fatal, disseminated infection following ZVL in Australia have come through the spontaneous reporting system. (69) This highlights the important ongoing role of spontaneous reporting in identifying rare, serious AEFI, and as a key element of any multi-faceted pharmacovigilance approach, given reporting occurs across the whole population.

There is potential to use strategic approaches, such as adaptation of active surveillance systems like AusVaxSafety-Active, to complement the existing spontaneous reporting system in a coordinated manner. For COVID-19 vaccines, AusVaxSafety-Active has expanded, under the COVID-19 pharmacovigilance plan, to include a survey at additional time points. (58) The US has also implemented CEM monitoring for COVID-19 vaccines through a new system, v-safe, modelled in part on AusVaxSafety-Active. (74) Data from this system has been used to develop a pregnancy registry and, in combination with data from the Vaccine Adverse Events Reporting System (VAERS), to characterise COVID-19 vaccine safety in pregnant women, demonstrating the ability of such a system to adapt, provide timely data and add value to a suite of pharmacovigilance resources. (108)

The timely availability of such data and the ability to rapidly communicate safety is particularly useful for COVID-19 vaccines, given the rapid implementation, high reactogenicity and reported vaccine hesitancy. (13, 109) AusVaxSafety-Active communicates data on all vaccines regularly through its website, adapting information to address emerging COVID-19 vaccine concerns, such as missed work due to systemic side effects, and anaphylaxis in individuals with a self-reported, relevant medical history. (58)

While CEM systems offer clear advantages as part of a suite of pharmacovigilance methods, later-onset AEFI that have not been identified in clinical trials are likely to be rare; large cohorts are required to reliably collect data to assess such conditions. Further, like spontaneous reporting systems, CEM systems are unable to determine risk relative to an unvaccinated cohort. (25) Active surveillance and epidemiological studies conducted within large cohorts are required to identify, investigate and understand potential safety signals, particularly for later-onset AEFI. An example of a novel approach within a large cohort is presented in the next chapter, again considering the safety of ZVL.

Chapter 4: Novel data sources and methods diversify surveillance mechanisms and contribute to hypothesis testing

4.1 Introduction

This next study introduces an epidemiological analysis within a large, primary care database (MedicineInsight, operated by the National Prescribing Service [NPS]). This represents a novel approach towards expanding vaccine pharmacovigilance capacity and incorporating more robust methods using a large, nationally representative database. In Australia, national healthcare databases, such as those coding hospital discharge data, are generally administrative, do not contain detailed clinical information, and are designed for allocation of resources rather than for research or health management purposes. Other specific healthcare databases, including the Australian Immunisation Register, are maintained separately and siloed. Despite a universal healthcare system and these numerous national or state-based healthcare databases, there is no national, systematically linked healthcare data available in Australia for the purposes of supporting health programs, including public health programs such as immunisation. (65)

MedicineInsight is a collection of de-identified data extracted from the patient management software programs of participating primary care sites – also known as general practices – across Australia, used to support medication safety. Although not linked data, it has potential to fill a gap by providing access to a large, national dataset incorporating both health and immunisation information that can be adapted for the purposes of pharmacovigilance. In 2018 and 2019, MedicineInsight data represented 13.2% of all patients who visited a general practitioner. (110) This proof-of-concept study was the first to utilise MedicineInsight data for vaccine safety, and facilitated collaboration and engagement with NPS to develop the methodology.

The study continues with the focus on live attenuated herpes zoster vaccine (ZVL), which is largely administered in primary care under the National Immunisation Program (NIP); pneumococcal and influenza vaccines were included to allow comparison of outcomes. The self-controlled case series (SCCS) approach was considered most appropriate for this analysis as it automatically controls for fixed confounding. (32) The method was developed for vaccine safety assessment and allows individuals to act as their own controls by assessing the risk of medical events in a pre-defined risk window following vaccination, compared to time window(s) distant from (and unlikely to be influenced by) vaccination. (32) The SCCS method was used to assess adverse events following immunisation (AEFIs) with ZVL within the Vaccine Safety Datalink (VSD) in the US (111); it has also

been used to investigate AEFIs following human papillomavirus (HPV) vaccine within the Clinical Practice Research Datalink (CPRD) in the UK. (36) While the SCCS method was used in Australia to investigate intussusception following rotavirus vaccines, based on data captured through the Paediatric Active Enhanced Disease Surveillance (PAEDS) system and other similar, hospital-based surveillance (37), it has not previously been applied to MedicineInsight data.

This study aims both to validate use of MedicineInsight for vaccine pharmacovigilance and to understand the risk of later-onset AEFIs. Specific adverse events of special interest (AESIs) were pre-defined, including rash, rash with antiviral prescription (as a marker of possible disseminated infection), myocardial infarction and stroke. Positive and negative control conditions (injection site reaction and burn, respectively) were included to validate the method.

4.2 Publication 4: Totterdell J, Phillips A[1], Glover C, Chidwick K, Marsh J, Snelling T, Macartney K. Safety of live attenuated herpes zoster vaccine in adults 70–79 years: a self-controlled case series analysis using primary care data from Australia's MedicineInsight program. Vaccine. 2020; 38 (23): 3968–3979. Available from: https://doi.org/10.1016/j.vaccine.2020.03.054

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Safety of live attenuated herpes zoster vaccine in adults 70–79 years: A self-controlled case series analysis using primary care data from Australia's MedicineInsight program

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ABSTRACT

Background: Australia introduced a funded shingles vaccination program for older adults in November 2016, administered predominantly in primary care clinics. MedicineInsight, a nationally representative primary care database, was used to investigate the risk of pre-specified outcomes following live attenuated herpes zoster vaccine (ZVL) in Australia.

Methods: Individuals aged 70–79 years who received ZVL between 1 November 2016 and 31 July 2018 were identified from MedicineInsight. The self-controlled case series (SCCS) method was used to estimate the seasonally-adjusted relative incidence (RI) of seven pre-specified outcome events (injection site reaction (ISR) [positive control], burn [negative control], myocardial infarction (MI), stroke, rash, rash with an antiviral prescription, and clinical attendance) during a plausible post-vaccination at-risk window compared with times distant from vaccination. Sensitivity analyses examined the effect of common concomitant vaccinations and restriction to first outcome events.

Results: A total of 332,988 vaccination encounters among 150,054 individuals were identified during the study period; over 2 million clinical attendances were observed. There was an increased RI of ISR in the seven days following ZVL (RI = 77.4, 95% CI 48.1–124.6); the RI of clinical attendance (RI = 0.94, 95% CI 0.94–0.95) and stroke (RI = 0.58, 95% CI 0.44–0.78) were lower in the 42 days following administration of ZVL compared to control periods. There was no evidence of a change in the RI of MI (RI = 0.74, 95% CI 0.41–1.33), rash (RI = 0.97, 95% CI 0.88–1.08), or rash with antiviral prescription (RI = 0.83, 95% CI 0.62–1.10) in the 42 days following ZVL compared to control periods.

Conclusion: No new safety concerns were identified for ZVL in this study based on a novel, Australian primary care data source. An expected increased risk of ISR was identified; findings in relation to cardiovascular disease were reassuring but require confirmation using additional data, including hospital records.

1. Introduction

Herpes zoster (HZ) is a localized, painful, vesicular skin rash resulting from reactivation of varicella-zoster virus (VZV). The incidence increases with age to an average lifetime risk of around 30% [1]. Prior to implementation of immunization programs, the incidence of HZ in Australia was reported to be 10 per 1000 persons aged 50 years and older [2], similar to rates observed in Europe

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[3] and the United States (US) [4]. The risk of post-herpetic neuralgia (PHN), a chronic neuropathic pain syndrome which may complicate HZ, also increases with age [5]. Disseminated disease, often characterized by diffuse vesicular rash, can occur in people who are immunosuppressed.

Live attenuated herpes zoster vaccine (ZVL) was registered for use in Australia in 2006 for people aged over 50 years but was in limited supply until 2014; it is recommended for immunocompetent adults over 60 years of age [6]. In November 2016, ZVL was funded (making it free for patients) under Australia's National Immunisation Program (NIP) for the ongoing cohort of adults aged 70 years, with catch-up for those aged 71–79 years funded until October 2021. Influenza and pneumococcal vaccines are also NIP funded for adults 65 years and over [6]. Vaccines in this age group are predominantly administered in primary care, via general practice clinics.

ZVL was evaluated in large, pre-licensure clinical trials with no increased risk of serious adverse events (SAE), hospitalized adverse events or death identified [7–9]; the rate of injection site reactions (ISR) was higher in vaccine than placebo groups (48% compared to 16% in adults 60 years or older) [7,9,10]. Data from post-licensure surveillance, predominantly reports of adverse events (AE) via spontaneous reporting systems, have suggested a safety profile consistent with data from clinical trials, although with lower rates of ISR [11–13]. Most reports (93%) to the Merck, Sharp, & Dohme Corp (MSD) global safety database [13] and 96% of reports to the United States (US) Vaccine Adverse Events Reporting System (VAERS) [11] and Australian Therapeutic Goods Administration's (TGA) Adverse Events Management System database [12] were non-serious. In all three post-marketing surveillance systems, ISR was the most commonly reported AE (20.5% in the MSD database and 16% in the AEMS, with injection site erythema reported in 27% and injection site swelling in 17% within VAERS), followed by HZ and rash.

While cardiovascular events (stroke and myocardial infarction (MI)) have been associated with wild-type ZV infection [14,15], no significant increase in risk has been identified following ZVL [10,16]. Among serious AE reports to the TGA AEMS, one causally-related death from disseminated Oka vaccine strain VZV infection was reported in a 71-year-old immunocompromised male vaccinated despite a contraindication [17,18]. Another immunocompromised male also died from disseminated vaccine VZV disease in the United Kingdom [19].

While spontaneous post-marketing reporting systems can detect safety signals, they are limited by incompleteness, imperfect data quality and the potential for selective reporting [11]. In Australia, AusVaxSafety is a multiple component active vaccine safety system that aims to address these limitations. The first and major component of AusVaxSafety consists of active participant-based surveillance that monitors AEs solicited directly from vaccine recipients in the community via an automated text message [20,21]. During the first two years of the ZVL program, specific survey data did not identify any safety signals amongst 18,655 adults aged 70–79 years; 8.3% of vaccinated individuals reported an adverse event (most commonly an ISR) and 0.3% reported medical attendance within three to five days after vaccination (a proxy measure of seriousness) [22].

Another component of the AusVaxSafety program was established to analyze routinely extracted longitudinal primary care data from MedicineInsight, a national database developed and managed by NPS MedicineWise. MedicineInsight data is used to support the safe use of new medicines along with quality improvement activities in participating practices [23,24]. Both AusVaxSafety and MedicineInsight receive funding support from the Australian Government Department of Health.

To examine the risk of specific outcomes following ZVL, we aimed to conduct a novel analysis of MedicineInsight data, which has not previously been used for vaccine safety assessment. We used the self-controlled case series (SCCS) method, an approach which controls for unmeasured time-invariant confounders by allowing individuals to act as their own control [25]. This method was developed for vaccine safety evaluation [26–28] and has been previously used to examine ZVL safety using data from managed care cohorts in the US [16], but has not been used with Australian primary care data. The objective of this study was to explore the risk of pre-specified potential adverse outcomes following ZVL (including ISR, rash and cardiovascular outcomes) in the target NIP cohort using the nationally representative (in terms of age and gender) MedicineInsight data and to make comparisons with data on outcomes following influenza and pneumococcal vaccines.

2. Methods

2.1. Study setting

The MedicineInsight data set consists of longitudinal, de-identified, whole-of-practice data extracted from the electronic clinical information systems (CIS) of participating primary care practices across Australia [23]. These include practices in major cities and in rural and remote areas, similar to the distribution of the Australian population in these areas [29]. At October 2018, participating practices represented 10.7% of the Australian patient population. Data is routinely extracted on patient demographics, practice encounters (excluding progress notes), diagnoses, vaccinations, prescriptions, pathology tests and referrals. Practice encounters can include clinical (a medical or nursing appointment) or non-clinical (administrative) encounters. Within-site individual identifiers are used to identify records common to an individual.

2.2. Study population

The NIP target population for ZVL during the study period was individuals aged 70–79 years; all Australians over 65 years of age are also eligible for funded 23-valent pneumococcal (23vPPV) and influenza vaccines under the NIP. Although the primary vaccine of interest was ZVL, all individuals who had received 23vPPV and seasonal inactivated influenza vaccines were also included for two reasons: ZVL may be commonly co-administered with these two vaccines meaning that any outcome events identified might be attributable to these other vaccines; and to estimate the relative incidence (RI) of outcome events in other vaccines using the same data source and methods as comparators for the ZVL estimates. All MedicineInsight records were obtained for individuals 70–79 years of age who received ZVL, 23vPPV or influenza vaccine(s) between 1 November 2016 (the commencement of the funded ZVL program) and 31 July 2018.

Individuals with a history of stroke and MI were identified by a search of practice encounters and diagnoses related to these conditions using information from the diagnosis (medical history), reason for encounter, and reason for prescription fields, and included both coded and free-text data. Individuals with records for historical events of stroke and MI (occurring before the start of the study period) were excluded. Primary care records are not formally linked to hospitalization records in Australia, although general practitioners (GPs, primary care providers in Australia) may record hospitalization and new diagnoses in their CIS. Individuals who died were censored on 31 December of the preceding year because only the year of death was available.

2.3. Study design

We undertook a retrospective SCCS analysis of outcomes following ZVL using MedicineInsight data. The method estimates the relative incidence of an outcome event within a risk window following exposure (i.e. vaccination) compared to a control period distant from vaccination (Fig. 1) [30]. Only individuals who have experienced the outcome event of interest are included in the analysis and the design inherently controls for time-invariant confounders [25].

This study investigated the incidence of seven pre-specified outcome events: ISR [positive control], burn [negative control], MI, stroke, any rash, rash with a prescription for an antiviral medication within 2 days of the rash-related encounter, and any clinical attendance in a post-vaccination at-risk window compared with the incidence of these outcome events during control periods. ISR was included as a positive control given consistent evidence of an increased risk of ISR in pre-licensure and post-licensure studies. Burn was included as a negative control because of the absence of a plausible causal relationship with vaccination. Rash with antiviral prescription was specified because antivirals (e.g. valaciclovir) are prescribed to reduce the severity and duration of HZ infection [31]; prescription of an antiviral medication was considered to be a proxy for an HZ-like rash.

We defined an individual's observation period in terms of their record of activity at the site and recorded year of death (if applicable). An individual's observation start date was defined as the latest of 1 November 2016, or 365 days after their first recorded activity at the site (any encounter, diagnosis, or prescription). The lead time of 365 days from an individual's start of site activity was specified to ensure adequate patient follow-up was available to assess historical diagnoses. An individual's end date of observation was defined as 31 December in the year prior to their death for individuals who had year of death recorded, and 31 July 2018 for individuals who had no year of death recorded. Therefore, the maximum observation period for any individual was 638 days.

Exposure (vaccination) was defined as any record in the CIS immunization field for any of the three vaccines under study with a date of administration occurring within the individual's observation period. Vaccination prescriptions recorded only in the prescription field were excluded as these prescriptions may not have been filled at the time the prescription was provided. While some vaccines administered were clinically coded, others were free text entries; vaccination records for the study vaccines were identified via targeted, free-text search criteria (see Appendix A for search terms). The date of vaccination was set as the administration date specified in the immunization field. Individuals with multiple vaccination records for ZVL or 23vPPV during their observation period were excluded as these vaccines are generally recommended to be given as a single dose for older adults. We enforced a minimum time between influenza vaccinations of 126 days because a single dose is generally recommended each season. Any records occurring within 126 days of an individual's previous influenza vaccination were excluded to avoid overlapping risk windows (refer to Section 2.4). Any vaccines with the same recorded date of administration were assumed to be co-administered.

Except for clinical attendance, outcome events were identified using free-text regular expression searches of the reason for encounter, reason for diagnosis and reason for prescription fields (see Appendix A for search terms). In CIS software, the same event can be recorded in multiple locations on similar (but not necessarily identical) dates. Therefore, to ensure the earliest time point was selected for each event for each individual the following process was used: for each record matching an outcome event, we matched encounters, diagnoses, and prescriptions on their respective dates to identify likely-related events and then selected the date of first occurrence. Records of clinical attendance were identified as any site encounter excluding those identified to be non-clinical (administrative), which were identified by a free-text search of the encounter type and encounter reason fields for specific terms identified as administrative in nature (see Appendix A).

2.4. Definition of risk windows

At-risk windows were defined for all vaccine types based on biologically plausible windows supported by evidence. For ISR, the risk-window was 1–7 days post vaccination and for all other outcomes was 1–42 days post vaccination. The basis for the length of the risk window for systemic adverse events was the 42 day window used in pre-licensure clinical trials [7,9,10,32] and post-licensure studies [16,33]. This time period is also biologically plausible for MI and stroke events, which have been observed following wild-type VZV, particularly one to four weeks following infection [14,15], with viral replication in arterial walls the proposed mechanism for stroke [34]. Considering rash within 42 days was appropriate given that varicella-like rash more than 6 weeks after vaccination is more likely to represent primary wild-type VZV infection or reactivation of latent VZV as HZ (in older individuals), which remains possible due to modest vaccine efficacy for HZ [7,13]. The risk windows for burns (the negative control) and clinical attendance were chosen to be consistent with the risk window for systemic events. For ISR, the risk window was based on the short median time to ISR (~2 days) in the Shingles Prevention Study (SPS) and post-licensure surveillance [10,13] and the identification of a signal for cellulitis within 7 days in another post-licensure SCCS [16].

To account for the potential for medical events to negatively affect the likelihood of vaccination (healthy vaccinee bias) [25,35], a washout period of 42 days pre-vaccination was defined. A 42 day post-risk washout period was also included (except in the case of rash with an antiviral prescription) to minimize the potential for any risk attributable to vaccination carrying over into the control period (Fig. 1) [35]. For rash with an antiviral prescription, an indefinite post-risk period was specified to allow for exploration of the impact of vaccination on HZ; for this outcome event, only the first recorded influenza vaccination was considered for analysis to avoid overlapping risk periods.

Pre-exposure and post-risk washout periods were excluded from the control period. The day of vaccination (day 0) was excluded from all risk windows because only the date and not the time of clinical encounter, vaccination, nor medical event was recorded. As a result, we could not reliably distinguish vaccine

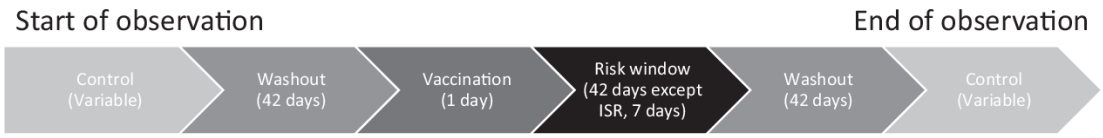

Fig. 1. Self-controlled case series design for the analysis of outcome events following administration of live attenuated herpes zoster vaccine to 70–79 year old adults using primary care data.

administration encounters from same-day encounters for medical events (occurring before or after vaccination) or unrelated reasons, including opportunistic coding. All other time periods an individual was under observation were allocated to their control period.

2.5. Statistical methods

Relative incidence estimates were obtained by the SCCS model using the windows defined in Section 2.4. The primary analysis modelled all vaccine exposures jointly; each outcome event was modelled independently and all outcome events occurring during the observation period contributed to the relative incidence estimates. Given that the study period spanned 1 November 2016 to 31 July 2018, we additionally specified fixed windows to adjust for seasonal effects by specifying cut-points: 1 December, 1 March, 1 June, and 1 September in each year. Weekly periodicity of events, such as regular GP attendances on the same day of the week noted for some patients, was accounted for indirectly by the specification of risk-windows in terms of full-week cycles.

Lack of independence of outcome events violates the Poisson assumption of the SCCS model and may bias estimates. Therefore, sensitivity analyses were undertaken which only included the first outcome event observed and assessed each vaccine independently, excluding co-administered vaccines.

The relative incidence and 95% confidence intervals for each outcome were estimated using conditional Poisson regression with the length of each window included as offset terms to account for the period of time under study. No adjustments were made for multiple comparisons. All analyses were conducted using R 3.5.1 [36] and the gnm package version 1.1–0 [37].

2.6. Ethical approval

The MedicineInsight program was approved through the Royal Australian College of General Practitioners National Research and Evaluation Ethics Committee (NREEC) in December 2017 (NREEC 17–017). Approval for use of MedicineInsight data in this study was received from the NPS MedicineWise external Data Governance Committee on 23 November 2016 and an amended version on 29 September 2017. This study was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee (HREC/17/SCHN/159).

3. Results

3.1. Vaccinations and outcome events

A total of 337,294 vaccination records for 150,756 individuals from 456 MedicineInsight primary care practices were obtained. After excluding those with multiple ZVL or 23vPPV vaccinations or multiple influenza vaccinations within 126 days of each other, a total of 332,988 vaccination encounters (ZVL: 92,857; 23vPPV: 21,480; and influenza: 218,651) for 150,054 individuals were included. Most individuals (93%) were under observation for the entire study period, according to our pre-specified criteria.

ZVL vaccinations were clustered at the beginning of the study period following inclusion under the NIP. Weekly and seasonal fluctuations in vaccinations were observed for the three vaccines investigated (Fig. 2). The number of vaccination records declined with age, apart from a small increase in ZVL just prior to 79 years of age (the upper age limit of the catch-up cohort) (Fig. 3). Of ZVL doses, 82% were administered alone, 16% with influenza vaccine and 2% with 23vPPV. Of influenza vaccine doses, 89% were administered alone while 47% of 23vPPV doses were administered alone.

Over 2 million clinical attendances were observed among exposed individuals during their observation periods. The next most common outcome event was any rash, with 12,309 events observed. The least common outcome event was injection site reaction, with 177 events observed; 40% were recorded less than 8 days after vaccination. Vaccination centered event plots show

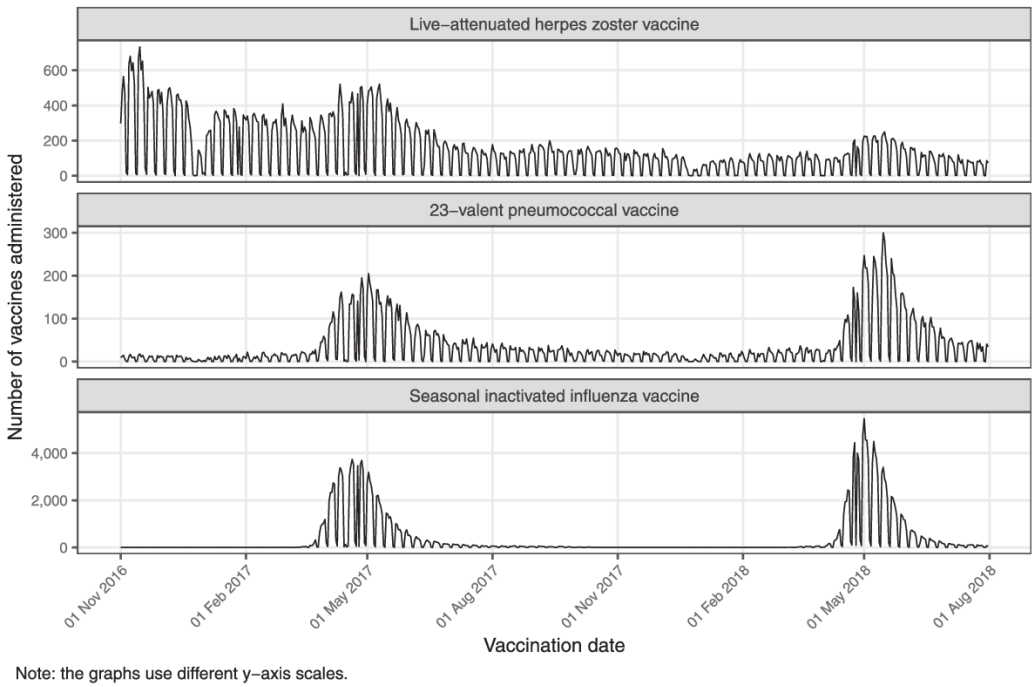

Fig. 2. Daily counts of vaccines administered to 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018, by vaccine.

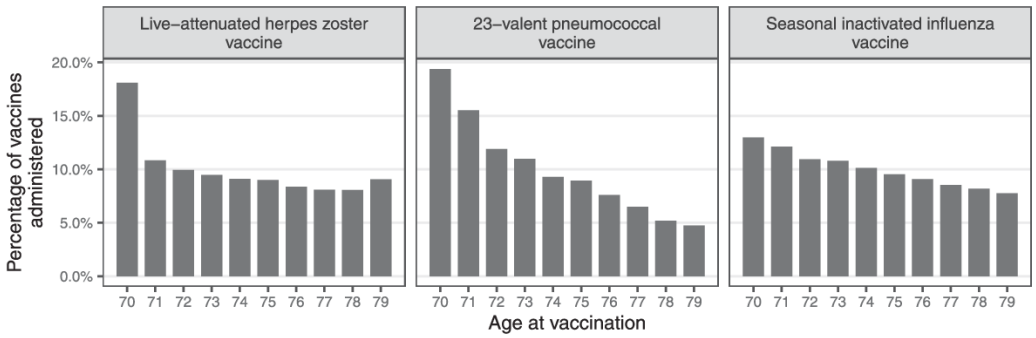

Fig. 3. Distribution of age of vaccination for vaccines administered to 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018, by vaccine.

the number of events per-person days under observation for the positive control (ISR) peaks soon after ZVL vaccination, whereas for the other medical events, including the negative control (burns), there was no obvious elevation in the event rate in the 12 weeks after vaccination (Fig. 4).

3.2. Self-controlled case series analysis

3.2.1. Injection site reactions

An increase in the relative incidence of injection site reactions was observed in the 7-day risk window following all three vaccines in the main analysis (Table 1). Results of sensitivity analyses excluding co-administered vaccines were consistent (Table 2). The incidence of ISR remained elevated in the 42-day post-risk washout period following ZVL (RI = 3.42, 95% CI 1.81–6.49) (Appendix B); on further exploration, risk was elevated only in the early part of the post-risk washout period (8–14 days post-vaccination (RI = 16.2, 95% CI 6.77–38.7), before returning to control period levels (Appendix C).

3.2.2. Myocardial infarction (MI)

There was no evidence of an increased risk of MI in the 42-day risk window following any vaccine in the primary analysis (Table 1) or when including first events only as part of the sensitivity analysis (Table 2). There was evidence of an increased relative incidence of MI in the post-risk washout period (days 43–84 post exposure) for ZVL (RI = 1.68, 95% CI 1.11–2.54) (Appendix B). On further exploration, the increased relative incidence was observed in days 57–63 and 71–77 (Appendix D); small event numbers

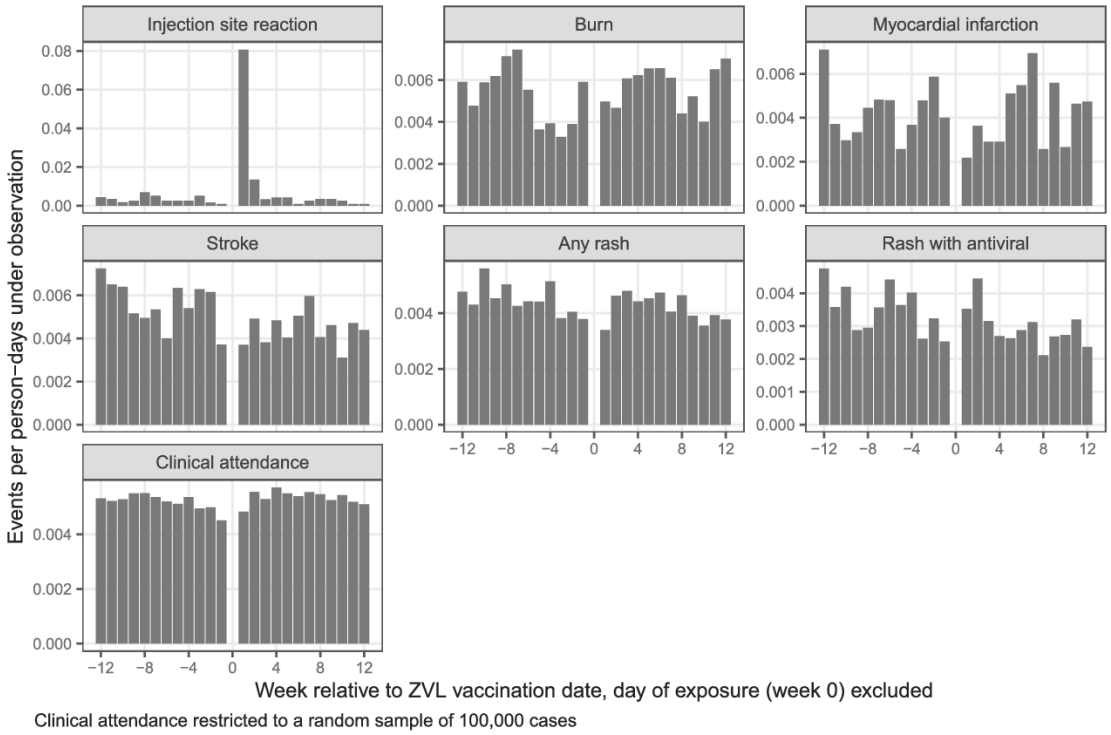

Fig. 4. Event rates by outcome relative to date of vaccination with live attenuated herpes zoster vaccine (ZVL), for vaccines administered to 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018, by vaccine.

Table 1
Relative incidence (at-risk window versus control period)[a] of outcome events following vaccination of 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018 (outcome events modelled independently with all vaccines included jointly, adjusted for season).

	Zoster vaccine			Pneumococcal vaccine			Influenza vaccine		
Outcome	At-risk n (PD)	Control n (PD)	RI (95% CI)	At-risk n (PD)	Control n (PD)	RI (95% CI)	At-risk n (RD)	Control n (PD)	RI (95% CI)
Injection site reaction	37 (833)	104 (96 876)	77.4 (48.1, 124.6)	30 (378)	138 (102,318)	65.0 (31.6, 133.6)	29 (1,071)	102 (84,934)	6.62 (3.42, 12.8)
Burn	72 (23,798)	1,282 (511,166)	1.23 (0.97, 1.57)	8 (5,259)	1,455 (564,087)	0.55 (0.27, 1.13)	145 (57,946)	1,036 (407,960)	0.93 (0.76, 1.14)
Myocardial infarction	12 (8,327)	436 (221,244)	0.74 (0.41, 1.33)	2 (2,729)	469 (237,376)	0.39 (0.09,1.59)	47 (23,226)	324 (176,808)	1.17 (0.82, 1.66)
Stroke	50 (35,113)	1,984 (793,445)	0.58 (0.44, 0.78)	15 (9,081)	2,132 (868,410)	0.72 (0.42, 1.21)	197 (88,397)	1,500 (633,321)	1.06 (0.89, 1.26)
Any rash	422 (228,311)	10,381 (4,990,170)	0.97 (0.88, 1.08)	115 (52,961)	11,959 (5,497,005)	1.01 (0.84, 1.23)	1,124 (564,634)	8,645 (3,982,480)	1.06 (0.98, 1.14)
Rash with antiviral	61 (33,800)	1,570 (856,854)	0. 83 (0.62, 1.10)	22 (10,571)	1,931 (1,099,845)	1.23 (0.77, 1.95)	104 (73,998)	917 (455,454)	0.78 (0.62, 0.97)
Clinical attendance	79,352 (3,726,764)	1,799,288 (79,138,828)	0.94 (0.94, 0.95)	19,616 (848,864)	2,032,393 (87,483,370)	1.06 (1.04, 1.07)	200,785 (8,840,389)	1,368,928 (63,862,675)	1.03 (1.02, 1.03)

CI: Confidence interval, n: number of events, PD: person days, RI: Relative incidence.
[a] At risk window is 42 days following vaccination except for injection site reaction (7 days). The control period is time periods an individual was under observation with the exception of the risk window, day of vaccination and 42-day washout periods before vaccination and following the at-risk window.

Table 2
Sensitivity analyses: Relative incidence (at-risk window versus control period[a]) of outcome events following vaccination with live attenuated herpes zoster vaccine (ZVL) in 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018 (with and without concomitant vaccines (influenza and 23-valent pneumococcal polysaccharide vaccine vaccine) and considering all events or first events only).

	All vaccines modelled together, for all events	ZVL modelled independently (concomitant vaccines excluded), for all events	All vaccines modelled together, for first events only	ZVL modelled independently (concomitant vaccines excluded), for first events only
	RI (95% CI)	RI (95% CI)	RI (95% CI)	RI (95% CI)
Injection site reaction	77.4 (48.1, 124.6)	60.5 (37.4, 97.9)	71.2 (43.6, 116.1)	57.3 (34.8, 94.3)
Burn	1.23 (0.97, 1.57)	1.12 (0.86, 1.47)	1.08 (0.78, 1.50)	1.12 (0.80, 1.58)
Myocardial infarction	0.74 (0.41, 1.33)	0.70 (0.35, 1.36)	0.90 (0.49, 1.66)	0.80 (0.39, 1.64)
Stroke	0.58 (0.44, 0.78)	0.51 (0.37, 0.71)	0.54 (0.37, 0.77)	0.51 (0.34, 0.76)
Any rash	0.97 (0.88, 1.08)	0.96 (0.86, 1.07)	1.01 (0.90, 1.14)	1.01 (0.89, 1.14)
Rash with antiviral	0. 83 (0.62, 1.10)	0.67 (0.49, 0.92)	0.80 (0.59, 1.09)	0.64 (0.45, 0.90)
Clinical attendance	0.94 (0.94, 0.95)	0.94 (0.93, 0.94)	NA[b]	NA[b]

RI: Relative incidence, CI: Confidence interval.
[a] At risk window is 42 days following vaccination except for injection site reaction (7 days). The control period is time periods an individual was under observation with the exception of the risk window, day of vaccination and 42-day washout periods before vaccination and following the at-risk window.
[b] Clinical attendance was not considered sufficiently rare to conduct sensitivity analysis using first events only.

within this post-hoc analysis limited the ability to investigate these more granular patterns.

3.2.3. Stroke

A reduced relative incidence of stroke was observed in the 42-day window following ZVL but not following 23vPPV or influenza vaccine (Table 1). This persisted when including first events only as part of the sensitivity analysis (Table 2). This reduced incidence following ZVL persisted into the post-risk washout window (RI = 0.72, 95% CI 0.55–0.93) in the primary analysis (Appendix B).

3.2.4. Rash

There was no change in the relative incidence of rash or rash with antiviral prescription in the 42-day window following ZVL compared to the control period in the primary analysis (Table 1), although a reduced relative incidence was noted in the post-risk washout period compared to control-windows (RI = 0.67, 95% CI 0.54–0.83, for rash with antiviral prescription) (Appendix B). A reduced risk was observed in the at-risk window when ZVL was given alone (Table 2).

3.2.5. Clinical attendance

Compared to control periods, there was a small reduction in the risk of clinical attendance in the 42-day risk window following ZVL but not following 23vPPV or influenza vaccines (Table 1). The results of sensitivity analyses excluding concomitant vaccines was consistent for ZVL (Table 2).

3.2.6. Burn

No change in the incidence of burn, which was used as a negative control, was observed for any of the vaccines.

3.2.7. Pre-exposure risk

A reduced relative incidence of clinical attendance was observed for ZVL and influenza vaccines in the pre-exposure washout window (ZVL RI = 0.95, 95% CI 0.95–0.96; Influenza RI = 0.93, 95% CI 0.93–0.94) compared to control-windows in the primary analysis (Appendix B). A lower relative incidence of MI (RI = 0.44, 95% CI 0.21–0.94) and rash with antiviral prescription (RI = 0.69, 95% CI 0.51–0.94) were observed during the pre-exposure window compared to control period for ZVL (Appendix B).

4. Discussion

This analysis of outcome events following 332,988 eligible ZVL, influenza and 23vPPV vaccination encounters in 150,054 individuals in the Australian primary care setting found no evidence of an increase in the risk of serious outcomes in the pre-defined risk periods, while confirming an increase in ISR following ZVL and other vaccines. The risk of ISR following ZVL in the safety sub study [10] of the pivotal ZVL randomized controlled clinical trial was 48% in vaccine recipients compared to 16% in placebo recipients, with fewer than 1% reported as severe. Consistent with clinical trial data, the risk of ISR in our study was elevated both for ZVL alone and ZVL administered concomitantly with influenza vaccine [38]. While ISR occurred a median of 2.3 days following vaccination in the sub study [10], and has been observed a median of 2 days following vaccination in post-marketing surveillance [13], we observed an elevated incidence of ISR documented at primary care practices up to 14 days following ZVL, which likely relates to delay in reporting ISR to the GP.

The absence of any increase in clinical attendance following ZVL vaccination, identified in our study, is reassuring. Similarly, AusVaxSafety active surveillance data has demonstrated a low rate of reported medical attendance following ZVL [22]. A reduced relative incidence of clinical attendance in the pre-exposure period in this study provides evidence to support the healthy vaccinee effect, which was minimized by the use of the pre-exposure washout window. A reduced relative incidence of MI, but not stroke, was seen in the ZVL pre-exposure period.

Although wild-type VZV reactivation causing HZ has been associated with ischemic [14,15] and hemorrhagic stroke [15] and MI [14] in the one to four weeks following infection [34], the SPS [10] did not identify an increased risk for cardiovascular events. We identified a reduced relative incidence of stroke following ZVL; whether this is attributable to HZ vaccine efficacy and reduced risk of wild-type HZ associated complications requires further study. While death due to stroke and heart disease have been reported to post-marketing spontaneous reporting systems [11], some deaths from these causes would be expected in this age group irrespective of vaccination; no unusual pattern has been observed in surveillance data that would suggest a causal relationship to ZVL [11]. SCCS methodology aims to reduce confounding and other biases that may affect spontaneous reporting systems; other post-marketing studies (including SCCS) have not identified an increased risk of cardiovascular or cerebrovascular events following ZVL [16,33].

While no increase in the relative incidence of MI was observed in the pre-specified risk-window period, we observed a higher relative incidence of MI in the post-risk washout period (between 43- and 84-days following vaccination). On *post hoc* exploration an increased risk was not observed consistently during this period suggesting this may be a chance finding. Our findings may be affected by poor ascertainment of serious events like stroke and MI due to the use of primary care rather than hospital data; the study may not have been adequately powered for these rarer outcomes. Further investigation within emergency department and hospital data may provide greater sensitivity in identifying and validating cardiovascular and cerebrovascular outcome events.

While ascertainment of these serious events may be limited in the primary care setting, rash is common [39]. Rash has been considered a non-specific finding in post-marketing observational studies [16]; the pairing of rash with antiviral prescription is likely to be more specific for herpetiform, varicella- or zoster-like rashes. A reduced relative incidence of rash with antiviral prescription following ZVL was observed, which is most likely attributable to vaccine-induced effectiveness against HZ. The finding is reassuring given that a varicella-like rash in the days following vaccination may indicate disseminated infection with vaccine virus in immunocompromised patients [17]. In a recent survey of immunization providers in the US, family physicians report recommending ZVL to certain immunocompromised patients, despite a contraindication to ZVL vaccination [40]. Following the death of an Australian man from disseminated Oka vaccine VZV infection in 2016 [17] there was widespread education targeted toward GPs regarding vaccine contraindications and appropriate administration of ZVL [17,41].

There are limitations to the use of MedicineInsight data, in addition to those inherent in routinely collected data more generally, and the methods which could be applied in this study [23]. An assumption of the analysis is that an unbiased set of events occurring during an individuals' observation period have been ascertained. However, the quality of data used is dependent on GP data entry into the practice CIS, which is likely to vary by site; where an outcome was not recorded, it is not possible to know whether this reflected an absence of the outcome or failure of documentation, particularly for minor outcomes such as ISR. Outcomes such as stroke and MI would be more likely to present initially to an emergency department than to primary care; primary care data may be insufficiently sensitive to capture these events, without linkage to hospitalization data. For example, there was no reduced incidence of stroke identified in the pre-exposure period, which might have been expected if a healthy vaccinee effect is evident. Delayed coding of hospitalization information by GPs (due to delayed receipt of information such as hospital letters and laboratory test results) may also mean events that occurred in the pre-vaccination window are documented in the post-vaccination window. Inaccurate onset dates could also be reported for milder events, such as ISR, if they are recorded as a recent historical event during a routine primary care visit, which may explain the pronged period post vaccination over which ISR was observed. Due to lack of specific information on date of death, patients who died were censored on 31 December of the preceding year so that MI or stroke events occurring immediately prior to death may not have been captured.

The generalizability of the findings of this study are limited by the exclusion of patients with a past history of MI or stroke. In addition, it was not possible to determine an individual's level of immunocompromise due to the complexity of classifying the immune status of individual patients based on limited information; immune status may affect the experience of adverse events [17,42].

As not all MedicineInsight data were coded, exposures and outcome events were identified by regular expression searches of text strings, which were not validated. Additionally, individual identifiers were only available at the site level, meaning any individuals attending multiple practices, which can occur due to non-capitation of patients to a single primary care practice in the Australian context, were treated as distinct individuals. This meant that outcome events occurring at a site other than the practice attended for vaccination would not be ascertained. However, evidence suggests multiple practice attendance is low in older age groups, with only 12.9% of adults over 70 years of age reporting attending multiple practices in a recent survey [43].

The systematic exploration of the use of general practice data and the SCCS design in vaccine pharmacovigilance in this study is a critical step in moving beyond spontaneous reporting systems in Australia, given the inherent limitations of passive post-marketing adverse events surveillance. Although many Australian patients, especially older patients, see a regular GP and GPs are commonly the immunization provider, electronic primary care

data is rarely used for vaccine safety research in Australia; one proof of concept paper using a different (smaller) primary care database validated a safety signal of an increase in ISR with repeat 23vPPV vaccination, resulting in removal of a recommended vaccine dose [44]. There is significant scope to better utilize routinely collected primary care data for vaccine safety surveillance once the limitations and applications are more fully understood and further validation of the approach has been undertaken. For more severe adverse events, the application of SCCS to hospitalization data has been effective internationally [26,28]. Linkage with hospitalization data in Australia could make primary care data a richer source of information.

5. Conclusion

No new safety concerns were identified for ZVL in this study which used a novel data source and the SCCS design. Expected findings in relation to an increased risk of ISR following ZVL, influenza and pneumococcal vaccination support the validity of the SCCS in this setting, using primary care data. Findings in relation to MI and stroke were reassuring, but are subject to limitations including data completeness, delayed reporting and hospital presentation. Further work should focus on validation of identified exposures and outcomes and linkage with hospitalization data. The finding of reduced rash with antiviral prescription following ZVL suggests this data source could be examined to explore ZVL vaccine effectiveness in Australia, using a suitable study design.

Statement

This paper contains original unpublished work and is not being submitted for publication elsewhere. This work was submitted as a report to the Australian Government Department of Health.

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Author contributions

AP and JT contributed equally to the authorship of the manuscript. AP developed the study protocol, assisted with data interpretation and drafted and revised the manuscript; JT revised the study protocol, conducted the analysis and contributed to interpretation and revision of the manuscript; JM revised the study protocol and contributed to analysis and interpretation; CG, TS and KM provided input in the protocol, interpretation and manuscript; KC provided input into the protocol, provided the data and assisted with data interpretation and revision of the manuscript; all authors reviewed and approved the final manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kendal Chidwick is an employee of NPS MedicineWise. The other 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.

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Appendix A. Free text search criteria for vaccine and outcomes events, and to exclude non-clinical attendances, within NPS MedicineInsight data

Vaccine regular expression search terms[a]

Vaccine	Search Terms
Zoster	zost|herp|varic|shing
Pneumococcal	pn|ppv
Influenza	flu|ufl|quad|tetra|vaxig|intanza
Exclusions[b]	decl|ref|past|prev|not |priorix|no |quadracel|proquad|7 val|13 val

[a]The symbol|indicated 'or' within regular expression searches.[b]We generally undertook two regular expression searches: one to identify potential matches to the vaccine or condition of interest for inclusion; one to identify and exclude any matched records which were not of interest.

Outcome event regular expression search terms[a]

Outcome event		Search Criteria
Injection site reaction	Inclusions	(inje|vacc|admin|site|loca).*brui|(inje|vacc|admin|site|loca).*cell|(inje|vacc|admin|site|loca).*eryt|(inje|vacc|admin|site|loca).*indu|(inje|vacc|admin|site|loca).*infe|(inje|vacc|admin|site|loca).*infla|(inje|vacc|admin|site|loca).*nodu|(inje|vacc|admin|site|loca).*oede|(inje|vacc|admin|site|loca).*pain|(inje|vacc|a

(*continued on next page*)

Outcome event regular expression search terms (*continued*)

Outcome event		Search Criteria
		dmin|site|loca).*petech|(inje|vacc|admin|site|loca).*prur|(inje|vacc|admin|site|loca).*rash|(inje|vacc|admin|site|loca).*redn|(inje|vacc|admin|site|loca).*reac|(inje|vacc|admin|site|loca).*sore|(inje|vacc|admin|site|loca).*swel|(inje|vacc|admin|site|loca).*urti|post[p].*(inje|vacc|admin)
	Exclusions	zostavax injection|zostavax vaccn|shingle vaccination/|shingles vaccine/|zoster vaccine,|appointuit|postpone|pain clinic|parasite|fluvacc|knee - graze|vaccination,|vaccinations,|bee|sting|tick|bite|insect|incision site|concern of|carcinoma|spc site|catheter|(b12|b-12) injection|^shingles vaccination $|postpone vacc|travel |prolia|denosumab|vaccination//|vaccinations ,|vaccination ,|steroid +|re-vaccination
Burns	Inclusions	burn
	Exclusions	burning|craig
Myocardial infarction	Inclusions	^ami|ami$| ami myocar.*infar|posteri.*infar|anteri.*infar|septal.*infar|lateral.*infar|heart.*infar|heart.* attac
	Exclusions	fear|risk|lacunar|cortex|cerebell|1989|1999|1996|2008|transfer|undisplaced|amission|stopped|amiodarone|amiadarone|amiodorone|hypercholesterami|exported|family|prevent|fracture|aminoglycoside|tele|amiloid|renal|badami|cerebral|robyn|amine|amiodar|amioa|aminio|amigrai
Stroke	Inclusions	stroke|trans.*isch|^tia$\|^tia \| tia$| tia
	Exclusions	heat|sun|[pr]*event|family hist|\\?|week|risk|post |advice|protect|engage sms|engage email
Any rash	Inclusions	rash|shingles|zoster|vesic
	Exclusions	imm|vac|vax|injec|appointuit|letter|crash|water brash
Antiviral	Inclusions	acyclo|aciclo|famciclo|famvir|notaris

[a]The symbol | indicated 'or' within regular expression searches.

Free text encounter type and encounter reason terms used to exclude non-clinical records[a]

Encounter type	Encounter reason
access session|admin|admin notes|administration|administrative (clinical)|administrative procedure|allied health|clinical notes provided|closure|correspondence received|ctg registration|diabets educator|dietitian|ecc care coordination|ecc consultation|ecc family session|ecc outreach session|ecc phone intervention|ecc session|ecc tertiary liaison|engagement session|fax|infusion bay - nurse|intake|it testing|medical record transfer|medical records|medicare check|mhis|nh fax message|no consultation|non attendance/late cancellation warning|notes - patient not in attendance|nurse|nurse admin|nurse attendance|nurse consult|nurse consultation|nurse consultation|nurse encounter|nurse visit|nurse visit|nursing|nursing consult|nursing consultation|nursing staff consult|nursing visit|out of office|pathology recall by rn|patient consent|pcehr assisted registration|peer support|physio consultation|physiotherapy|practice admin|practice consultation|practice nurse|practice nurse|practice nurse consultation|practice nurse surgery consultation|psychology session|reception|reception colleen|registered nurse|sms|social worker|step session|surgery visit - nurse|treatment room - rn|tristar konnect|websterpak	^cc$\|^een$|^en$\|^fta$|aboriginal health work|administration office|administrative proced|ahpacc liason officer|ahpacc worker|ain|allied health assistan|care coordinator|chaperone|chart review|child health worker|chinese access support|clinical services mana|community health worke|counsellor|dermagen consultant|diabetes educator|did not attend|dietitian|een nurse|endorsed enrolled nurs|enrolled nurse|exercise physiologist|failed to attend|family services worker|file review|ips vocational worker|jven peer worker|left message|letter posted|letter written no consu|medical student|mental health nurse|midwife|non[ ]? urgent recall|notes and record|nurse|nurse assistant|nurse practitioner|nurse support of|nursing student|occupational therapis|on recall appoint|optomertrist|pap remind|pathology request|peer worker|phone result|phone[ ]?call|physiotherapist|podiatrist|practice manager|practice nurs|prescription no consul|prescription renewal|primary health worker|psychologist|recall|receptionist|record and notes|referral letter no con|registered nurse|reminder manage|repeat prescription no|research assist|researcher|review file no con|senior case manager|social worker|telephone|triage telephone|urgent recall|youth peer worker

[a]The symbol | indicated 'or' within regular expression searches.

Appendix B. Relative incidence (at-risk, pre-exposure and post-risk washout windows versus control period[a]) of outcome events following vaccination of 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018 (all outcomes modelled independently with all vaccines included jointly, adjusted for season)

		Zoster vaccine (Exposures = 92,857)			Pneumococcal vaccine (Exposures = 21,480)			Influenza vaccine (Exposures = 218,651)		
Outcome	Risk period	n	PD	RI (95% CI)	n	PD	RI (95% CI)	n	PD	RI (95% CI)
Injection site reaction	Control	104	96,876	1.00	138	102,318	1.00	102	84,934	1.00
	At risk	37	833	77.4 (48.1, 124.6)	30	378	65.0 (31.6, 133.6)	29	1,701	6.62 (3.42, 12.8)
	Pre-exposure	6	4,472	2.05 (0.83, 5.08)	1	2,268	0.36 (0.04, 2.97)	11	10,206	0.60 (0.28, 1.32)
	Post-risk	15	4,978	3.42 (1.81, 6.49)	2	2,260	1.38 (0.30, 6.32)	17	10,194	1.11 (0.58, 2.12)
Burn	Control	1,282	511,166	1.00	1,455	564,087	1.00	1,036	407,960	1.00
	At risk	72	23,798	1.23 (0.97, 1.57)	8	5,259	0.55 (0.27, 1.13)	145	57,946	0.93 (0.76, 1.14)
	Pre-exposure	44	21,042	0.87 (0.64, 1.18)	6	5,296	0.42 (0.18, 0.95)	117	58,097	0.73 (0.58, 0.92)
	Post-risk	61	22,851	1.07 (0.82, 1.39)	6	4,661	0.47 (0.21, 1.07)	140	54,043	1.06 (0.85, 1.32)
Myocardial infarction	Control	436	221,244	1.00	469	237,376	1.00	324	176,808	1.00
	At risk	12	8,327	0.74 (0.41, 1.33)	2	2,729	0.39 (0.09,1.59)	47	23,226	1.17 (0.82, 1.66)
	Pre-exposure	7	7,618	0.44 (0.21, 0.94)	8	2,746	1.41 (0.67, 2.99)	55	23,310	1.50 (1.04, 2.14)
	Post-risk	26	7,892	1.68 (1.11, 2.54)	4	7,892	0.77 (0.28, 2.14)	42	21,383	0.90 (0.61, 1.32)
Stroke	Control	1,984	793,445	1.00	2,132	868,410	1.00	1,500	633,321	1.00
	At risk	50	35,113	0.58 (0.44, 0.78)	15	9,081	0.72 (0.42, 1.21)	197	88,397	1.06 (0.89, 1.26)
	Pre-exposure	72	31,886	0.90 (0.71, 1.15)	25	9,100	1.08 (0.72, 1.64)	217	88,990	1.19 (1.00, 1.42)
	Post-risk	60	33,674	0.72 (0.55, 0.93)	16	8,147	0.86 (0.52, 1.44)	184	82,132	0.97 (0.81, 1.16)
Any rash	Control	10,381	4,990,170	1.00	11,959	5,497,005	1.00	8,645	3,982,480	1.00
	At risk	422	228,311	0.97 (0.88, 1.08)	115	52,961	1.01 (0.84, 1.23)	1,124	564,634	1.06 (0.98, 1.14)
	Pre-exposure	392	209,613	0.97 (0.88, 1.08)	105	53,735	0.89 (0.73, 1.09)	1,09	567,207	1.08 (1.00, 1.17)
	Post-risk	346	217,586	0.85 (0.76, 0.95)	87	46,214	0.96 (0.77, 1.20)	1,018	523,365	1.01 (0.93, 1.09)
Rash with antiviral	Control	1,570	856,854	1.00	1,931	1,099,845	1.00	917	455,454	1.00
	At risk	61	33,800	0.83 (0.62, 1.10)	22	10,571	1.23 (0.77, 1.95)	104	73,998	0.78 (0.62, 0.97)
	Pre-exposure	48	31,811	0.69 (0.51, 0.94)	17	10,694	0.86 (0.51, 1.43)	134	74,279	1.03 (0.83, 1.27)
	Post-risk	371	254,613	0.67 (0.54, 0.83)	84	56,541	0.79 (0.56, 1.10)	891	572,406	0.82 (0.72, 0.94)
Clinical attendance	Control	1,799,288	79,138,828	1.00	2,032,393	87,483,370	1.00	1,368,928	63,862,675	1.00
	At risk	79,352	3,726,764	0.94 (0.94, 0.95)	19,616	848,864	1.06 (1.04, 1.07)	200,785	8,840,389	1.03 (1.02, 1.03)
	Pre-exposure	73,941	3,426,143	0.95 (0.95, 0.96)	20,795	863,058	1.02 (1.01, 1.04)	181,871	8,876,058	0.93 (0.93, 0.94)
	Post-risk	80,653	3,574,331	0.98 (0.97, 0.98)	16,586	739,952	1.01 (1.00, 1.03)	189,822	8,164,901	1.05 (1.04, 1.06)

CI: Confidence interval, n: number of events, PD: person days, RI: Relative incidence.

[a]At risk window is 42 days following vaccination except for injection site reaction (7 days); pre risk window is 42-days before vaccination; post risk window is 42-days following the at risk window; all other time periods an individual was under observation were allocated to the control period.

Appendix C. Relative incidence (at-risk, pre-exposure, post-risk washout and 7-day partitioned post-risk windows versus control period[a]) of injection site reaction following vaccination with live attenuated herpes zoster vaccine (ZVL) in 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018 (adjusted for season)

Risk period	n	PD	RI (95% CI)
Control	104	96,876	1.00
Pre-exposure	6	4,472	1.92 (0.76, 4.87)
At risk (1–7 days)	37	833	86.2 (53.0, 140.3)
Post-risk (8 – 49 days)	15	4,978	3.42 (1.81, 6.49)
Post-exposure risk period: 7-day partition			
Post-risk (8–14 days)	6	833	16.2 (6.77, 38.7)
Post-risk (15–21 days)	2	833	3.88 (0.91, 16.6)
Post-risk (22–28 days)	3	833	3.32 (0.87, 12.7)
Post-risk (29–35 days)	3	833	3.06 (0.78, 12.0)
Post-risk (36–42 days)	0	826	0.00 (0.00, Inf)
Post-risk (43–49 days)	1	820	0.67 (0.08, 5.67)

CI: Confidence interval, n: number of events, PD: person days, RI: Relative incidence.

[a]At risk window is 7 days following vaccination; pre risk window is 42-days before vaccination; post risk window is 42-days following the at risk window; all other time periods an individual was under observation were allocated to the control period.

Appendix D. Relative incidence (at-risk, pre-exposure, post-risk washout and 7-day partitioned post-risk windows versus control period)[a] of myocardial infarction following vaccination with live attenuated herpes zoster vaccine (ZVL) in 70–79 year old adults in primary care between 1 November 2016 and 31 July 2018 (adjusted for season)[b]

Risk period	n	PD	RI (95% CI)
Control	436	221,244	1.00
Pre-exposure	7	7,618	0.44 (0.20, 0.93)
At risk (1–42 days)	12	8,327	0.74 (0.41, 1.32)
Post-risk (43–84 days)	26	7,892	1.68 (1.11, 2.54)
Post-exposure risk period: 7-day partition			
Post-risk (43–49 days)	3	1,351	1.00 (0.32, 3.17)
Post-risk (50–56 days)	2	1,349	0.81 (0.20, 3.28)
Post-risk (57–63 days)	8	1,330	3.15 (1.54, 6.46)
Post-risk (64–70 days)	3	1,310	1.27 (0.40, 3.99)
Post-risk (71–77 days)	7	1,288	2.96 (1.38, 6.35)
Post-risk (78–84 days)	3	1,264	1.10 (0.35, 3.47)

CI: Confidence interval, n: number of events, PD: person days, RI: Relative incidence.

[a]At risk window is 42 days following vaccination; pre risk window is 42-days before vaccination; post risk window is 42-days following the at risk window; all other time periods an individual was under observation were allocated to the control period.

[b]Changes to RI estimates compared to Table 2 are due to changing overlap of season and risk windows when using a different partition.

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4.3 Implications of publication 4

This study represents a useful and unique exploration of a different approach to vaccine pharmacovigilance in the Australian context. The analysis successfully identified an expected risk of injection site reaction following ZVL, pneumococcal and influenza vaccines, with and without concomitant vaccination, in this older cohort. The potential to adapt this methodology to examine vaccines given in real-world conditions under the NIP, including concomitant administration, adds to its value. Further, the absence of risk associated with burns (the negative control) following vaccination supports the validity of the method. The use of rash with antiviral prescription as an indicator of disseminated vaccine-virus disease was a novel approach that may improve specificity when considering a common condition such as rash.

However, the study did identify limitations that are likely to restrict the usefulness of this approach and which were anticipated by the study team and in the hypotheses underpinning this thesis. In particular, the quality of data is reliant on practitioner documentation during routine provision of clinical care, and it is not audited routinely, nor collected purposively for research or surveillance purposes, despite practices enrolling in the MedicineInsight program. In addition, unlike hospital or emergency department data, entries in most fields are not linked to disease or other standardised coded outputs; however, a vaccine field does exist, which supported identification of the exposure variable for this study. Further, in Australia, individuals are not limited to one primary care provider and records are not linked; for a patient vaccinated at one site, any presentation to a different site for a medical event would not be captured.

Incomplete information on emergency department presentations and hospital admissions within primary care data is a significant limitation, given that key serious AESIs (i.e. myocardial infarction and stroke) are likely to present in these settings. While Australian primary care data have been used in a limited way to explore less serious AEFIs (injection site reactions) (112), the inclusion of data on hospitalisations is essential to enable assessment of the full spectrum of AEFIs within this rich and relatively untapped data source.

Internationally, robust epidemiological methods, including SCCS and cohort studies, are used to investigate signals through interrogation of linked databases such as the CPRD (36, 113-115) and VSD (31, 34, 111, 116, 117), and large linked databases in Europe. (33, 80, 118) The VSD incorporates administrative, hospitalisation, primary care and vaccination data from nine healthcare organisations in the US (34), while the CPRD links patient data from primary care practices across the UK with secondary healthcare data including admission, emergency department and death data. (35)

Such methods enable comparison of vaccinated and unvaccinated cohorts (or time periods), including for rare and hospitalised events. (6) These databases are also used to establish background incidence rates for specific AESIs, which can be compared to the number of spontaneous reports received during vaccine program implementation to determine whether the observed rate is greater than would be expected. (36, 119, 120)

For Australia to assess AESIs and later-onset AEFIs through a truly multi-faceted vaccine pharmacovigilance system, access to analytic cohorts based on linked data is a key additional modality that requires development. This will entail identification of and linkage between key healthcare databases and with the Australian Immunisation Register; unlike some other countries, there is no universal national patient identifier in Australia to facilitate matching (121), and significant administrative barriers have been identified in linking state and national databases. (65) If linkage can be streamlined, the use of such data will require a strategic approach to the development of analytic cohorts and consolidation of appropriate methodology if Australia is to develop a truly multi-faceted and adaptive vaccine pharmacovigilance system. The final chapter of this thesis uses a qualitative methodology to explore this and other gaps and opportunities that may enable Australia to strengthen its vaccine pharmacovigilance systems.

Chapter 5: From program suspension to the pandemic: a qualitative examination of Australia's vaccine pharmacovigilance system over 10 years

5.1 Introduction

Chapters 1 to 4 provided examples of the contribution of Australia's current vaccine pharmacovigilance methods, including traditional spontaneous reporting and more novel methods that have developed over time and in response to specific safety issues. The validity and usefulness of each component have been explored using quantitative methods to assess the data source directly for specific vaccines. Yet Australia's vaccine pharmacovigilance framework is complex and includes interactions across systems, among stakeholders, and between state and national governments (Figure 2). Qualitative methods offer an opportunity to explore the perceptions of key stakeholders and the influence of social and political factors to develop a richer understanding of complex public health systems. (122) This study was undertaken in collaboration with four co-authors (see Authorship attribution statement); a modified version of the content presented here has been submitted for publication and has undergone initial peer review.

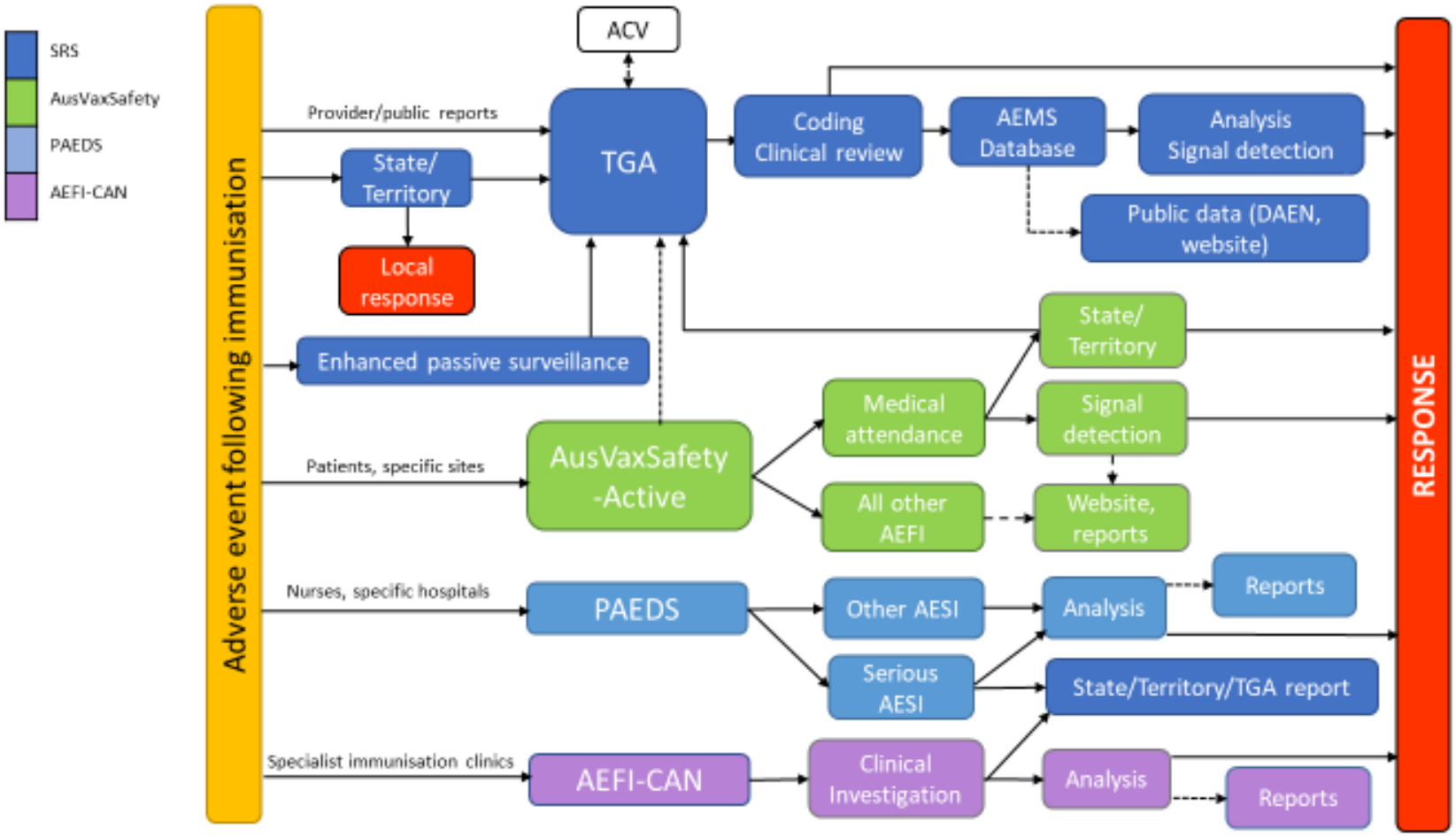
The influenza vaccine-associated events of 2010 represented a turning point in Australia's vaccine safety journey, resulting in the commissioned national *Review of the management of adverse events associated with Panvax and Fluvax*, led by former Chief Medical Officer Professor John Horvath ('the Horvath Review') (53), and the development of AusVaxSafety-Active. (56, 57) The Horvath Review identified the need for improved timeliness, clarification of roles and responsibilities, and increased transparency around the vaccine safety surveillance process. The Australian Government accepted all seven of the review's recommendations with a 2-year implementation timeframe, overseen by the Department of Health and the Therapeutic Goods Administration (TGA). (123) Reforms were linked to another TGA initiative (*TGA reforms: a blueprint for TGA's future*) released in December 2011. (124) All recommendations of the Horvath Review were addressed by government within the implementation timeframe (123); however, no formal evaluation has been completed.

Ten years on, a number of new vaccines or expanded eligibility for existing vaccines have been introduced onto the National Immunisation Program (NIP), including diphtheria-tetanus-pertussis vaccine for pregnant women, quadrivalent meningococcal vaccine for adolescents, and live attenuated herpes zoster vaccine for older adults. (125) This qualitative study was undertaken in 2020 as Australia was preparing to implement a COVID-19 immunisation program. The World Health

Organization (WHO) recommends that countries like Australia, which already have mature pharmacovigilance systems, take extra steps to implement active surveillance systems for adverse events of special interest (AESIs), research identified safety concerns (including comparative studies of vaccinated and unvaccinated populations), use local safety data to inform communication strategies, and contribute data and knowledge on the safety profile of COVID-19 vaccines. (25) In the context of public scrutiny around the novel technology and rapid deployment of COVID-19 vaccines, robust pharmacovigilance is essential to maintain public confidence and high coverage to enable recovery from the significant health, social and economic impacts of the COVID-19 pandemic. (25)

This study aimed to understand vaccine safety experts' perspectives on the evolution of Australia's vaccine pharmacovigilance mechanisms since 2010, identifying any perceived gaps and considering system readiness to monitor safety of the COVID-19 immunisation program. We aimed to provide the findings to policymakers to inform the development of pharmacovigilance systems and, specifically, national COVID-19 vaccine safety monitoring.

Figure 2 Schematic representation of Australia's vaccine pharmacovigilance systems



ACV – Advisory Committee on Vaccines; AEFI – adverse events following immunisation; AEFI-CAN – Adverse Events Following Immunisation – Clinical Assessment Network; AEMS – Adverse Events Management System; AESI – adverse events of special interest; DAEN – Database of Adverse Event Notifications; PAEDS – Paediatric Active Enhanced Disease Surveillance; SRS – spontaneous reporting system; TGA – Therapeutic Goods Administration

Solid lines represent AEFI reporting, analysis and response; dashed lines represent communication around AEFI reports and pharmacovigilance.

5.2 Methods

5.2.1 Study design

This qualitative study used thematic analysis to examine semi-structured interviews with Australian vaccine safety experts and key government representatives.

5.2.2 Participants and setting

Participants were purposively selected experts in vaccine safety who were either current or former members of national advisory groups or held key operational roles in Australia's pharmacovigilance systems. Potential participants were identified through review of current member lists of the Australian Technical Advisory Group on Immunisation, National Immunisation Committee, Advisory Committee on Vaccines and AusVaxSafety Expert Leadership Group. Former advisory group members who had played a key role in vaccine safety in Australia since 2010 were identified based on the authors' knowledge of vaccine safety stakeholders over this time period. Potential participants who held an operational role as part of a surveillance system (AusVaxSafety or the spontaneous reporting system) or who held a role within national government were identified based on these roles.

Selection was further guided by the socioecological model (SEM) framework. (126) The SEM framework enables understanding of the multiple levels of influence on public health policy, including jurisdictional and national policy-setting perspectives, as well as public health, specialist clinician, primary care and consumer perspectives. The final selection of vaccine safety experts was agreed through discussion amongst four authors.

The identified vaccine safety experts were invited by email to participate and provided with an information sheet. If there was no response within 2 weeks, a single reminder email was sent. An interview time was mutually arranged with those who agreed to participate. The information sheet stated that completion of an interview would be accepted as consent; verbal consent was provided at interview. In order to protect their identity, participants were described by their pseudonym (e.g. participant 1), rather than by identifying the individual or the role(s) they have within vaccine safety surveillance in Australia. If a participant was not available, another potential participant with a similar professional background was approached.

5.2.3 Data collection

Interviews were conducted between July and October 2020, prior to implementation of the COVID-19 immunisation program. Data were collected through semi-structured interviews, based on an interview guide developed by the investigators and informed by the Centers for Disease Control and Prevention's (CDC's) *Updated guidelines for evaluating public health surveillance systems* (127), the *National Immunisation Strategy for Australia 2019 to 2024* (128), the Horvath Review (53), and the requirements identified by the WHO's *Global manual on surveillance of adverse events following immunisation*. (5) The interview guide (Appendix C) included questions on current safety systems and their integration; data analysis and reporting; signal investigation and causality assessment; roles, responsibilities and governance; communication; and gaps and future directions. All question areas included a focus on changes since 2010 and requirements for COVID-19 vaccine pharmacovigilance. Questions were slightly tailored to the relevant experience of the participants. Question prompts were used to explore participants' views in greater depth. All but one of the interviews were conducted using Microsoft Teams videoconferencing features (one participant elected to provide a written response based on the interview guide). Data collection continued until saturation was reached; this was defined as no additional, unique data outside the coding framework.

5.2.4 Data analysis

Interviews were recorded and transcribed verbatim. Two authors (AP and SC[2]) coded the first three interviews, using a codebook developed through a deductive (also known as thematic or 'top down') approach described by Braun and Clarke (129), based on the interview guide. Coding was confirmed or revised through agreement between both authors, after which AP[2] coded the remaining interviews. All coding was undertaken in NVivo (QSR International; Version 12). Thematic analysis was conducted using the method described by Braun and Clarke. (129) Potential themes were developed from the codes through interpretive analysis and the generation of mind maps. All authors reviewed the initial themes and agreed on the refined thematic conceptualisation.

[2] See authorship attribution statement

5.2.5 Ethics

This study was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee (2020/ETH00884).

5.3 Results

In total, 23 vaccine safety experts were approached and 17 participated. Almost all participants (n=16) were current or former national advisory or expert group members; most had several concurrent roles in vaccine safety and two participants were national government employees (Table 2). Based on their main role, participants represented all perspectives within the SEM framework including national policy (n=6), jurisdictional policy (n=2), public health (n=3), specialist clinician (n=3), primary care (n=2) and consumer (n=1). However, based on their broad experience, most participants offered multiple perspectives. Six individuals declined participation, including three representing a national policy perspective, two representing a primary care perspective and one specialist clinician. Five of the six did not respond to the email invitation or follow-up reminder; one replied that they were unable to participate due to competing demands of the COVID-19 pandemic.

Table 2 Participant demographics and roles in vaccine safety

Characteristic	Category	Number
Number of participants		17
Median interview duration, minutes (range)		41 (29–50)
Sex	Male	10
	Female	7
Role[a]	Current or former national advisory or expert group membership[b]	16
	Operational role in a surveillance system	5
	Specialist clinician in vaccinology (physician or nurse)	5
	Public health practitioner	6
	State or territory role and/or representative	5
	National government representative	2
	Primary care practitioner	2
	Consumer representative	1

[a] Most participants had several concurrent or historical roles in vaccine safety.

[b] Advisory and expert groups included the Australian Technical Advisory Group on Immunisation (ATAGI), National Immunisation Committee, Advisory Committee on Vaccines, AusVaxSafety Expert Leadership Group and ATAGI COVID-19 working group.

Sixteen participants were interviewed, and one submitted a written response based on the interview guide, which was included in the analysis. Six overarching themes were identified, encompassing participants' views on system improvements, future needs, governance and information sharing, communication, and the challenges of a COVID-19 immunisation program.

5.3.1 Improvement, innovative local systems and a foundation for COVID-19 vaccine safety surveillance

Participants described local innovation as a feature of vaccine pharmacovigilance in Australia. Many specified AusVaxSafety-Active as the '*stand-out*' innovation and '*pivotal change*' since 2010, given its ability to obtain near-real-time safety data through active, SMS-based surveillance in primary care settings. Several stated that AusVaxSafety-Active was '*relatively nationally representative*', providing a '*quasi-national*' system with good response rates and sample size, which had improved over the past 10 years.

In terms of the longstanding spontaneous reporting system, some participants commented on innovative approaches that had emerged within some states, including sophisticated electronic reporting systems, which, in conjunction with improved timeliness and data completeness, put Australia in a '*vastly better position*' than in 2010. Participants noted that the spontaneous reporting system, which participants referred to as passive surveillance, was an '*important component*' and '*core platform*' that most thought benchmarked reasonably well against similar passive surveillance systems internationally. Paediatric Active Enhanced Disease Surveillance (PAEDS) was considered a '*good mechanism*' for surveillance of specific hospitalised AEFI and signal investigation; a few participants mentioned the value of emergency department-based surveillance for specific syndromes in one state.

Several participants stated that a safety signal could be detected within current systems, particularly a signal for AEFI occurring soon after vaccination. Looking toward the future, some participants discussed '*refining and calibrating*' the signal detection methods within AusVaxSafety-Active and the Adverse Events Management System (AEMS), including using real-time data analytics and reporting.

The current surveillance systems were considered '*fundamentals*' that could be enhanced, scaled up and adapted for COVID-19 vaccine safety monitoring. In particular, participants mentioned the need to maximise reporting to the spontaneous reporting system and expand coverage of AusVaxSafety-Active to settings and populations relevant for COVID-19 vaccine, including pharmacy and aged care settings, and increase representation from Aboriginal and Torres Strait Islander populations. Some participants noted that enhancements were underway as part of COVID-19 vaccine planning.

'I truly believe we have one of the most comprehensive systems in the world as far as both active and passive surveillance. That's not to say it's perfect and that's not to say it can't evolve and continue to change. Certainly, the breadth of active surveillance I think is really astounding that's occurring in Australia at the moment.'
(participant 1)

'I think we've got a basic framework for monitoring which we're obviously going to need to adapt to a COVID vaccine specifically. And maybe adapt it in a number of different ways…But I think we have the backbone and we have the infrastructure to be able to do that.'
(participant 8)

5.3.2 Ongoing evolution – barriers and drivers for change

Participants perceived a need to develop a more systematic approach to population-level active surveillance, including through vaccine safety analyses using large linked databases. Several suggested this approach to better capture later-onset events, given the focus of AusVaxSafety-Active on shorter-term events. Others mentioned the utility of data linkage to capture hospitalised or rare events, which they perceived were underreported by hospital staff to the spontaneous reporting system. While participants noted the benefit of the existing sentinel hospital-based active surveillance system (PAEDS), several noted that this was limited to selected hospitals and was '*paediatric based*'. Expansion of active, hospital-based surveillance was mentioned, including the potential to '*repurpose*' the national Influenza Complications Alert Network (FluCAN) for COVID-19 vaccine safety surveillance.

Several participants reflected on established data linkage systems in other high-income countries, including the US Vaccine Safety Datalink (VSD). Lack of timely and systematic data linkage for the purposes of pharmacovigilance in Australia was described as a major gap, despite being considered by most as technically '*quite feasible*'. The Australian Immunisation Register was considered a '*unique*' system to include in data linkage for vaccine safety, in conjunction with established electronic national healthcare and administrative databases.

Participants highlighted a number of organisational barriers to timely and structured access to linked data for use in vaccine safety analyses. While one participant described '*restrictions and caveats placed around the use and access*' to data as appropriate (participant 11), many others expressed

frustration at the barriers to linkage, with one stating that '*this is really what is expected of a modern-day health system*' (participant 1).

Several participants talked about the importance of data linkage for COVID-19 vaccine safety surveillance and considered that the current '*emergency situation*' could be a driver for '*significant enhancement*', reflecting that the 2010 influenza vaccine experience had similarly '*galvanised the then-government to decide that further investment was needed*' (participant 6). A vaccine injury no-fault compensation scheme was also highlighted by several participants as a '*pillar of vaccine safety surveillance*' (participant 14) that exists in most other industrialised countries and a '*critical*' component to meet the challenges of COVID-19 vaccination in Australia.

> *'Essentially for me the big hole is still the lack of linking in real-time fashion, immunisation data from a very good register to health encounter datasets that already exist. And that's sort of like a huge omission in my opinion, if you want to take vaccine safety seriously.'* (participant 14)

> *'I think it's feasible to get a large level population data-linked system up and running quickly. I think to do it at a national level is incredibly hard, and would rely on an immense amount of jurisdictional collaboration and barrier crunching, but I think you could develop a variety of models that would enable something functional to be established within several months, that would have vaccine safety utility at a representative population level.'* (participant 15)

5.3.3 Greater integration is essential

Many participants talked about a lack of integration between AusVaxSafety-Active and the AEMS, describing '*parallel systems*' where notifications may either '*fall through gaps*' or be duplicated. Data governance and system compatibility were raised as potential barriers to integration. Some described shared data summaries and networks between individuals and organisations (such as joint meeting attendance) as proxies for system integration; enhancements were identified as being underway.

Some participants described the national spontaneous reporting system as '*fragmented*' and said that jurisdictional processes had not necessarily evolved in a '*coordinated way*' with '*everyone…doing it slightly differently*' (participant 1). Participants perceived that integration should

be driven from the national level to develop a '*coordinated federal system*' with '*consistent uniform passive surveillance*' (participant 1) and harmonisation of jurisdictional systems. A few participants noted that some jurisdictions were independently working towards electronically merging their data.

> *'I would just love to have an overarching national safety surveillance system and having the active and the passive all combined in one. I just think that's got to be our future.'* (participant 12)

> *'There are multiple existing links between Australia's active and passive surveillance systems…the [COVID-19 pharmacovigilance] plan aims to…strengthen linkages between the active and passive surveillances systems.'* (participant 10)

5.3.4 Causality assessment improved but room to enhance timeliness and adult assessment

Many participants discussed improvements in causality assessment in recent years and some stated that the current process was professional, responsive and sensitive, with use of an expert panel. A number of participants cited recent '*detailed examination*' of AEFIs following live attenuated herpes zoster vaccine as evidence of the improved process. However, participants talked about a lack of visibility of causality assessment processes and lack of feedback to the immunisation provider community. Several participants raised concerns about the timeliness of causality assessment ('*it may take months before something is in the public space*' [participant 1]) and called for a standing (rather than ad hoc) causality assessment committee '*built into the actual framework of the surveillance syste*m' (participant 3), particularly in preparation for COVID-19 vaccines.

Participants noted that state- and territory-based AEFI clinics and the Adverse Events Following Immunisation Clinical Assessment Network (AEFI-CAN) were key elements which provide individual-level assessment and reassurance. Several participants raised concerns about the availability of similar clinics to provide services for adults with complex immunisation-related concerns in some jurisdictions, and one participant articulated a need to engage adult services and provide training for clinicians for the rollout of COVID-19 vaccines.

> *'I think the last couple of years with the formation of the causality group by the TGA, that's been done far better and far more responsively.'* (participant 15)

> *'We do have a clinical service for adults…I think every state needs to have an avenue to try and seek adult review and assessment.'* (participant 1)

5.3.5 Improved relationships, networks and information sharing; importance of robust federal leadership

Close working relationships between the TGA and jurisdictions, as well as the National Centre for Immunisation Research and Surveillance (NCIRS), were reported to be '*fundamental to ensuring timely communication around signals of concern*' (participant 10). The monthly TGA teleconferences (Table 1) were considered an '*information sharing forum*' and participants perceived that the quality of AEMS data presented had '*improved massively in the last year*' (participant 15), with newer data visualisation approaches more useful than traditional line-listed data. Participants said that reports from AusVaxSafety-Active were clear and regular, with one participant stating that monthly reports were '*just so reassuring as a program manager*' (participant 12).

Participants described a '*greater network of clinicians and vaccine safety experts*' (participant 11) that the TGA had developed over recent years; in particular, the Advisory Committee on Vaccines (Figure 2, Table 1) was described as '*an important new step*' (participant 5). The AEFI-CAN network, in which members of the TGA pharmacovigilance branch also participate, was also considered an effective communication forum.

Most participants stated that federal leadership was essential, although a few highlighted '*collective responsibility*' and '*collaborative relationships*' between stakeholders. Most said that overall responsibility resided with the TGA as the regulatory authority with '*the legislative power to undertake rapid regulatory action*' (participant 10); however, several participants commented on the need for support from external organisations and other government departments. Some participants articulated a greater need for '*robust federal leadership*' and said there was '*compartmentalisation of responsibilities*'. Several participants stated that an independent delegated authority or agency could have governance over vaccine pharmacovigilance but did not necessarily perceive this as a realistic and achievable option. The COVID-19 immunisation program was considered an opportunity to clarify and improve governance.

> *'I think it is…appropriate to contract groups that have expertise…to get a project done or to get a system running or even maintain that system. But ultimately…the vision and the responsibility and the investment should be with the federal government.'* (participant 14)

> *'If we really start to wish upon a star we could say, well, we need a national agency of a CDC kind which…has statutory authority and independence.'* (participant 6)

5.3.6 Communication, transparency and the unprecedented challenge of COVID-19

Participants thought that AusVaxSafety-Active had '*done a really good job of raising the profile of vaccine safety*' (participant 14) for both consumers and providers, and was an '*incredibly powerful tool*' for public confidence, demonstrating transparency ('*we are not afraid of our own data*' [participant 17]). The AusVaxSafety website was described as '*well-presented and very readily consumable*' (participant 13), particularly through the use of infographics, although several participants commented that providers and consumers may not be aware of the website and that communication strategies needed to evolve or were already evolving.

Participants said that the availability of spontaneous reporting system reports online through the Database of Adverse Event Notifications (DAEN) (Table 1, Figure 2) provided transparency, although one stated this was not user-friendly and '*would be very easy to misconstrue or misinterpret*' (participant 3). Participants acknowledged that TGA advisories and information on vaccine registration processes were available online, although one commented '*we don't hear about the good news very often*' (participant 9). Some participants were concerned that providers may not be adequately aware of the spontaneous reporting system process or reporting requirements, and that education may be required for COVID-19 vaccines.

Participants perceived a high level of vaccine confidence in Australia and a solid base to deal with the unprecedented challenges in relation to public scrutiny of COVID-19 vaccines. However, some participants were still concerned about the effect of temporally associated AEFI on public confidence. Most participants described a need for more transparent communication to build trust, with one describing this as similar to '*the way that the Australian authorities have informed the public around the decision-making for COVID-19 vaccines*' (participant 15). Acceptability of COVID-19 vaccines to healthcare workers was raised as an important issue, particularly given the influence of providers on public confidence. Several participants noted that work and planning is ongoing in the public communications space, including through international collaboration.

> *'When I've done presentations to GPs [general practitioners], I've certainly shown them what's available. And when they see what's available, particularly on AusVaxSafety, they really like that and think*

it's a good communication tool for patients who might be concerned.' (participant 13)

'And the way that people responded then when the scourge of polio was very visible doesn't seem to be the way people are responding to COVID-19, despite the fact that the death rate overseas has been enormous…If we're going to have to deal with similar disinformation here, then that's an enormous task in terms of vaccine safety.' (participant 17)

5.4 Discussion

This study highlights the progressive yet substantial improvement in Australia's vaccine pharmacovigilance systems since the Australian Government's (Horvath) review of vaccine safety in 2011. The advances identified in terms of innovation, information sharing and transparent communication suggest that Australia is very well placed to conduct ongoing post-marketing surveillance for COVID-19 vaccines. However, we also identified weaknesses and barriers; there is an opportunity to augment pharmacovigilance approaches to capture later-onset events and a need for greater system integration. Interviews were undertaken in mid-2020 in the knowledge that system improvements would be developed to address the heightened complexity of safety surveillance for COVID-19 vaccines. Changes are being driven through the national COVID-19 vaccine safety monitoring plan (130) and recent renewal of the Australian Government-funded AusVaxSafety consortium; the findings of this study have been shared with the Australian Government and TGA to further inform system developments.

Participants in our study considered AusVaxSafety-Active a leading innovation, and its effectiveness for influenza vaccine post-marketing surveillance and signal detection has been demonstrated. (59) In line with our participants' comments that AusVaxSafety-Active would need to expand to capture additional settings and populations for COVID-19 vaccine pharmacovigilance, partnerships with state and territory health departments have enabled expansion, with participation of state-run mass vaccination clinics. (58) Other sites such as pharmacies, Aboriginal medical services and aged care facilities are also being incorporated for COVID-19 vaccine surveillance. However, as described, AusVaxSafety-Active aims to monitor early-onset events (generally within 1 week), and our participants noted that such methods were not necessarily suited to the detection of later-onset events. As explored in Chapter 3, participant-based surveys administered at a time distant from vaccination may be of limited value given the potential for recall bias and ascertainment of

unrelated medical events. Conversely, while later-onset AEFI may be captured through spontaneous surveillance, underreporting is a well-recognised limitation of such systems (27); our participants particularly noted underreporting by hospital staff in relation to AEFI that may present late and/or to hospitals. Until recently, AusVaxSafety-Active and the spontaneous reporting system have not been integrated and have operated as parallel systems; increasingly, with implementation of the COVID-19 immunisation program, states and territories have been more focused on reviewing medically attended AEFI detected via AusVaxSafety-Active.

The need to develop more systematic approaches for population-level active surveillance to capture later-onset AEFI, including those presenting to hospitals and particularly for AESIs following COVID-19 vaccination, was clear from this study. Currently, sentinel hospital-based active surveillance is the key modality, outside of spontaneous reporting, through which later-onset and hospitalised AEFIs can be captured in Australia. Both PAEDS and FluCAN have been adapted to capture data on COVID-19 cases and complications, and PAEDS has been previously tailored to monitor specific AESIs, such as intussusception and febrile seizures. (29, 131) While both systems have the capacity to expand to AESIs related to COVID-19 vaccines, hospital-based surveillance is resource intensive and limited by the number of participating sites. (29) However, for very rare, late-onset events, such as the newly described thrombosis with thrombocytopenia syndrome (TTS) which occurs at an estimated rate of approximately 1 per 100,000 after the first dose of the AstraZeneca COVID-19 vaccine (18), patients could present infrequently and to any potential location, including secondary and rural hospitals. While spontaneous reporting systems can capture such events, systematic approaches to actively monitor large, electronic population cohorts would significantly augment surveillance capability.

The key modality missing from Australia's suite of resources, as identified in our study, is structured and timely access to linked sources of relevant health and demographic data for the purpose of pharmacovigilance. This reflects the findings from the quantitative work in this thesis around the need for epidemiological analysis using large population-level databases, including those with linked data. In this, Australia lags behind other developed countries. The US VSD has been operating since 1990 and is used not only for testing hypotheses generated from the Vaccine Adverse Events Reporting System (VAERS) but also for active surveillance through rapid cycle analysis, comparing vaccinated and unvaccinated populations in near-real time. (34) In the UK, the Clinical Practice Research Datalink (CPRD) has been operating for 30 years (35); for COVID-19 vaccines, rapid cycle analysis is being undertaken. (75)

Our participants highlighted barriers to establishing vaccine-specific analyses in large linked databases in Australia, despite the existence of many comprehensive, stand-alone electronic health databases. Unlike some European countries (33), Australia does not have a unique, personal identification number to enable deterministic linkage between health registers, so probabilistic matching is required. (121) Further, in contrast to the nine healthcare organisations participating in the US VSD, which maintain both individual electronic immunisation records and comprehensive healthcare information (31), the Australian Immunisation Register is maintained by the national government while timely access to hospital inpatient and emergency department data is facilitated by state and territory governments. (65, 132)

Proof-of-concept studies have linked the Australian Immunisation Register with various healthcare datasets, including the National Death Index (121) and hospitalisation data from selected states and territories. (132) However, participants in our study echoed previously published concerns around complex application, approval and administrative processes, which have led researchers to suggest that linkage of the immunisation register with other datasets is not feasible for real-time surveillance (65, 66), although it certainly has value for signal investigation and examination of AESIs. In addition, vaccine doses are underreported to the immunisation register by providers (133), particularly for adults, which has limited its usefulness for linkage. Mandatory reporting of vaccinations to the register, implemented in 2021, should improve usefulness in this regard. (134)

Australia's National Immunisation Strategy 2019–2024 identifies the need to 'facilitate opportunities for linkage between national immunisation registers and other data collections' to enhance vaccine safety monitoring systems (128, p.23); some of our participants expressed optimism that implementation of the COVID-19 immunisation program may be a driver for change, if identified barriers can be overcome. Currently, work is ongoing within Australian states and territories to link data for the purposes of COVID-19 vaccine pharmacovigilance, including broader, jurisdictional access to the Australian Immunisation Register. Further, two Australian organisations (NCIRS and Monash Health) are partners in the Global Vaccine Data Network (GVDN), a multinational network of researchers with capacity in vaccine data linkage, established to conduct coordinated active surveillance of vaccines, including COVID-19 vaccines. (135) Subject to necessary ethics and governance approvals for all participating countries and data sources, the GVDN seeks to combine data from multiple settings to study AESIs at a global level.

While our study highlighted improvements in both governance and communication since the Horvath Review, with established networks and the creation of the Advisory Committee on Vaccines, participants still reflected on a need to clarify and improve governance. In comparable countries,

governance of vaccine safety is variably maintained by regulatory medicines authorities and/or government public health agencies. (24, 136, 137) Our participants discussed governance options including the creation of a central agency, or increased utilisation of external organisations to support government. In implementing the COVID-19 immunisation program in Australia, relationships between the TGA and independent organisations such as NCIRS have strengthened as implementation of more enhanced pharmacovigilance strategies (such as access to linked data to determine background rates of key AESIs) has become imperative .

Participants indicated they believed that transparency has improved, which may reflect implementation of reforms aimed at improving community understanding of TGA processes and enhancing public trust (124), along with provider and consumer participation in AusVaxSafety-Active. However, lack of visibility and timeliness around the causality assessment process undertaken by the TGA was highlighted as a concern. Participants echoed international calls for transparent communication to address the challenges of COVID-19 immunisation program implementation.(138, 139) As the pandemic immunisation program has been implemented in Australia, there has been a notable increase in content communicated publicly by the TGA, including weekly website updates, information on the role and function of the TGA, and safety alerts. (140, 141) Similarly, the Australian Government has published multiple consumer and health provider communications in relation to COVID-19 vaccine safety. (18) The AusVaxSafety website also provides weekly data updates and information, with additional detail for COVID-19 vaccines. (58) Further, the TGA has periodically communicated the findings of the Vaccine Safety Investigation Group, which has brought together individuals with relevant expertise to conduct regular and timely causality assessments for cases of TTS following the AstraZeneca COVID-19 vaccine. (140)

A strength of our study was the broad background of our participants, representing multiple stakeholder perspectives in relation to Australia's post-marketing surveillance systems, including consumer, provider, system and government representatives. However, as we selected participants based on their roles and expertise, it is possible that we may have obtained a biased perspective, as some participants had an ongoing role in vaccine pharmacovigilance in Australia and may have felt compelled to provide a positive account of the current systems. In reality, we found many participants provided candid assessments, particularly those with more extensive experience, which may have been because they were aware that the data would be de-identified and because a number were independent of government or the TGA. We were limited by the unavailability of six participants who were unable to participate directly in interviews during the COVID-19 pandemic; reasons for non-response were not actively sought, but one individual indicated that they were

willing to participate but did not have capacity. Where participants did not respond, we ensured that we had representation from others who were involved in similar roles; many participants had multiple roles. However, the views of participants may not necessarily reflect the views of all relevant stakeholders.

5.5 Conclusion and implications

There is significant potential for the COVID-19 vaccine safety monitoring plan and program implementation to strengthen Australia's pharmacovigilance system and drive the improvements identified here, including an enhanced ability to capture later-onset or very rare AEFIs. While evidence of improvement is already apparent, further work is required to build an integrated, comprehensive national system. It is also important that this occurs for all vaccines used in Australia, and particularly those under the NIP, from both risk and public perception points of view; enhancements driven by the implementation of Australia's COVID-19 immunisation program should be embedded in routine safety surveillance for all vaccines.

As part of a pharmacovigilance strategy for the NIP and to ensure the public are supported to accept rare vaccine-related risk, our participants identified the need for a no-fault vaccine injury compensation scheme. These schemes exist in most other, similar developed countries, such that any person with a serious injury causally related to vaccination can be compensated, promoting confidence in the beneficence of the system. (142)

This study offers a unique perspective of a key 10-year period in Australia's vaccine safety journey, bookended by a significant vaccine safety event in 2010 and implementation of the COVID-19 immunisation program in 2021. The perspectives of vaccine safety experts in Australia are hugely valuable at this critical point in time. While the innovative approach used by AusVaxSafety-Active may be valuable for other countries implementing a COVID-19 immunisation program (and is already implemented as v-safe in the US), Australia can equally learn from other well-developed systems internationally, particularly those with established data linkage systems that are utilised for pharmacovigilance. Australia has the opportunity to leverage the current momentum to establish and sustain population-level active surveillance and clear governance processes, both for COVID-19 immunisation and future programs.

Conclusion

The last decade – how far have we come?

Over the past decade, Australia's vaccine pharmacovigilance approach has developed into a diverse suite of systems. This thesis has explored several of those systems, contextualising both the value and limitations of each in the context of specific, topical vaccines (Table 3). A variety of analytical methods has been used to interrogate data and explore the contribution of the systems to complex questions. The quantitative analyses presented have demonstrated the breadth of information gained from descriptive analysis of surveillance data over time, the added value of detailed cohort event monitoring (CEM), and the need for assessment of risk using epidemiological methods such as the self-controlled case series analysis. The review article presented in Chapter 1 draws out the appropriate use of all vaccine pharmacovigilance methods, guiding the strategic implementation of a multi-faceted suite of methods. The qualitative analysis demonstrates the relevance of the rich insights that stakeholder perceptions can bring to evaluating and informing the system as a whole.

Individually, the strengths of each vaccine pharmacovigilance method have been demonstrated. A spontaneous reporting system is an essential, base component of any vaccine pharmacovigilance system to enable early ascertainment of rare, potentially serious, and unexpected events, to identify signals and generate hypotheses that require further testing. (5, 23, 143) The qualitative study presented in Chapter 5 suggests that Australia's spontaneous reporting system benchmarks well with similar systems in other developed countries. This is supported by the useful information gained and published in the longitudinal analysis of human papillomavirus (HPV) vaccine in Chapter 2, with findings comparable to an analysis of the same vaccine within the US Vaccine Adverse Events Reporting System (VAERS) database. (100) Further, analysis of Australian data was enriched by accurate denominator data on doses administered and by data from an enhanced surveillance period. However, the usefulness of spontaneous reporting systems is limited in isolation. Its value can be extended by combining it with other data sources. For example, comparison of spontaneous reports of fatigue syndromes with background rates calculated from the Clinical Practice Research Datalink (CPRD) as part of the UK's enhanced pharmacovigilance strategy for HPV vaccine provided valuable information indicating an absence of association between vaccination and those syndromes. (36)

Similarly, the value of AusVaxSafety-Active in monitoring short-term adverse events following immunisation (AEFIs) following influenza vaccine has been validated through published studies (59,

71, 107), and the unique pharmacovigilance study of herpes zoster vaccine presented in Chapter 3 supports the usefulness of AusVaxSafety-Active in providing near-real-time data on reactogenicity, including in older adults. The system has potential to further support the rollout of vaccines in sub-populations; for example, the US v-safe system, which is modelled in part on AusVaxSafety-Active, has been used to generate much needed data on the safety profile of COVID-19 vaccines in pregnant women, and to create a pregnancy registry for COVID-19 vaccines. (108) AusVaxSafety-Active utilises information technology approaches to vaccine pharmacovigilance through mhealth; other technological advances in pharmacovigilance, such as advanced statistical techniques to analyse patterns within large datasets, are also required. (143)

Table 3 Strengths and limitations of key pharmacovigilance systems in Australia

System	**Methodology**	**Value**	**Limitations**
Adverse Events Management System (AEMS)	Passive surveillance	Identification of rare and later-onset, unexpected events Well established Rapid signal identification if reporting is timely	Underreporting Stimulated reporting Incomplete data Lack of denominator data No unvaccinated comparator population Jurisdictional differences
AusVaxSafety-Active	Cohort event monitoring	Profiling of reactogenicity Rapid data accumulation Less resource intensive than other active surveillance	Lack of denominator data No unvaccinated comparator population Not well suited to surveillance for later-onset events
Adverse Events Following Immunisation Clinical Assessment Network (AEFI-CAN)	Network of vaccine specialist clinics and staff	Individual clinical assessment Detailed case information and case validation	Resource intensive Lack of denominator data No unvaccinated comparator population
Paediatric Active Enhanced Disease Surveillance (PAEDS)	Sentinel hospital-based active surveillance	Identification of rare and later-onset pre-specified events Detailed case information and case validation	Resource intensive Lack of denominator data No unvaccinated comparator population
Healthcare databases (e.g. MedicineInsight)	Epidemiological study	Unvaccinated comparator population (or self-controlled) Large population Can potentially be used for both signal detection and investigation	Lack of case validation Data linkage needed to include all health events (e.g. hospitalised) Data access not timely or streamlined so not useful in real time Lag in data coding

Despite its benefits, CEM is limited when used in isolation and integration with passive surveillance is required. In some jurisdictions, AusVaxSafety-Active reports that involve medical attendance are escalated to the spontaneous reporting system and individuals reporting an AEFI are linked into adverse events clinics. (47, 48, 144) Systematic integration would leverage the potential for AusVaxSafety-Active to identify such serious AEFIs or, through adaptation of surveys, to confirm signals that may have been identified through passive surveillance. To handle solicited reporting from AusVaxSafety-Active, any integration would need to identify the reporting source and use the marker of medical attendance as a proxy for serious AEFIs. Further, overarching governance structures would be required to facilitate integration and a coordinated response to vaccine safety issues.

As described in Chapter 3, and further highlighted in Chapter 5, CEM may not be suited to the detection of later-onset AEFI. While these may be identified through spontaneous reporting systems, it is well recognised that signals generated by passive surveillance require confirmation, and resulting hypotheses require testing. (5, 143) One important step is to compare the rate of an identified adverse event of special interest (AESI) with the background rate of the condition of interest, as described above in the example of HPV vaccine and fatigue syndromes from the UK. The 'background rate' is the incidence observed in a population in the absence of the vaccine; comparing the observed incidence in a vaccinated population to the expected background incidence will provide information about whether the reported AESI has occurred by chance. (102) Establishing background rates – in different populations, ages, countries and time periods – requires a list of AESIs to be generated as part of immunisation program planning; this necessitates a strategic and coordinated approach. Access to electronic healthcare data in which to conduct analyses is also required so that rates are generated from contextual, recent and population-specific data. (102)

While providing useful evidence to assess signals, comparison to background rates alone does not determine causality. To definitively test hypotheses, it must be demonstrated that the risk in vaccinated individuals is greater than the risk in unvaccinated people. (5) As indicated throughout this thesis, population-level active surveillance and epidemiological studies conducted within large databases are critical elements of a robust, multi-faceted and adaptive vaccine pharmacovigilance system. Epidemiological studies can be designed and implemented for specific AESIs; active surveillance within population-level databases (such as rapid cycle analysis within the US Vaccine Safety Datalink [VSD]) can be adapted to compare specific AESIs in vaccinated and unvaccinated individuals in near-real time. (31, 34)

Chapter 1 highlighted the value of such methods in providing high-quality data to confirm the safety profile of HPV vaccine and in refuting unsubstantiated claims that damage vaccine confidence. Chapters 2, 3 and 4 documented the value of Australia's existing pharmacovigilance mechanisms but highlighted the need to take this information to the next level and test hypotheses within large, electronic healthcare databases linked to both hospitalisation data and the Australian Immunisation Register. Finally, Chapter 5 provided a rich understanding of the perspective of Australian experts, demonstrating that active, population-level surveillance is critical to address vaccine safety challenges now and in the future.

Barriers to implementing data linkage approaches in Australia have been previously explored and described. (65, 66) The absence of these mechanisms within Australia's public health infrastructure, including for vaccine pharmacovigilance, is increasingly in contrast to comparable countries. However, efforts to expand activity in this space have occurred and may be gaining pace in the context of the pandemic vaccine rollout. The Population Health Research Network was conceived 10 years ago to establish cross-jurisdictional data linkage, and has become a national network for data linkage units, a secure data laboratory and a support service for researchers that has been used for formal research studies on vaccine effectiveness. (145) More recently, the National Integrated Health Services Information (NIHSI) Analysis Asset has the potential to provide a national repository of information and include immunisation register data in the future. (146) However, currently, there is no established, routine data linkage for vaccine safety in Australia and no nationally coordinated approach to either active surveillance or epidemiological analysis within population-level datasets.

The pandemic – current and future impacts

This thesis was conceived in 2016, 4 years before the COVID-19 pandemic. Many of the findings around the limitations of current systems and the need for adaptive, multi-faceted approaches within a strategic implementation context have come into sharp focus with the rollout of COVID-19 immunisation programs – both in Australia and globally. For COVID-19 vaccines, the use of novel platforms and the simultaneous widespread use of multiple vaccines, largely under emergency use authorisation and in a pandemic context, is lifting vaccine safety science well beyond what was expected at the outset of this thesis.

At the time of writing, the end of the pandemic was not in sight; yet COVID-19 vaccines have already sparked safety concerns globally and the importance of a robust approach to assess the ongoing balance of benefit and risk could not be more important at this time. Some of the early issues, such as the occurrence of expected immediate adverse events (described as 'influenza-like symptoms'),

are related to the recognised immune response or reactogenicity of the vaccine, but without clear communication, may have a significant impact on vaccine uptake. (15) These AEFIs are well suited to surveillance via AusVaxSafety-Active and rates have been regularly communicated on the AusVaxSafety website, allowing program managers, providers and the public to understand what to expect following vaccination. (58) Others AEFIs, such as anaphylaxis, are well captured by spontaneous reporting systems, given that the event occurs soon after vaccination and is serious so likely to be reported. (147) Pre-defined AESIs such as vaccine-associated enhanced disease are well suited to monitoring through active, sentinel hospital-based surveillance such as Paediatric Active Enhanced Disease Surveillance (PAEDS). (148) Now more than ever, the multi-faceted and adaptive suite of resources described in this thesis is needed to monitor the spectrum of safety issues potentially related to COVID-19 vaccines.

The detection in Europe of a syndrome of thrombosis with thrombocytopenia (TTS) following the AstraZeneca COVID-19 vaccine created global concern. (16) Subsequently, there were similar reports of the syndrome following the Janssen COVID-19 vaccine (which uses a similar platform) in the US. (149) In Europe, the UK and the US, extensive work was undertaken after the signal was identified to compare rates of reported, unusual thromboses with background rates, thereby confirming the signal. (150, 151) Some of these analyses relied on access to linked data, including through the VSD in the US (152); a population-based cohort study using linked data from Scandinavian healthcare registers concurrently explored thromboembolism, thrombocytopenia and bleeding following vaccination with the AstraZeneca COVID-19 vaccine. (120)

At the time of writing, the World Health Organization (WHO) has called for epidemiological studies to understand the risk of TTS, including in specific sub-populations (by age and sex). (19) It is likely that vaccine safety issues will continue to emerge for COVID-19 vaccines, either due to real, unexpected events related to the new platforms, or to heightened media attention and increased reporting influenced, at times, by tenuous vaccine confidence. For example, at the time of writing, a signal from one country is emerging for myocarditis following vaccination with mRNA COVID-19 vaccines, underpinning the importance of understanding population-specific background rates (153) and having capacity to rapidly estimate risk in vaccinated and unvaccinated populations. (154) For Australia, the ability to rapidly and systematically interrogate population-level data to determine age- and sex-specific background rates and to investigate, confirm and respond to safety signals is urgently required, both to ensure the ongoing benefit–risk balance of the immunisation program in Australia and also to enable a greater global contribution.

Australia in a global context

Australia is part of a global community, the reality of which has become intensely clear through the COVID-19 pandemic and associated immunisation program. While it is imperative that Australia has the capacity for comprehensive country-level pharmacovigilance, we also have a responsibility, as a developed country, to contribute globally and to support low- and middle-income countries in our region.

It is recognised that vaccine pharmacovigilance, particularly for the detection and validation of rare and population-specific safety signals, requires the use of data within large collaborative networks as well as in individual countries. (6) These collaborative networks ('distributed data networks') use common protocols and analysis methods, either analysing data locally with subsequent meta-analysis, or pooling data across sites and countries. These methods increase both sample size and heterogeneity, but technical and coding solutions and governance frameworks must be carefully established. (6, 155) In Europe, the multinational Vaccine Monitoring Collaboration for Europe (VAC4EU) project is a dedicated network allowing rapid and systematic assessment of vaccine benefits and risk; it is monitoring COVID-19 vaccines across eight European countries. (155) For Australia, participation of two key organisations (the National Centre for Immunisation Research and Surveillance, and Monash Health) in the multinational Global Vaccine Data Network will hopefully fast-track development and consolidation of capacity in vaccine data linkage and coordinated active surveillance of vaccines. (135)

The WHO's Immunisation Agenda 2030 is underpinned by the need for partnerships and for evidence-based decision-making, to extend the benefits of vaccines, globally and across the life course. (4) There will be an ongoing need for vaccines to prevent morbidity and mortality from both existing and emerging diseases, and safety challenges will continue to arise. As vaccine science evolves, novel platforms that have been successful in the COVID-19 pandemic (particularly mRNA vaccines) may be used more broadly. These new vaccines are expected to have different characteristics from traditionally used products, which will require adaptation of pharmacovigilance approaches. (156) Further, emerging research into 'adversomics', which studies the drivers of AEFIs at a molecular level through immunogenomics, will underpin a need for tailored and adaptable methods to examine associations in specific populations. (157) Globally, there must be capacity to rapidly and accurately assess the balance between benefit and risk. (143)

Summary and recommendations

This thesis hypothesised that multi-faceted and adaptive vaccine pharmacovigilance methods are necessary to monitor vaccine safety in real-world conditions in Australia and ensure an ongoing positive benefit–risk balance for vaccines and immunisation programs. The pharmacovigilance landscape has evolved over time and now represents a more complex system, including a range of modalities that have demonstrated their value and adaptability to address various vaccine safety scenarios over the past decade. Clearly lacking, however, is a structured approach to active surveillance based on population-level data, including linked data.

What is now apparent, and has been brought into sharp focus through the COVID-19 immunisation program, is the need to overcome barriers and facilitate streamlined and timely access to linked healthcare data to enable comparison of vaccinated and unvaccinated populations. Further, while Australia's systems are diverse, adaptive and complementary, coordination and integration are needed to ensure a strategic approach to implementing surveillance now and into the future. Finally, through strengthening its own systems, Australia has the opportunity to make a contribution to an international body of evidence, which will in turn support our own programs.

This thesis therefore concludes with the following recommendations:

1. *Develop nationally coordinated and systematic approaches for population-level active surveillance within a strategic framework that facilitates streamlined access to large, linked patient cohorts; analysis using robust epidemiological methods; and rapid adaptation to new pharmacovigilance challenges.*

A major limitation of Australia's pharmacovigilance system is the lack of a systematic approach to identify safety signals, or to confirm and investigate vaccine safety issues, particularly for later-onset and rare AEFIs and AESIs. To become comparable with similar countries, a nationally coordinated approach to routine population-level active surveillance is required, similar to systems used in the US (Vaccine Safety Datalink [VSD]), the UK (Clinical Practice Research Datalink [CPRD]) and Scandinavia.

2. *Better integrate Australia's suite of pharmacovigilance resources to create a multi-faceted and adaptive system that can rapidly respond, in a coordinated manner, to vaccine safety challenges under real-world conditions.*

Improved integration of passive and active surveillance systems is needed to ensure that planning, data collection, analysis and response are coordinated, utilising the strengths of each system and allowing overlapping methodologies to fill gaps that would be created by relying on singular systems. While some gains have been made since the COVID-19 immunisation program commenced, greater efficiency and effectiveness will stem from having a 'whole-of-system' approach to integrated surveillance.

3. *Vaccine pharmacovigilance should be focused, purposive and informed by clear governance structures that value and drive innovation, with representation from both government and public health organisations, and benchmarking through a regular monitoring and evaluation framework.*

To ensure a strategic approach to coordination and cohesion, pharmacovigilance activities should be planned and articulated, governance arrangements should be clear, and monitoring and evaluation should occur routinely.

4. *Peak national organisations should leverage opportunities to contribute to an international body of evidence in vaccine pharmacovigilance as part of a global community.*

Australia is often an early adopter of vaccines and, through a comprehensive and funded National Immunisation Program, often achieve high coverage rapidly. Through strengthening country-based systems, Australia can make a greater global contribution to the vaccine safety landscape and, through these networks and relationships, continue to adapt and implement progressive and technology-focused vaccine pharmacovigilance systems.

5. *Ensure that the healthcare community and the public contribute to vaccine pharmacovigilance and are well informed about the risk of vaccines in relation to their benefit.*

As immunisation programs become more complex and extend across the lifespan, and as novel pandemic vaccines are broadly implemented, providers and consumers must be aware of the risk profile of individual vaccines, as well as understand their value, both for individual protection and population-level immunity.

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Appendices

Appendix A: Appendices to publication 1

This appendix includes the supplementary material related to the study in Chapter 1. Five tables are presented which list and summarise all HPV vaccine safety studies included in this review article. Articles are categorised by study type to demonstrate the levels of published evidence assessed.

Electronic Supplementary Material (ESM) 1

Safety of human papillomavirus vaccines: An updated review

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ESM 1A and 1B: Summary of select data on adverse events reported in HPV vaccine clinical trials in generally healthy subjects (i.e. those without known immunocompromising or auto-immune medical conditions) published from 10 May 2012 – 11 August 2016

1A: Studies comparing HPV vaccine with a placebo or control (non-HPV vaccine) group

Reference (Sponsor)	Region	No. of participants by vaccine & control (type)	Selected Adverse Events (AEs)[a]	Frequency of AEs in vaccine recipients, % or number [95% confidence interval shown where available]	Frequency of AEs in control recipients, % or number [95% confidence interval shown where available]
Studies with 2vHPV vaccine					
Angelo et al 2014[1] (GSK)	40 countries, 42 trials (pooled)	33 339 2vHPV 24 241 control (various)	Unsolicited AE MSC SAEs: full study, 30-day FU PIMD	30.8% [30.2-31.3] 9.6% [9.3–10.0] 7.9%, 0.5% 0.2%	29.7% [29.1–30.3] 10.4% [10.0–10.8] 9.3%, 0.6% 0.2%
Skinner et al 2014 [2] (GSK)	Multi: 12 countries	2881 2vHPV 2871 placebo (AlOH)	ISR Solicited general symptoms Unsolicited symptoms MSC SAE (vaccine-related) NOCD, NOAD	85% 65% 40% 41% 10% (<1%, n=5) 5%, <1%	67% 58% 41% 40% 9% (<1%, n=8) 6%, <1%
Hildesheim et al 2014 [3] (GSK)	Costa Rica	3727 2vHPV 3739 control (Hepatitis A vaccine)	Solicited local AE Solicited general AE Unsolicited AE SAE (vaccine-related) Death NOCD, NOAD Neurological condition	53.7% 90.5% 43.9% 24.5% (1.4%, n=53) 0.2% 10.3%, 0.6% 16.8%	19.9% 89.1% 41.1% 23.8% (1.0%, n=39) 0.2% 11.2%, 0.6% 15.8%
Sow et al 2013 [4] (GSK)	Senegal & Tanzania	450 2vHPV 226 placebo (AlOH)	Local AE General AE Unsolicited AE MSC SAE (vaccine-related) NOCD, NOAD Death	59.7% [57.0–62.4] 35.1% 25.3% [23.0-27.8] 69.3 [64.8–73.6] 3.8 [2.2–6.0] (0) 2.4 [1.2–4.3], 0.4% [0.1–1.6] 0% [0.0-0.8]	43.1% [39.2–47.0] 35.1% 30.2% [26.6–33.9] 75.2 [69.1–80.7] 6.2 [3.4–10.2] (0) 4.9 [2.5–8.5], 0.9% [0.1–3.2] 0% [0.0-1.6]
Zhu et al 2014a [5] (GSK)	China	750 G 9-17 yrs; 1212 W 26-45 yrs 980 2vHPV 982 placebo (G: AlOH; W:	Grade 3 local symptoms Unsolicited symptoms MSC SAE (vaccine-related) NOAD	G: 5.2%; W: 3.0% G: 37.2% [32.3–42.3]; W: 5.3% [3.6–7.4] G: 3.7% [2.1–6.2]; W: 0.8% [0.3–1.9] G:1.3%[0.4–3.1](0); W: 0.5%[0.1–1.4](0) G: 0% [0.0–1.0]; W: not reported	G: 2.0%; W: 0.3% G: 33.2%[28.5–38.3]; W: 5.9%[4.2–8.1] G: 2.9% [1.5–5.2]; W: 1.2% [0.5–2.4] G: 0.5%[0.1–1.9](0); W:0.5%[0.1–1.4](0) G: 0.5% [0.1–1.9]; W: not reported

Reference (Sponsor)	Region	No. of participants by vaccine & control (type)	Selected Adverse Events (AEs)[a]	Frequency of AEs in vaccine recipients, % or number [95% confidence interval shown where available]	Frequency of AEs in control recipients, % or number [95% confidence interval shown where available]
		hepatitis B vaccine)	PIMD	G: Not reported; W: 0	G: Not reported; W: 0
Zhu et al 2014b [6] (GSK)	China	3026 2vHPV 3025 placebo (AlOH)	IS pain, redness, swelling Unsolicited symptoms SAE (vaccine-related) MSC NOCD, NOAD	62.6%, 14.5%, 14.4% 26.2% 1% (n=1) 5.2% 0.3%, 0.1%	42.5%, 7.6%, 5.8% 25.6% 1.8% (n=1) 5.2% 0.4%, 0.1%
Lim et al 2014 [7] (GSK)	Malaysia	135 2vHPV 136 placebo (AlOH)	IS pain, redness, swelling Unsolicited AE MSC SAE (vaccine-related)	76.4%, 22.1%, 17.3% 22.2% 7.4% n=5 (0)	49.4%, 14.1%, 6.9% 26.5% 8.1% n=3 (0)
Szarewski et al 2012 [8] (GSK)	14 countries	9319 2vHPV 9325 control (hepatitis A vaccine)	*HPV-DNA negative(SN/SP)* ISR overall IS pain, redness, swelling Systemic AE Fever *HPV-DNA positive (SN/SP)* ISR IS pain, redness, swelling Systemic AE Fever	*SN (Seronegative) /SP (seropositive)* 82.0% [81.0–82.9] / 78.0% [75.9–80.0] 80.8%,29.2%,26.2%/76.8%,25.4%,23.5% 66.7% [65.5–67.9] / 62.2% [59.8–64.5] 4.9% [4.3–5.4] / 6.4% [5.3–7.7] *SN (Seronegative) /SP (seropositive)* 86.9% [82.5–90.6] / 79.8% [78.1–81.4] 86.6%,24.1%,19.2%/78.7%,25.6%,23.5% 69.3 [63.7–74.6] / 63.7 [61.7–65.7] 5.9 [3.5–9.2] / 6.4 [5.4–7.4]	NR (reported elsewhere)[9, 10]
Naud et al 2014 [11] (GSK)	Brazil	219 2vHPV 213 placebo (AlOH)	SAE MSC NOCD, NOAD	8.9% [5.5–13.5] 26.5% [21.1–33.1] 2.7% [1.0–5.7], 1.8% [0.5–4.5]	5.2% [2.6–9.1] 17.8% [12.9–23.7] 1.4% [0.3–4.1], 0.5% [0.0–2.6]
Roteli-Martins 2012 [12] (GSK)	Brazil	223 2vHPV 213 placebo (AlOH)	SAE (vaccine-related) MSC NOCD, NOAD	4.5% [2.2-8.1] (0) 17.9% [13.1-23.6] 2.2% [0.7-5.2], n=2	3.3% [1.3-6.7] (0) 11.3% [7.4-16.3] 0.9% [0.1-3.4], n=2
Konno et al 2014 [13] (GSK)	Japan	358 2vHPV 348 control (hepatitis A vaccine)	SAE (vaccine-related) MSC NOCD, NOAD Death	5.0% [3.3-7.3] (n=1) 18.9% [15.6–22.5] 1.2% [0.4–2.5], 0.6% [0.1-1.7] 0.2% [0.0–1.1]	6.5% [4.6–9.0] (n=0) 22.1% [18.6–25.9] 1.5% [0.7–3.0], 0.2% [0.0-1.1%] 0.0% [0.0–0.7]

Reference (Sponsor)	Region	No. of participants by vaccine & control (type)	Selected Adverse Events (AEs)[a]	Frequency of AEs in vaccine recipients, % or number [95% confidence interval shown where available]	Frequency of AEs in control recipients, % or number [95% confidence interval shown where available]
Studies with 4vHPV					
Mugo et al 2015 [14] (Merck)	Ghana, Kenya & Senegal	227 4vHPV 19 placebo (Aluminium adjuvant); 9-12yrs	ISR: 9-12y, 13-16y, 16-26y Systemic AE:9-12y, 13-16y, 16-26y (vaccine related) SAE: 15-day follow-up	68.4%, 72.4%, 73.9% 48.1% (36.7%), 58.6% (51.7%), 61.3% (35.3%) 0%	47.4% 57.9% (47.4%) 0%
Li et al 2012 [15] (Merck)	China	302 4vHPV 298 placebo (Aluminium adjuvant)	Any AE ISR, ISR pain, IS swelling Systemic AE(vaccine-related) SAE Allergic reaction	50.7% 21.9%, 20.2%*, 3.0%* 42.7% (28.8%) 0% 2.6%*	44.0% 13.4%, 13.1%*, 0.7%* 39.9% (27.5%) 0.3% 0.7%*
Clark et al 2013 [16] (Merck)	Europe, Americas	307 4vHPV 393 placebo (Aluminium adjuvant)	ISR Systemic AE (vaccine-related) SAE (vaccine-related)	49.0% 35.8% (23.8%) 1.7%	41.0% 29.1% (18.2%) 1.6%
Studies with 9vHPV					
Garland et al 2015 [17] (Merck)	8 countries	618 9vHPV 306 Placebo(saline) All received prior 4vHPV	ISR Systemic AE (vaccine-related) SAE (vaccine-related)	91.1% / 43.9% 59.7% (30.6%) 0.5% (n=1)	43.9% 55.7% (25.9%) 0.3% (n=1)

1B: Studies where all participants received HPV vaccine

Reference (Sponsor)	Region	No. of participants by vaccine type (group)	Selected Adverse Events (AEs)[a]	Frequency of AEs in Group A recipients, % or number [95% confidence interval shown where available]	Frequency of AEs in Group B recipients % or number [95% confidence interval shown where available]
Studies with 9vHPV vaccine used in all subjects (no placebo arms)					
Castellsague et al 2015 [18] (Merck)	17 countries	2520 9vHPV 1101 women (A) 1419 men (B)	ISR Severe pain Systemic AE (vaccine-related) SAE (vaccine-related)	84.1% 1.9% 48.8% (23.4%) 2.4% (0)	67.2% 0.6% 37.1% (16.0%) 1.6% (0)
Van Damme et al 2015 [19] (Merck)	17 countries	2800 9vHPV 1800 girls 9-15y (A1) 600 boys 9-15y (A2) 400 women 16-26y (B)	ISR, Severe IS pain Systemic AE (vaccine-related) Fatigue Headache Fever SAE (vaccine-related) Death	A1: 81.9%, 4.1% A2: 72.8%, 0.5% A1:45.0%(20.8%)A2:41.8%(21.8%) A1: 1.0% A2: 0.5% A1: 9.5% A2: 9.1% A1: 6.7% A2: 8.6% A1: 0.9% (n=0) A2: 1.7% (n=1) A1: 0.1% A2: 0%	85.4%, 2.6% 57.1% (26.0%) 2.6% 9.9% 6.9% 3.2% (n=1) 0.2%
Kosalaraksa et al 2015 [20] (Merck)	6 countries	1054 9vHPV 525 concomitant(A) & 528 non-concomitant Tdap-IPV (B)	ISR PD-1, 2, 3 PD-1 IS pain, erythema, swelling PD-any IS pain erythema, swelling Systemic AE PD-1, 2, 3 SAE (vaccine-related)	93.9%, 60.7%, 68.3% 59.2%, 8.2%, 13.0%[#] 84.8%, 30.5%, 40.6% 48.6%, 19.2%, 21.5% 1.7% (0)	90.1%, 60.2%, 66.1% 60.5%, 5.7%, 8.2%[#] 83.7%, 24.1%, 31.1% 48.6%, 18.0%, 19.8% 1.3% (0)
Schilling et al 2015 [21] (Merck)	5 countries	1241 9vHPV 621 concomitant(A) & 620 non-concomitant MCV4 & Tdap (B)	ISR PD-1, 2, 3 ISR PD-1 pain, erythema, swelling Systemic AE PD-1, 2, 3 SAE (vaccine-related)	80.9%, 46.7%, 52.1% 58.3%, 10.0%, 14.4%[#] 43.1%, 16.1%, 14.8% 0.8% (0)	80.4%, 46.5%, 48.4% 55.0%, 8.9%, 9.4%[#] 42.4%, 15.0%, 16.2% 0.8% (0)
Moreira et al 2016 [22] (Merck)	31 countries, Post-hoc pooled analysis (7 trials)	15,776 all 9vHPV (A) 12,583 female 9vHPV (B1) 3,193 male 9vHPV (B2)	ISR IS pain, swelling, erythema Systemic AE (vaccine-related) Fever Syncope SAE (vaccine-related) NOCD (n=15,875) Death	84.8% 83.2%, 36.1%, 30.8% 51.9% (26.7%) 6.1% (n=955) 0.2% (n=36) 2.3% (n=7) 2.4% <0.1% (n=7)	B1: 88.1%; B2: 71.6% B1: 86.9%, 39.1%, 32.9% B2: 68.3%, 24.4%, 22.4% B1:53.8%(27.8%); B2:44.2%(22.5%) B1:5.8%(n=734); B2:6.9%(n=221) B1: 0.3% (n=34); B2: <0.1% (n=2) B1: 2.5% (n=6); B2: 1.4% (n=1) NR B1: 0.1 (n=7); B2: 0

Reference (Sponsor)	Region	No. of participants by vaccine type (group)	Selected Adverse Events (AEs)[a]	Frequency of AEs in Group A recipients, % or number [95% confidence interval shown where available]	Frequency of AEs in Group B recipients % or number [95% confidence interval shown where available]
Studies comparing 9vHPV and 4vHPV					
Joura et al 2015 [23] (Merck)	18 countries	7071 9vHPV (A) 7078 4vHPV (B)	ISR Severe IS Pain Systemic AE (vaccine-related) SAE (vaccine-related) Death	90.7% 4.3% 55.8% (29.5%) 3.3% (n=2, <1%) 0.1%	84.9% 2.6% 54.9% (27.3%) 2.6% (n=2, <1%) 0.1%
Vesikari et al 2015 [24] (Sanofi Pasteur/ Merck)	6 countries	299 9vHPV (A) 300 4vHPV (B)	ISR IS swelling Systemic AE (vaccine-related), Fever SAE (vaccine-related)	91.6% 47.8%[#] 47.5% (20.7%), 5.0% 0.3% (0)	88.3% 36.0%[#] 52.0% (24.3%), 2.7% 0.7% (0)
Studies comparing 2vHPV and 4vHPV					
Einstein et al 2014a [25] (GSK)	USA	205 2vHPV(A) 216 4vHPV (B)	SAE (vaccine-related) NOCD, NOAD MSC Spontaneous abortion	6.7% (4.8–9.1) (n=1) 6.0% [4.1–8.3], 1.3% [0.5–2.6] 45.4% [41.2–49.6] 13%	6.1% [4.3–8.5] (n=1) 6.0% [4.1–8.3], 2.2% [1.1–3.8] 39.1% [35.0–43.3] 15%
Einstein et al 2014b [26] (GSK)	USA	159 2vHPV (A) 156 4vHPV (B)	SAE (vaccine-related) NOCD, NOAD MSC Spontaneous abortion (no anomaly)	8.0% [5.8–10.5] (n=1) 7.1% [5.1–9.5], 1.3% [0.5–2.6] 46.8% [42.6–51.1] 15.6%	6.7% [4.8–9.1] (n=1) 7.8% [5.7–10.3], 2.4% [1.3–4.0] 40.9% [36.7–45.1] 14.5%
Gilca et al 2015 [27] (Investigator)	Quebec, Canada	366 randomised 1:1 2vHPV (A) or 4vHPV (B). All 2 prior doses 4vHPV	IS Pain (grade 3), swelling, redness Systemic AE SAE	89.1%* (9%*), 26.2%*, 28.4% 58% 0	72.1%* (2%*), 17.5%*, 21.9% 59% 0
Leung et al 2015 [28] (GSK)	4 countries	359 2vHPV 2 dose (A) 358 4vHPV 2 dose (B1) 358 4vHPV 3 dose (B2)	ISR IS pain, redness, swelling IS pain grade 3 Solicited Systemic AE, Fever Unsolicited AE (grade 3) SAE (vaccine-related) MSC PIMD	93% 91.6%, 53.2%, 45.4% 11.7% [8.6–15.5] 74%, 14.8% 25% (5%) 3.6% (0) 14% 0.8% (n=3)	B1: 81%; B2: 86% B1: 77.3%, 37.5%, 27.5%; B2: 82.9%, 44.1%, 33.1% B1:4.8%[2.8–7.5];B2: 5%[3.0–7.9] B1: 75%, 16.5%; B2:74%, 13.2% B1: 27% (2%); B2: 28% (6%) B1: 0.6% (0); B2: 0.3% (0) B1: 16%; B2: 13% B1: 0.8% (n=3); B2: 0

Reference (Sponsor)	Region	No. of participants by vaccine type (group)	Selected Adverse Events (AEs)[a]	Frequency of AEs in Group A recipients, % or number [95% confidence interval shown where available]	Frequency of AEs in Group B recipients % or number [95% confidence interval shown where available]
Nelson et al 2013 [29] (Investigator)	Hong Kong	*Pilot*: 10 males, 5 2vHPV (A), 5 4vHPV (B) *Main study*: 40 females, 19 2vHPV (A), 21 4vHPV (B)	*Pilot (intradermal administration)*: ISR *Main study (various doses/ methods)*: ISPain,Redness,Swelling,Tenderness Headache Tiredness Muscle ache Dizziness	n=5 n=18*, 12, 11, 17* n=4 n=4 n=3 n=2	n=5 n=11*, 11, 8, 10* n=2 n=10 n=5 n=3
Sangar et al 2015 [30] (Investigator)	India	31 2vHPV (A) 31 4vHPV (B)	Any AE post-dose 1, 2, 3, any IS pain Solicited symptom SAE	51.6%*, 17.9%, 38.1%, 36.25%* 80.6% 28 of 80* 0	19.4%*, 7.1%, 13.0%, 13.4%* 29.0% 11 of 82* 0
Studies with 2vHPV or 4vHPV and no control group					
Luna et al 2013 [31] (Merck)	Columbia	1360 4vHPV	New onset medical condition	13%	No control group
Watson-Jones et al 2012 [32] (Investigator)	Tanzania	5532 4vHPV	AE SAE	N=11 N=3	
Giuliano et al 2015 [33] (Merck)	US, Mexico	145 males 4vHPV	Total AEs (vaccine-related) Vaccine-related ISR Vaccine-related systemic Vaccine-related grade 3 AE	N=144 (107 in 63 men (42%)) N=50 N= 57 N=1	
Walter et al 2015 [34] (Investigator)	USA	72 4vHPV (concomitantly with other vaccines)	IS Pain	Higher pain score in HPV vaccine site	
Levi et al 2013 [35] (Investigator)	Italy	271 2vHPV	IS pain, IS swelling Medical attention post-dose 1	83.4%, 20.8% 0.9%	

Footnotes for ESM 1A and 1B: Abbreviations: AE – adverse event; AlOH – aluminum hydroxide; d – day; G – girls; GSK – GlaxoSmithKline; IS – injection site; ISR – injection site reaction; IPV – inactivated polio vaccine; MCV4 – quadrivalent meningococcal conjugate vaccine; MSC: medically significant conditions; NOAD – new onset autoimmune disease; NOCD – new onset chronic disease; PD – post-dose; PIMD – potential immune-mediated disease; SAE – serious adverse event; Tdap – tetanus, diphtheria, acellular pertussis vaccine; VLP – virus like particles; yo – year olds; SN – seronegative; SP – seropositive; NR – not reported; yrs – years; FU – follow-up; PD – post dose; W – women. *Significant at $p<0.05$

[a]The terms used regarding adverse events reflect those presented and defined within each individual study, thus are not necessarily consistent across this summary of data. In general, a solicited AE includes those for which information was specifically sought from the study participants. Unsolicited AEs were those that were spontaneously reported by the subject. Solicited local AEs typically included injection-site pain, erythema, swelling and/or redness. AE given as 'vaccine-related' are those determined by the study investigators. MSCs were conditions prompting emergency room or physician visits that were not related to common diseases or routine visits for physical examination or vaccination, or SAEs not related to common disease (which included upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury). SAEs were typically predefined as any AE that resulted in death, were deemed by the investigator to be life-threatening, resulted in a persistent or significant disability or incapacity, resulted in or prolonged an existing in-patient hospitalisation or was a congenital anomaly, a cancer or an "other important medical event". SAEs were typically followed for the entire duration of patient follow-up, unless otherwise specified in the table.

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Electronic Supplementary Material (ESM) 2

Safety of human papillomavirus vaccines: An updated review

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ESM 2: Summary of selected data from studies on HPV vaccine safety from spontaneous reporting systems, by statistical method, published from 10th May 2012 to 11 August 2016

Reference	Period & vaccine	Surveillance system, Setting	Measured outcome	Reporting rate per 100 000 doses distributed (unless marked) [95% confidence interval where available]			
Angelo et al 2014 [1]	2007-2011 2vHPV	Reports to GSK & trial data, Global	IS pain Pyrexia Dizziness IS swelling Malaise Syncope VIIth nerve paralysis GBS Optic neuritis SLE MS	9.18 6.61 3.33 2.29 2.21 1.94 0.066 0.048 0.028 0.024 0.017			
Stokley et al 2014 [2]	2006-2014 2vHPV/4vHPV	VAERS, USA	Any AE	37.2[a]			
Harris et al 2014 [3]	2007-2011 4vHPV	Provincial notifiable diseases system (12-15 year olds), Canada	Any AE (serious) ISR Rash Anaphylaxis Allergic reaction (skin) Allergic reaction (respiratory) Allergic reaction (gastrointestinal) Allergic reaction (not specified) Severe (including syncope) Occulorespiratory syndrome Seizure	19.2 (serious 7.5%) 3.8 4.2 0.3 4.8 0.9 0.7 0.3 5.1 0.4 0.3			
NCIRS 2014 [4]	2007-2011 4vHPV	TGA, Australia	Any AE Serious AE Syncope Convulsion Anaphylaxis GBS	34.8 [33.1–36.5] [b] 2.5 [2.0–2.9] [b] 4.40 [b] 1.36 [b] 0.31 [b] 0.04 [b]			
TGA 2015 [5]	2013 4vHPV	TGA enhanced surveillance, Australia		*Male 12-13yrs*	*Male 14-15yrs*	*Female 12-13yrs*	*Overall*
			Any AE	101	44	122	88.2
			Syncope	28.2	14.2	49.5	37.0
			ISR	6.2	4.5	12.7	7.7

			Allergic reaction Anaphylaxis Syncopal seizure ED presentation or hospitalisation	6.5 NR 5.9 6.9	6.6 NR 1.4 1.7	8.2 NR 5.6 5.2	7.1 0.12 4.2 4.6
Alguacil-Ramos et al 2016 [6]	2005-2011	Spanish Immunization/ AE register reports (SIV) Spain	Any AE (by report) Any AE (by AE term) Nervous system[c] disorders Headache Syncope Local reactions	87.1 [75.5-100.6][b] 168 [152.1-186.9] 72.6 [62.0-84.9] 18.7 14.1 22.5 [16.1-28.8]			
Rodriguez-Galan et al 2014 [7]	2007-2011 4vHPV	Pharmacovigilance Centre in the Valencian Community,Spain	Any AE Syncope or LOC Syncope or LOC with seizure Pre-syncope	103[b] 17 [11.1- 23][b] 3.2 [0.6-5.7] [b] 3.2 [0.6-5.7] [b]			
Subelj et al 2016 [8]	2009-2013 4vHPV	Statutory reporting to registry within school-based program, Slovenia	Any AE Serious AE(≥1day hospitalisation) Headache Fever >38 IS pain IS swelling Syncope Seizures	149.5 8.4 40.3 35.3 35.3 20.2 13.4 3.4			
Oberle et al 2016 [9]	2008-2010 2vHPV/4vHPV	Paediatrician cards & passive reports, Germany	Anaphylaxis (BCCD 1-3 with hospital admission)	0.223 [0.221–0.31][b]			
Cheng et al 2015 [10]	2007-2013 4vHPV	SAEFVIC, Australia	Anaphylaxis	0.32 [0.29, 0.35] [b]			
Huygen et al 2015 [11]	2007-2013 2vHPV	GSK safety database, Global	CRPS	0.01[d]			
Pellegrino et al 2013a [12]	2006-2012 2vHPV/4vHPV 2007-2013 4vHPV	VAERS TGA Australia	MS (new or relapse) MS (new or relapse)	0.8 0.14			
Pellegrino et al 2015 [13]	? - 2013	VAERS	'ASIA syndrome'	3.6 [3.4–3.7]			

Reference	Period & vaccine	Surveillance system, Setting	Measured outcome	Includes Observed (Obs) vs Expected (Exp) analyses
MHRA 2012 [14]	2008-2012 2vHPV	Yellow card, UK	Any AE CRPS[e] CRPS[e] Anaphylaxis/Anaphylactoid	~100 per 100 000 doses administered Obs/Exp=0.03 [0.01-0.07] Obs/Exp=0.16 [0.06-0.35] ~ 1 per 100 000 doses administered
Donegan et al 2013 [15]	2008-2010 2vHPV	Yellow card, UK	Fatigue syndromes	Obs<Exp for real-time analyses except in specific sensitivity analyses assuming 10% of cases reported.
Reference	**Period & vaccine**	**Surveillance system, Setting**	**Measured outcome**	**Proportional reporting ratio (PRR)**
Ojha et al 2014 [16]	2010-2012 4vHPV	VAERS, USA	GBS	PRR=0.54 [0.26-1.1]
Reference	**Period & vaccine**	**Surveillance system, Setting**	**Measured outcome**	**Proportion**
Jain et al 2013 [17]	2008-2010 2vHPV/4vHPV n=1313	Survey (enhanced surveillance) Uganda/Vietnam	Any AE Medical advice/clinic	10.5% of doses administered 1.2% of doses administered
Moro et al 2015 [18]	2006-2013 4vHPV	VAERS (pregnancy)	Spontaneous abortion Elective terminations Major birth defect No AE	10.2% of pregnancy reports (n=15) 4.1% of pregnancy reports (n=6) n=2 70.1% of pregnancy reports
Goss et al 2015 [19]	2006-2012 4vHPV	Pregnancy registry US, France, Canada	Live births No anomalies Spontaneous abortion Major birth defects Fetal death	86.6% of reports with known outcome 94.6% of reports with known outcome 6.7% [5.5-8.2] 2.4% [1.7-3.3] 0.8% [0.4-1.4]
Reference	**Period & vaccine**	**Surveillance system, Setting**	**Measured outcome**	**Case counts (N) without denominator data**
Weinbaum et al 2015 [20]	2006-2015 2vHPV/4vHPV	VAERS, USA	CRPS	N=22 (0.07% of reports)
Mahajan et al 2015 [21]	2013 4vHPV	TGA, Australia	Any AE (serious) ISR Syncope Pre-syncope Urticaria GBS	N=786 (N=20) N=60 (8% of reports) N=339 (43% of reports) N=85 (11% of reports) N=30 (4% of reports) N=1
Menge et al	2006-2009	VAERS & case	Neuromyelitis optica	N=4

2012 [22]		reports, USA		
Woo et al 2014 [23]	1990-2012	VAERS, USA	Cranial nerve palsies	N=7
Holt et al 2014 [24]	2006-2012	National Registry of Drug-Induced Ocular Side effects (USA); WHO; FDA (USA)	Uveitis	N=24
Pellegrino et al 2013b [25]	2005-2012 2vHPV/4vHPV	VAERS/EVPM, Europe	ADEM	VAERS n=24 EVPM n=49
Staltari et al 2013 [26]	2012 2vHPV	Italian Drug Agency reports, Italy	Urticaria	N=1
Dorij et al 2015 [27]	2010 4vHPV	Program implementation, Bhutan	Any AE	N=218 reports (dose 1) N=14 (dose 2) N=14 (dose 3)
Lee et al 2012 [28]	2008-2010	Mandatory registry, Taiwan	Any AE	N=2
Reference	**Period & vaccine**	**Surveillance system, Setting**	**Measured outcome**	**Inappropriate analyses not matched to the data characteristics**
Geier et al 2015 [29]	2006-2012 4vHPV	VAERS, USA	Multiple	Case control design used within VAERS, which not provide sufficiently unbiased data to design or test an association using this methodology[30]

Abbreviations: ADEM – acute disseminated encephalomyelitis; AE – adverse event; ASIA – autoimmune/inflammatory syndrome induced by adjuvants; BCCD – Brighton Collaboration case definition; CRPS – complex regional pain syndrome; Exp – expected; EVPM- EudraVigilance post-authorisation module; FDA-US Food and Drug Administration; GBS – Guillain Barre Syndrome; IS – injection site; LOC – loss of consciousness; MS – multiple sclerosis; NR- not reported; Obs – observed; PRR – proportional reporting ratio; SAEFVIC- Surveillance of Adverse Events Following Vaccination In the Community; SLE – systemic lupus erythematosus; TGA-Therapeutic Goods Administration; VAERS – Vaccine Adverse Events Reporting System.

[a]Calculated based on data in manuscript

[b]Rate per doses administered

[c]Nervous systems disorders includes headache & syncope

[d]Rate based on 5 cases confirmed to meet criteria by independent panel out of 17 reported (including all cases, rate = 0.08 UK & 0.14 Japan)

[e]Two different estimates of background incidence

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Electronic Supplementary Material (ESM) 3

Safety of human papillomavirus vaccines: An updated review

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ESM 3: Summary of selected safety data from observational studies using population-based data sources from 10th May 2012 to 11 August 2016

Reference	Period/ vaccine	Data source, study type	Study cohort			Measured outcome	Main finding [95% confidence interval where reported]
USA							
Liu et al 2016 [1]	2006-2014 2vHPV/ 4vHPV	Data linkage Descriptive	Females ≥ 9 yrs; n =196, 270; 528 913 doses			Any AE	37.3 per 100 000 doses administered
Naleway et al 2016 [2]	2008-2011 4vHPV	VSD SCCS	Females 9-26 yrs; n=650			VTE	1-7day window: IRR = 1.47 [0.47-4.64] 1-14d window: IRR = 0.97 [0.36-2.65] 1-28d window: IRR 0.72 [0.31-1.63] 1-60d window: IRR = 0.92 [0.54-1.57]
Yih et al 2016 [3]	2006-2013 4vHPV	Insurance claims data from Mini-Sentinel Data Partners/ immunisation registries, SCRI	Females 9-26 yrs; n= 53			VTE (first episode)	Risk window 1-28d: RR=0.7 [0.33-1.43] Risk window 1-7d: RR = 0.43 [0.07-1.50]
Langer-Gould et al 2014 [4]	2008-2011 4vHPV	MCO Nested case control	Cases Females 9-26 yrs; n=92 Controls 9-26 yrs, n=459			MS or acquired CNS demyelinating syndromes up to 3yrs post vaccination	OR 1.05 [0.62-1.78]
Baxter et al 2016 [5]	2007-2013 4vHPV	MCO Case-centred	Females with SSHL immunised up to 9 months prior Controls matched to MCO members receiving same vaccine in 9 mnths prior to onset date in case			SSHL	OR 4.155 [0.17-29.13]
Pellegrino et al 2014 [6]	2006	National /Kids Inpatient Sample Ecological	Females & males <17 yrs post-2006 vs pre-2006			SLE	No increase in hospitalisations (data not reported)
Macarthy et al 2016 [7]	2005-2011 4vHPV	VSD Case-centred	Females & males 9-26yrs (1 355 535 doses administered)			Death 0-30 days after vaccine	Non-external causes: RR=1.28[0.44-3.68] All causes: RR=1.12 [0.62–2.03]
				Total	*0-30 days*		
			Non-external causes	N=34	N=4		
			All causes	N=117	N=13		

Reference	Period/ vaccine	Data source, study type	Study cohort	Measured outcome	Main finding [95% confidence interval where reported]
UK					
Donegan et al2013 [8]	2006-7 2009-11 2vHPV	CPRD Ecological	Females & males, 2009-11 vs 2006-7	Fatigue syndromes	Females 12-20yrs: IRR = 0.094 [0.78–1.14] Adults 21+ yrs: IRR: 0.96 [0.93–1.01] Males: IRR 0.66 [0.50–0.87]
	2008-2011 2vHPV	CPRD SCCS	Females 12-20 yrs; n=187	Fatigue syndromes	IRR: 1.07 [0.57–2.00] (p = 0.84)
Baril et al 2015 [9]	2008-2011 2vHPV	CRPD	Females 15-25 yrs, first day gestation -30 to +45 d after any dose (exposed) vs Females 15-25 yrs, first day gestation 120 d to 18 mnths after last dose(unexposed)	Spontaneous abortion	HR = 1.30 [0.79–2.12]
Cameron et al 2016[10]	2004-2012 2v/4vHPV Scotland	Hospital admissions Ecological	Males & Females 12-18yrs; 2004-2012	59 conditions[a]	No significant change in incidence in 54 conditions.
	2011-12 2v/4vHPV Scotland	Date linkage Cohort/trend analysis	Females 12-13 yrs; n=12	Bell's palsy	4 of 12 cases aged 12-13yrs were vaccinated
Denmark, Sweden					
Arnheim-Dahlstrom et al 2013[11]	2006-2010 4vHPV	Data linkage Cohort	Vaccinated (n=296 826) vs unvaccinated females 10-17 yrs; n=997 585	23 outcomes (AID, neurological & VTE), *selected shown*: Hashimoto's thyroiditis Hypothyroidism Crohn's disease Ulcerative colitis Juvenile arthritis SLE ITP Bell's Palsy ON VTE Bechet's syndrome Raynaud's disease T1DM	*RR not significant for 20 of 23 conditions* RR=1.12 [0.82-1.52] RR=0.90 [0.71-1.14] RR=0.85 [0.62-1.17] RR=0.71 [0.49-1.03] RR=0.99 [0.78-1.26] RR=1.35 [0.69-2.67] RR=1.18 [0.65-2.17] RR=1.02 [0.72-1.43] RR=0.67 [0.27-1.64] RR=0.86 (0.55 - 1.36) *RR significant for 3 of 23 conditions** RR= 3.37 [1.05 - 10.80] RR = 1.67 [1.14 - 2.44] RR= 1.29 [1.03 - 1.62]

Reference	Period/ vaccine	Data source, study type	Study cohort	Measured outcome	Main finding [95% confidence interval where reported]
Scheller et al 2015 [12]	2006-2013 4vHPV	Data linkage Cohort	Vaccinated (n=789 082) vs unvaccinated females 10-44 yrs MS n=3 978 271; Other n=3 980 716	MS ON, neuromyelitis optica, TM, ADEM	IRR = 0.90 [95%CI, 0.70-1.15] IRR = 1.00 [95%CI, 0.80-1.26]
	2006-2013 4vHPV	Data linkage SCCS	Vaccinated females MS=4322 Other n=3300	MS ON, neuromyelitis optica, TM, ADEM	IRR = 1.05 [95%CI,0.79-1.38] IRR = 1.14 [95%CI, 0.88-1.47]
Scheller et al 2014 [13]	2006-2013 4vHPV	Data linkage SCCS	Females 10-44 yrs n=500 345	VTE	IRR (adjusted for oral contraceptive use) = 0.80 [0.55-1.16]
Netherlands					
Schurink-Van't Klooster et al [14]	2008–2010 2vHPV	ICPI GP database Ecological	Males & Females 12-16 yrs, 2009-10 vs 2008; n=321 certain[b], n=127 uncertain[b] migraine	Migraine	IRR (certain migraine) = 1.14 [0.82–1.62]
	2008–2010 2vHPV	ICPI GP database Cohort	Vaccinated (n=11) & unvaccinated (n=11) females 12-16 yrs with incident migraine	Migraine	IRR in monthly periods following dose 1 vs unvaccinated/pre-vaccinated ranged from 0.0-3.0 (none significant)
	2008–2010 2vHPV	ICPI GP database, SCCS	Vaccinated females born 1993-1997, n=11	Migraine	RR 6.3 [0.80–49.1] adjusted for school holidays
France					
Grimaldi-Bensouda et al 2014[15]	2007-2011 4vHPV	PGRx programme Case control	Cases: Females 14–26 yrs, n=211 Controls: matched, n=875	AID ITP MS CTD T1DM	Adj OR = 0.9 [0.5–1.5] OR = 1.0 (0.4–2.6) OR = 0.3 (0.1–0.9) OR = 0.8 (0.3–2.4) OR = 1.2 (0.4–3.6)
ANSM 2015 [16]	2008-2012 2vHPV/ 4vHPV	French health insurance scheme, Cohort	Vaccinated (n= 842,120) vs unvaccinated (n=1410596) females 13 – 16 yrs	AID IBD GBS	HR = 1.07 [0.99-1.16] HR = 1.19 [1.02-1.39] HR = 4.00 [1.84-8.69]

Abbreviations: ADEM - acute disseminated encephalomyelitis; AID - autoimmune disease; CPRD - Clinical Practice Research Datalink; CNS - Central nervous system; CTD - connective tissue disease; d – days; ICPI - GBS - Guillain Barre Syndrome; HR - hazard ratio; IBS - inflammatory bowel disease; ITP - immune thrombocytopenic purpura; Integrated Primary Care Information Database; IRR - incidence rate ratio; MCO – Managed Care Organizations; mnths – months; MS - multiple sclerosis; ON - optic neuritis; OR - Odds ratio; PGRx - Pharmacoepidemiologic General Research Extension; RR - relative risk; SCCS - Self-controlled case series; SCRI - Self-controlled risk interval; SLE - systemic lupus erythematosus; SSHL - Sudden sensorineural hearing loss; TM - transverse myelitis; T1DM - type 1 diabetes mellitus; VSD - Vaccine Safety Datalink; VTE - Venous thromboembolism; yrs – years.

* Only met 1 of 3 pre-defined 'signal strengthening' criteria; not considered to be temporally associated with vaccination

[a]Based on Medicines and Healthcare Products Regulatory Agency listing of conditions possibly linked to HPV vaccination plus 'other disorders of autonomic nervous system'[10]

[b]Certain migraine was defined as 'patients with definite migraine and menstruation-related migraine', uncertain migraine was defined as 'unclear/possible migraine and typical aura without headache'[14]

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Electronic Supplementary Material (ESM) 4

Safety of human papillomavirus vaccines: An updated review

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ESM 4: Summary of case series and case reports following HPV vaccine published between 10 May 2012 – 11 August 2016

Diagnosis	Reference	Region	Brief case overview	Comments
POTS/CFS	Brinth et al 2015a; Brinth et al 2015b; Brinth et al 2015c [1-3]	Denmark	Three studies variously reporting on subsets of 35, 53 and 39 females aged 12-39 yrs among a group of patients referred for investigation of orthostatic intolerance as a suspected adverse effect of HPV vaccination; a further subset met the criteria for POTS and/or CFS/ME.	The three Danish publications report on various number of females; it is unclear how the three cohorts relate to each other although there is overlap. Cases are from a single centre with significant case ascertainment bias (referral for symptoms attributed to HPV vaccine; cases were excluded if symptoms prior to vaccination or onset more than 2 months after vaccination). There was potential for solicited interview responses and recall bias (0-5 years between onset and examination). There was inconsistent timing with vaccination and indications that case series is compatible with background epidemiology of POTS.[4]
	Tomljenovic et al 2014 [5]	US	14yo girl reported to have CFS/POTS/ASIA	
	Blitshteyn 2014 [6]	US	6 cases of POTS reported	
Primary ovarian failure	Colofrancesco et al 2013 [7]	Israel/other	Siblings aged 13 and 14; another girl aged 21 yrs.	Investigation for other potential causes of POF was not stated; the authors noted most cases of POF have no aetiology; there was variable temporal relationship with vaccination and inadequate case definitions.[8]
	Little et al 2012 [9]	Australia	16-year-old girl.	
Proposed 'ASIA syndrome'	Anaya et al 2015 [10]	Columbia	3 females aged 16, 20 and 19 yrs with different diagnoses (arthritis/SLE)	There was significant case ascertainment bias (e.g. referral to specific centres); the syndrome not accepted and lacks clear definition or consistent application of criteria; the collection of symptoms overlaps with many other conditions; there was a variable temporal relationship to vaccination and no evidence of causation.[11, 12]
	Palmieri et al 2016 [13]	Italy	18 females aged 12-24 yrs referred for neuropathy/autonomic dysfunction with various symptoms (e.g. asthenia, headache, cognitive dysfunctions, myalgia, tachycardia, rash).	
	Poddighe et al 2014 [14]	Italy	A 14-year-old girl with symptom onset 60 minutes after vaccination; diagnosed with pseudo-neurological syndrome and later a chronic fatigue-like syndrome.	
SLE or SLE-like disease	Gatto et al 2013 [15]	Italy/Israel	Six females aged 13-32 yrs. All patients had personal or family history of autoimmune-rheumatic conditions.	Cannot assess causality given the background rate of this condition in this cohort.[16]
CRPS and Fibromyalgia	Kinoshita et al 2014 [17]	Japan	40 girls aged 11-17 yrs with peripheral nerve dysfunction; 18 diagnosed with CRPS (according to various criteria); orthostatic hypotension and POTS diagnosed in some cases.	Representative case reports detailed in the Japanese study do not fulfil criteria for CRPS; other heterogeneous conditions were presented. There was limited clinical detail provided and variable/unclear temporal relationship to vaccination. Referrals were to a single centre with ascertainment bias. Also, significant case ascertainment bias for fibromyalgia cases with variable temporal relationship to vaccination (24 hours to 5.4 weeks).[4, 18]
	Martinez-Lavin 2014 [19]	Mexico	An 11-year-old girl diagnosed with fibromyalgia and CRPS and a 14-year-old girl with fibromyalgia after HPV vaccination.	
	Martinez-Lavin et al 2015 [20]	Worldwide	45 individuals aged 9-19 yrs identified via blogs and email correspondence with authors; 53% fulfilled fibromyalgia diagnostic criteria.	

Various other conditions	Cerami et al 2013 [21]	Italy	Mostly single case reports of various conditions (acquired neuromyotonia, optic neuritis, tubulointerstitial nephritis and uveitis syndrome (2 cases), interstitial lung disease, juvenile idiopathic arthritis, acute chorea, acute cerebellar ataxia) in various ages and at variable time post HPV vaccination.	Cannot infer causality based on case reports.[22]
	Chang et al 2016 [23]	South Korea		
	Sawai et al 2016 [24]	Japan		
	Yamamoto et al 2015 [25]	Japan		
	Decio et al 2014 [26]	Italy		
	Yonee et al 2013 [27]	Japan		
	Akioka 2014 [28]	Japan		
Death	Tomljenovic et al 2012 [29]	Canada	Post-mortem tissue examined in 2 cases	Criticised by CDC and WHO for substantial methodological concerns and flawed causality assessment.[30, 31]
	Lee 2012 [32]	USA	Post-mortem tissue examined in 1 case	

Abbreviations: ASIA - Autoimmune/inflammatory syndrome induced by adjuvants; CDC - US Centres for Disease Control; CFS - Chronic Fatigue Syndrome; CRPS - Complex Regional Pain Syndrome; ME - Myalgic encephalitis; POTS - Postural orthostatic tachycardia syndrome; SLE - Systemic Lupus Erythematosus; WHO - World Health Organisation; yrs – years.

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Electronic Supplementary Material (ESM) 5

Safety of human papillomavirus vaccines: An updated review

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ESM 5: Summary of select data on adverse events from clinical trial of HPV vaccines in persons with specific immunocompromising or auto-immune medical conditions published from 10 May 2012 – 11 August 2016

Reference	Region, period & vaccine	Follow up period	Study design	Population & sample size	Summary of adverse events
HIV infected populations					
Denny et al 2013 [1]	South Africa 2008-2011 2vHPV	Solicited AEs: 7d PD; unsolicited AEs: 30d PD; SAEs:12mnths PD1	Phase I/II partially blind, partially-randomised placebo-controlled trial (placebo: AlOH)	Women 18-25 yrs (WHO clinical stage 1) HIV+ HPV vaccine group n=61 HIV+ placebo group n=59 HIV- group n=30	Local and systemic AEs similar in HIV+ and HIV- women who received 2vHPV, but higher than in HIV+ women who received the placebo. Headache 19.7% and 23.7% of HIV+ and HIV- vaccine recipients respectively vs. 13.3% placebo.
Giacomet et al 2014 [2]	Italy 4vHPV	7 days	Prospective, non-randomised, controlled, open-label clinical study	Persons aged 13-26 yrs HIV+ n=46 HIV- n=46	AEs more frequent in HIV+ subjects vs. HIV-negative (particularly IS pain and erythema, headache, malaise and fever).
Kahn et al 2013 [3]	US and Puerto Rico 2008-2011 4vHPV	All AEs: 7 d; serious (grade 3+) AEs: 4 wks post-last dose	Phase II multicentre open-label clinical study	HIV+ women aged 16-23 yrs ART group n=30 Non-ART group n=69	26.3% reported at least 1 local AE (pain was the most common). Fever 12.1%. 1 vaccine-related serious AE – grade 3 fatigue.
Kojic et al 2014 [4]	Global 2008-2011 4vHPV	28 wks PD 1	Phase II, open-labelled, single-arm clinical trial	HIV+ women 13-45 yrs Grouped by CD4 count: Group A: >350 cells/μL (n=127) Group B: 201–350 cells/μL (n=95) Group C: ≤200 cells/μL (n=93)	17% experienced grade 3 or higher adverse events. Fever (grade 1 or higher) in 16 participants: Group A n=5; Group B n=4; Group C n=7. Laboratory abnormalities more common in more immunocompromised participants.
Toft et al 2014 [5]	Denmark 2011 2vHPV/ 4vHPV	Solicited AEs: 4 d; unsolicited AEs: 15d; SAEs: 12 mnths PD 1	Double-blind, randomised controlled head-to head trial of 2vHPV vs. 4vHPV	HIV+ men and women ≥ 18 yrs N=91 (61 male, 30 female) 2vHPV n=45 4vHPV n=46	ISR more common in the 2vHPV group than the 4vHPV group (91.1% vs. 69.6%, p=0.02). The difference in frequency of systemic AEs between the two groups was not statistically significant.

Reference	Region, period & vaccine	Follow up period	Study design	Population & sample size	Summary of adverse events
Pre-existing autoimmune disease					
Esposito et al 2014 [6]	Italy 2vHPV	Local and systemic AEs: 14 d PD; SAEs:12 mnths PD 1	Open-label controlled trial in females with and without JIA	Cases: Females 12-25yrs stable JIA n=21 Controls: healthy females with similar age distribution n=21	The frequency of local and systemic reactions was not statistically different between patients and controls.
Jacobson et al 2013 [7]	US 2008-2009 4vHPV	7 months PD 1	Cohort open-label study	Female IBD patients, immunosuppressive therapy 9 to 26 yrs n=37	Almost half reported soreness at injection site after each dose. Other local AEs were less common (<20%) and systemic AEs were uncommon (<10%, n≤3).
Mok et al 2013 [8]	Hong Kong 2009-2011 4vHPV	12 months PD 1	Prospective - controlled study in females with SLE (vaccinated and unvaccinated) and healthy controls	Cases: Females 18-35 yrs with SLE receiving stable dose of immunosuppressive agents within 3 mnths of entry, n=50 Healthy controls: aged matched females without chronic medical illness, n=50 SLE controls: age- and disease-duration matched controls (no intervention) n=50	Erythema and pain at the injection site 6% vs. 4% in cases and controls. Systemic reactions were rare. There were no serious AEs and no withdrawals. The rate of disease flare in the SLE cases was 0.22/patient/yr, compared with 0.20/patient/year in the unvaccinated SLE controls (p=0.81).
Soybilgic et al 2013 [9]	USA 4vHPV	7 months PD 1	Open-label prospective pre-post intervention study	Females SLE patients aged 9-26 yrs n=27	9/27 (33.3%) had a mild-moderate flare during the study period, typically with symptoms similar to those prior to vaccination. Vaccination did not result in an increase in mean SLE Disease Activity Index scores.

Abbreviations: AE – adverse event; AlOH – aluminum hydroxide; ART – anti-retroviral therapy; d – days; HIV – human immunodeficiency virus; IBD – inflammatory bowel disease; IS – injection site; ISR – injection-site reaction; JIA – juvenile idiopathic arthritis; mnths – months; PD – post dose; SAE – serious adverse event; SLE – systemic lupus erythematosus; WHO – World Health Organization; wks – weeks; yrs – years.

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Appendix B: Author's reply in response to comment on publication 1 – Macartney K, Phillips A, Patel C, Pillsbury A, Brotherton J. Authors' reply: Safety of human papillomavirus vaccines. Drug Safety. 2018; 41 (5): 541–543.

This letter was written in response to two commentary letters that were published following publication of the review article in Chapter 1. This letter demonstrates the ongoing need to reinforce the importance of undertaking epidemiological studies in large populations to test hypotheses generated by case series and passive reporting systems. While some authors within the scientific community continue to reinforce the validity of lower levels of evidence, there is a risk that programmatic decisions will be made on the basis of inadequate evidence, with an associated risk of reductions in vaccine confidence and harm from vaccine-preventable diseases.

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LETTER TO THE EDITOR

Authors' reply: Safety of Human Papillomavirus Vaccines

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We strongly disagree with the assertions made by Chandler et al. [1] and Martinez-Lavin [2] regarding our use of evidence [3] and with the validity of the alternative information presented by the authors.

Chandler et al. [1] contend that a hierarchy of evidence is outdated and that we use epidemiological evidence to "trump" the findings of case reports and case series. The evidence hierarchy used to structure our review is a globally accepted paradigm in modern clinical medicine and healthcare [4]. Modifications to this hierarchy routinely place case series and case reports as the lowest level of evidence [5], reflecting their high risk of bias. We note that both Chandler et al. [1] and Martinez-Lavin [2] cite multiple very small and largely observational studies with no controls, several of which have been criticized [6, 7]. This is despite Martinez-Lavin [2] questioning the validity of "small" clinical trials.

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The vast majority of evidence-based reviews on any topic do not include case series or case reports at all because of their inherent biases. In our review, we included such reports and acknowledged that they can have a role in raising potential safety issues; we did not characterize them as "anecdotes" or "coincidence," as suggested by Chandler et al. [1]. Case reports allow patients and physicians to raise concerns and may contribute to hypothesis generation [3]. This has been recognized for decades and has underpinned the development of specialist adverse events clinics and networks in some countries which not only provide assessment and support for those who have experienced an adverse event but also facilitate systematic gathering of data to investigate concerns [8–11]. In the case of human papillomavirus (HPV) vaccines, this has occurred. As described in our two reviews [3, 12], in addition to an extensive body of clinical trial evidence demonstrating the safety of HPV vaccines, dozens of robust well-designed studies to investigate specific concerns have been conducted.

Chandler et al. [1] discuss variability in immunological responses to vaccination and appear to contend that case reports present data on individuals of "unusual susceptibility" to adverse events too rare to detect in epidemiological studies [1]. Yet, the opposite is true. Well-designed epidemiologic studies have, at their center, carefully validated case definitions, such as those published for potential adverse events by multi-disciplinary experts from the Brighton Collaboration. Martinez-Lavin [2] cites publications, including Chandler et al. [13], that describe symptoms such as headache, fatigue, dizziness, and musculoskeletal pain at highly variable times post-

vaccination. These are common concerns; their occurrence does not imply they are caused by vaccination. In contrast, well-designed population-based studies have been used to investigate signals for, and determine the post-vaccination risk of, clearly defined and validated adverse events, including Guillain-Barré syndrome following influenza vaccination [14], narcolepsy following adjuvanted pandemic influenza vaccine [15], thrombocytopenia following the measles, mumps, and rubella (MMR) vaccine [16], and anaphylaxis following numerous individual vaccines [17].

With regard to the new era of "predictive vaccinology" discussed at length by Chandler et al. [1], we agree future developments in this field will undoubtedly help us to better understand observed individual variation in immunogenicity, efficacy, and reactogenicity to vaccines. However, the inference, if intended, that further developments in this field give validity to unsupported assumptions of causal relationships between vaccination and adverse events based on temporal associations alone is dangerous. There is potential, over the coming decades, for immunogenomics and systems biology approaches to study vaccine effects and perhaps, in years to come, provide the ability to identify predictive biomarkers for different outcomes [18, 19]. Yet even then, practical applications would need careful consideration [18]. Vaccines routinely recommended at a population level are currently held to the highest possible standards with respect to safety and overall benefit:risk profile, underpinned by extensive high-quality evidence as detailed in our and others' reviews of HPV vaccines [3].

Martinez-Lavin [2] also presents an analysis of clinical trial data from a previously published letter [20] that has been criticized by others [21]. The additional ad hoc analyses presented are flawed and do not account for a lack of temporal association [22], with no clear methodology provided for the calculation of number needed to vaccinate. Overwhelmingly, our and other quality reviews have demonstrated the safety of HPV vaccination and a positive benefit:risk profile. Regarding some of the other conditions cited in his letter, as stated in our paper [3], the European Medicines Agency (EMA) [23] and the World Health Organization's Global Advisory Committee on Vaccine Safety [24] also concluded there was no evidence of an association between HPV vaccine and postural orthostatic tachycardia syndrome or complex regional pain syndrome; the EMA reviewed the work by Martinez-Lavin [21] for their report.

HPV vaccines are highly effective in reducing HPV infections, genital warts, and pre-cancerous lesions of the cervix [25, 26]; reductions in cervical cancers are expected to occur imminently in vaccinated populations. As evidenced in our review [3], and that of other independent groups [23, 24, 27, 28], robust scientific evidence from around the globe supports the safety of these vaccines.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the preparation of this study.

Conflicts of interest Kristine Macartney, Anastasia Phillips, Alexis Pillsbury and Cyra Patel have no conflicts of interest that are directly relevant to the content of this study. Julia Brotherton is employed as the Director of the National HPV Vaccination Program Register, which is owned and funded by the Australian Government Department of Health. She has been an investigator on investigator-initiated HPV epidemiology studies that have received unrestricted partial funding for laboratory components from Seqirus (cervical cancer typing study) and Merck (recurrent respiratory papillomatosis study) but has never received any personal financial benefits.

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Appendix C: Interview guide for Chapter 5: From program suspension to the pandemic: a qualitative examination of Australia's vaccine pharmacovigilance system over 10 years

Participant from a Government organisation or national advisory group			
Q	**Topic**	**Guiding questions**	**Planned follow up questions**
1	Introduction	Tell me about your role in vaccine safety in Australia	
2	Current systems and integration	What are your views on the various vaccine safety systems available in Australia currently?	How do you think vaccine safety monitoring systems in Australia have changed over the past ten years? Do you think that vaccine safety arrangements are aligning with international best practice? What are your views on the TGA's passive vaccine safety surveillance system? What are your views on the AusVaxSafety active surveillance system? What are your views on AEFI-CAN? How well integrated are these systems? Are there any jurisdictional vaccine safety surveillance systems that are performing particularly well? What lessons can we learn from these? What are the limitations of the current systems? Are there gaps? Are systems sufficient to monitor the rapid roll out of a pandemic vaccine? Are there emerging opportunities for data linkage, as outlined in the National Immunisation Strategy?
3	Reporting and analysis	What are your views on the analysis and reporting of AEFI data in Australia?	How well do you think analysis and reporting is aligned with international best practice? Would signal detection be possible based on current analysis and reporting?

4	Investigation and causality assessment	What are your thoughts on Australia's process for the investigation of individual AEFIs and clusters, and for causality assessment?	How well do you think investigation and causality assessment is aligned with international best practice? Do you have any suggestions for how the processes could be improved?
5	Roles and responsibilities	I'm interested in your thoughts on how various organisations are undertaking their roles and responsibilities in vaccine safety.	Are roles and responsibilities sufficiently clear and embedded? Do you think that timeliness and completeness of AEFI notification, a key action in the National Immunisation Strategy, is improving? Do you think providers are sufficiently aware of AEFI notification systems?
6	Communication	How does communication around vaccine safety in Australia impact on community confidence in the immunisation program?	Has there been a change over the past 10 years? Are there examples of where Australia has done well? Are there examples where communication could have been improved? How well is Australia placed to communicate vaccine safety messages during the roll-out of a pandemic vaccine?
7	Governance	What are your thoughts about the governance of vaccine safety in Australia?	Which organisation do you feel is the focal point for vaccine safety surveillance in Australia? Is this appropriate? What are your views on the effectiveness of vaccine safety plans?
8	Future	The current National Immunisation Strategy prioritises continuing to enhance vaccine safety monitoring systems. What can you point to that suggests this is occurring?	What are the key gaps? How can the Australian Immunisation Register be improved to enhance vaccine safety monitoring systems? What is the role for data linkage? Is the system sufficiently robust to monitor the safety of a rapidly rolled-out pandemic vaccine?

Participant from Primary Care			
Q	**Topic**	**Guiding questions**	**Planned follow up questions**
1	Introduction	Tell me about your role in immunisation and vaccine safety in Australia	
2	Current systems and integration	What are your views on the various vaccine safety systems available in Australia currently?	How do you think vaccine safety monitoring systems in Australia have changed over the past ten years? Are current vaccine safety arrangements appropriate and 'fit for purpose' from a primary care perspective? What are your views on the TGA's passive vaccine safety surveillance system? What are your views on the AusVaxSafety active surveillance system? What are your views on specialist (tertiary) vaccine safety clinics for individual patient review? How well integrated are these systems? Are there any state or territory-based vaccine safety surveillance systems that are performing particularly well? What lessons can we learn from these? What are the limitations of the current systems? Are there gaps? Are systems sufficient to monitor the rapid roll out of a pandemic vaccine?
3	Reporting and analysis	Based on what you have seen in your role, what are your views on the analysis and reporting of AEFI data in Australia?	How useful do you think current vaccine safety reporting is for primary care?

4	Investigation and causality assessment	What are your thoughts on Australia's processes for investigating reported cases of AEFI?	How appropriate/useful do you think current processes for reviewing and assessing AEFI from a primary care perspective? Do you have any suggestions for how the processes could be improved?
5	Roles and responsibilities	I'm interested in your thoughts on how various organisations are undertaking their roles and responsibilities in vaccine safety.	What do you see as the role for primary care? Is this role clear to providers? Do you think that timeliness and completeness of AEFI notification by providers, a key action in the National Immunisation Strategy, is improving? Do you think providers are sufficiently aware of AEFI notification systems?
6	Communication	From your position in primary care, does communication around vaccine safety in Australia impact on community confidence in the immunisation program?	Has there been a change over the past 10 years? Are there examples of where Australia has done well? Are there examples where communication could have been improved? How well is Australia placed to communicate vaccine safety messages during the roll-out of a pandemic vaccine?
7	Governance	What are your thoughts about the oversight of vaccine safety in Australia?	Which organisation do you feel is the focal point for vaccine safety surveillance in Australia? Is this appropriate?
8	Future	The current National Immunisation Strategy prioritises continuing to enhance vaccine safety monitoring systems. What can you point to that suggests this is occurring?	What are the key gaps? Is the system sufficiently robust to monitor the safety of a rapidly rolled-out pandemic vaccine?

Consumer participant			
Q	**Topic**	**Guiding questions**	**Planned and potential follow up questions**
1	Introduction	Tell me about your knowledge of and interest in immunisation and vaccine safety in Australia	
2	Current systems and integration	What are your views on the various vaccine safety systems available in Australia currently?	How do you think vaccine safety monitoring systems in Australia have changed over the past ten years? How are vaccine safety arrangements viewed by Australian consumers, including in comparison to other countries? Are you confident in the adequacy of vaccine safety systems in Australia to monitor the rapid roll out of a pandemic vaccine? **Potential more specific questions depending on pre-existing knowledge**: What are your views on the TGA's passive vaccine safety surveillance system? What are your views on the AusVaxSafety active surveillance system? What are your views on specialist (tertiary) vaccine safety clinics for individual patient review? How well integrated are these systems? Are there any state or territory-based vaccine safety surveillance systems that are performing particularly well? What lessons can we learn from these? What are the limitations of the current systems? Are there gaps?

3	Reporting, analysis and communication	Based on what you know, what are your views on how vaccine safety information is analysed and publicly reported in Australia?	How well do you think vaccine safety information is communicated to consumers? How does communication around vaccine safety in Australia impact on community confidence in the immunisation program? Are there examples of where Australia has done well? Are there examples where communication could have been improved? How is Australia placed to communicate vaccine safety messages during the roll-out of a pandemic vaccine?
4	Roles and responsibilities	I'm interested in your thoughts on the roles and responsibilities of various organisations and groups in vaccine safety.	Are the roles of immunisation providers clear and well defined? Are the roles of government organisations clear and well defined? What do you think is the role of consumers? Do you think that consumers are sufficiently aware of the importance of reporting AEFI? Do you think that immunisation providers are sufficiently aware of the importance of reporting AEFI?
5	Governance	What are your thoughts about the oversight of vaccine safety in Australia?	Which organisation do you think has oversight of vaccine safety monitoring in Australia? Is this appropriate?
6	Future	The current National Immunisation Strategy prioritises continuing to enhance vaccine safety monitoring systems. What can you point to that suggests this is occurring?	Do you think there are any gaps or issues with vaccine safety monitoring in Australia?

Appendix D: Additional letter: McIntyre P, Phillips A, Brotherton J, Tatley M. Improving detection of rare or poorly defined adverse events – analysis poorly grounded in evidence [Letter re: Chandler R. Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events]. BMJ Rapid Responses. 9 July 2019: 365: I2268. https://doi.org/10.1136/bmj.l2268

This letter was written in response to an analysis piece that selectively cited the literature, did not address background incidence and supported the inappropriate use of passive surveillance data. It was written to counter emerging themes from some authors that, when published, increase the risk of harm from vaccine-preventable disease through reducing vaccine confidence.

Intended for healthcare professionals

Rapid response to:

Analysis

Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events

BMJ 2019; 365 doi: https://doi.org/10.1136/bmj.l2268 (Published 31 May 2019) Cite this as: BMJ 2019;365:l2268

- Article
- Related content
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- Rapid responses
- Response

Rapid Response:

Re: Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events

Improving detection of rare or poorly defined adverse events – Analysis poorly grounded in evidence

The Analysis published on May 31st in the BMJ, opens by linking gaps in “vaccine safety infrastructure” to lapses in public confidence in vaccines, vaccine hesitancy and the re-emergence of measles. However, it quickly becomes apparent this is a smokescreen for the notion of “suspected harm” from HPV vaccine, specifically that investigating links to postural orthostatic tachycardia syndrome (POTS) has been impeded in various ways. (1)

The numerous problems in this piece – among them selective citation of the literature and inappropriate application of pharmacovigilance methods to the complexities of POTS - are not immediately apparent, because on superficial reading the arguments appear well-structured and to raise legitimate questions. Dr Chandler states that POTS is a complex disorder – so far, so good - but the references cited lack relevant background for adolescents. (2-4) First, POTS overlaps chronic fatigue syndrome (CFS) which is common – around 0.5% of adolescents, with common symptoms (chronic fatigue and/or nausea, and/or dizziness, and/or pain) identified as POTS by “intermittent intolerance of upright positions associated with postural tachycardia of more than 40 beats per minute.” (2) Importantly, clinical evidence of POTS is found in 25-50% of CFS cases. (3) Second, symptoms typically arise within a year or two of the beginning of puberty, 70% in girls. (4) Third, about two thirds of POTS patients have headaches, and the most common cause of headache in adolescents is migraine, which shares symptoms with POTS. (2). POTS is more common in Caucasians and around 15% of affected adolescents have a parent or sibling with similar symptoms, suggesting genetic predisposition. (2)

As POTS, viewed as a subset of CFS, is common, with onset in early to mid-adolescence and strong female predominance, reports after HPV vaccine are not surprising. What is surprising is the notion that data mining of the global pharmacovigilance database VigiBase is any more than hypothesis generation. (1) Numerically, VigiBase reports are predominantly from countries with high Caucasian populations where young adolescent

females have been targeted for broad HPV vaccine programs (5), and association with fatigue and/or headache and/or syncope inevitable. (2-4) In the analysis of which Dr Chandler is the lead author, among 40,000 reports associated with HPV vaccine, 76% of 694 subjects in four clusters were identified by individual review as "relevant to ongoing safety concerns." (6) In contrast, analysis of reports to the US Vaccine Adverse Event Reporting System (VAERS) found no signal for POTS and HPV vaccination. Among 160 potential subjects from 40, 735 reports, only 29 fully met POTS criteria and 20/29 had a pre-existing medical condition, CFS in five. (7) It is notable that only two reports came from Australia, which has high HPV coverage and historically high reporting to VigiBase (5), whereas 88 came from Denmark with 20% of Australia's population. (6)

Carefully validated case definitions are essential to determine the post-vaccination risk of validated adverse events, and initial findings can be overturned by subsequent studies of higher quality, as with venous thromboembolism and HPV vaccination (8). In our view, three studies, not referred to in the Analysis, have design characteristics to validly evaluate the POTS-HPV signal. Although they examine CFS, rather than POTS specifically, clinical overlap supports extrapolation. (2, 3) The methodologically strongest study is from Norway, where the ICD-10 code G93.3 is assigned by paediatricians using specific Norwegian guidelines for CFS, and HPV vaccination status recorded on a national register. (9) Among 176,453 girls born 1997-2002, 82% had at least one dose of 4v HPV vaccine and 407 cases of CFS were identified. HPV vaccine was not associated with CFS during total follow-up (adjusted hazard ratio (aHR) 0.86 (95% CI 0.69-1.08) or the first two years (aHR 0.96; 95% CI 0.64-1.43). Over the study period, reported incidence of CFS increased to a similar extent in boys and girls, despite only girls being eligible for HPV vaccination. Two other studies used the self-controlled case series method to calculate relative incidence (RI) pre and post HPV among CFS cases. No association was found in 187 cases (RI 1.07; 95% CI 0.57-2.00) in the UK (10) or 37 in the Netherlands (RI 0.62; 95% CI 0.07-5.49) (11).

However, lack of epidemiological evidence is insufficient to satisfy Dr Chandler, who argues a search for immune and genetic markers of individual susceptibility is needed. She cites the case of a 42 year old man with GBS after each of three doses of tetanus toxoid as exemplifying individual-level risk. However, a study of 989 vaccines given to people with previous GBS, identified only 6 cases of recurrence, only one tenuously vaccine-exposed (Measles-Mumps-Rubella vaccine 4 months prior). (12) It is difficult to see how a 1978 case report represents the "even-handed look at the evidence"required of a BMJ Analysis.

The final plank of Dr Chandler's argument is that POTS, and other severe adverse events, are concealed by incomplete clinical trial reporting. Although barriers to accessing clinical trial data are lamentable, retrospective examination of individual trial records is onerous and problematic for non-specific and unmeasured events, such as POTS. What is needed is high quality post-marketing studies (9-11) and well delineated background rates. A prescient study looked at pre-HPV incidence of autoimmune conditions in a US female adolescent cohort, (13) and for POTS was recently reported from Finland. (14)

Understandably, anxiety about debilitating symptoms of unknown cause, such as with POTS, is front of mind while cancer prevention is more distant. However, the basis for a true HPV-POTS association is flimsy, in contrast to strong evidence that HPV programmes have prevented pre-cancerous lesions in many countries (15) and could ultimately eliminate cervical cancer as a public health problem globally. (16)

High quality pharmacovigilance is an essential component of any vaccination program. Unfortunately, the Analysis of May 31st combines selective citation with unjustified, impractical calls for individual risk assessment, both lines of argument reminiscent of broader anti-vaccine tropes. (17) Its publication in a quality journal bestows unwarranted credibility, risking validating unjustified anxieties. Anxieties which, if they take further hold, threaten to deny a generation of young people protection against cervical and other cancers.

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Competing interests: Peter McIntyre was from 2004-2017 Director of Australia's National Centre for Immunisation Research and Surveillance (NCIRS) which receives funding from the Australian and New South Wales governments, including funds to support vaccine safety surveillance activities. NCIRS also receives funding from competitive research grants but no monies from vaccine manufacturers. He was in 2008 a member of a panel convened by the Australian Therapeutic Goods Administration to examine reported cases of multiple sclerosis following HPV vaccination and in 2009 of a panel convened by the NSW government to examine reports

of anaphylaxis after HPV vaccination but has not been a member of any advisory groups for manufacturers. He was a member of the Australian Technical Advisory Group on Immunisation (ATAGI) from 1998 to 2017 which considered HPV on multiple occasions over this period. He is a member of World Health Organisation committees and relevant travel costs are paid; his declaration of interests is also available on the WHO website. Statements in this rapid response are his alone in consultation with his co-authors.Julia Brotherton was Medical Director of Australia's National HPV Vaccination Program Register from 2010-2018, operated under contract to the Australian government. She is in receipt of competitive grant funding from Australia's National Health and Medical Research Council, The Australian Research Council, and Victorian Cancer Agency. She has served on non renumerated government technical advisory committee's in relation to HPV vaccines in Australia and has been an external advisor to WHO on HPV vaccines with travel costs reimbursed Anastasia Phillips is a public health physician, and PhD candidate in the area of vaccine safety including HPV with NCIRS, who is also employed by the Western Australian Department of Health. She has no financial interests to declare. Michael Tatley is Director of the New Zealand Pharmacovigilance Centre which contributes reports to VigiBase. The pharmacovigilance centre receives funding from the NZ Ministry of Health but does not receive any funding from pharmaceutical manufacturers.

09 July 2019

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Appendix E: Additional publication: Phillips A, Beard F, Macartney K, Chan J, Gilmour R, Saravanos G, McIntyre P. Vaccine-preventable child deaths in New South Wales from 2005 to 2014: How much is preventable? Journal of Paediatrics and Child Health. 2018; 54 (4): 356–364.

This paper is included to provide background on the benefit of vaccines. While the thesis focuses on vaccine pharmacovigilance and the risk side of the benefit-risk equation, it is important to reinforce the benefits of vaccination, particularly in an era of complacency.

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ORIGINAL ARTICLE

Vaccine-preventable child deaths in New South Wales from 2005 to 2014: How much is preventable?

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Aim: To identify and describe potentially vaccine-preventable child deaths in New South Wales (NSW).

Methods: Child deaths in NSW from 2005 to 2014 potentially preventable by vaccination were identified from the NSW Child Death Register (maintained by the NSW Ombudsman) and the Notifiable Conditions Information Management System (NSW Health). Medical and post-mortem records were reviewed. Cases were classified as vaccine-preventable based on the strength of evidence for the relevant infection causing death and likelihood that death was preventable through vaccination. A two-source capture–recapture method was used to estimate the true number of deaths. Age-specific mortality rate and number of deaths by disease, area of residence and comorbidity were analysed. Deaths were classified as preventable based on vaccine availability, eligibility under the National Immunisation Program, age and presence of any contraindications.

Results: Fifty-four deaths were identified as definitely or probably due to diseases for which a vaccine was available, with a total average annual mortality rate of 0.33 per 100 000 children and 2.1 per 100 000 infants. Two thirds of deaths occurred in children with no identified comorbidities. Twenty-three deaths were classified as preventable or potentially preventable by vaccination, with influenza (12 deaths) and meningococcal disease (five deaths) most common. An additional 15 deaths would be potentially preventable as of August 2016 due to immunisation recommendation changes including maternal vaccination.

Conclusion: Maternal vaccination along with increased uptake of childhood influenza vaccination could reduce child deaths, particularly from influenza.

Key words: Australia; child; death; immunisation programmes; influenza vaccines; vaccination.

What is already known on this topic?

1 Deaths from vaccine-preventable diseases in children are now rare in Australia.
2 There is a lack of recent, comprehensive assessment of such deaths.

What this paper adds?

1 Deaths preventable or potentially preventable by vaccination continue to occur in Australian children.
2 There is scope to prevent further deaths, particularly due to influenza, meningococcal disease and pertussis.
3 Increased uptake of vaccination in children with and without underlying medical conditions, particularly for influenza, could reduce residual child deaths.

Deaths due to vaccine-preventable diseases in Australia have declined significantly despite substantial increases in the population.[1] The current National Immunisation Program (NIP) Schedule, funded for all children, protects against 16 infectious diseases; a small number of additional doses or vaccines are also funded for specific high-risk groups.[2] Some vaccines, although registered for use and recommended in the *Australian Immunisation Handbook*, are available only through private purchase.[3]

Although vaccine-preventable deaths among children are now rare, reported cases often cause considerable public interest and distress. Ascertaining complete and accurate identification about such deaths can be problematic, as data from death certificates and notifications to the National Notifiable Diseases Surveillance System may be divergent and incomplete.[1] This study was conducted on behalf of the Child Death Review Team (CDRT) of the New South Wales (NSW) Ombudsman, who review all child deaths in NSW and provide annual reports to the Parliament. It aimed to provide a detailed description of deaths among children residing in Australia's largest state and to identify missed

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Conflict of interest: None declared.

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Table 1 Case definition for deaths due to pathogens/diseases of interest†

	Laboratory and epidemiological evidence	Clinical and post-mortem evidence
Confirmed	Laboratory definitive evidence‡ of pathogen of interest from a clinical specimen	Post-mortem or clinical evidence of severe disease consistent with the disease of interest
Probable	Laboratory suggestive evidence‡ of pathogen of interest from a clinical specimen OR Laboratory evidence of a pathogen of interest from a post-mortem specimen OR Epidemiological link to a case of disease of interest	Post-mortem or clinical evidence of severe disease consistent with the disease of interest
Uncertain	Laboratory evidence clinical or post-mortem specimen) of a pathogen of interest OR Epidemiological link to a case of disease of interest	Absence of post-mortem or clinical evidence of severe disease consistent with the disease of interest
Not a case	No laboratory evidence of pathogen of interest	

†Case definition for confirmed/probable/uncertain requires evidence listed in both columns. ‡Consistent with national notifiable diseases case definitions, where available.

opportunities for vaccination. A report and recommendations based on this work were tabled in NSW State Parliament by the NSW Ombudsman.[4]

Methods

Deaths among live-born children from diseases of interest were investigated. Diseases of interest were defined as those caused by a pathogen for which a vaccine is currently available on the NIP (excluding human papillomavirus), regardless of disease subtype. Specifically, this included diphtheria, *Haemophilus influenzae* infection, hepatitis A and B, influenza, measles, meningococcal disease, mumps, pertussis, pneumococcal disease, poliomyelitis, rotavirus, rubella, tetanus and varicella. Cases were identified from two independent sources of routinely collected data over the period 2005–2014: The Child Death Register (CDR), maintained by the CDRT, and the Notifiable Conditions Information Management System (NCIMS), maintained by NSW Health.

CDR data are based on death certificates and coroners' reports coded using the International Statistical Classification of Diseases (ICD) system, 10th revision, modified for Australia (ICD-10-AM), for all deaths under 18 years of age in NSW. The CDRT provided a data set containing all deaths potentially due to infectious diseases; deaths potentially due to diseases of interest were identified through ICD-10-AM coding for cause of death and associated cause of death, and from free text in any field. A triage system was used to narrow case selection to those cases specifying a disease of interest or relevant pathogen. Clinical syndromes (such as pneumonia, sepsis or gastroenteritis) without reference to a disease of interest or relevant pathogen were not further analysed. From NCIMS, we identified notified cases of diseases of interest under the age of 15 years where a death was also recorded. Data from the two sources were matched using personal identifiers including date of birth and surname. Data were also requested from neighbouring jurisdictions (Queensland, Victoria and the Australian Capital Territory) on deaths in children normally residing in NSW.

For each case, all available medical records, post-mortem examination reports, coronial findings and laboratory results were reviewed. A standardised set of demographic, clinical and laboratory information were collected. Vaccination history was obtained from clinical notes and/or NCIMS. All cases of diseases of interest were included, regardless of whether the pathogen subtype was included in the vaccine available at that time or whether the child was eligible for the vaccine under the NIP.

Cases were classified as confirmed, probable or uncertain using a rating scale for the strength of evidence for the disease as having caused death, developed for the study (Table 1). Uncertain cases were excluded from the main analysis.

Confirmed and probable cases were further classified as to whether they were likely to be preventable through vaccination (Fig. 1); non-preventable cases were assessed as to whether they would be preventable as of August 2016. Vaccines available, recommended and funded from 2004 to 2016 are shown in Table 2. In classifying deaths as preventable, 100% vaccine efficacy was assumed.

Data were analysed using STATA (Stata Statistical Software: Release 14, 2015; StataCorp LP, College Station, TX, USA) and Microsoft Excel (2010; Microsoft Corporation, Redmond, WA, USA). Mortality rates were presented as annual average rates per 100 000 child population. Postcode data were linked to the Australian Standard Geographic Classification Remoteness Structure data provided by the Australian Bureau of Statistics in order to classify deaths by remoteness.[5] Population data by remoteness were obtained from the Centre for Epidemiology and Evidence, NSW Ministry of Health.

Based on the assumption of independence of the two data sources, a capture–recapture method was used to estimate the total number of deaths. This estimation is based on the formula $n = ((a + 1)(b + 1)/(c + 1)) - 1$, where n is the total estimated cases, a is the total number of cases ascertained from the primary source (CDR), b is the total number ascertained from the secondary source (NCIMS) and c is the number of cases common to both sources.[6]

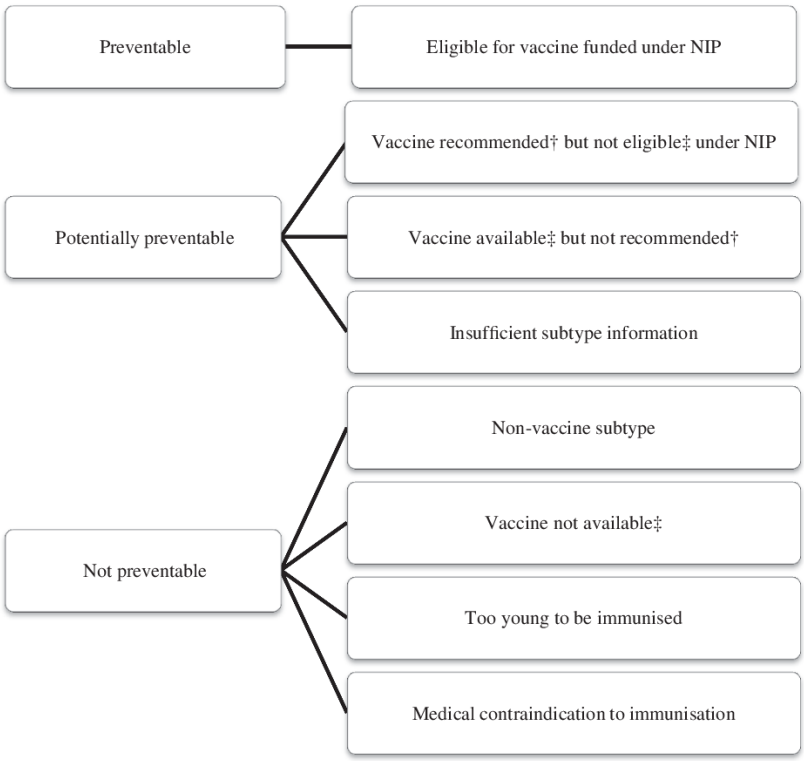

Fig. 1 Framework for assessing potential for prevention by vaccination. †Refers to recommendations in the *Australian Immunisation Handbook* as on August 2016 (http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home). ‡Child eligible under the National Immunisation Program (NIP) or vaccine available prior to the time of the child's death (http://www.immunise.health.gov.au/).

The CDRT reviews all deaths of children in NSW under the auspices of the NSW Ombudsman. This study was commissioned by the CDRT on behalf of the NSW Ombudsman and conducted under the Community Services (Complaints, Review and Monitoring) Act 1993. Ethics committee review was not required under this Act. Both data sources used in this study are statutory collections and the CDRT provided all data to the research team under their appointment as expert advisor within the Act.

Results

Cases of death due to diseases of interest

Seventy-three cases of death potentially related to a disease of interest were identified (Fig. 2). Sufficient data were available to assess deaths among NSW residents who died in two of three neighbouring states. Of the 73 included cases, 54 were considered confirmed or probable according to the case definition in Table 1. Case vaccination status for the disease was documented in the clinical notes or NCIMS for around half of the cases. Where vaccination status was not documented in the clinical notes or NCIMS, it was not possible to ascertain this information from the Australian Childhood Immunisation Register (ACIR) as ACIR records are not available for deceased children. No child was documented to have been vaccinated for the disease of interest except for one case of invasive pneumococcal disease due to serotype 19A, who had received three doses of 13-valent pneumococcal vaccine (13vPCV). This case was considered a vaccine failure and not further classified. In almost all cases not vaccinated for the disease of interest, the family was not documented as specifically objecting to vaccination.

All confirmed and probable cases

The overall mortality rate was 0.33 per 100 000 child population (95% confidence interval (CI) 0.25–0.43) and 2.1 per 100 000 infants under 12 months of age (95% CI 1.29–3.25). The highest number of deaths in any 1-year age group was in children under 12 months of age (Fig. 3). Male children were over-represented (39/54 cases). The highest number of deaths occurred in major cities (n = 31), but the rate of death was highest in inner regional areas (0.63 compared to 0.31 in major cities and 0.4 deaths per 100 000 child population in outer regional, remote and very remote areas). Children from inner regional areas were twice as likely to die (relative risk = 1.99, 95% CI 1.03–3.71) compared with children from major cities. There was no statistically significant difference in the risk of death in children in outer regional, remote and very remote areas compared to major cities (relative risk = 1.29, 95% CI 0.33–3.64).

Meningococcal deaths appeared to decrease over the study period, while influenza deaths appeared to increase (Fig. 4). Meningococcal serogroup B accounted for 8 of the 12 meningococcal deaths and influenza A was identified in 14 of 15 influenza deaths, with H1N1 identified in 5 cases. Two thirds of deaths classified as confirmed or probably due to diseases of interest were in children without known comorbidities (n = 36). Of the

Table 2 Australian National Immunisation Schedule as implemented in New South Wales (NSW), 2005–2014

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Notes
DTP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NA
Polio	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NA
MMR	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NA
Varicella	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	Also recommended from 2003
Hib	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NA
Meningococcal C	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NA
Meningococcal ACWY	R-SRG	R-SRG	R-SRG	R-SRG	R-SRG	R-SRG	R-SRG	R-SRG	R-SRG	R-SRG	R-SRG	R-SRG	For high-risk medical conditions and travel†
Meningococcal B	NA	NA	NA	NA	NA	NA	NA	NA	NA	R	R	R	For infants and young children <2 years; adolescents 15–19 years
Hepatitis B	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NA
Hepatitis A	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	Funded under NIP for Indigenous children 12–24 months in some states (not NSW). Also recommended for travellers >1 year to endemic areas (unfunded)
Rotavirus	NA	R	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NIP	NA
Influenza													
Individuals >6 months at risk of severe influenza and pregnant women	R	R	R	R	R	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	Funded under NIP in 2010 but previously subsidised under PBS. List of underlying medical conditions expanded in 2013
Indigenous people ≥15 years	A	A	A	R	R	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NA
Indigenous children 6 months to 5 years	A	A	A	A	A	A	A	A	R	R	NIP -SRG	NIP -SRG	NA
Children >6 months to <5 years	A	A	A	A	A	A	A	A	R	R	R	R	Funded in Western Australia from 2008 (not NSW)
Pandemic H1N1 2009	NA	NA	NA	NA	NIP	NA	NA	NA	NA	NA	NA	NA	NA

(*Continues*)

Table 2 (Continued)

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Notes
Pneumococcal													
7-Valent PCV	NIP	NIP	NIP	NIP	NIP	NIP	NA	NA	NA	NA	NA	NA	Catch-up for all children <2 years; replaced 23-valent PPV as booster for high-risk children at 12 months of age from 2005
13-Valent PCV	NA	NA	NA	NA	NA	NA	NIP	NIP	NIP	NIP	NIP	NIP	Replaced 7-valent PCV July 2011; NIP-funded catch-up for children 12–35 months (additional dose); booster for children with high-risk medical conditions from 2013 if dose of 13-valent PCV not previously received (in addition to 23-valent PPV)
23-Valent PPV	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	NIP-SRG	Funded dose for Indigenous children in some states (not NSW) at 18–24 months from 2001 to 2011; booster for children with specified underlying medical conditions at 12 months from 2001 (replaced by 7-valent PCV in 2005) and 4–5 years from 2003 (second dose in 5–10 years recommended from 2013)

†Adolescent programmes funded by some states and territories in 2017. Data taken from National Centre for Immunisation Research and Surveillance,[3] with permission. A, available; DTP, diphtheria, tetanus and pertussis; Hib, *Haemophilus influenzae* type b; MMR, measles-mumps-rubella; NA, not applicable; NIP, funded under National Immunisation Program; NIP-SRG, funded under National Immunisation Program for special risk group only; PBS, Pharmaceutical Benefits Scheme; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; R, recommended; R-SRG, recommended for special risk groups only.

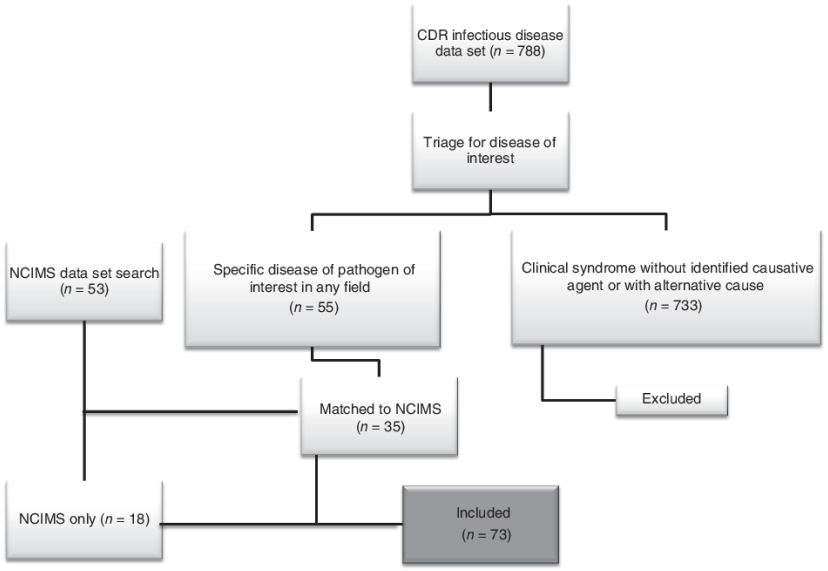

Fig. 2 Process for assessing cases of disease of interest and final included cases. CDR, Child Death Register; NCIMS, Notifiable Conditions Information Management System.

18 children with comorbidities, 12 were eligible for NIP-funded vaccine (including all influenza cases) or additional vaccine doses (including all pneumococcal cases) due to their risk category. None of these children were documented as having been vaccinated for the disease of interest.

Preventable and potentially preventable deaths

Among the 54 confirmed and probable cases of death due to diseases of interest, 23 were considered preventable (n = 5) or potentially preventable (n = 18), most commonly influenza (n = 12) and meningococcal disease (n = 5) (Table 3). Five influenza deaths considered preventable or potentially preventable occurred in children with comorbidities who were eligible to receive funded vaccine. A further seven potentially preventable influenza deaths occurred in children without known comorbidities, most (n = 5) in children aged from 6 months to less than 5 years of age, where influenza vaccine was recommended but not funded under the NIP.

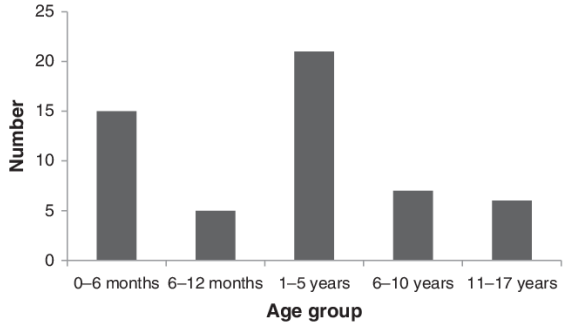

Fig. 3 Number of confirmed and probable cases of death due to diseases of interest by age group, 2005–2014.

Five meningococcal deaths and four pneumococcal deaths were considered preventable or potentially preventable. Preventable deaths occurred in children eligible for catch up programmes (n = 3), including the NIP-funded meningococcal C vaccine and 7-valent pneumococcal conjugate vaccine (7vPCV) catch-up programmes. Potentially preventable meningococcal deaths were due to serogroups (B, C and Y) for which an unfunded vaccine was available for the relevant age group at the time of death.

Non-preventable deaths

Thirty deaths were not considered preventable by vaccination (Table 3). Nine were in children too young to be vaccinated (aged 2 months or less) including deaths due to pertussis and influenza (n = 4). Although not preventable through vaccination of the

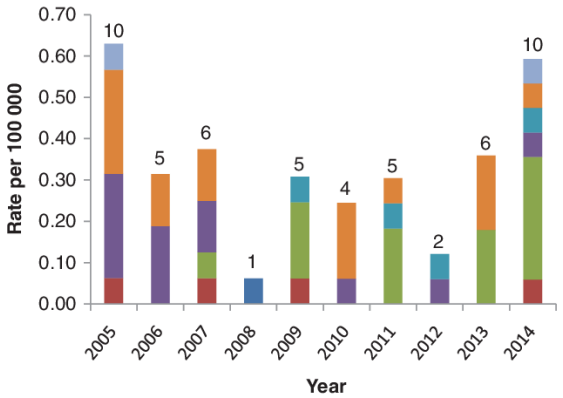

Fig. 4 Rate of deaths due to diseases of interest over time by disease (number of deaths above bars). (■), Varicella; (■), pneumococcal; (■), pertussis; (■), meningococcal; (■), influenza; (■), *Haemophilus influenzae*; (■), hepatitis A.

Table 3 Confirmed and probable cases of death due to disease of interest and potential for prevention by vaccination

Disease	Total	Number preventable or potentially preventable†	Number not preventable†	Number not preventable that may be preventable in 2016
Influenza	15	12	3	3
Meningococcal	12	5	7	6
Pneumococcal‡	15§	4	11	3
Others¶	11	NR	9	3
Total	53	23	30	15

†As determined by the assessment framework in Figure 1. ‡Eight of these deaths were classified based on samples obtained post-mortem (five were untyped). §One additional pneumococcal death occurred due to a vaccine strain (19A) in a fully vaccinated child and was considered a vaccine failure; the case was not classified regarding potential for prevention by vaccination. ¶Amalgamated data due to small cell sizes. NR, not reported due to small cell size.

child, these deaths may have been preventable through maternal vaccination during pregnancy.

Deaths occurred where the subtype of the pathogen was not covered by the relevant available vaccine, and these were considered non-preventable. These included deaths due to 13vPCV pneumococcal serotypes which were not included in the 7vPCV available at the time, and H1N1 influenza deaths prior to availability of the H1N1 pandemic vaccine. Seven deaths due to meningococcal B disease (six aged under 12 months) occurred before a meningococcal B vaccine was available (most would have been old enough to be vaccinated). Several varicella deaths in immunocompromised children were also considered non-preventable due to vaccine contraindications. Deaths from untyped *H. influenzae* were not considered preventable due to the low likelihood that the infecting strain was type b (Hib), given the very low proportion of invasive *H. influenzae* of known serotype due to type b.[7]

Of the 30 deaths classified as non-preventable, half would now be potentially preventable through maternal vaccination (infant influenza and pertussis deaths (n = 4)) and vaccines incorporating new disease subtypes (meningococcal B, pneumococcal and influenza (n = 11); Table 3).

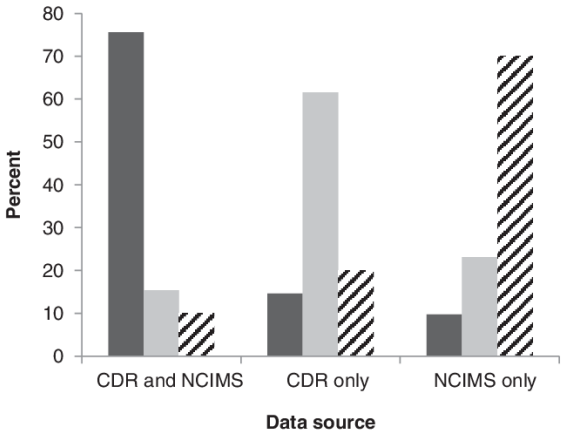

Fig. 5 Case classification by data source for all cases of death due to diseases of interest, 2005–2014. (■), Confirmed; (▩), probable; (▨), uncertain. CDR, Child Death Register; NCIMS, Notifiable Conditions Information Management System.

Data source comparison

Confirmed cases were more likely to have been identified from both data sources (Fig. 5). Of the 54 confirmed and probable cases, 47 were identified from the CDR, 40 from NCIMS and 33 matched from both sources. The capture–recapture analysis estimated a total of up to 57 confirmed and probable cases (95% CI 53–61), indicating that three additional cases may have been captured if case ascertainment had been complete.

Discussion

We identified influenza as the most common cause of childhood death preventable or potentially preventable by vaccination. Influenza was the confirmed or probable cause of 15 deaths in NSW children over the 10-year period of our study. As 14 of 15 influenza deaths occurred from 2009 onwards, identification may reflect increased testing following the pandemic year, with an increase in all-age influenza notification rates also noted nationally over this time period.[8]

An excess of influenza deaths (7/15) occurred in children with comorbidities. While influenza vaccination is recommended and funded under the NIP for children with specified medical conditions,[2] low vaccination coverage has been well documented.[9,10] Another seven influenza deaths occurred in children over 6 months of age with no documented comorbidities and all influenza cases who died before arrival at hospital were previously healthy children under 5 years of age. Previously healthy young children with influenza have been shown to have high hospital admission rates[11] and may be more likely to die before hospital admission or within 3 days of symptom onset, compared to those with underlying medical conditions.[12] While influenza vaccination is recommended in Australia for all children between 6 months and 5 years of age, it is only funded under the NIP for those at higher risk[2] and coverage is very low.[13,14] Coverage recorded in ACIR was less than 2.5% in children aged 6 months to less than 5 years of age between 2005 and 2014 (excluding Western Australia, where a funded seasonal influenza immunisation programme for children commenced in 2008).[14] A number of other high income countries provide free influenza vaccination for all young children.[15,16]

Influenza deaths in young infants were rarely confirmed as the cause of death in our study. Several deaths were classified as

uncertain and attributed at post-mortem to sudden unexplained death in infancy. Sudden unexplained death in infancy is multifactorial, and although signs of infection are often found at autopsy, minor respiratory infections in infants are common and in many cases not thought to be the primary factor contributing to death.[17] Despite a lack of clarity around the cause of death, these infants may have been protected by maternal vaccination, recommended for pregnant women and funded under the NIP since 2010,[2] although the duration of neonatal protection following vaccination in pregnancy is uncertain.[18] In addition, this study only investigated deaths among live-born children and did not examine the burden of stillbirth, which may also be potentially preventable through maternal immunisation.[19]

We identified 12 deaths due to meningococcal disease over the 10-year study period, substantially less than the 26 deaths identified in NSW in children less than 15 years between 2000 and 2007.[20] There has been a dramatic decline in meningococcal C disease since the introduction of the meningococcal C immunisation programme in 2003.[21] The meningococcal C deaths in our study occurred between 2005 and 2007, with most children eligible for meningococcal C vaccine catch-up programmes under the NIP. Although meningococcal C vaccination coverage has been high (93%), coverage is lower in catch-up cohorts (70%).[21] Most meningococcal deaths in our study were due to meningococcal B disease; most occurred before the meningococcal B vaccine (which is now recommended but not funded under the NIP for young children, particularly those aged <24 months, adolescents aged 15–19 years and those with specific medical conditions[2]) became available in 2014. Although serogroup B was predominant in Australia over the study period, its incidence has declined concurrently with the decline in serogroup C disease.[21]

Of the pertussis deaths identified in our study, most were less than 2 months of age. Similarly, 10 of 11 pertussis deaths reported nationally between 2006 and 2012 were in infants less than 2 months of age.[22] Such deaths are likely to be preventable through pertussis vaccination during pregnancy,[23] which was recommended in the *Australian Immunisation Handbook* in April 2015 and provided free of charge by all states and territories from mid-2015.[2,22]

Our analysis assumes deaths were preventable or potentially preventable when a vaccine was available and/or funded under the NIP. However, our conclusions are limited by the efficacy of the vaccines available for each disease. The estimated effectiveness of influenza vaccine in prevention of hospitalised influenza was 55.5% in a recent Australian study.[13] Vaccine effectiveness against death was 65% (95% CI 54–74%) among children aged 6 months to 17 years in a recent US study, and 51% (95% CI 31–67%) in a subgroup of children with high-risk conditions.[24] Acellular pertussis vaccines in infants are estimated to have an efficacy of 84% against hospitalisation,[25] and the effectiveness of maternal pertussis vaccination against early infant death from pertussis is estimated as 95%.[26] Meningococcal B vaccination protects against 73–88% of strains in the UK, where it has been introduced into the routine national programme.[27]

Capture–recapture analysis estimated that three additional confirmed or probable cases would have occurred due to the diseases of interest. Capture–recapture methodology allows estimation of the total number of deaths in the population based on two independent data sources and has been previously used to estimate the incidence of congenital rubella syndrome[28] and acute flaccid paralysis in Australia.[29] This study was enhanced by the use of two independent data sources, although it is limited by the potential for underestimation of child deaths due to absence of specific pathogen information in some CDR records, which were excluded for review by our triage process. While this study was limited to one state in Australia, it provides detailed review of 10 years of data from all children in a state contributing 32% of the Australian child population (aged up to 19 years)[30] and the findings are likely apply nationally.

Conclusion

While the number of deaths in children from infectious diseases has decreased markedly since the pre-vaccine era, we identified an estimated 23 deaths potentially preventable by vaccination in a 10-year period in NSW, particularly in young infants. There is scope to reduce child deaths, particularly from influenza, meningococcal B and pertussis. In particular, increased uptake of currently funded influenza vaccination for children with comorbidities, as well as maternal vaccination for influenza and pertussis, may reduce child deaths. This study quantifies influenza-attributable deaths among children without underlying medical conditions, which would be a key component of cost-effectiveness analysis required to consider funding of universal childhood influenza vaccination under the NIP.[31] More detailed recommendations to reduce the number of vaccine-preventable child deaths are described in the report of this study tabled in the NSW State Parliament.[4]

Acknowledgements

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Appendix F: Peer-reviewed conference presentations based on PhD work

Totterdell J, Phillips A, Glover C, Chidwick K, Marsh J, Snelling T, Macartney K. Safety of live attenuated herpes zoster vaccine in adults 70 to 79 years: a self-controlled case series analysis using primary care data from the MedicineInsight program. Public Health Association of Australia 17th National Immunisation Conference; 2021: Perth, Australia.

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Quinn H, Pillsbury A, Phillips A, Macartney K. Searching for swollen little limbs: AusVaxSafety expands to monitor pertussis booster vaccines. Public Health Association of Australia Communicable Diseases Control Conference; 2017: Melbourne, Australia.