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

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ABSTRACT

Background: In 2010, the Australian seasonal influenza vaccination program for children under 5 years of age was suspended due to an unexpected increase in fever and febrile convulsions causally associated with one particular influenza vaccine brand. A subsequent national review made seven recommendations to improve vaccine pharmacovigilance. Ten years on, in advance of implementing the COVID-19 immunisation program, we evaluated views on the capacity of Australia's vaccine pharmacovigilance system to promptly detect, examine and communicate a signal.

Methods: Semi-structured interviews were conducted between July and October 2020 with individuals with expertise in vaccine safety in Australia using an interview guide informed by key Australian and international frameworks. Interviews were digitally recorded and transcribed verbatim. Thematic analysis was used to code data using a deductive approach.

Results: Interviews with seventeen participants enabled six themes to be identified. Participants described improvement and significant innovation within Australia's vaccine pharmacovigilance system over the decade since 2010, particularly through establishment of a new active, cohort event monitoring system using short message service surveys. Participants thought Australia had a good foundation for COVID-19 vaccine safety surveillance; implementation of the COVID-19 immunisation program was seen as a potential driver for ongoing enhancement through: a) improved integration of the active surveillance and spontaneous reporting systems, and; b) development of population-level active surveillance, including through data linkage. Transparent communication was considered essential to address the unprecedented challenges of COVID-19 and broader vaccine safety concerns.

Conclusions: Vaccine safety experts in Australia convey confidence in the innovative pharmacovigilance systems implemented over the past 10 years. While Australia has a multifaceted system incorporating both active surveillance and spontaneous reporting systems, COVID-19 vaccine implementation represents an opportunity to enhance current systems and to develop new, systematic approaches to vaccine pharmacovigilance that should make both a local and global contribution.

1. Introduction

Australia has a strong history in the delivery of safe and effective immunization programs, and is recognized globally for achieving high coverage for childhood vaccines under a comprehensive national immunization program (NIP) [1]. Invariably, adverse events will be reported following vaccination but do not necessarily have a causal relationship with the vaccine. Pharmacovigilance mechanisms must be robust and agile enough to rapidly investigate temporal associations, assess causality, determine whether the benefit-risk profile remains favourable, and provide data for effective communication [2,3]. Vaccine pharmacovigilance activities in Australia have been valuable, identifying and responding to early safety concerns around human papillomavirus (HPV) vaccine (in 2007–8) [4], and providing an early understanding of the

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incidence of intussusception following rotavirus vaccines (2007–10) [5], among other issues.

However, vaccine pharmacovigilance came under scrutiny in Australia in 2010 when a major safety incident occurred with an unexpected increase in fever and associated febrile convulsions in children following influenza vaccination with one particular brand. This led to temporary suspension of the seasonal influenza vaccination program for children under 5 years of age [6,7] and long-term impacts on influenza vaccine confidence and coverage in children [8,9]. The resulting commissioned national '*Review of the management of adverse events associated with Panvax and Fluvax*' led by the former Chief Medical Officer, Professor John Horvath (the Horvath Review) [7], 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 recommendations with a two year implementation timeframe overseen by the Department of Health and the Australian medicines regulator, the Therapeutic Goods Administration (TGA) [10]. Reforms were linked to another TGA initiative (*TGA reforms: A Blueprint for TGA's Future*) released in December 2011 [11]. Concurrently, other expert commentators echoed concerns around governance and transparency and highlighted the inherent limitations of spontaneous (passive) reporting systems (SRS), the need for complementary active surveillance systems and the potential for use of large linked databases for pharmacovigilance [6]. Large linked databases are used in a number of developed countries to investigate safety signals identified through spontaneous reporting systems, with epidemiological studies comparing risk in vaccinated and unvaccinated cohorts; these data may also be used in near real time to monitor vaccine safety [12]. All recommendations of the Horvath Review were addressed by Government within the implementation timeframe; however, no formal report or evaluation of the response was completed [10].

Australia has a longstanding SRS, operated by the TGA, with reporting predominantly occurring via surveillance mechanisms in Australia's eight States and Territories; enhancements have been made under both the Horvath Review and TGA reforms [10,11]. Following the events of 2010, early efforts to monitor parent reports of fever in recipients of childhood influenza vaccine led to the local development of two active, electronic cohort event monitoring systems (SmartVax and Vaxtracker), which were subsequently brought together as AusVaxSafety-Active [13–15]. Australia also has an active, prospective hospital-based surveillance system (the Paediatric Active Enhanced Disease Surveillance network [PAEDS]) [16,17] and an Adverse Events Following Immunisation Clinical Assessment Network (AEFI-CAN) [18] (Fig. 1, Table 1). In addition, ad-hoc specialised studies, including using large linked databases, are conducted by research groups [19,20] and emergency department surveillance is undertaken in some States [21]. Australia has a national immunization register which has captured data on all childhood immunizations since 1996 and was extended to include vaccines given to people of all ages in 2016 [1].

Ten years on, a number of new vaccines (or expanded eligibility for existing vaccines) have been introduced onto the NIP, including diphtheria, tetanus and pertussis vaccine for pregnant women, quadrivalent meningococcal vaccine for adolescents and live attenuated herpes zoster vaccine for older adults [22]; both active surveillance and the SRS have been used to monitor these new programs [15,23]. The Australian COVID-19 immunization program commenced in 2021 and will only include vaccines registered for use by the TGA based on safety and efficacy data from phase 3 clinical trials [24]. To enable ongoing monitoring of the benefit-risk ratio of the available vaccines and provide timely data to further characterise their safety profiles, vaccine pharmacovigilance will need to facilitate the early detection, investigation and analysis of adverse events following immunization (AEFI) and adverse events of special interest (AESI), including rare or population-specific events [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]. The World Health Organization recommends that countries, like Australia, which already have mature pharmacovigilance systems, take extra steps to implement active surveillance systems for AESI, 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].

This study, conducted between July and October 2020, 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 immunization program. We aimed to synthesise the findings and make recommendations to inform vaccine safety surveillance development and specifically national COVID-19 vaccine safety monitoring.

2. Methods

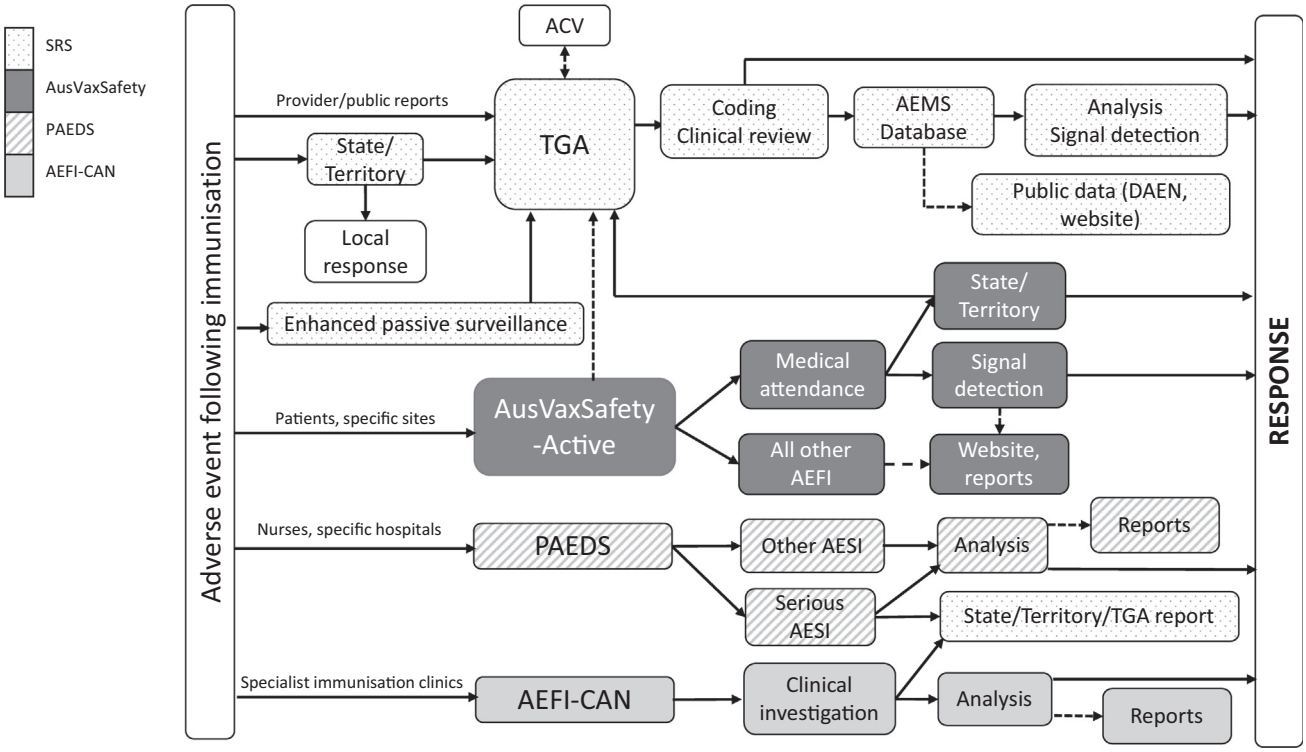
2.1. Study design

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

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 (the National Immunisation Technical Advisory Group), the National Immunisation Committee (advising on program implementation), the Advisory Committee on Vaccines (advisory to the TGA on pre- and post-market vaccine activities), and the AusVaxSafety (active vaccine safety program) 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 SRS) or held a role within national government (the Australian Government Department of Health or the TGA) were identified based on these roles. Those selected from national government roles were not individuals who had been personally involved in the Horvath Review, although others within their organization would have been involved with vaccine safety over various time periods, including dating back to the Horvath review. Selection was further guided by the socioecological model (SEM) framework [26]. 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 (KM, AP, MD and FB).

The identified vaccine safety experts were invited by email to participate and provided with an information sheet. If there was



ACV – Advisory Committee on Vaccines; AEFI-CAN - Adverse Events Following Immunisation – Clinical Assessment Network; AEMS - Adverse Events Management System; PAEDS – Paediatric Active Enhanced Disease Surveillance; TGA – Therapeutic Goods Administration. Solid lines represent AEFI reporting, analysis & response; dashed lines represent communication around AEFI reports and pharmacovigilance.

Fig. 1. Key components and interactions within Australia's current vaccine pharmacovigilance system.

no response within two weeks, a single reminder email was sent. For those who agreed to participate, an interview time was mutually agreed. If a participant was not available, another potential participant with a similar professional background was approached. 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.

2.3. Data collection

Interviews were conducted between July and October 2020, prior to implementation of the COVID-19 immunization 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 (CDC) *Guidelines for Evaluating Public Health Surveillance Systems*, [27] the *National Immunisation Strategy for Australia 2019 to 2024*, [28] the Horvath Review [10], and the requirements identified by the World Health Organization's *Global Manual on Surveillance of Adverse Events Following Immunization* [3]. The interview guide (Table A1) 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 interviews were conducted by AP using Microsoft Teams videoconferencing features (one participant elected to provide a written response on behalf of their organization, based on the interview guide). Data collection continued until saturation was reached; this was defined as no additional, unique data outside the coding framework.

2.4. Data analysis and synthesis

Interviews were recorded and transcribed verbatim. Two authors (AP and SC) coded the first three interviews using a codebook developed through a deductive (also known as thematic or 'top down') approach as described by Braun and Clarke, [29] which was analyst driven with coding based on the interview guide. Coding was confirmed or revised through agreement between both authors after which AP 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 [29]. Potential themes were developed from the codes through interpretive analysis and the generation of mind maps.

Findings from the thematic analysis were synthesised to distil recommendations, which reflected the dominant themes. All authors reviewed the initial themes and agreed on the refined thematic conceptualisation and recommendations.

2.5. Ethics

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

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 con-

Table 1
Key components of Australia's vaccine pharmacovigilance system.

System/year	*Description*	*Data collection*	*Data analysis*	*Response & communication*	*Governance*
AEMS Pre-2000	Spontaneous (passive) reporting system Enhanced surveillance for specific vaccines (detailed vaccine safety plans)[1]	Statutory reporting requirement for health providers in most States & Territories[2] Submitted via some State & Territory surveillance programs Consumer & pharmaceutical company reporting	Local follow up in some States Coded using standardised MedDRA® terms Clinical review of AESI & serious AEFI Signal detection (PRR & other methods)[3]	Monthly teleconferences with stakeholders (TGA AEFI JIC meeting) Data transmitted to Vigibase/ UMC Searchable Database of Adverse Event notifications (DAEN)[4] Safety advisories[5] & provider letters Regulatory action	TGA (manages) ACV (independent advice)[6] Vaccine safety investigation & causality assessment panels (as required)
AusVaxSafety-Active [7] 2014[a]	Cohort event monitoring system (active surveillance)	AEFI reports solicited via automated, SMS surveys from 375 + participating immunisation provider settings[b] Within 1 week following vaccination (longer for some vaccines)	AEFI rates Medical attendance rates Signal detection (FIR CUSUM & Bayesian analyses)[8]	Website reports Reports to stakeholders Vaccine specific reports and publications[9] Case follow up by States and Territories	AusVaxSafety consortium led by NCIRS Expert Leadership Group Advisory Committee Government funded
AEFI-CAN 2014[c]	Clinical network[10]	Specialised immunisation clinics in most States and Territories	Selected AEFI entered into database Analyses as needed	Regular teleconferences with members and TGA Publications	AusVaxSafety consortium led by NCIRS Government funded
PAEDS 2007[11]	Hospital-based active surveillance system	Specialist nurses screen hospital admissions, ED records & lab data in 8 tertiary, paediatric hospitals to identify selected AESI[d]	Epidemiological analysis Case review	Annual reports Reporting via SRS	National collaboration led by NCIRS Reference Group Government funded

ACV – Advisory Committee on Vaccines; AEFI - adverse event/s following immunisation; AEFI-CAN - AEFI – Clinical Assessment Network; AEMS - Adverse Events Management System; ED - emergency department; FIR CUSUM - fast initial response cumulative summation; JIC – Jurisdictional (State or Territory) Immunisation Coordinator; MedDRA – Medical Dictionary for Regulatory Activities; NCIRS – National Centre for Immunisation Research and Surveillance; PAEDS – Paediatric Active Enhanced Disease Surveillance; PRR - proprotional reporting ratio; SMS - short message service; SRS - spontaneous reporting system; TGA – Therapeutic Goods Administration; UMC – Uppsala Monitoring Centre. [a] Active participant-based surveillance (cohort event monitoring) began in 2014, with the name 'AusVaxSafety' adopted in 2016. [b] Sites include primary care, hospitals, schools, pharmacies, community clinics and Aboriginal Medical Services. [c] Clinician network meetings formalised and network secretariat established. [d] Includes intussusception, febrile seizures, serious adverse neurological events (SANE), COVID-19 & Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-COV-2 (PIMS-TS).

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Table 2
Participant demographics and roles in vaccine safety.

Characteristic	Category	Number (range)
Number of participants		17
Median interview duration (minutes)		41 (29–50)
Gender	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 (ACV), AusVaxSafety Expert Leadership Group and ATAGI COVID-19 working group.

current roles in vaccine safety and two participants were national government employees (Table 2). Based on only their main role, participants represented all perspectives within the SEM framework; based on their broad experience, most participants offered different levels of perspective. 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 competing demands of the COVID-19 pandemic.

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 immunization program.

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, given its ability to obtain near-real time safety data through active, SMS-based surveillance in primary care settings, as the '*stand-out*' innovation and '*pivotal change*' since 2010. 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 SRS, 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 SRS (and associated AEMS database), 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. PAEDS was considered a '*good mechanism*' for surveillance of specific hospitalised AEFI and for 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 early-onset AEFI. Looking toward the future, some participants discussed '*refining and calibrating*' the signal detection methods within AusVaxSafety-Active and the 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 SRS and expand coverage of AusVaxSafety-Active to settings and populations relevant for COVID-19 vaccines, including pharmacy and aged care settings, and to increase representation of 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**

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 SRS. 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 United States (US) Vaccine Safety Datalink. 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 would be 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, immunization data from a very good register to health encounter data sets 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, population level, 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**

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 SRS 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 with between the active and passive surveillances systems.'* **Participant 10**

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 immunization 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 system*' (participant 3), particularly in preparation for COVID-19 vaccines.

Participants noted that State and Territory-based AEFI clinics and the AEFI-CAN clinical network 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 immunization-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**

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-Jurisdictional Immunisation Committee (TGA AEFI JIC) meetings (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 (Fig. 1, 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 immunization 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**

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 public availability of SRS reports online through the Database of Adverse Event Notifications (DAEN) (Table 1, Fig. 1) 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 SRS 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 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, 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**

Table 3
Recommendations for Australia's pharmacovigilance system, based on identified themes.

Recommendation	Thematic underpinning
Better integrate Australia's suite of pharmacovigilance resources to create a multi-faceted and adaptive system that can rapidly respond, in coordinated manner, to vaccine safety challenges under real world conditions, including through rapid causality assessment and access to no-fault vaccine injury compensation, when relevant.	3.2 Ongoing evolution – barriers and drivers for change 3.3 Greater integration is essential 3.4 Causality assessment improved but room to enhance timeliness and adult assessment 3.5 Improved relationships, networks and information sharing - importance of robust federal leadership
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 experts, and benchmarking through regular evaluation.	3.5 Improved relationships, networks and information sharing - importance of robust federal leadership 3.6 Communication, transparency and the unprecedented challenge of COVID-19
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.	3.2 Ongoing evolution – barriers and drivers for change 3.5 Improved relationships, networks and information sharing - importance of robust federal leadership
Enhance current vaccine pharmacovigilance capacity for COVID-19 vaccine safety surveillance and for the future, including expanding existing systems and implementing new approaches to pharmacovigilance, governance and communication.	3.1 Improvement, innovative local systems and a foundation for COVID-19 vaccine safety surveillance 3.2 Ongoing evolution – barriers and drivers for change 3.6 Communication, transparency and the unprecedented challenge of COVID-19

3.7. Recommendations

Based on synthesis of the identified themes, four recommendations were developed for the Australian pharmacovigilance system (Table 3).

4. Discussion

Our study highlights the progressive 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 post-marketing surveillance for COVID-19 vaccines. We also identified weaknesses, barriers, and the opportunity to augment pharmacovigilance approaches to capture later-onset events together with the need for greater system integration. Our 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* [30], recent renewal of the Australian Government funded AusVaxSafety consortium and juridictional approaches. Importantly, 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 post-marketing surveil-

lance and signal detection has been demonstrated [31]. In line with our participants' comments that AusVaxSafety-Active would need to expand to capture additional settings and populations for COVID-19 vaccine surveillance, partnerships with state and territory health departments have enabled expansion, with participation of state-run mass vaccination clinics [15]. Other sites such as pharmacies, Aboriginal medical services and aged care facilities are also now being incorporated for COVID-19 vaccine surveillance. The US CDC has also implemented an active, text-messaging based post-vaccination survey (V-Safe), modelled in part on AusVaxSafety, for COVID-19 vaccine safety [32].

However, AusVaxSafety-Active aims to monitor early onset events (generally within one week) and our participants noted that such methods were not particularly well suited to the detection of later onset events. Participant-based surveys administered at a time distant from vaccination are of limited value given the potential for recall bias and for attribution of unrelated medical events to vaccination. Conversely, while later onset AEFI may be captured through spontaneous surveillance, underreporting is a well-recognised limitation of such systems [33]; our participants particularly noted underreporting by hospital staff in relation to AEFI that may present with an onset date distant from vaccination. Further, AusVaxSafety and the SRS are not integrated and operate as parallel systems, although this is also being addressed to an extent at jurisdictional level in the context of the COVID-19 immunization program.

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 AESI following COVID-19 vaccination, was clear from our study. Currently, sentinel hospital-based active surveillance is the key modality, outside of spontaneous reporting, through which later-onset and hospitalised AEFI can be captured in Australia. Two sentinel hospital-based surveillance networks, PAEDS and FluCAN, have been adapted to capture data on COVID-19 cases and complications, and PAEDS has been previously tailored to monitor specific AESI, such as intussusception and seizures [5,17,34]. While both systems have the capacity to expand to AESI related to COVID-19 vaccines, hospital based surveillance is resource intensive and limited by the number of participating sites [17]. In addition, for very rare, late-onset events, such as the newly described Thrombosis with Thrombocytopenia Syndrome (TTS) [35], patients could present infrequently and to any potential location, including secondary and rural hospitals. This reinforces the need to ensure hospital-based clinicians are aware of and rapidly report AEFI, as was highlighted by our participants. Further, systematic approaches to identify and investigate AEFI and AESI within large electronic population cohorts, including through linked data sources, would significantly augment system capabilities, particularly in the context of epidemiologic analysis of vaccine-attributable risk.

The key modality missing from Australia's current post-marketing vaccine safety monitoring framework, identified in our study, is structured and timely access to linked sources of relevant health and demographic data for pharmacovigilance. Data linkage is a central vaccine pharmacovigilance approach in several other countries, including the US [36], UK [37], Denmark and Sweden [38], where data can be used to both identify signals and test hypotheses, including in real time through rapid cycle analysis within the US Vaccine Safety Datalink [39]. Hypothesis testing through the conduct of observational studies, such as cohort and self-controlled case series analyses, enables comparison of vaccinated and unvaccinated cohorts and the estimation of risk, and contributes to causality assessment [2,12].

Our participants highlighted barriers in establishing vaccine specific analyses in large linked databases in Australia, despite the existence of many comprehensive, stand-alone electronic health databases. Unlike Denmark and Sweden [40], Australia does not maintain a unique, personal identification number to enable linkage between registers and probabilistic matching is required [19]. Further, in contrast to the nine healthcare organisations participating in the US Vaccine Safety Datalink, which maintain both individual electronic immunization registries and comprehensive healthcare information [36], in Australia, the national immunization register is maintained by the federal government while timely access to hospital inpatient and emergency department data is facilitated by State and Territory governments [20,41].

Proof of concept studies have linked the Australian Immunisation Register with various health care datasets, including the National Death Index [19] and hospitalisation data from selected States and Territories [20]. However, participants in our study echoed previously published concerns around complex application, approval and administrative processes [41], which have previously led researchers to suggest that linkage of the immunization register with other data sets is not feasible for routine or real-time surveillance [41,42], although it certainly has value for signal investigation and examination of AESI. In addition, vaccine doses are under-reported to the immunization register by providers [43], 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 [44].

The *National Immunisation Strategy for Australia 2019 to 2024* identifies the need to 'facilitate opportunities for linkage between national immunisation registers and other data collections' to enhance vaccine safety monitoring systems [28, p.25]; some of our participants expressed optimism that implementation of the COVID-19 immunization program may be a driver for change, if identified barriers can be overcome. Currently, work is ongoing within Australian jurisdictions to link data for the purposes of COVID-19 vaccine pharmacovigilance, including via jurisdictional linkage with 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 [45]. 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 AESI at a global level. Globally, distributed data networks are being implemented with common protocols, analytics and case definitions to assess vaccine safety using real world data, particularly for rare and population-specific events [12].

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 internationally, governance of vaccine safety is variably maintained by regulatory medicines authorities and/or government public health agencies [46–48]. Our participants discussed governance options including the increased utilisation of external organisations to support Government. In implementing the COVID-19 immunization program in Australia, relationships between the TGA and independent expert organisations have strengthened as the need to implement more enhanced pharmacovigilance strategies have become imperative.

Participants indicated they believed that transparency has improved over the past 10 years, which may reflect implementation of TGA reforms which aimed to improve community understanding of TGA processes and enhance public trust [11], 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 immunization program implementation [49]. As this 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 [50]. Similarly, the Australian Government has published multiple consumer and health provider communications in relation to COVID-19 vaccine safety [35]. The AusVaxSafety website also provides weekly data updates and information, with additional detail for COVID-19 vaccines [15]. Further, the TGA has periodically communicated the findings of a Vaccine Safety Investigation Group (VSIG), which has brought together individuals with relevant expertise to conduct regular and timely causality assessments, for example, for cases of anaphylaxis following COVID-19 vaccines and for TTS following the AstraZeneca COVID-19 vaccine [51].

There is significant potential for the *COVID-19 vaccine safety monitoring plan* and program implementation to strengthen the system and drive improvements identified here, including an enhanced ability to capture later onset AEFI. While evidence of improvement is already apparent, there is further work 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 a risk and a public perception point of view; enhancements driven by the implementation of Australia's COVID-19 immunization program should be embedded in routine safety surveillance for all vaccines. Equally, the need for a no-fault vaccine injury compensation scheme as part of the COVID-19 immunization program and for the NIP, was articulated by our participants and noted by other expert commentators to be '*overdue and essential*' [52]; we note this is ever more so in the context of vaccine attributable events such as TTS. We synthesised the thematic analysis to develop recommendations which are relevant both to the COVID-19 immunization program and the ongoing NIP (Table 3). These recommendations highlight the need for an integrated, multi-faceted and coordinated system, established within a clear governance framework. Systematic approaches for population-level active surveillance are an essential element of the vaccine pharmacovigilance system. The COVID-19 immunization program presents an opportunity to enhance capacity and sustain improvements for immunization programs going forward.

Our study offers a unique perspective of a key, ten-year period in Australia's vaccine safety journey, bookended by a significant vaccine safety event in 2010 and implementation of the COVID-19 immunization program in 2021. A strength of our study was the broad background of our participants, representing multiple levels of the post-marketing surveillance system, 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 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 availability 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. Conclusion

The perspectives of vaccine safety experts in Australia are hugely valuable at this critical point in time, ten years following the Horvath Review and during implementation of the COVID-19 immunization program. While AusVaxSafety-active is an innovative approach that may be valuable for other countries implementing a COVID-19 immunization program, 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 immunization and future programs.

Declaration of Competing Interest

The National Centre for Immunisation Research and Surveillance holds the AusVaxSafety contract from the Australian Government Department of Health.

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We thank the participants for sharing their time, expertise and insights.

Appendix 1

Interview guides Table A1.

Table A1
Interview guides.

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?

Table A1 (*continued*)

Participant from a Government organisation or national advisory group			
Q	Topic	Guiding questions	Planned follow up questions
			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

(*continued on next page*)

Table A1 (*continued*)

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?

Table A1 (*continued*)

Consumer participant			
Q	Topic	Guiding questions	Planned and potential follow up questions
			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?

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