Applied Epidemiology of Infectious Diseases in Western Australia

by

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A bound volume submitted to the Australian National University
to fulfil the requirements for the degree of Master of Philosophy in Applied Epidemiology (MAE)

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Government of **Western Australia**
Department of **Health**

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Author's Declaration

I hereby declare that the work herein now submitted as a bound volume for the degree of Master of Philosophy in Applied Epidemiology (MAE) of the Australian National University is the result of my own investigations, and all references to the ideas and work of other researchers have been specifically acknowledged. I hereby certify that the work embodied in this bound volume has not already been accepted in substance for any degree, and is not being currently submitted in candidature for any other degree.

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A note about terminology

I use the term ‘Aboriginal’ throughout this work to refer to the original inhabitants of Australia, that is all Aboriginal and Torres Strait Islander peoples. I use this term for conciseness and in preference to ‘Indigenous’.

Abstract

I commenced the Master of Philosophy in Applied Epidemiology (MAE) in February 2015. My field placements were shared between the Communicable Diseases Control Directorate, Public Health Division at the Western Australia Department of Health (CDCD) and the Telethon Kids Institute (TKI), both located in Perth.

Two of the three projects that I completed at the CDCD involved a statewide protracted mumps outbreak that went on for the duration of my MAE and reached almost 900 cases. The epidemiology of this outbreak including a discussion about vaccination is presented in Chapter 1. This satisfies the outbreak investigation requirement of the MAE.

Chapter 2 comprises a late draft manuscript that explores the vaccine effectiveness (VE) of the measles-mumps-rubella vaccine among paediatric cases during the mumps outbreak. I designed and carried out a matched case-control study using paediatric outbreak cases and controls from a population database. I measured VE using a conditional logistic regression model and compared it with the screening method. Both methods yielded a very low VE this population. This is likely due to a multitude of factors that are discussed in the chapter.

My work at TKI involved a data analysis using linked-administrative data on a total population birth cohort involving all children born in Western Australia between 1996-2012. I explored the burden of hospital separations that resulted from otitis media (OM), the most common infectious disease in children, and a common related procedure, myringotomy with ventilation tube insertion (MVTI). I calculated the age-specific hospitalisation rates for OM and MVTI over the study years. The second part of this analysis involved investigating the maternal and infant risk factors and population attributable fractions for OM-related hospitalisation in early life. This work was important because of its implications for practice. All of this is presented in Chapter 3.

Chapter 4 is an evaluation of SmartVax, a novel, real-time Adverse Events Following Immunisation (AEFI) surveillance system using SMS text messages to communicate directly with vaccinees after their vaccination. This was the third project that I completed at the CDCD. The chapter begins with a peer-reviewed publication, Continuous active surveillance of adverse events following immunisation using SMS technology, that describes the system and analyses data outputs for children <5 years from 2011-2015. I have included the publication first to provide a brief system overview including summarised surveillance data, to give context to the evaluation since SmartVax is a relatively new and developing system. The publication is followed by the formal evaluation.

Finally, I include a summary of the teaching exercises that I was involved in during my MAE. The first was a "lesson from the field" where I prepared an exercise for my fellow scholars. The exercise was useful for me and the feedback from my colleagues was positive. The second was a collaborative teaching exercise about confounding that we taught to the first year MAE scholars on their last day of courseblock.

These combined activities at both placements have enriched my understanding of epidemiology while working in health and research environments.

Acknowledgements

Now all glory to God... Eph 3:20

Without my family I would not have been able to complete the MAE. My wife Asha Bowen has been very supportive and provided excellent feedback throughout the course. She did not hesitate to look over my work and give constructive feedback like 'your sentences are too long" or "where did this denominator come from?" She was also a great sounding board for talking about infectious diseases and helping me to understand the concepts that were new to me. Mostly she has been there, filled in when I needed to write, given me time to do the work which meant not being able to do some of the work she needed to get done. Thank you. Also to my children who have given me perspective and laughter throughout the sometimes stressful times. I'm now looking forward to going on bike rides, reading books and going to the park!

Also a shout out to my mother-in-law Narelle for not hesitating to make the flight from Sydney to help keep things going at home when I was away at courseblock. You are an important part of the family and we all appreciate and love you very much.

I have had the opportunity to meet and work with a number of people over the two years of my MAE, all of whom have enriched my experience.

My field supervisors Paul Effler and Hannah Moore. I have been very fortunate to work with Paul and be welcomed into the Prevention and Control team. I've learned more about epidemiology from him than I ever could have from a textbook. I gleaned from the conversations we had about the mumps outbreak and vaccine safety surveillance. His passion for his work is evident. My writing has improved greatly from his 'editorial review' and I will "use my words wisely" and never forget the difference between sensitivity and specificity.

I have benefited from working under Hannah Moore's leadership. She has carefully guided me through the process of linked data analysis while giving me opportunities to expand and hone my data analysis skills by challenging me. She was very easy to approach when I had a question and was prompt with feedback about my work. I have learned a lot from her. Thank you. And…we still need to do the Cox Regression!

My supervisor at NCEPH, Stephanie Williams. To say I couldn't have done it without her would be an understatement. I was very fortunate to have Stephanie pushing me when I didn't want to be pushed, challenging my thinking when I wanted to take the easy way out. She has also helped me improve my writing skills by asking questions and forcing me to come up with the answers. I have benefitted from her expertise and have appreciated every bit of it. Well, all but this comment when I thought I was almost finished, "all the elements of the chapter are here, I think it is about 35% finished."

Deborah Lehmann has been an amazing support at the Telethon Kids Institute. Her knowledge about otitis media and willingness to share that knowledge is one of the reasons I've succeeded. She was always happy to answer my questions and posed great thoughts to consider. And, there's always a good reason for a party!

I'd also like to acknowledge and thank Parveen Fathima, Janice Lim, Tasnim Abdulla on my team. Particularly Parveen and Janice for a lot of the data cleaning that took place before I started, that made my life a little easier! Of course for that laughs, laughs and more laughs…and chocolate.

Kingsley Wong, Nick De Klerk and Peter Jacoby for being willing to help with my stats questions.

Peter Richmond for your support through two years of SmartVax, mumps and otitis media.

Chris Blyth who helped make my MAE field placements possible. He went out of his way to help organise my placements here in Perth and did so out of his kind generosity and for that I'm grateful. Without his connections and effort, I may not have had such an awesome experience.

為せば成る
為さねば成らぬ何事も
成らぬは人の為さぬなりけり

Japanese Poem

Translation
If you try, you may succeed
If you don't try you will not succeed. This is true for all things.
Not succeeding is the result of not trying.

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Summary of Competencies required for the degree of Masters of Philosophy in Applied Epidemiology, February 2015 – November 2016

	Chapter 1	Chapter 2	Chapter 3	Chapter 4	Chapter 5
	Epidemiology of a protracted mumps outbreak in Western Australia	Vaccine effectiveness during a mumps outbreak: a matched case-control study	The burden of otitis media in a Western Australian birth cohort	Vaccine safety surveillance using SMS: an evaluation of SmartVax	Teaching and lessons from the field
Investigate a disease outbreak	✓	✓			
Analyse a public health dataset			✓	✓	
Evaluate a surveillance or other health information system				✓	
Design and conduct an epidemiological study		✓			
Conduct a literature review	✓	✓	✓	✓	
A relevant report to non-scientific audience			✓		
Preparation of an advance paper for publication		✓		✓	
Abstract and oral presentation at national or international conference	✓	✓	✓	✓	
Plain language summary			✓		
Teaching					✓

Summary of MAE presentations and travel awards

International Conferences

Westphal DW. Surveillance of adverse events following immunization using text messages. The Council of State and Territorial Epidemiologists Annual Conference. Anchorage AK USA 18-22 June 2016 (Oral presentation).

Westphal D, Williams S, Effler P. The epidemiology and vaccine effectiveness of a large mumps outbreak in Western Australia. European Society of Pediatric Infectious Diseases (ESPID). Brighton UK 10-13 May 2016 (Oral presentation).

Westphal D, Williams S, Leeb A, Effler P. Using SMS technology for real-time surveillance of adverse events following immunisation. European Society of Pediatric Infectious Diseases (ESPID). Brighton UK 10-13 May 2016 (Oral presentation).

National Conferences

Westphal D, Lehmann D, Richmond P, Lannigan F, Williams S, Moore H. The burden of otitis media in a Western Australian birth cohort. Otitis Media in Australia (OMOz) Conference 2016. Newcastle NSW Australia 13-15 September 2016 (Oral presentation).

Effler P, **Westphal D**, Giele C, Levy A, Chua J, Dowse G. A large prolonged mumps outbreak in highly vaccinated Aboriginal Western Australians. Australian Society of Microbiology 2016 Annual Meeting. Perth 2-4 July 2016 (Oral presentation by co-author).

Westphal D, Quinn H, Williams S, Effler P. Vaccine Effectiveness during a mumps outbreak in Western Australia. Public Health Association of Australia, National Immunisation Conference. Brisbane 7-9 June 2016 (Oral presentation).

Westphal D, Williams S, Leeb A, Effler P. SmartVax: Real-time surveillance of adverse events following immunisation. Public Health Association of Australia, National Immunisation Conference. Brisbane 7-9 June 2016 (Oral presentation).

Westphal D, Giele C, Levy A, Chua J, Williams S, Effler P, Dowse G. A Second Prolonged Mumps Outbreak in Highly Vaccinated Aboriginal Western Australians. Public Health Association of Australia, National Immunisation Conference. Brisbane 7-9 June 2016 (Poster).

Oral presentations at local meetings

Westphal D, Lehmann D, Richmond P, Lannigan F, Williams S, Moore H. Otitis media hospitalisations and risk factors in Western Australian children: a retrospective population cohort study using linked data. Scientific Retreat, Telethon Kids Institute 14-15 November 2016 (Oral presentation).

Westphal D, Quinn H, Williams S, Effler P. Vaccine Effectiveness during a mumps outbreak in Western Australia. PHAA National Immunisation WA Road Show. 1 August 2016 (Oral presentation).

Westphal D, Williams S, Leeb A, Effler P. SmartVax: Real-time surveillance of adverse events following immunisation. PHAA National Immunisation WA Road Show. 1 August 2016 (Oral presentation).

Westphal D, Williams S, Leeb A, Effler P. Using SMS technology for real-time surveillance of adverse events following immunisation. Inspired by Infectious Diseases Breakfast Meeting, Telethon Kids Institute, 7 April 2016.

Westphal D, Dowse G. Epidemiology of Mumps in Western Australia. Public Health Nurses Statewide Update. Communicable Disease Control Directorate, Public Health Division, Western Australia Department of Health 24 November 2015.

Westphal D, Leeb A. Adverse events following immunisation surveillance in General Practice. Biennial Communicable Disease Control Network Australia Conference, WA Road Show. Perth 22 October 2015

Travel Awards

1. Vice Chancellor Travel Grant, Australian National University, awarded $1,500 to attend the Council of State and Territorial Epidemiologists meeting in Anchorage, Alaska to present an oral abstract.
2. Peter Baume Travel Scholarship, National Centre for Epidemiology & Population Health, awarded $1,000 to attend the European Society of Pediatric Infectious Diseases meeting in Brighton UK to present two oral abstracts.
3. Centre of Research Excellence in Ear and Hearing Health of Aboriginal and Torres Strait Islander Children, awarded conference registration fees, conference dinner and $500 toward travel expenses to attend OMOz 2016, the Australian Otitis Media annual meeting in Newcastle NSW to present an oral abstract
4. Friends of the Telethon Kids Institute, awarded $679.10 to cover additional expenses to attend OMOz 2016, the Australian Otitis Media annual meeting in Newcastle NSW to present an oral abstract

The epidemiology of a protracted mumps outbreak in remote Western Australia predominantly among highly vaccinated Aboriginal people

List of abbreviations

ACIR	Australian Childhood Immunisation Register
ATAGI	Australian Technical Advisory Group on Immunisation
CDCD	Communicable Disease Control Directorate
IgG	immunoglobulin G
IgM	immunoglobulin M
MMR	measles mumps rubella
MMRV	measles mumps rubella varicella
NCIRS	National Centre for Immunisation Research & Surveillance
NIP	National Immunisation Program
PCR	polymerase chain reaction
PHAA	Public Health Association of Australia
PHU	public health unit
RNA	Ribonucleic acid
SH	small hydrophobic
VE	vaccine effectiveness
WA	Western Australia
WACHS	Western Australia Country Health Service
WANIDD	Western Australia Notifiable Infectious Diseases Database

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Prologue

Role

My primary role was coordinating surveillance and response to the outbreak on a statewide basis under the leadership of the medical epidemiologist, Dr. Gary Dowse, in the Communicable Disease Prevention and Control Directorate (CDCD), Public Health Division, Western Australia Department of Health (WA Health). I became involved two months after the outbreak began. As part of my role, I gathered epidemiological information throughout the outbreak, collected and analysed data, prepared epidemiological curves for our team and for the regions affected by the outbreak and supplied epidemiological data related to the outbreak to present at meetings. I also communicated with individuals in the public health units, answered questions and provided information as needed. There was frequent, and at times, daily communication between the public health units in the regions and the CDCD in Perth. I wrote and revised this chapter and completed the analyses. Dr. Gary Dowse compiled and provided data used in **Table 7**.

Lessons learned

- It is challenging but not insurmountable to action infectious disease control in Aboriginal communities. It requires patience and perseverance.
- The complexities of delivering health care in remote communities.
- The importance of communication and collaboration with those on the ground, in the regions, controlling the outbreak to ensure continuity.

The final point was challenging because many of the health region staff were already stretched thin with the work required to control this outbreak as well as the other work they needed to do. For example, in the Kimberley early during the mumps outbreak there was also a syphilis and Leprosy outbreak that needed health service attention. At the CDCD we had an

expectation that information would be entered into the WA notifiable infectious diseases database (WANIDD) within two days by staff in the regional PHUs, however that was difficult when mumps was not the only thing going on. I was also stretched thin. I had three other projects that I needed to work on and, at times, I found it difficult to negotiate the time. I made a commitment to provide epidemic curves to the Kimberley and then the other regions as the outbreak spread throughout the state. Weekly updates soon became monthly. This outbreak continued for the whole duration of my MAE.

If I had the chance to do it over again I would schedule monthly teleconferences with the affected regions just to stay connected and have the opportunity to share stories.

Public health impact

I organised and convened a national mumps outbreak control forum in April 2016. This meeting brought together high level decision makers in WA from health, research and laboratory backgrounds to discuss current outbreak control activities and possible research to prevent future mumps outbreaks in this population. In addition to local attendees, the meeting also had representation by teleconference from the National Centre for Immunisation Research and Surveillance and the Australian Technical Advisory Group on Immunisation. After the meeting I prepared the minutes and scheduled a follow-up meeting for a smaller mumps research group. The agenda and minutes of the outbreak control forum are in **Appendix 1**.

For three days in December 2015, I had the opportunity to accompany a small group of nurses on a visit to a remote Aboriginal community in the Western Desert to support them in provision of community-wide measles-mumps-rubella vaccinations. My role on the trip was "logistician." I helped the public health nurses obtain informed consent from residents and prepared the vaccination supplies. I did not vaccinate as I am not a registered health

professional. On the first day, we began vaccinating opportunistically in the clinic. When it slowed we discussed going out into the community, where the residents were, to take the intervention to them. It was a hot day and many of the residents told us later that they just wanted to stay in the shade. We went out into the community door-to-door and talked to people, explained why we were there, asked if they would like to be vaccinated, which many people took up. In fact, one woman close to 70 insisted that she be vaccinated. After the nurse explained that it wasn't necessary for her she wouldn't hear of it, so she got one too. We believe that we vaccinated approximately 60% of the community. No further transmission beyond a single incubation period was reported in this community. I learned that being flexible, having an open mind and being able to deviate from the plan made a big difference. We did the walking, met people where they lived and did not expect people to come to us, we were able to make a difference.

There were several opportunities to present details about this outbreak over the period of my MAE. The first was at the Public Health Nurses Statewide Update meeting on 25 November 2015 where I presented the epidemiology of mumps in Western Australia (WA) including the epidemiology of the current outbreak. The next opportunity was when I presented an oral abstract at the European Society of Pediatric Infectious Diseases (ESPID) in Brighton, United Kingdom (UK) in May 2016. It was a combined World Health Organization/European Centre for Disease Prevention and Control session that was very well attended. A number of conference delegates approached me after the talk to discuss the outbreak and vaccine effectiveness (Chapter 2). One person was managing a mumps outbreak in the UK and we discussed the control activities we were using in WA. The slides from this presentation can be found in Chapter 2, Appendix 2. I also prepared a poster about this outbreak and presented it at the Public Health Association of Australia (PHAA) National Immunisation Conference in June 2016 (**Appendix 2**).

At the time of writing, transmission had slowed but had not yet ceased, although we believe it will soon. I intend to work closely with a writing group comprised of individuals from the public health regions in WA Country Health Service (WACHS). These staff were involved in the day-to-day control of the outbreak in their respective regions. We hope to document this outbreak and the lessons learned to feed back to the regions and publish in a scientific medical journal. My hope is that the forthcoming manuscript will be of interest and use to others. There is also ongoing work to plan future studies that will help us to understand what happened that caused so many vaccinated Aboriginal Western Australians living in remote parts of the state to get mumps.

Acknowledgments

First of all, I would like to thank all of the staff in the Public and Population Health Units, both as part of the Western Australia Country Health Service and the North and South Metropolitan Health Services. These nurses and staff worked tirelessly to keep ahead of this outbreak, worked overtime, and provided valuable information that went into compiling this chapter.

I would like to thank Dr. Gary Dowse for his leadership, guidance and no nonsense approach to managing this outbreak. I learned a great deal from him. To Paul Effler, for the many discussions and musings about the outbreak and hypothesising. I learned about how to go about answering some of those questions. I appreciated being able to glean from his experience and expertise. Carolien Giele, for the chats and help along the way. To Avram Levy and Joanna Chua at PathWest for graciously indulging my questions about genotyping and laboratory procedures. Thanks to Clare Huppatz and Gary Dowse for proof-reading the chapter and providing feedback.

Abstract

Background

Between 2009 and 2014, an average number of 23 cases of mumps were notified annually in Western Australia (WA). This primarily reflected overseas acquisition of mumps with some limited local transmission. Prior to this, in 2007 to 2008, there was a large outbreak due to genotype J mumps virus. This outbreak primarily affected young highly vaccinated Aboriginal people from the Kimberley, a geographically remote region of the state. We describe here the investigation of an even larger outbreak that commenced in the Kimberley region in March 2015 before spreading to other remote parts of the state and metropolitan boarding schools.

Methods

Mumps is notifiable by laboratories in WA. Cases were either laboratory confirmed or epidemiologically linked to a laboratory-confirmed case. Laboratory diagnosis was by polymerase chain reaction and/or serology. I extracted case information from the WA notifiable infectious diseases database and described demographic characteristics, vaccination status, outbreak control activities and laboratory details.

Results

Between 3 March 2015 and 30 September 2016, 884 outbreak-related mumps cases were notified. Of these, 89.1% were Aboriginal and 51.7% were male. The median age was 21 years (range 8 months to 64 years). The highest proportion of cases was among Aboriginal Australians aged between 10-19 years. Of cases <20 years, 25/410 (6.1%) were partially (1 dose) and 353/410 (86.1%) fully (2 doses) vaccinated against mumps. Overall, 40/884 (4.5%) of cases were hospitalised and 28/457 (6.1%) of males reported symptoms of orchitis. A total of 170/225 (75.6%) mumps samples were successfully genotyped and all were genotype G.

Discussion

This is another example of a growing number of mumps outbreaks reported in recent years in highly vaccinated populations. That this outbreak disproportionately affected Aboriginal Western Australians living in remote WA, and only 7 years after a similar outbreak, is exceptional. Further studies that help to explain the apparent higher susceptibility of Aboriginal people in WA to mumps are needed.

1.0 Background

1.1 Mumps illness

Mumps is an acute, vaccine-preventable viral disease. It is an enveloped, negative-strand RNA virus in the *Paramyxoviridae* family, genus Rubulavirus.[1,2] A classic feature of mumps infection is swelling of one or both of the parotid salivary glands, known as parotitis.[3,4] Mumps illness transmission is by droplet or by contact with contaminated fomites.[3,4] The incubation period is between 16-18 days (range 12-25 days) and maximum infectivity is from two days before to five days after the onset of symptoms. Approximately 30-40% of infections are asymptomatic, despite this they are still infectious.[1,3,5]

Following incubation, the prodromal period is marked by low grade fever, headache, malaise and myalgia which often precede parotitis.[1] Whilst primarily mild and self-limiting, mumps complications include orchitis in males and oophoritis in females. Orchitis is the most commonly occurring complication in post-pubescent males and prior to widespread vaccination it affected up to 30% of clinical cases.[3] Orchitis among vaccinated cases is lower, however, generally <10%.[6]

Mumps orchitis is an important complication, known to cause sterility, albeit rare. It can cause subfertility,[5] testicular atrophy and azoospermia.[7] While a number of studies have tried to find an association between mumps orchitis and testicular cancer,[8-10] only one reported an association, but with a very small sample size.[11] Post-pubescent females can experience oophoritis and mastitis[12] but these are uncommon. Other less common but serious complications include meningitis, pancreatitis, encephalitis[13] and sensorineural deafness.[14]

1.2 Mumps vaccine in Australia

The monovalent, live attenuated mumps vaccine (Jeryl-Lynn strain) was first registered for use in Australia in 1980 and recommended for children at 12 months of age in 1981, before a transition to the combined measles-mumps vaccine in 1982.[15] In 1989, the measles-mumps dose at 12 months of age was replaced with measles-mumps-rubella (MMR) vaccine and in 1992 a two-dose MMR schedule was recommended and funded for all children (**Table 1**). In 1998 a catch-up was offered to children between 4-16 years such that anyone born from 1981 and, hence aged below 33 years when the

outbreak began, would have been eligible for two doses of a mumps-containing vaccine.[16] However, those born between 1978 and 1982, *i.e*. aged 33-37 years, were less likely to have been vaccinated (including the catch-up campaign) and less likely to have natural immunity from wild-type mumps exposure due to decreasing mumps disease incidence.[16] Since widespread vaccination for mumps in Australia, there has been a subsequent decline from 59,000 cases in 1969[17] to an average of 198 per year between 2000-2014.[18]

Table 1. Key dates in mumps vaccine scheduling in Australia[15,19]

Year	First dose 12 months	Second dose 18 months	Second dose 4-5 years	Second dose 12 years
1981	M			
1982	MM			
1989	MMR			
1992	MMR			MMR
1998	MMR		MMR	
2013	MMR	MMRV		

Abbreviations: M, mumps; MM, measles-mumps; MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella

1.3 Setting and population

Western Australia (WA) is Australia's largest state, covering one-third of the landmass of the country. Outside of the south-western corner, the state is sparsely populated. There are only 2.5 million residents, 1.9 million of whom live in the southern capital, Perth.[20] Outside of Perth, the state is generally divided into seven regional areas for administrative purposes, including provision of medical and public health services. These areas make up the WA Country Health Service (WACHS). They are the Kimberley, Pilbara, Midwest, Goldfields, Wheatbelt, South West, and Great Southern (**Figure 1**). Four percent of the WA population identify as Aboriginal, however a greater proportion of Aboriginal people reside outside of the capital (**Table 2**)[21]

Table 2. Population of Western Australia by region and proportion by Aboriginal status, 2013[20,22]

Region	Aboriginal			Non-Aboriginal			Total
	n	% of region	% of state	n	% of region	% of state	
Kimberley	17,153	43%	18%	22,737	57%	1%	39,890
Pilbara	10,608	16%	11%	55,690	84%	2%	66,298
Midwest	8,136	12%	9%	59,664	88%	2%	67,800
Goldfields	7,157	12%	7%	52,481	88%	2%	59,638
Wheatbelt	3,951	5%	4%	73,528	95%	3%	77,480
Great Southern	2,338	4%	2%	59,184	96%	2%	61,522
South West	4,412	3%	5%	165,270	97%	7%	169,682
Metropolitan	41,714	2%	44%	1,928,286	98%	80%	1,970,000
Total	95,468		4%	2,416,842		96%	2,512,310

1.4 Mumps in WA

In 2007—2008 a mumps outbreak occurred in the Kimberley region in the northern part of the state covering 423,517 km^2. In total, 183 cases were notified, 153 (83.6%) of whom lived in the Kimberley or were epidemiologically-linked to the Kimberley outbreak. This outbreak disproportionately affected Aboriginal Australians 141/153 (92.2%). Details of the 2007-2008 outbreak are reported elsewhere.[23] Prior to this, between 1995 and 2007 a total of only 10 mumps cases were reported from the Kimberley (Communicable Disease Control Directorate (CDCD), unpublished data). Between 2009 and 2014 an average of 23 mumps cases were notified in the state each year (range 14-45),[18] primarily representing overseas acquired illness with some limited local transmission (CDCD, unpublished data).

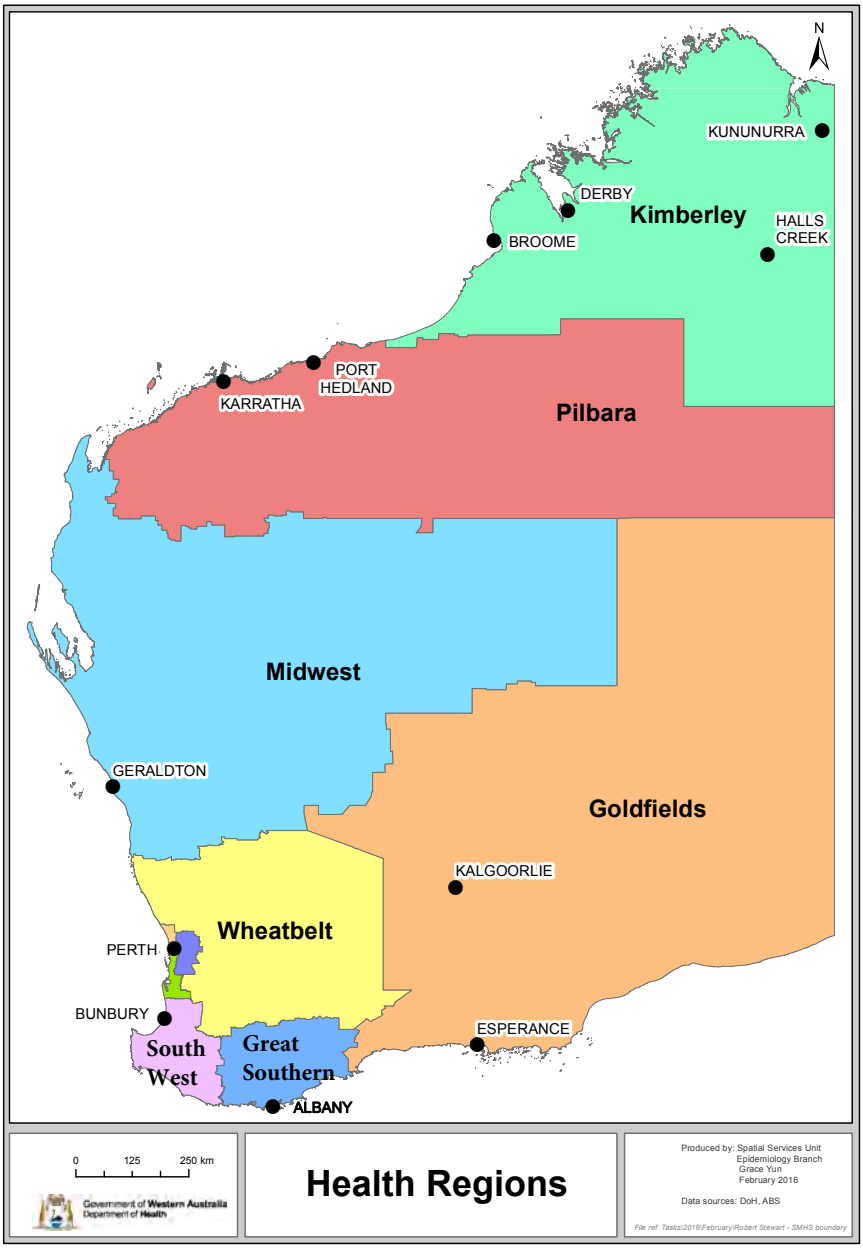

Figure 1. Health and geographic regions of Western Australia
(map reproduced with permission)

1.5 Mumps disease control guidelines in Western Australia

Mumps is one of 79 notifiable infectious diseases under the WA Health Act 1911. Case confirmation is based on the case definition published in *Surveillance Case Definitions for Notifiable Infectious Diseases and Related Conditions in Western Australia*[24] and by the Communicable Diseases Network of Australia.[25]

When suspected mumps cases are identified, laboratory confirmation is performed, usually using buccal swab polymerase chain reaction (PCR) or serology.

As per standard procedure, following notification to the Department of Health, public health nurses or a public health physician employed by regional Public (or Population) Health Units (PHU), contact cases to ascertain disease acquisition details, vaccination status, and identify any contacts that may be at risk (i.e. under-vaccinated). Cases in this outbreak were advised to self-isolate (refrain from attending school or work) for up to five days following the onset of parotitis. Contacts identified through case-interview were given advice about mumps symptoms in case they contracted it. Contacts were also advised to get vaccinated, but that vaccination would only prevent disease if they had not already been exposed.

When a greater than expected number of cases are identified in a community, based on the epidemiological context, an "outbreak" may be identified, with an escalation of the public health response. Once confirmed to meet the case definition, cases are entered onto the WA Notifiable Infectious Diseases Database (WANIDD) by the WANIDD clerk at CDCD. This is done for all (statewide) laboratory-notified cases and doctor-notified cases from metropolitan Perth; or by a regional public health officer for doctor-notified cases in country regions. Given the multi-jurisdictional nature of this outbreak, the WACHS PHU staff in conjunction with the CDCD developed mumps control guidelines for this outbreak, however they were not in widespread use until November 2015.

1.6 Outbreak surveillance

In April 2015, four mumps cases were notified by PathWest, the state tertiary reference laboratory, three from the same East Kimberley remote community. Weekly notifications were discussed at an epidemiology team meeting at CDCD in Perth. The Centers for Disease control and Prevention (CDC) in the United States of America (US) define a mumps outbreak as three or more cases linked by time and place.[26] These three notifications represented an increase from the expected background rates. This cluster led to a local alert to healthcare providers in the region for enhanced surveillance.

A fifth case who lived in a nearby community was retrospectively identified through routine case follow-up. She spent the school holidays in the same community in which the three cases resided. This case had an illness onset date of 3 March 2015, around one incubation period before the other three notified cases. This case was considered to be the index case, however no source was identified, and the 3rd of March 2015 was considered the first day of the outbreak.

1.7 Aims of Investigation and control activities

The aim was to describe the epidemiological features of the outbreak including: incidence by time, place and personal characteristics (age, sex, Aboriginal status, vaccination status); the frequency of hospitalisation and complications; and laboratory features. Outbreak control activities – which involved vaccinating contacts who were not appropriately vaccinated for age and administering booster doses of MMR vaccine (usually a third dose) in boarding schools and Aboriginal communities where cases had occurred in an attempt to interrupt transmission.

2.0 Methods

2.1 Epidemiological analysis

Descriptive epidemiological analyses of the mumps outbreak were performed.

Outbreak case definition

Cases were notified between 1 March 2015 and 30 September 2016

AND

lived in or visited a community in WA where there was active mumps transmission, *i.e.* there were other confirmed mumps cases with disease onset within the case's incubation period.

AND

were classified as either confirmed or probable outbreak cases where

a confirmed case:

- was laboratory-confirmed by polymerase chain reaction (PCR) for mumps or had isolation of mumps virus **OR**
- had clinical evidence, *i.e.* acute parotitis or swelling of other salivary glands lasting two or more days and detection of mumps IgM (where there was no recent mumps vaccination) **OR**

- had acute parotitis or swelling of other salivary glands **and** had an epidemiological link to a laboratory-confirmed case by PCR or mumps isolation

where an epidemiological link involved contact between two or more people where at least one person was infectious and the other contracted disease within the incubation period (*i.e.* between 12-25 days) and at least one person in the chain was laboratory-confirmed.[25]

A probable case was a person who:

- had clinical evidence of mumps illness (in the absence of another possible diagnosis).

All probable and confirmed cases meeting the case definition were included and reporting combined for this analysis.

Case information including demographics, clinical and laboratory details, Aboriginality and vaccination status was also available in the WANIDD. Confirmation of vaccination status was through the Australian Childhood Immunisation Register (ACIR), a population register with vaccination records for all children born after 1995, who are enrolled in Australia's publicly-funded health system,[27] Health Care and Related Events (HCARe), or a medical record management system used by the regional PHUs, particularly for older individuals who were vaccinated before the commencement of the ACIR.

2.2 Data extraction

De-identified data for notified mumps cases in WA (with date of onset between 1 March 2015 and 30 September 2016) were extracted from WANIDD.

2.3 Control measures including vaccination

In the absence of mumps outbreak guidelines in Australia, local guidelines were developed early in the outbreak, and were informed by the US CDC mumps outbreak control guidelines[26] and other sources.[3] In short, prevention and control strategies included prompt follow-up of cases and provision of information and advice regarding isolation and infection control; contact tracing (with provision of information to contacts); community and region-wide awareness-raising (through mass media, posters, etc.); alerts to doctors and clinics with information promoting catch-up vaccination and the need for prompt diagnosis, appropriate laboratory testing and notification of all cases; and booster vaccination

strategies designed to limit ongoing transmission within and between communities, by reducing the number of people susceptible to mumps due to waning immunity or under-vaccination. Booster vaccination took the form of 1) vaccination of all members of households and other close contacts of cases (*e.g.* classmates or sports teammates) and where appropriate 2) an intervention involving an additional dose of MMR (usually MMR3) in boarding schools or other defined community setting (*e.g.* population small enough to achieve high vaccination coverage within a short period of time). Vaccination control measures were implemented using a sequential approach that included:

1. In communities where cases had not yet been identified but where there was transmission elsewhere in the region, age-appropriate catch-up vaccination was offered within the entire region with oversight by the PHUs;
2. When the first sporadic case in a community or at a boarding school was identified, vaccination catch-ups or booster doses were offered to all household members (or boarding school houses) and defined close contacts;
3. When the second or more cases were identified in a community, MMR booster vaccinations (usually MMR3) were offered to all community members or boarders aged between 8 and 40 years (or similar age-range), where logistically feasible.

2.3.1 Household vaccination

In households with an identified mumps case, the vaccination status of children aged <8 years was checked to ensure they were up to date and if not, they were offered a catch-up dose. Other household members between 8 and 40 years (or similar age-range) in whom vaccination was not contraindicated (*e.g.* pregnant women) were offered a booster dose, irrespective of their previous MMR vaccination history due to the possibility of waning vaccine immunity.

2.3.2 Booster MMR intervention

Booster doses (usually MMR3, at least in individuals aged <25 years in whom documentation of prior vaccination history was most reliable) were provided as a ring-fencing strategy to prevent further spread within and beyond boarding schools and discrete communities, where feasible. Vaccination

status was not checked and all residents aged 8 to 40 years (or similar range) were offered a dose of MMR.

These communities and boarding schools were monitored for further transmission to determine the effectiveness of the intervention in preventing further cases.

2.4 Laboratory testing

Specimen collection for suspected mumps cases included urine, buccal (mouth or throat) swabs and/or blood. Testing was mostly undertaken at PathWest Laboratory Medicine in Perth because the remote regions in which most cases occurred are serviced in the main by PathWest. Detection of mumps specific Immunoglobulin (Ig) M and IgG antibodies was performed using enzyme immunoassay and immunofluorescence. Real time PCR targeting the nucleoprotein gene was completed on oral swabs and urine samples, only at PathWest (including on samples referred from private pathology providers).

For PCR, an amplification curve with crossing threshold value (CT) of below 40 was considered positive, repeatable CT above 40 was considered equivocal and no amplification curve was negative (Avram Levy, PathWest scientist, personal communication). All PCR-positive and IgM positive cases were reported directly to the CDCD. Genotyping of mumps virus was completed by PathWest scientists on selected cases—usually the first new case in a community, initial cases in a new region (that had not previously had mumps cases in the current outbreak), intermittently on subsequent cases in order to document genetic changes; and on those requested by the CDCD (*e.g.* to rule out possible vaccine-induced infection in recently vaccinated cases) using small hydrophobic (SH) sequence analysis and methods described by the World Health Organization (WHO).[28] The prototype sequence (genotype G) for the 2015/2016 outbreak was first identified in Perth in 2013, and this was used as the comparator sequence throughout the current outbreak.

2.5 Statistical analysis

Demographic characteristics of cases were presented as proportions and compared using chi-squared or Fisher's exact tests, where appropriate. Analyses were conducted using Stata 14.2.

2.6 Ethics statement

Ethics approval was not required as this outbreak investigation was conducted in the context of legally required notification and public health control under the WA Health Act 1911, as part of the author's formal student attachment to CDCD in the WA Department of Health.

3.0 Results

3.1 Epidemiological investigation

In WA, between 3 March 2015 and 30 September 2016, a total of 920 mumps cases were reported to the CDCD. A total of 36 cases did not meet the case definition (*e.g.* had overseas acquired disease or no epidemiological link to outbreak). A total of 884 cases met the outbreak case definition and were included in the analysis.

After the first cluster of cases in the East Kimberley region, there was sustained disease spread across the region to other remote communities and towns, including Broome, the regional administrative centre. In May 2015, cases with epidemiological links to confirmed cases in the Kimberley were identified in a boarding school in the Goldfields in the southern part of the state, and in June at a boarding school in Perth. In July, cases from the Pilbara region were notified following a regional football match involving Kimberley and Pilbara teams. In September, cases from the Goldfields region were reported, followed in October by cases from the Midwest (**Figure 1**). After an initial decrease of case notifications from the Kimberley in November 2015, there was a second wave in late December and January 2016 that continued for another six months with a trickling of cases through September 2016. The second wave affected towns in the East Kimberley that were not affected during the early part of the outbreak. At the end of October another cluster of cases at a different Perth boarding school to the previous, epidemiologically-linked to the Pilbara, were notified.

Of the 884 cases, 444 (50.2%) were residents from the Kimberley, 228 (25.9%) Pilbara, 117 (13.2%) Goldfields, 52 (5.9%) Midwest, 34 (3.9%) metropolitan Perth and the remaining 9 (1.0%) were from other regions in WA. One case that was included in the Kimberley was visiting WA from another state. There were two cases who acquired disease in WA and then relocated to another state during

their incubation period to attend a boarding school, those two cases, while meeting the outbreak case definition, were not included in these analyses because of lack of access to case information. The total number of cases from each region and the proportion of cases that were Aboriginal compared with the population of that region is summarised in **Table 3**.

Figure 2 shows the weekly number of notified cases by region. There were two temporal peaks in the notification of cases, October 2015 and February 2016, as well as an additional aberrant peak in early August 2015.

Table 3. Proportion of Aboriginal mumps outbreak cases compared with the proportion of Aboriginal residents, by region

Region	Aboriginal cases/all cases (%)	Proportion of region population identifying as Aboriginal (%)
Kimberley	396/444 (89.2)	44.0
Pilbara	209/228 (91.7)	16.0
Midwest	39/52 (75.0)	11.5
Goldfields	111/117 (94.9)	9.7
Wheatbelt	8/9 (88.9)	4.9
Perth	24/34 (70.6)*	2.0

*17 of the 24 Aboriginal cases in Perth attended boarding schools and were epidemiologically linked to rural and remote parts of the state. Only 7 Aboriginal cases were residents of Perth.

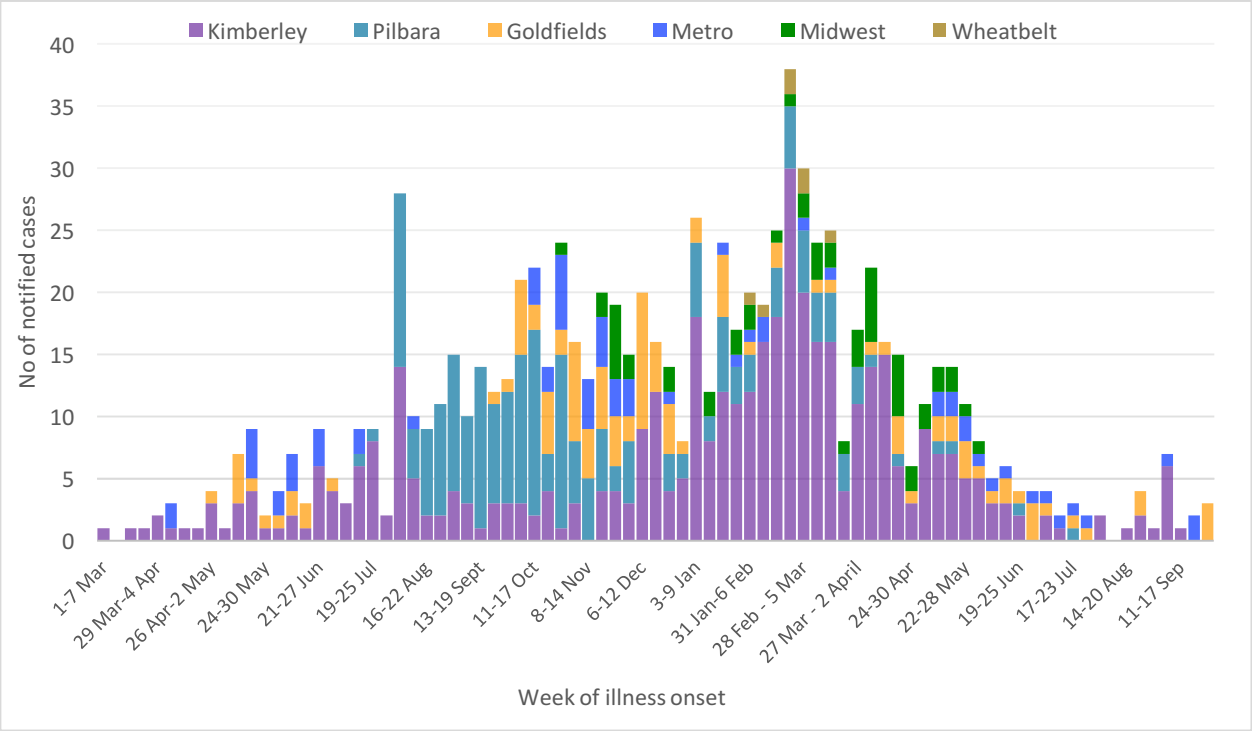

Figure 2. Epidemic curve of mumps outbreak cases in Western Australia by region affected from March 2015 through September 2016 (n=884)

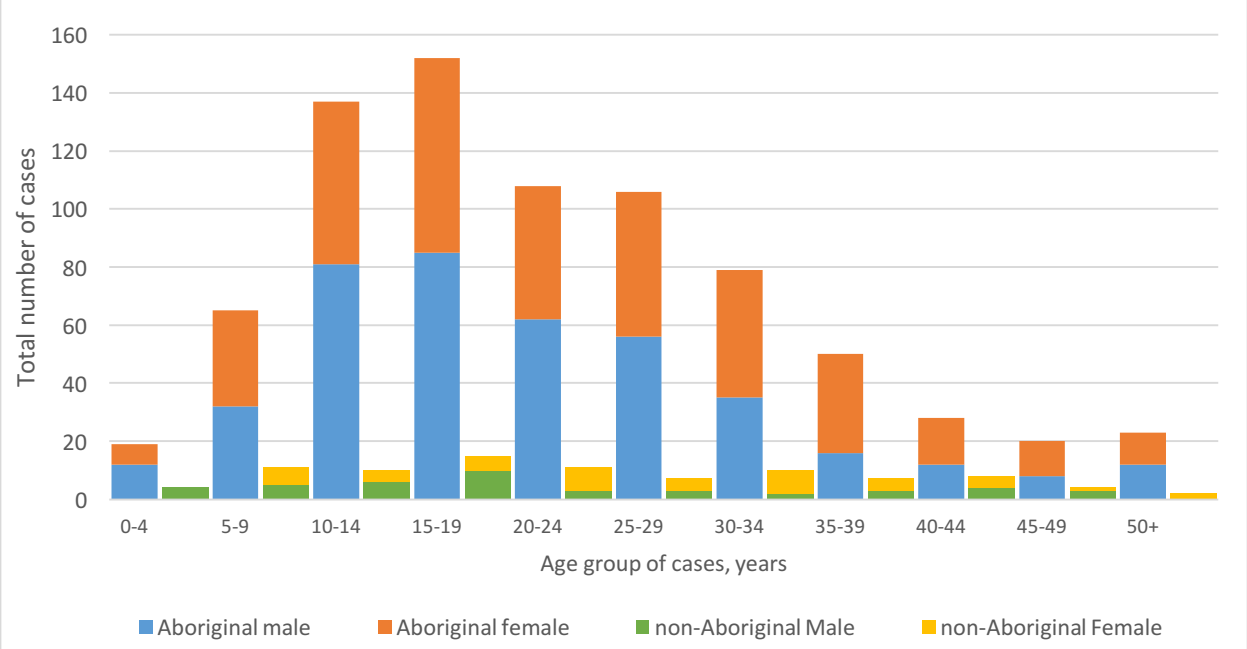

Figure 3. Total number of mumps cases by age group, sex and Aboriginal status, Western Australia 2015-2016, (n=884)

Just over half of the 884 cases were male 457 (51.7%) (**Figure 3**). Of all cases, 785/884 (88.8%) were Aboriginal and two were Torres Strait Islanders. There were eight cases where Aboriginal status was

not recorded. Of the Aboriginal cases, 779/787 (99.0%) were from rural and remote regions of the state compared to only 7/787 (0.9%) Aboriginal cases in metropolitan Perth.

The highest proportion of cases for both Aboriginal and non-Aboriginal people were aged 15-19 years. The total number of mumps cases by age group, sex and Aboriginal status is presented in

Figure 3.

There was a total of 824/884 (93.2%) confirmed cases and 60/884 (6.8%) probable cases.

3.2 Hospitalisation and complications

Clinical information was not available for all cases. The most common symptom documented in WANIDD was parotitis (either unilateral or bilateral), which was reported in 671/884 (75.9%) of cases. However, it was assumed that parotitis would have been the presenting symptom for the great majority of cases.

PHUs were asked to document hospitalisation (a fixed field) or complications of mumps such as orchitis, oophoritis or meningitis in the free text clinical comments field in the case's WANIDD record. No complication other than orchitis were reported.

Orchitis was reported in 26 of 457 (5.7%) male cases. There were 40 of 884 cases hospitalised during the outbreak, three of whom reported orchitis.

The relationship between vaccination status and either orchitis or hospitalisation was assessed. Those who had completed a full course of vaccination appeared to have reported fewer hospitalisations or orchitis, although this observation was complicated by the high rate of missing data making data on this table difficult to interpret (**Table 4**) The age of males who reported orchitis ranged from between 15-44 (mean age 26 years) and the highest proportion of cases who were hospitalised were in the 15-19 year age group (**Table 5**).

Table 4. Risk of hospitalisation or orchitis related to vaccination status during a mumps outbreak in Western Australia, 2015-2016

	Vaccination status			
All cases	Unknown/missing n= 222	Unvaccinated n=28	One Dose n=107	Two Doses n=527
Hospitalised n(%) N=884	4 (1.8%)	2 (7.1%)	9 (8.4%)	25 (4.7%)
Male only	n=99	n=14	n=61	n=283
Orchitis n=457	8 (8.1%)	0 (0%)	5 (8.2%)	13 (4.6%)

Table 5. Age of cases reporting hospitalisation or orchitis during a mumps outbreak in Western Australia, 2015-2016

Age group, years	Hospitalised n=40/884 n(%)	Orchitis n=26/457 n (%)
0-4	3 (7.5%)	0
5-9	2 (5.0%)	0
10-14	6 (15%)	0
15-19	9 (22.5%)	6 (23.1%)
20-24	3 (7.5%)	6 (23.1%)
25-29	6 (15%)	5 (19.2%)
30-34	4 (10%)	3 (11.5%)
35-39	6 (15%)	5 (19.2%)
40+	1 (2.5%)	1 (3.8%)

3.3 Vaccination Status

Six cases were under 12 months of age and would not have been eligible for vaccination. Vaccination status was available for 388/415 (93.5%) cases who were aged between 1 and 19 years (the age group with the best documentation of vaccination status available because of the ACIR). Of these, 5 (1.2%) were unvaccinated, 27 (6.5%) had one recorded MMR dose and 356 (85.8%) had two recoded doses of MMR. There were 27 (6.5%) cases with vaccination information missing or unavailable in this age group.

The proportion of cases with zero doses, unknown or missing status was higher among those 25 years and above, and particularly those 35 years or older (**Table 6**) consistent with lower vaccine coverage and lack of systematic documentation of vaccination in older individuals. However, there were relatively few cases aged >34 years.

Table 6. Vaccination status of cases by age group, mumps outbreak in Western Australia 2015-2016

age group, years (n)	**Vaccination status of cases**			
	Two Doses	One Dose	Unvaccinated	Unknown/missing
	n (%)	n (%)	n (%)	n (%)
1-4 (17)	16 (94.1)	1 (5.8)	0 (0)	0 (0)
5-9 (77)	69 (89.6)	3 (3.9)	0 (0)	5 (6.5)
10-14 (148)	131 (88.5)	9 (6.1)	1 (0.68)	7 (4.7)
15-19 (168)	137 (81.6)	12 (7.1)	4 (2.4)	15 (8.9)
20-24 (121)	75 (62.0)	25 (20.7)	2 (1.7)	19 (15.7)
25-29 (113)	49 (43.4)	21 (18.6)	1 (0.89)	42 (37.2)
30-34 (91)	40 (44.0)	16 (17.6)	1 (1.1)	34 (37.4)
TOTAL (735)	**517 (68.3)**	**87 (13.1)**	**9 (1.4)**	**122 (16.6)**
35-39 (57)*	4 (7.0)	11 (19.3)	5 (8.8)	37 (64.9)
40+ (85)*	3 (3.5)	7 (8.2)	13 (15.3)	62 (72.9)

Abbreviations: MMR, measles-mumps-rubella vaccine

3.4 Vaccination control measures

Community-wide MMR booster vaccination interventions were carried out in multiple communities, while household and close contact vaccination was a standard strategy for all cases. Overall, there were 6,605 additional doses of MMR shipped to the involved regions for outbreak control measures. This is in addition to MMR ordered and used for routine vaccinations related to the National Immunisation Program (NIP).

Provisional data relating to MMR booster vaccination interventions were reviewed for nine selected boarding school and community settings (compiled by and kindly provided by Dr Gary Dowse). Where the intervention was carried out soon after the identification of the first case in the boarding

school or community and maximum vaccination coverage achieved, further transmission in the community beyond a single incubation period appeared to have been prevented.

However, where the intervention was gradual, that is it took place over several visits or where a high proportion of residents had been absent from the community, transmission continued beyond a single incubation period (**Table 7**). In Boarding School A, for example, the public health response was delayed due to resources and staffing. Two visits were made to the school two weeks apart to vaccinate contacts. The result was that transmission continued for more than one incubation period. Conversely, in Boarding School B, 100% coverage was achieved at the first visit and there were no further cases beyond a single incubation period. Similarly, in discrete remote communities (not identified for ethical reasons) and larger towns (such as Broome, Port Hedland and Kununurra) where comprehensive booster vaccination programs were not undertaken at all because of practical and logistic difficulties, transmission was extended over multiple generations of cases over many weeks to months.

Table 7. Effectiveness of a measles-mumps-rubella vaccination intervention*

Location	Intervention delivery	Coverage, n(%)	Effectiveness
School A	Gradual, at two visits two weeks apart	31/43 (72%) students at second visit	Cases continued for two incubation periods
School B	Targeted delivery	58/58 (100%) students 18/18 (100%) staff at first visit	No cases beyond one incubation period
School C	Targeted delivery	105/123 (85%) coverage of 123 students	No cases beyond one incubation period
School D	Targeted delivery	73/87 (84%) of boarders, 55/82 (67%) of day students	No cases beyond one incubation period
Community A	Targeted delivery with further opportunistic vaccination in community clinics	291/347 (84%) community members	No cases beyond one incubation period
Community B	Targeted with little or no opportunistic vaccination in community after	42/90 (47%) of community members	Transmission continued, impact unknown
Community C	Targeted delivery	50/75 (72%) of community members	Some continued transmission
Community D	Targeted delivery	52/71 (73%) of community members	No further cases for four months, then single case
Community E	Targeted delivery	34/52 (65%) of community members	No further cases beyond one incubation period

**Data collected by public health officers in the regions, and further transmission ascertained through surveillance data. Compiled and provided by Dr Gary Dowse, CDCD.*

3.5 Laboratory results

A total of 742/884 (84.0%) cases were laboratory confirmed. Genotyping was successful on 175 (67.8%) of 258 PCR-positive mumps samples on which it was attempted. All were genotype G. Within the genotype there was little variation in the SH gene sequence. However, a lineage with a single SH gene mutation emerged in the town of Broome in the Kimberley region in June 2015 and then spread through the West Kimberley and Pilbara regions but not the East Kimberley where the prototype outbreak sequence (G) continued to circulate (personal communication, Avram Levy, PathWest scientist).

4.0 Discussion

This was the largest mumps outbreak in Australia since the disease became notifiable in 1995, in which a total of 884 mumps cases met the outbreak case definition. Most cases were vaccinated Aboriginal people. The outbreak was ongoing from March 2015 to September 2016, with a small number of cases continuing to be reported in October 2016. Many remote communities, towns and several boarding schools were affected by this outbreak and transmission covered a very large geographic area, more than 2,100,000 km^2. Most of the affected communities were located in remote areas, some of which were only readily accessible by four-wheel drive vehicle or light aircraft which made outbreak control challenging.

Mumps outbreaks among highly vaccinated populations have been reported in Europe,[29-32] the US,[12,33-35] Canada,[36] and previously in Western Australia.[23] These were primarily reported in environments favouring intense exposure, *e.g.* university dormitories or religious schools. The suggested causes for outbreaks in these settings include suboptimal vaccine coverage[34,37] and waning of vaccine induced immunity.[23,36,38-41] In a review summarising calculated vaccine effectiveness (VE) during mumps outbreaks, Dayan and Rubin[42] reported that the effectiveness of the Jeryl-Lynn vaccine strain (the strain used in Australia and other countries) ranged between 73% and 91% for one dose and between 91% and 94% for two doses.[42] Using the screening method, researchers in Canada reported that VE for two doses was between 66% and 88%.[36] A cross-sectional study that compared the attack rates of primary school-aged cases with their household contacts found VE of 95% amongst school children

but only 67% among older vaccinated household contacts;[32] suggesting decreased VE as time since vaccination increases. Another study explored waning immunity during an outbreak and reported an increased odds of 27% with each year since vaccination (OR 1.27 95% confidence interval (CI) 1.16,1.38).[43]

Immunity also wanes when no natural exposure to disease occurs.[2] Prior to the decline of mumps incidence due to vaccination, immunity was boosted by re-exposure as the mumps wild-type virus circulated. However, as vaccination rates increased and endemic circulation of mumps virus has been eliminated in developed populations with high vaccine coverage, such exposures have become uncommon,[13] which could be another reason that transmission was sustained in our population. None of the 2007-2008 Kimberley outbreak cases were also cases in the current outbreak, which suggests better and more long-lasting immunity provided by natural infection (CDCD, unpublished data).

The herd immunity threshold for mumps has been reported by some between 70-90%[44,45] and others estimate a higher threshold (90-92%).[46] In our outbreak, the age groups with the highest proportion of cases were also those with the highest two-dose MMR vaccination coverage (86.1% among all cases <20 years). Others have hypothesised that the herd immunity threshold may need to be higher to achieve population protection during an outbreak,[47-49] consistent with our experience. It is unlikely that adequate herd immunity existed in our outbreak population (68% for cases < 40 years), similar to 2007-2008 Kimberley outbreak.[23]

To our knowledge, there have been only three other mumps outbreaks reported that disproportionately affected ethnic or religious subgroups within a population. These include the WA mumps outbreak during 2007-2008,[23] discussed earlier, where 141/153 (92%) of outbreak cases were Aboriginal people, primarily in the Kimberley region. Of those in the age group with the highest proportion of cases (15-19 years), 26/34 (76%) had two documented prior doses of MMR, while 32 of 34 (94%) had at least one documented dose.[23] Secondly, in 2009-2010 an outbreak in New York City affecting 3,502 cases, 97% of whom were Orthodox Jewish persons. Of these 89% had two doses of MMR while 8% had received only one dose. Transmission to non-Jewish persons in the affected

communities was neither frequent nor sustained. The authors suggested that intense exposure associated with Orthodox Jewish study practices among adolescent boys may have contributed to the continued transmission during this outbreak.[35] This is consistent with the droplet nuclei and fomite transmission properties of the mumps virus which requires relatively close contact, within one metre of the index case, compared with other infectious diseases like measles or varicella which are airborne.[4]

Thirdly, there was a mumps outbreak in Guam during 2009-2010 where attack rates of two minority ethnic groups, Chuukese and Pohnpeian were significantly higher compared with other Guam residents.[50] These two subpopulations were reported to have the highest household crowding indices, with Chuukese and Pohnpeian cases reporting 3.0 and 3.1 persons per bedroom, respectively, compared with the Guam average of 2.3.[50] This intense exposure from crowded households could have been a factor in the higher attack rates in these Island subpopulations.

On 9 November 2016, a large mumps outbreak in north-western Arkansas, USA was reported in the International Society for Infectious Diseases ProMed-mail. According to the Arkansas Department of Health, over 1000 mumps cases had been reported since mid-August 2016, predominantly among Marshallese residents (65%) of the affected county. Transmission spread to 53 schools, businesses and churches (http://outbreaknewstoday.com/mumps-cases-top-1000-arkansas-16004/). No further information about the outbreak was available, however a VE study is ongoing by the US CDC.

Aboriginal Australians have been reported to have inadequate housing (*e.g.* major structural problems, or homelessness)[51] and crowded living conditions, particularly in remote communities, which may have played a role in the continued and sustained transmission that we observed in WA. Studies from the Northern Territory (NT) have reported that Australian remote communities have households with an average of 3.4 residents per bedroom.[52] Other studies in similar communities reported a median of between 2.3 and 7.5 residents per bedroom.[53,54] We did not collect household size information from cases during this outbreak. However, anecdotal information shared by some of the public health nurses who followed-up cases indicated that some case households were "crowded." One example was that a house had more than 20 residents at one visit and on returning the following week

many of the residents had changed. It was not uncommon for public health nurses to visit homes with 20 to 30 occupants.

Aboriginal Australian's are also highly mobile and social, consistent with their historically nomadic culture.[55] This mobility involves moving between remote communities and town centres to access education and essential services as well as movement for continuity of land practices, to preserve important familial relationships and cultural or ceremonial practices.[56] Mobility in and between communities and crowded household environments were postulated to have been contributors to mumps transmission during the 2007-2008 outbreak in this population[23] and are likely as well to have played a role in mumps virus transmission during the current outbreak as well.

Very little has been published supporting a booster MMR3 dose as a control measure during mumps outbreaks. This was also the first time that a MMR3 was used for outbreak control in WA, *i.e.* it was not used during the 2007-2008 mumps outbreak in the Kimberley.

Among cases in North Eastern New York, a MMR3 intervention was temporarily associated with a decline in cases and was thought to have helped control a mumps outbreak.[57] In Guam a substantially lower attack rate was reported after implementation of an MMR3 intervention during a mumps outbreak.[50] However, this intervention was implemented after peak transmission in the community had occurred and the authors could not determine whether it was the intervention that made the difference or if it was coincidental timing.

The US CDC have recommended collecting data on the impact of MMR3 control activities when used as a public health intervention during outbreaks to help inform control strategies for future outbreaks.[26] As an outbreak control measure and particularly among cases ≥15 years old, administration of MMR3 has been shown to result in an anamnestic reponse.[58] However the value of MMR3 beyond outbreak control may be limited.[59] In a study measuring antibody response to mumps in young adults, a MMR3 dose was administered and mumps neutralising antibody titres were assessed at baseline, one and 12 months post immunisation. Though elevated one-month post vaccination, the mumps neutralising antibody titres had returned to near baseline levels within a year. This result

suggests the utility of using a MMR3 as an outbreak control method but that longer term benefit as part of a scheduled vaccination program may not be sustained.[59] Our experience, based on preliminary analyses of data from communities where ring-fence type MMR booster doses were provided, shows that a MMR3 appears to be a useful tool for outbreak control where it is carried out promptly and with high coverage. However, it is possible that the effect observed in these communities could have been the result of naturally declining transmission unrelated to the intervention. While randomisation of communities to vaccine booster intervention versus standard practise might be the most direct way to determine effectiveness, this would be an ethically difficult study to undertake. However, it was notable that in those communities and towns where logistic and other factors prevented prompt and comprehensive booster dose coverage, ongoing mumps transmission was much more likely.

Recording of vaccination status among cases who were too old to have an ACIR record was likely to have been incomplete (at the time of this outbreak children <18 would have complete records and children approximately <23 years could have had an ACIR record with a single 4-5 year old MMR dose recorded). Some older cases were not able to recollect or provide evidence of earlier vaccination. Public health officers in the PHUs attempted to ascertain vaccination status from other sources, where possible. This information would be missing if the case moved into the region after having received care in a different PHU region or state. These issues most likely resulted in an under-ascertainment of the proportion of cases who were, in fact, partially or fully vaccinated. Vaccination status in cases aged <18 years was more complete because of our ability to confirm vaccination status from the ACIR. In September 2016, the ACIR was expanded to become a whole of life register and hence forward will capture all immunisation information from birth to death.[60]

In a previous study following a mumps outbreak, the authors found that cases who had two doses of MMR were less likely to be hospitalised or report orchitis compared to those who were unvaccinated.[61] We were unable to ascertain whether vaccination had any effect on the severity of mumps illness because of the high number of cases with missing or incomplete vaccination information.

Immune escape is another plausible explanation for continued disease spread during this outbreak, due in part to the mismatch between the Jeryl Lynn (genotype A) vaccine strain and the genotype G outbreak strain. Assaying consecutive serum samples from children at different intervals after vaccination, Rubin *et.al.* reported that geometric mean antibody titres to an outbreak G strain were half that of the Jeryl Lynn strain. In 22% of samples there was a ≥4 fold reduction in ability to neutralise the outbreak G strain compared with the vaccine strain with decreasing neutralising ability as time since vaccination increased.[62] While the outbreak G strain was successfully neutralised at all time points, the minimum level of neutralising antibody required to prevent infection by heterologous strains in "real life" has not been established.[62] Previous reports from serological studies have shown that the Jeryl-Lyn derived vaccine offers some cross-protection against heterologous infection. However, it is unknown how much protection or if any cut off exists or what the role of other factors like waning immunity or increased infection risk in intense exposure settings may play.[40]

Health inequalities and social determinants are thought to play a significant role in explaining the disparity of health outcomes, generally, among Aboriginal Australians.[63] Socioeconomic disadvantage introduces several factors that contribute to poor health in communities,[64] one of these is the effect of psychosocial factors and how they could have affected the disproportionate impact on Aboriginal people. This has not specifically been tested among Aboriginal Australians but lends to an ecological comparison. Immune function is affected by psychological stress[65] and Aboriginal people proportionally suffer significantly higher stress than non-Aboriginal people.[66] The association between stress and antibody response to influenza[67] and Hepatitis A[68] vaccination has also been established. Higher levels of cumulative stress have been shown to lead to both slower antibody production and production at a lower level.[67] This theory was also supported in a meta analysis[69] and among older caregivers.[70] We were unable to assess these factors in the current outbreak, however they may have contributed to lower immunogenicity from prior mumps vaccination and to the ongoing and sustained transmission. We recognise that this ecological comparison could be biased by ecological fallacy. Studies would be required to explore this at an individual level in this population.

Future immunologic research should focus on testing avidity of antibodies to mumps virus, including comparing Aboriginal and non-Aboriginal Australians, as current serological testing is not reliable in terms of predicting who is at risk.[40,71] Specifically, research should explore why mumps outbreaks appear to affect some populations disproportionately, *i.e*. whether this simply reflects exposure intensity or is the result of other factors affecting the immunogenicity of the vaccine in these groups. Although we know that neutralizing antibody titres are a correlate of protection, and the correlates of protection for measles and rubella have been established, the surrogate immunological marker for mumps has not yet been established.[2,13,72-74] Future research should attempt to do this.

5.0 Conclusions

A large, sustained mumps outbreak predominantly affected well-vaccinated Aboriginal people in WA. Incidence was higher in older teenagers and young adults, suggesting waning of vaccine-induced immunity. The outbreak was caused by a genotype G mumps virus, against which the Jeryl Lynn vaccine strain may not have provided sufficient protection. Further studies are underway to help determine the immunological, social and other factors that might have contributed to this outbreak.

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Appendix 1. Meeting Summary of the WA Mumps Outbreak Control Forum

Held 6 April 2016 at Grace Vaughan House (DRAFT)

1. BACKGROUND

The current outbreak in WA is the largest that has occurred in Australia in the post-vaccination era, yet the second in 8 years affecting, predominantly, Aboriginal West Australians. No similar outbreaks have been reported in other indigenous populations nationally or internationally, excepting a large outbreak affecting Pacific Islander populations in Guam in 2009/10.

The WA Mumps Outbreak Control Forum brought together key experts and stakeholders to discuss the current mumps outbreak control activities and opportunities for research to elucidate the drivers of the outbreak in order to inform preventative measures for future mumps outbreaks in WA (and elsewhere).

2. OBJECTIVES

- To present the epidemiology of mumps in Western Australian prior to, and in the context of, the current mumps outbreak
- To review current outbreak control activities and decide whether additional measures are required
- To present laboratory characteristics of the outbreak
- To discuss hypotheses for the continued spread in remote WA
- To discuss avenues for research/evaluation activities that would enable better understanding of the outbreak and, therefore, help prevent future mumps outbreaks.

3. ATTENDANCE DETAILS

Attendees at Grace Vaughan House: Paul Armstrong (chair)[1], Chris Blyth[2], Jonathan Carapetis[2], Kate Cross[3], Gary Dowse[1], Johanna Dups[1], Paul Effler[1], Carolien Giele[1], Meredith Hodge[4], Tony Keil[5], Avram Levy[4], Sharon Nowrojee[6], Peter Richmond[2], David Smith[7], Tom Snelling[2], David Speers[7], Tania Wallace[8], Tarun Weeramanthri[1], Darren Westphal[1], Benjamin Witham[1]

Attendees by teleconference: Ross Andrews[9], Frank Beard[10], John Brazil[11], Jane Davies[12], Ashley Eastwood[13], Marama Haenga[13], Phillippa Jones[14], Kristine Macartney[10], Moira McKinnon[11], Lyn Symonds[11], Naru Pal[15]

1. WA Department of Health	**9. Australian Technical Advisory Group on Immunisation (ATAGI)**
2. Telethon Kids Institute	**10. National Centre for Immunisation Research and Surveillance (NCIRS)**
3. WA Country Health Service (WACHS)	**11.WACHS Midwest**
4.PathWest	**12.WACHS Goldfields**
5.PathWest PMH	**13.WACHS Kimberley**
6.North Metropolitan Health Service	**14.WACHS Pilbara**
7.QEII Medical Centre	**15.WACHS Southwest**
8. South Metropolitan Health Service	

Presentations

1.	Epidemiological aspects and background	Darren Westphal
2.	Possible causes for current outbreak	Gary Dowse
3.	Control measures	Gary Dowse
4.	Laboratory findings	David Smith

4. EPIDEMIOLOGY

Epidemiology of mumps in WA prior to the current outbreak

- Between 1995-2014 (in non-outbreak years) an average of 23 mumps cases were notified (range 10-39) per annum in WA. This reflects primarily imported cases, with limited local transmission, and very few cases in Aboriginal people.
- From July 2007 to June 2008, 183 mumps cases notified, 153 (82%) were epidemiologically linked to the Kimberley and 141 (92%) were Aboriginal Australians. The virus was genotype J. The outbreak started in the NT, however, most activity was in the Kimberley.
- From December 2012 to March 2013, a genotype G outbreak of 31 locally acquired cases in northern suburbs of Perth. Few identified links were found between cases, suggesting wider unrecognised transmission, but herd immunity prevailed.

Epidemiology of the current outbreak

- From March 2015-March 2016, more than 730 cases had been notified in an outbreak that started in a remote community in the East Kimberley and spread across the Kimberley and thence to the Pilbara, Goldfields and Midwest regions. Key features are as follows.
    - 88% were Aboriginal Australians.
    - Peak incidence in 15-19 year olds, most cases in age range 5-39 years.
    - Overall, of those between aged 2 and 20 years (the group who would have accurate vaccination records), 90% had at least one dose of MMR (95% of Kimberley Aboriginal cases aged 0-20 years have been fully vaccinated).
    - MMR vaccine (full) coverage at age 5-6 years in affected regions has averaged around 88-92% in the period since 2000, corresponding with the most affected age-groups.
    - Incidence increased with years since MMR2 dose, suggesting waning immunity.
    - In the Kimberley region, age-standardised incidence in the 2015/16 outbreak was double that of 2007/08, and 11 times higher in Aboriginal compared to non-Aboriginal people.
    - Highest incidence in 2015/16 outbreak (to date) has been in the Pilbara region.
    - No cases in 2015/16 occurred in people with notified mumps in 2007/08 and the relative proportion of cases in Kimberley communities and towns in the 2007/08 and 2015/16 outbreaks is inversely related, suggesting a protective boosting effect by prior infection.
    - 33 (4.5%) were hospitalised and 23 (6.5%) of males had orchitis.
    - Satellite outbreaks have occurred in several WA boarding schools in Perth, Esperance and Bindoon, primarily in facilities catering specifically for Aboriginal students, as well as in one school in Melbourne. There were less than a handful of cases in non-boarders or non-Aboriginal students in these schools.
    - The outbreak has largely affected those living in regional and remote communities. Other than the boarding school environments, there has been no evidence of transmission among Aboriginal people residing in urban Perth and the southwest of the state.
    - The outbreak genotype is Genotype G.
- Very little cross-border transmission to the NT in the current outbreak despite the high rate of mobility between the NT and WA.
- Recorded mumps outbreaks internationally, and in WA in 2007-2008, tend to last about a year.
- Decline in cases in past few weeks suggest the "Kimberley second wave" may be coming to an end and only occasional cases in the Pilbara, Goldfields and Midwest regions might be expected.

Evidence base for use of MMR third doses for outbreak control

- Evidence is limited: 2012 US guidelines – "...data are insufficient to recommend for or against the use of a third dose of MMR vaccine for outbreak control....".[26]
- A study of 656 young adults who had had 2x MMR in childhood showed increased neutralising antibody titres 1 month and 1 year after MMR3 (and seroconversion in sero-negatives), however, the authors concluded that although there may be benefit fore use in outbreak settings, there was not enough evidence for routine use in vaccinated populations.[59]
- MMR3 use in school students during US Orthodox Jewish and Guam outbreaks (both 2009/10) corresponded with decline in cases, more impressively in the former.[50,57]
- France now recommend MMR3 dose during outbreaks in semi-closed populations for those with > 10 years since MMR2 following outbreaks in 2013.[75]

Prevention and Control measures in WA 2015/16 outbreak

- Mumps outbreak disease control guidelines have been developed.
- Public health alerts, information and resources (posters etc.) have been developed and sent to local doctors, clinics and hospitals, local media, the community information.
- Fact sheets for cases and close contacts have been developed.
- Alerts were sent to all WA boarding schools.
- Isolation of cases for five days post onset of parotitis has been advised.
- Catch-up vaccinations to household and close contacts for those who were not age-appropriately vaccinated (usual control measure, but escalated to booster doses irrespective of vaccination history in outbreak scenario – see below).
- Age-appropriate catch-up MMR vaccination has been promoted across the regions from time of identification of first cases.
- MMR3 (booster) vaccinations have been used as a control measure in a sequential approach:
    - where no cases in community yet, but elsewhere, offer catch-up immunisation only
    - when first case recorded in remote community, town or boarding school, offer MMR3 to extended household and defined close contact circle (e.g. classmates) aged ~8-40 years (age range in which most cases occurred in 2007/08 and 2015/16 outbreaks)
    - when second or further cases in a remote or closed community occur, especially if outside contact circle of index case, where feasible, offer MMR3 to everyone in target age range as soon as possible in a 'ring-fencing' strategy.
- Where ring-fencing approach has been used early, quickly and comprehensively, it appeared to have been effective in preventing further cases beyond a single incubation period. Such implementation is easier in small communities and boarding school settings
- Resources, logistics and population mobility make control measures in larger communities and towns (e.g. Broome, Port Hedland, Kununurra) problematic.

Hypotheses on the causes of the outbreak

- Cold chain/vaccine manufacturing issues and primarily vaccine failure are not credible explanations.
- Secondary vaccine failure, i.e. waning immunity – supportive observational evidence from WA and other outbreaks internationally and evidence from immune studies.
- Most likely explanation for these WA outbreaks (as elsewhere) is a combination of:
    - chance introduction(s) to a community
    - crowded living conditions and social and mobility factors favouring transmission within and between communities
    - in context of waning immunity (despite high vaccine coverage) insufficient to reach threshold for herd immunity in intense transmission settings.
- Immune escape as a result of genotype mismatch with Jeryl-Lynn vaccine is also a possible contributory factor, given studies showing neutralising titres to non-vaccine genotypes tend to be

lower than those to the vaccine and decline with time. It is unclear what level of neutralising antibodies is sufficient for mumps protection.

- There is no specific evidence for genetic, nutritional or other factors that might increase susceptibility in Aboriginal people, but this requires consideration and further study.

Laboratory issues and potential immunological studies using existing specimens

- There are 12 mumps virus genotypes based on the sequence of the small hydrophobic (SH) gene
    - A-D, F-L, and N
    - Several sub genotypes.
- Of the ~720 outbreak cases, 258 samples were genotyped; 171 successful (66% success rate) with 24% case coverage.
- All were genotype G:
    - first G sequence observed in Perth in 2013
    - sporadic detections in Perth in 2013 and early 2015 prior to Kimberley outbreak
    - within genotype G, little variation in SH gene sequence has been seen during outbreak
    - a single substitution emerged in Broome in June (G261T) and became the dominant lineage in West Kimberley and Pilbara, but not East Kimberley
    - whole genome sequencing is underway.
- Genotyping is less useful for determining vaccine vs. wild-type infection.
- Genotyping PCR assays are less sensitive than screening assays, so can't genotype some of the PCR +ve cases
- Possibly low viral load following vaccination can be detected by screening but not genotyping.
- PathWest currently have several mumps isolates/PCR positives, serum and opportunistic serum samples for possible use as controls and for pre- and post-outbreak serosurveys
- Serum from cases include:
    - 33 samples from 27 patients who later got mumps
    - 20 patients identified with paired pre- and post-infection sera collected between October 2014 and March 2016
    - one patient who was mumps IgG negative in 2007 (with sera stored) then developed mumps in 2015/16 (ie. should have paired sera)
    - two patients who were mumps sero-negative in 2007 (with sera stored) then provided sera in 2015/16. Neither were notified in 2015/6 with mumps and paired samples were untested for mumps
    - 23 patients who were mumps IgG positive in 2007 (with sera stored) then provided sera in 2015-16 (unsure if mumps tested).
- Approximately 10,000 opportunistic serum samples identified from Aboriginal Kimberley residents, approximately 2000 from the Pilbara, and many more from non-Aboriginal residents in other areas of WA.
- It would be helpful to conduct whole genome sequencing of as many strains as possible from both lineages and sequence hemagglutinin-neuraminidase (HN) genes.

Main discussion points and recommendations

- The group concluded that no significant departure radical disease control activity is indicated.
- Continue the current MMR3 control approach as it looks effective in settings where implementation feasible.
- MMR booster vaccination in schools students was considered as a potential and feasible measure to attempt to limit transmission in larger towns, but logistic issues and concerns about sensitivity of targeting Aboriginal students meant this strategy has not been attempted. The feeling of the meeting was that the vaccination schedule already has Aboriginal-specific elements based on

evidence of susceptibility and, therefore, this approach should in fact be implemented if indicated.

- Research support was expressed by the representatives from ATAGI, NCIRS and Telethon Kids Institute.
- Worthwhile immunological investigations were identified previously by PathWest and CDCD staff but had not been progressed because of time pressures. There was a renewed resolve to progress these proposals.
- We need a better understanding of the role of social factors, including household crowding, mobility and kinship ties, in promoting transmission within and between communities.
- Closer analysis of disease transmission patterns in this and other recent outbreaks in WA (e.g. 2007/8 mumps outbreak, EV4 outbreak) may allow prediction of spread and identification of most at risk communities for future mumps outbreaks or other infectious diseases.
- The disease control nomenclature needs to be standardised and consistent and the outbreak guidelines updated to reflect this.

5. FUTURE RESEARCH ACTIVITIES

Item	Topic	Notes
1	Compare at-risk uninvolved community. Collect pre-vaccination sera, vaccinate, collect post-vaccination sera and mononuclear cells. During outbreak, early samples for PCR and culture. Sequential post outbreak samples for antibody and mononuclear cells.	
2	Prospective study of effect/duration of MMR3 booster dose on neutralising antibody levels in Indigenous and non-Indigenous adolescents.	Utilise opportunity of school-based vaccination program to provide MMR3, with collection of pre-dose and follow-up sera. Choice of schools will need to be considered carefully given there is already likely to have been a high rate of exposure to disease in outbreak areas, and some provision of MMR booster doses.
2	Utilising currently banked opportunistic sera at PathWest, importantly including those collected prior to the outbreak, to examine neutralising antibody levels, and compare between Aboriginal and non-Aboriginal people living in same/similar area	Need to progress study proposal and HREC application(s). Proposal should include formal linkage/other methods to ascertain ethnicity, vaccination history and other relevant demographic information.
3	PathWest has identified a small number (~27) of opportunistic sera specimens collected prior to diagnosis of mumps. It would be informative to compare their neutralising antibody titres with those of specimens collected around the same time in "matched" individuals (same community and theoretical potential exposure risk) who did not develop mumps.	Complications asymptomatic/undiagnosed infections in the control group
4	Compare neutralising antibody titres against different mumps strains and the vaccine strain to establish cross genotype neutralisation titres and cross-lineage neutralisation titres, Indigenous vs. non-Indigenous, those who got mumps and those who didn't, Kimberley/Pilbara vs. Goldfields vs. Southwest.	Need to know age, sex, location, vaccination history, race in order to pick appropriate samples for neutralisation.
5	Study of exposure risk vs. genetic role in increased	

	transmission	
6	Modelling of disease patterns in this and other recent outbreaks in WA (e.g. 2007/8 mumps outbreak, EV4 outbreak) may allow prediction of spread and identification of most at risk communities for future mumps outbreaks or other infectious diseases	
7	Studies to better understand the role of social factors, including household crowding, mobility and kinship ties, etc. in promoting transmission. Are differences in these factors between Aboriginal and non-Aboriginal people, and between Aboriginal people in the north-west versus those living in Perth and the southwest, sufficient to explain differences in incidence?	Telethon Kids may have access to relevant research already performed and/or know researchers who can collect such data?

NEXT STEPS

- Convene a Research Working Group to progress the various possible topics in the table above.
- Update the WA mumps disease control guidelines, as required.

Appendix 2. Poster presented at the National Immunisation Conference 2016 in Brisbane

A Second Prolonged Mumps Outbreak in Highly Vaccinated Aboriginal Western Australians

Darren Westphal[a,b,c], Carolien Giele[a], Avram Levy[d], Joanna Chua[d], Stephanie Williams[c], Paul Effler[a], Gary Dowse[a]

[a]Communicable Disease Control Directorate, Public Health Division, Department of Health (Western Australia), [b]Westarmer's Centre for Vaccines and Infectious Diseases, Telethon Kids Institute
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BACKGROUND

Western Australia (WA)

- WA has a population of 2.6 million; 4% are Aboriginal people of whom approximately 40% live in regional/remote areas.
- There are 9 public health regions (map).

Mumps

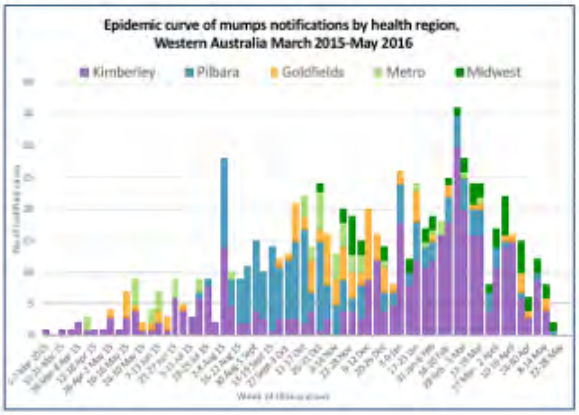
- Vaccine-preventable viral disease characterised by fever and parotid gland swelling; orchitis can occur in adult males. Approximately one-third of infections are subclinical.
- Transmitted through droplet nuclei; incubation period 14–25 days.
- 2 doses of Measles, Mumps, Rubella (MMR) vaccine are recommended at 12 and 18 months of age.
- In WA, an annual average of 23 cases of mumps were notified from 2010 to 2014, primarily reflecting overseas acquisition with some limited local transmission.
- In 2007 to 2008 there was a large outbreak (n=183) among highly vaccinated young Aboriginal residents of the remote Kimberley region caused by a genotype J mumps virus.

Aim

- To describe the epidemiological characteristics of a second mumps outbreak that commenced in the east Kimberley region in March 2015 before spreading throughout the region and to other parts of the state.

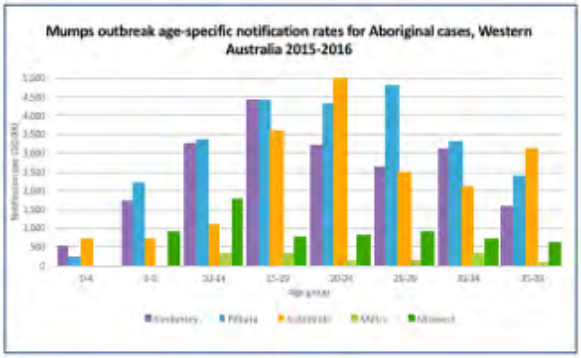
METHODS

- Mumps is a nationally notifiable disease.
- Cases were either laboratory confirmed (PCR and/or serology) or epidemiologically linked to a laboratory-confirmed case.
- Genotyping was performed on PCR positive cases without epidemiological links to the outbreak, first case in a community, or recently vaccinated cases.
- Demographic, clinical and vaccine status information was provided on each case by the diagnosing clinician or the public health staff following up cases. Vaccination status was obtained from the Australian Childhood Immunisation Register or Health Care and Related Encounters, the management software used in the public health regions.
- Mumps case information was extracted from the WA Notifiable Infectious Diseases Database for the period 3 March 2015 to 31 May 2016.



RESULTS

- 831 outbreak-related mumps cases were notified from 3 March 2015 to 31 May 2016 (Figure 1).
- 87% were Aboriginal, 52% male; median age of 20 years (range 8 months-64 years).
- Notification rates were highest among Aboriginal cases aged 15-24 years with >3% of the age group affected in the Kimberley and Pilbara (Fig 2).
- Of cases <20 years of age, 87% had received 2 doses of MMR (fully vaccinated) and 6% had received a single MMR dose (partially vaccinated).
- Thirty-eight (6%) cases were hospitalised and 6% of males (28/442) reported orchitis.
- Genotyping was available for 171 cases - All were genotype G.
- Outbreak-related clusters (from 4 - 10 cases) occurred in five boarding schools throughout the state after importation of infection. Two cases incubating mumps returned to a boarding school in another state.



DISCUSSION

Mumps outbreaks in highly vaccinated populations have been reported intermittently from overseas. This is the second outbreak among highly vaccinated Aboriginal young people living in remote WA communities. It is unclear why mumps is disproportionately affecting rural and remote Aboriginal Western Australians while their non-Aboriginal peers were largely unaffected. A number of factors that might contribute to widespread transmission of mumps in this population need further study, including: differences in household density and mobility patterns, waning vaccine immunity, and potential immune escape due to the mismatch between the wild-type and the vaccine virus genotypes.

CONCLUSIONS

We report a large mumps outbreak affecting highly vaccinated Aboriginal people living in remote areas in WA. This is the largest documented mumps outbreak in Australia since routine vaccination commenced in 1981 and one of the largest reported worldwide. More work is needed to determine the factors that led to the outbreak to guide future interventions to prevent mumps illness.

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Vaccine effectiveness during a mumps outbreak: a matched case-control study

List of abbreviations

ACIR	Australian Childhood Immunisation Register
CDCD	Communicable Disease Control Directorate
MMR	measles mumps rubella
MMRV	measles mumps rubella varicella
NCIRS	National Centre for Immunisation Research & Surveillance
PCR	polymerase chain reaction
VE	vaccine effectiveness
WA	Western Australia
WACHS	Western Australia Country Health Service
WANIDD	Western Australia Notifiable Infectious Diseases Database

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Prologue

This chapter is related to Chapter 1, The epidemiology of a protracted mumps outbreak in remote Western Australia predominantly among highly vaccinated Aboriginal people. The work in this chapter came about as a result of the sustained mumps outbreak. About 6 months into the outbreak, my supervisor Paul Effler, and I sought advice from others about what could be the cause. One researcher suggested that we do a matched case-control study to ascertain vaccine effectiveness (VE) as he had done previously for pertussis. I read that work, looked at other literature and VE estimates that were reported for other mumps outbreaks and outbreaks generally around the world. We hypothesized that the VE in our outbreak was lower than that reported elsewhere given the high vaccination two-dose coverage in our population. We set up a meeting with the National Centre for Immunisation Research & Surveillance (NCIRS) in which Professor Peter McIntyre and Dr. Helen Quinn (MAE 05) attended. We came up with a plan to use de-identified data from the Australian Childhood Immunisation Register (ACIR) that NCIRS has available to them. I would use this to obtain controls to match with our mumps cases for this matched case-control study. I wrote a research and data analysis plan. I then sought advice on whether I could use this project to satisfy the epidemiological project requirement for my MAE. In December I prepared a de-identified variable list of cases and sent them to Helen Quinn at NCIRS. We discussed the matching criteria before she matched the cases with controls using established methods and returned the data variables to me. I wrote the code, cleaned the data, conducted the statistical analysis, wrote the first draft and sent it around for comment. I met with my supervisor on several occasions to discuss the results and provide advice.

While I did this work myself, I recognise that I could not have done it without the advice and support of Paul Effler, Stephanie Williams and Helen Quinn. I also worked very closely with

Gary Dowse throughout the outbreak and he provided essential contextual guidance along the way and important advice on the final draft of this manuscript.

Public Health Impact

As with the public health impact described in Chapter 1, this work led to the mumps outbreak control forum (Chapter 1, Appendix 1) and ongoing discussions to answer the questions posed. Further discussions ensued which led to an idea to conduct serological studies to determine the level of serological protection that existed prior to the outbreak. This would be done using blood collected from residents for other reasons (*e.g.* pregnancy screening, sexually transmitted disease screening, etc). This work has not yet begun as approval by Human Research Ethics Committees is required prior to commencing this work.

I had the opportunity to present the information from this chapter at two conferences (European Society of Pediatric Infectious Diseases and the National Immunisation Conference) as oral presentations as well as some local meetings.

Vaccine effectiveness during a mumps outbreak: a matched case-control study

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1.0 Abstract

Introduction

Over the past decade, mumps outbreaks among highly-vaccinated populations have been reported with increasing frequency. In 2015 a protracted mumps outbreak occurred in Western Australia (WA), primarily in rural and remote areas. Aboriginal people comprise 4% of the state's population but were disproportionately affected during the outbreak. After nine-months of sustained transmission, we conducted a matched case-control study to estimate vaccine effectiveness (VE) of the mumps-containing measles-mumps-rubella (MMR) vaccine in children aged less than 18 years. We hypothesised that VE was lower than that reported from mumps outbreaks elsewhere.

Methods

Cases were included if they had clinically compatible illness, were aged <18 years, lived in or visited an area of WA where active mumps transmission was occurring, had disease onset between 3 March and 3 December 2015, and had laboratory-confirmed mumps or were epidemiologically linked to a laboratory-confirmed case. Controls, matched at a ratio of 11:1, were randomly selected from a population-based vaccination registry. A conditional logistic regression model was fitted to estimate the odds ratio (OR) and VE was calculated by 1-(OR)*100%. For comparison we calculated VE using the screening method: 1 – [PCV/(1-PCV)][(1-PPV)/PPV].

Results

A total of 144 cases were age and postcode matched with 1,584 controls. Cases were more likely to be Aboriginal compared with controls (89.6% vs. 37.2% p<0.001) and to have received two doses of MMR vaccine compared with controls, 93.1% vs. 89.5% p=0.19. Adjusted mumps VE was –110.7, (95% confidence interval (CI) –590.5 to 35.7) for two doses of MMR. VE derived from the screening method was –42.9% (95%CI -198.7 to 23.5).

Discussion

In this outbreak we found no protective effect in this population for two prior doses of MMR vaccine. Aboriginal people, most residing in rural and remote communities, were disproportionately affected compared to non-Aboriginal persons in the same communities. Future research should assess potential differences in mumps exposure-intensity in these communities and whether other factors associated with ethnicity play a role in determining the immunogenic response to mumps vaccine.

Key words

Vaccine effectiveness, Mumps, MMR vaccine, Mumps outbreak

2.0 Introduction

Mumps is a vaccine-preventable viral infection causing fever and inflammation of the salivary glands (parotitis).[1] Transmission is by respiratory droplets or by contact with contaminated fomites.[2] The incubation period is typically 16-18 days after exposure (range 12-25 days) and maximum infectivity is from two days before, until nine days after, the onset of parotitis. The most common complication is orchitis in post-pubescent men. Other complications are rare and include meningitis, pancreatitis and encephalitis.[1,2]

The monovalent, live attenuated mumps vaccine (Jeryl Lynn strain) was first registered for use in Australia in 1980 and recommended for children at 12 months of age in 1981, with a transition to the combined measles-mumps (MM) vaccine in 1982.[3] In 1989, the MM dose at 12 months of age was replaced with measles-mumps-rubella (MMR) vaccine and from 1992 a two-dose MMR schedule was recommended and funded for all children (**Table 1**).

Table 1. Key dates in mumps vaccine scheduling in Australia

Year	First dose 12 months	Second dose 18 months	Second dose 4-5 years	Second dose 12 years
1981	M			
1982	MM			
1989	MMR			
1992	MMR			MMR
1998	MMR		MMR	
2013	MMR	MMRV		

Abbreviations: M, mumps; MM, measles-mumps; MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella

In recent years, mumps outbreaks have been reported in many countries among highly vaccinated populations, primarily among adolescents and young adults,[4-6] raising concerns about the effectiveness of the MMR vaccine.

Two early clinical trials of the Jeryl-Lynn vaccine demonstrated an efficacy of 95% (95% confidence interval (CI), 88% to 98%) for one dose[7] and 96% (95% CI 88% to 99%) for two doses.[8] However,

vaccine effectiveness (VE) in the field has been lower than that reported in the clinical trials.[9] In a 2012 systematic review, VE of the MMR vaccine in preventing laboratory-confirmed mumps was reported to be between 64% and 66% for one dose and between 83% and 88% for two doses.[10] It was postulated that the short follow up period in typical clinical trials leads to falsely high estimates of mumps vaccine effectiveness as it does not allow for waning of vaccine-induced immunity.[11]

In March 2015 a mumps outbreak began in a small community in the remote Kimberley region of northern Western Australia (WA). It progressed to a large protracted outbreak, primarily among Aboriginal people, lasting more than a year and affecting most remote regions of WA, despite vaccine coverage levels of 90% or higher.

Using a matched case-control study, our primary aim was to estimate the VE of the MMR vaccine in children aged less than 18 years during the early phase of the 2015/16 WA mumps outbreak. We chose this age group because a population-based register was accessible from which to allocate controls. Due to the magnitude and extent of the outbreak in WA, we hypothesised that the VE in our population was lower than that reported elsewhere.[10]

3.0 Methods

3.1 Population and Setting

WA is a large state making up a third of the landmass of Australia (2.6 million km^2) and is sparsely populated with a total population of 2.5 million people, 1.9 million of whom live in the southern capital, Perth. Approximately 95,000 (4%) Western Australians identify as Aboriginal, 56% of whom live in regional and remote regions of the state. In some remote regions the proportion of persons who are Aboriginal is as high as 43%.[12]

3.2 Case selection

In Australia, all mumps cases meeting the Communicable Disease Network of Australia case definition must be reported to the state public health authorities.[13]

To be selected for the study, cases were:

notified between 1 March and 3 December 2015

AND

aged <18 years at the time of notification

AND

lived in or visited a community in WA where there was active mumps transmission, *i.e.* there were other confirmed mumps cases with disease onset within the case's incubation period.

AND

- was laboratory-confirmed by polymerase chain reaction (PCR) for mumps or had isolation of mumps virus **OR**
- had clinical evidence, *i.e.* acute parotitis or swelling of other salivary glands lasting two or more days **and** detection of mumps IgM (where there was no recent mumps vaccination) **OR**
- had acute parotitis or swelling of other salivary glands **and** had an epidemiological link to a laboratory-confirmed case *by PCR or mumps isolation*

where an epidemiological link involved contact between two or more people where at least one person was infectious and the other contracted disease within the incubation period (*i.e.* between 12-25 days) and at least one person in the chain was laboratory-confirmed.[25]

Outbreak cases were identified through the WA Notifiable Infectious Diseases Database (WANIDD).

3.3 Control selection

Controls, with names removed, were selected randomly from an extract of the Australian Childhood Immunisation Register (ACIR) held by the National Centre for Immunisation Research and Surveillance (NCIRS). The ACIR is a population-based immunisation register containing childhood vaccination records for all citizens and permanent residents who were born after 1995 and enrolled in Australia's publicly-funded health system.[14] More than 99% of children are enrolled in the ACIR by the time they reach 12 months of age, regardless of their vaccination status.[14]

3.4 Matching

Controls were individually matched to cases using date of birth and residential postcodes. Controls were born up to 30 days before or 30 days after (but not including) the birth date of the case, to ensure that cases were not matched with themselves. Matching was at a ratio of 11 controls to each case, to maximise precision of the estimates following the loss of power with exclusion of concordant pairs,[15] as required by matched case-control analysis. Controls with a combination of the same birthdate, sex, race and vaccination dates as any case were removed from the dataset to ensure that controls were not also cases in a different case-control set, prior to matching.

A subsequent comparison of the cases and controls was completed using birthdate, sex, race and vaccination dates to ensure that the control group was not contaminated with cases.

3.5 Vaccination Status

Vaccination status for both cases and controls was ascertained from the ACIR. Vaccine doses were included if they were received more than 14 days prior to illness onset. Both cases and controls were categorised into three groups: fully vaccinated, partially vaccinated and unvaccinated. Fully vaccinated was defined as having at least two doses of MMR where the first dose was received no earlier than 12 months of age and the second dose was received at least four weeks after the first dose.[16] Partially vaccinated individuals were defined as having only one dose of MMR, received no earlier than 12 months of age.[16] Any case who had a MMR vaccination with a subsequent illness onset within two weeks was considered to have been incubating mumps at the time of the vaccination and that vaccine dose was not included.

3.6 Statistical Analysis

Baseline demographic characteristics and vaccination status of cases and matched controls were compared using McNemar's chi-square and Fisher's exact test of proportions where appropriate.

A conditional logistic regression model was fitted to estimate the odds ratios (OR) for one or two doses of MMR controlling for sex and Aboriginality, with unvaccinated individuals used as the

reference group. A subgroup analysis was completed separately for Aboriginal and non-Aboriginal cases. Aboriginal status was missing for 203 (11.8%) controls who were not included in the subgroup analysis. Sex was included in the model as a potential confounder. VE was calculated as (1 − odds ratio) × 100%[17] and reported with 95% confidence intervals (CI). The VE for 2-doses derived from the matched case-control design was compared with VE calculated using the screening method.[18] VE = 1 − [PCV(1-PPV)]/[(1-PCV)/PPV], where the PPV is the proportion of the population vaccinated and PCV is the proportion of mumps cases that are vaccinated. We calculated the average annual PPV for the three regions with the highest cases using annual vaccination coverage rates between 2002 and 2014 as determined from the ACIR. Because the number of cases varied by region, we used a weighted proportion to ensure that the VE estimate in each region contributed equally to the overall result.

4.0 Results

4.1 Outbreak characteristics

Over 9 months, 147 cases met the inclusion criteria. Three cases were subsequently removed because eligible controls could not be identified. Laboratory confirmation was available for 130/144 (90.3%) cases.

A total of 144 cases were age and postcode matched with 1,584 controls. The median age of cases was 13 years (interquartile range [IQR] 10-16 years), 34% were female and 89% were Aboriginal (**Table 2**). Cases were more likely to be male than controls (66% [n=95] compared with controls, 52% [n=832]; *P*=0.001) and Aboriginal (90% [n=129] compared with 37% [n=589]; *P* <0.001). The proportion of cases that were fully vaccinated was higher than that of controls, 134/144 (93.1%) compared with 1,417/1,584 (89.5%) p=0.19 but this difference was not statistically significant (**Table 2**).

Table 2. Characteristics of mumps cases compared with their matched controls

Characteristics	Mumps Cases (n=144) No. (%)	Controls (n=1,584) No. (%)	P Value*
Female	49 (34.0)	761 (48.0)	0.001
Aboriginal status	129 (89.6)	589 (37.2)	<0.001
Missing data	0	203 (11.8)	
Vaccination status			
1 dose MMR	7 (4.9)	98 (6.2)	0.89
2 doses MMR	134 (93.1)	1,417 (89.5)	0.19
Unvaccinated	3 (2.1)	69 (4.4)	0.85

Abbreviations: MMR, measles-mumps-rubella
*McNemars Chi-squared p-value

4.2 Vaccine effectiveness

Overall, the adjusted VE was –110.7%, (95% CI –590.5 to 35.7) for two doses (**Table 3**). Restricting analysis to only Aboriginal Australians yielded a VE of –61.7% (95% CI –1298.0 to 81.3) for those fully vaccinated. The VE point estimate for non-Aboriginal Australians was 32.4% (95% CI –285.9 to 88.2) (**Table 4**). The results did not change substantially when sex was removed from either model. The overall VE we obtained using the screening method for two doses was –42.9% (95% CI –198.7 to 23.5) which corroborated our findings.

Table 3. Comparison of vaccine effectiveness of MMR vaccine during a mumps outbreak in Western Australia 2015, using a matched case-control method and the screening method

Estimated VE Model	Number of discordant pairs	Cases, No. (n=144) No. (%)	Controls, No. (n= 1,584) No, (%)	VE, % (95% CI) Matched Design	VE, % (95% CI) Screening Method
No. of Doses					
0	51	3 (2.1)	69 (4.4)	1 [Reference]	
1	70	7 (4.9)	98 (6.2)	–51.7% (–520.5 to 62.9)	n.a.
2	93	134 (93.1)	1,417 (89.5)	–110.7% (–590.5 to 35.7)	–42.9% (–198.7 to 23.5)

Abbreviations: VE, vaccine effectiveness; 95% CI, 95% confidence interval
Controlled for sex and Aboriginal status

Table 4. Comparison of estimated vaccine effectiveness for Aboriginal and non-Aboriginal residents during a mumps outbreak in Western Australia 2015

Estimated VE Model	Number of discordant pairs	Cases, No.	Controls, No.	VE, % (95% CI) Matched design	VE, (95% CI) Screening method
		No. (%)	No, (%)		
No. of Doses					
Aboriginal		n=129	n=589		
0	8	1 (0.7)	7 (1.2)	1 [Reference]	
1	46	7 (5.4)	50 (8.5)	39.8% (-536.2 to 94.3)	
2	50	121 (93.8)	532 (90.3)	–61.7% (–1298.0 to 81.3)	-108.4 (-394.7 to 0)
non-Aboriginal		n=15	n=792		
0	34	2 (13.3)	46 (5.8)	1 [Reference]	
1	0	0	36 (4.5)	n.a.	
2	53	13 (86.7)	710 (89.6)	32.4% (–285.9 to 88.2)	43.1% (-441.5 to 88.2)

Abbreviations: VE, vaccine effectiveness; 95% CI, 95% confidence interval

5.0 Discussion

Not surprisingly, our study found calculated VE was very poor because cases were as highly and completely vaccinated as controls. To our knowledge, the VE reported in our study was the lowest ever reported for mumps.[10,11,19-27]

While we believe that our estimation of vaccination status was accurate, the VE that we reported is the lowest ever reported. During an outbreak among university students in the US state of Iowa, 89% of whom had two-doses of MMR, VE was calculated at 84% for one and 82% for two doses.[28] Using the screening method during an outbreak in England, primarily among cases aged 19-23 years, one and two dose VE was estimated at 88% for one dose and 95% for two doses, however these estimates declined as time since vaccination increased.[11] During another outbreak in England, cases <18 years had VE calculated at 69% for any MMR vaccination.[22] In Germany a small outbreak affected a primary school where 23 cases were aged 8-10 years, 2-dose VE was estimated at 92%.[26]

In other settings two-dose VE was reported between 66% to 93%.[20,25] A study from the Netherlands, found vaccine protection to be satisfactory amongst schoolchildren but ineffective among older vaccinated household contacts,[25] suggesting VE against mumps may wane over time. In other outbreaks that have been reported in highly vaccinated communities including the 2007/2008 outbreak among Aboriginal Western Australians, case incidence increased with age.[5,11,19,29-33]

Our results confirm what we know from other mumps outbreaks among highly vaccinated populations; highly vaccinated does not mean highly immune.[34] With mumps, vaccination status should not be used as a proxy for immunity given the strong evidence for the waning effect of immunity as the time since vaccination increases. Many post-vaccine mumps outbreaks have occurred in high population density settings such as schools or dormitories.[4,28,31,35,36] Although the current outbreak primarily affected Aboriginal people living in remote, sparsely populated areas, high household density and crowding are features of Aboriginal communities[37-39] which may have contributed to the sustained mumps transmission.

While we were unable to assess this in the current study, the timing of the second dose of mumps vaccine may impact VE. Eriksen and colleagues have suggested that more time between doses provides better protection against mumps outbreaks.[40] This is also consistent with Davidkin and colleagues who suggest better protection is observed if the time between the first and second dose is greater than two years.[41] However, a short interval between mumps vaccine doses cannot explain susceptibility in our study population as the vaccine schedule applicable to the age cohort under 18 years has recommended doses at 12 months and between 4-5 years. The Australian immunisation schedule changed in 2013, whereby MMR vaccines are now given at 12 and 18 months of age to provide increased protection against measles and to incorporate varicella into a quadrivalent vaccine at 18 months.[42,43] The US Centers for Disease Control and Prevention recommends that the second mumps-containing vaccine be given between four and six years after the first dose at 12 months.[44]

Calculating VE in a highly vaccinated population such as ours is a challenge that has been previously identified.[45] Both cases and their matched controls were highly vaccinated, thereby reducing the number of discordant pairs that would contribute data in our matched analysis, despite having a large control to case ratio. We also had wide confidence intervals in our estimates and discrepant findings such as a higher VE estimate for one compared to two doses in Aboriginal people. Use of the screening method also resulted in low estimates in part due to the high proportion of cases that were fully vaccinated.

Fine and Zell[45] suggested several factors that could lead to an underestimation of VE, including vaccine failure. This bias would be increased if these vaccine failures were clustered in the population, thus reducing herd immunity.[45] We think it unlikely that bias due to clustering of vaccine failure could account for our low VE estimates. It was not possible to calculate secondary attack rates in households in this outbreak, a method that has been identified previously to reduce this bias.[17]

There may be other factors that could have contributed to the disproportionate impact on Aboriginal people in this outbreak. Aboriginal Australians have higher incidence of low birthweight and preterm birth than their non-Aboriginal peers.[46] These factors leading to reduced immunity have been

associated with increased infection-related hospitalisations among Aboriginal children in WA up to 18 years of age.[47] Immune function has also been reported to be affected by psychological stressors[48] and Aboriginal people suffer significantly higher stress than non-Aboriginal people.[49] These factors may have contributed to lower immune response to mumps vaccine and consequent enhanced transmission in the context of this outbreak.

Another possibility considered for low VE during this outbreak, was primary vaccine failure due to poor vaccine manufacturing, inadequate cold chain or other issues. This was not credible for a number of reasons. First, the high notification rates spanned widely across different regions with different vaccine supply mechanisms and a large number of health care providers. Second, the wide age range of cases would require systematic and ongoing problems over many years, but primarily affecting only Aboriginal people. Non-Aboriginal residents who would have been vaccinated in the same clinics at the same time and who live in the same towns have been largely unaffected during this outbreak.

As controls were matched to cases by residential postcodes and therefore sourced from the outbreak area, we cannot rule out the fact that some controls may have been subclinical cases, cases not otherwise notified, or went on to become cases (confirmed or otherwise) after matching. Any of these scenarios will have impacted our calculated VE which may have significantly changed the results. Limiting our control selection to those who were laboratory-confirmed would have been ideal, however, was not logistically practical.

We have shown that despite high vaccine coverage, VE of the mumps-containing vaccine during this outbreak is very low among Aboriginal Western Australians albeit with wide confidence intervals. The disproportion of Aboriginal people in this outbreak could suggest that immunogenicity is impacted by socio-demographic (*e.g.* household crowding, population mobility), genetic, nutritional, psychological stressors or other factors amongst this population. Despite a sparsely populated and vast rural area, transmission has been ongoing for more than a year.

Future research should explore why mumps outbreaks appear to affect Aboriginal Australians disproportionately, *i.e.* whether this simply reflects exposure intensity or is the result of other factors affecting the immunogenicity of the vaccine in this population. While the correlates of protection for measles and rubella have been established, the surrogate marker for mumps is still to be determined.[50-52] Further studies are required to determine the relative contribution of immunologic and other factors in explaining the apparent higher susceptibility of Aboriginal people to mumps.

Authors' contribution

DW, HQ and PE designed the study. DW conducted the statistical analysis and wrote the initial draft of the manuscript. HQ, SW, GD and PE revised the manuscript, helped with the interpretation of the data and offered important conceptual suggestions. All authors approved the final version of the manuscript.

Conflicts of interest

No authors have any conflicts of interest to declare.

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Appendix 1. Tables not shown in the manuscript

Table 5. Effectiveness of the MMR vaccine during a mumps outbreak, by years since completion of the two dose MMR series (Fully Vaccinated)

Estimated VE Model	No. Vaccinated			
	Cases, No. (%)	Controls, No. (%)	mOR, (95% CI)	VE, % (95% CI)
Time Since Vaccination, yr				
unvaccinated	3 (2.1)	69 (4.4)	1 [Reference]	1 [Reference]
0-8 years	65 (45.1)	669 (42.2)	2.88 (0.79 – 10.5)	-188.1% (-949.7 – 20.9)
9-14 years	76 (52.8)	846 (53.4)	1.86 (0.55-6.26)	-85.7% (-526.3 – 44.9)

Abbreviations: VE, vaccine effectiveness; MMR, measles mumps rubella; mOR, matched odds ratio; 95% CI, 95% confidence interval.

Table 6. Vaccine effectiveness of the MMR vaccine during a mumps outbreak, time (interval) between dose one and dose two

Estimated VE Model	No. Vaccinated			
	Cases, No. (%)	Controls, No. (%)	mOR, (95% CI)	VE, % (95% CI)
Interval between Dose 1 & Dose 2, yr				
Unvaccinated	3 (2.2)	69 (4.8)	1 [Reference]	1 [Reference]
1-2 years	53 (39.3)	451 (31.0)	2.9 (0.86 – 9.7)	-188.9 (-866.3 to 13.6)
3-5.9 years	79 (58.5)	934 (64.2)	2.0 (0.60 – 6.5)	-97.7 (-550.4 to 39.9)

Abbreviations: VE, vaccine effectiveness; mOR, matched odds ratio; 95% CI, 95% confidence interval.

We were unable to find an assocaition between time since vaccination and interval between doses in the current study.

Table 7. Comparison of estimated vaccine effectiveness using the screening method among Aboriginal and non-Aboriginal residents aged <18 years, by region during a mumps outbreak in Western Australia 2015

Estimated VE	VE, % (95% CI) Screening method
Aboriginal (cases)	
Kimberley (54)	-34.8% (-577.6 to 57)
Pilbara (50)	-247.2% (-1639.4 to -12)
Goldfields (15)	-42.1% (-1197.0 to 67.8)
non-Aboriginal	
Kimberley (4)	71.6% (-1392.9 to 97.7)
Pilbara (7)	14.32% (-3841.2 to 89.6)
Goldfields (0)	n.a.

Abbreviations: VE, vaccine effectiveness; 95% CI, 95% confidence interval

Appendix 2. Slides from oral presentation at the European Society of Pediatric Infectious Diseases (ESPID) Conference 2016 in Brighton UK

EPIDEMIOLOGY AND VACCINE EFFECTIVENESS DURING A LARGE MUMPS OUTBREAK IN WESTERN AUSTRALIA

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Disclosure

X	No, nothing to disclose
	Yes, please specify:

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership/ Equity Position	Employee	Other (please specify)

Part 1: Epidemiology of Outbreak

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Background

- Western Australia is Australia's largest state
- Sparsely populated
- 4% of population identify as Aboriginal

Mapfrappe.com

Mumps – the disease

- Viral illness
- Complications are rare
- All confirmed cases are notified in Australia
- Prevention with MMR vaccine

Mumps – Vaccine scheduling in Australia

Key dates in mumps scheduling in Western Australia				
Year	First dose 12 months	Second dose 18 months	Second dose 4-5 years	Second dose 12 years
1981	Mumps			
1983	MM			
1989	MMR			
1994	MMR			MMR
1998	MMR		MMR	
2013	MMR	MMRV		

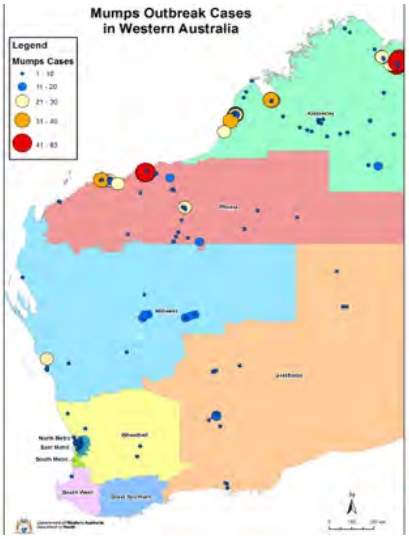
Mumps – Outbreak in Western Australia, 2015-2016

- From 1995-2014 approximately 23 mumps cases/yr
- Primarily overseas acquired

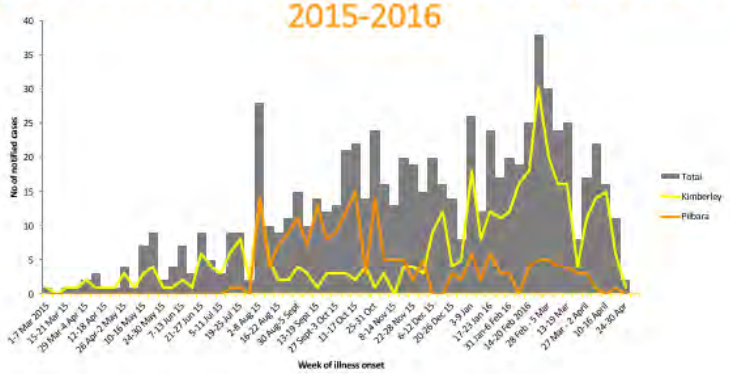
- The current outbreak began in March 2015
- Further irregular spread across the region
- Subsequent spread to other remote parts of the state
- Genotype G

Mumps – Outbreak in Western Australia, 2015-2016

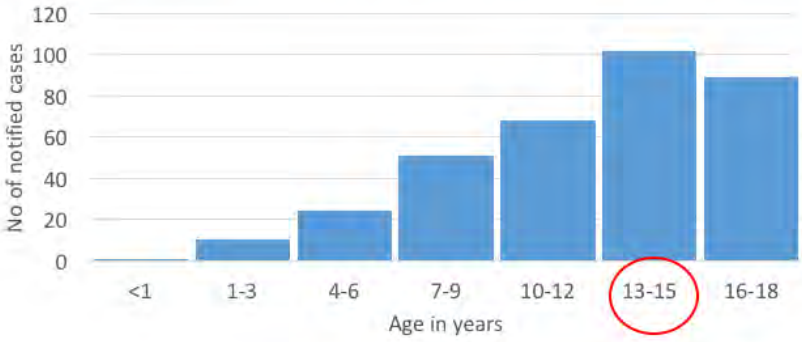
- March 2015-April 2016, 796 cases notified
- 5 school clusters of between 4-10 cases
- 2 exported cases to another state



Epidemic curve of Western Australia Mumps Outbreak, 2015-2016



Age Distribution of Cases 0-18 years



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Demographics	N (%)
Overall N=796	
Sex	
male	421 (53)
Age, median (range)	21 (8 mos – 64 yrs)
Aboriginal	687 (88)
Vaccination status cases aged 2-18 N=337 (42%)	
2 doses MMR	292 (88)
1 dose MMR	21 (6)
Aboriginal	301 (89)

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Part 2: Matched Case-Control Study for Vaccine Effectiveness

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Methods

- In December 2015 we conducted a matched case-control study
- Aim: to calculate VE for MMR in cases <18
- Matched with population controls at ratio of 1:11
- VE= (1-OR) * 100
- Conditional logistic regression model
- Subgroup analysis: Aboriginal vs non-Aboriginal Australians

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Results

- 144 cases under 18 years matched with 1584 controls

Estimated VE Model	Cases, No. (n=144)	Controls, No. (n= 1,584)	VE, % (95% CI) Matched Design	VE, % (95% CI) Screening Method
	No. (%)	No, (%)		
Fully Vaccinated	134 (93.1)	1,417 (89.5)	-122.8% (-626.5 – 31.7)	-55.7% (-232.1 – 17.9)

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Limitations

- Methodology,
  - A study design where we were unable to use half our cases
  - High population vaccination coverage (PPV)
- VE is often underestimated in outbreaks
- Confounding: cases and controls too much alike?

Summary

- Largest Australian mumps outbreak since vaccine
- Another example of outbreaks among the highly vaccinated
- Further research currently in planning
- Mumps vaccine?

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Co-authors
Helen Quinn, Stephanie Williams, Paul Effler

CDCD epidemiologists: Gary Dowse, Carolien Giele

PathWest Laboratory scientists

Nurses and staff at Public Health Units

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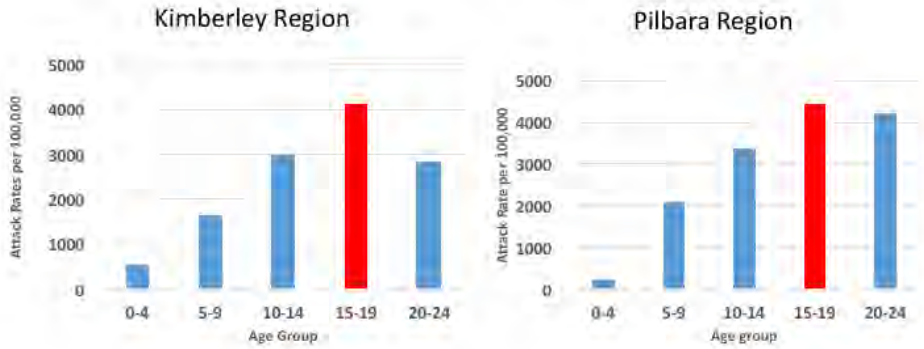
Attack Rates per 100,000 population, Aboriginal



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Epidemiology of Otitis Media hospitalisations in Western Australia: a retrospective population cohort study (1996-2012)

List of abbreviations used in this chapter

7vPCV	7 valent pneumococcal conjugate vaccine
ABS	Australian Bureau of Statistics
AOM	acute otitis media
ARIA	Accessibility/Remoteness Index of Australia
CSOM	chronic suppurative otitis media
ED	Emergency Department
GP	General Practitioner
HMDC	Hospital Morbidity Data Collection
ICD-AM	International Classification of Disease-Australian Modification
IRR	incidence rate ratio
MNS	Midwives' Notification System
MVTI	myringotomy with ventilation tube insertion
NICU	neonatal intensive care unit
OM	otitis media
OME	otitis media with effusion
ENT	Otorhinolaryngologist (ear-nose-throat) specialist
PCV	pneumococcal conjugate vaccine
POBW	percentage of optimal birthweight
PTAR	person time at risk
SEIFA	Socio Economic Index For Area
US	United States

WACHS	Western Australia Country Health Service
WADLS	Western Australia Data Linkage Service
WHO	World Health Organization

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Prologue

Role

I was very fortunate to work on this project for my *analysis of a public health dataset,* a requirement for the MAE. It was a fantastic experience to use statistical and analytical skills that I hadn't used before and to be a part of this important work that hasn't been done before. It will help to build the evidence in the area of otitis media hospitalisations, particularly among Aboriginal Australians.

I was responsible for designing this project and analysing the otitis media (OM) outcomes from this large public health dataset. I wrote the data analysis plan, cleaned and recoded the data for the OM outcomes, set up the statistical models and analysed the final dataset.

I developed the aims and objectives with the help and advice of Hannah Moore, Deborah Lehmann and Peter Richmond. Hannah Moore also provided important guidance in building the model and in presenting and interpreting the data.

Lessons

I learned a great deal about linked data analyses and the complexities of merging outcomes from one dataset to another. It was also very confronting to see the disparity of OM-related hospitalisations between Aboriginal and non-Aboriginal children in Western Australia. Otitis media was a new research area for me so I had to rely heavily on 'the experts': Deborah Lehmann, Peter Richmond and Francis Lannigan. While the learning curve was steep, I gained a lot of knowledge about the subject area. I attended the Otitis Media Australian Conference (OMOz) which gave me perspective about the burden of middle ear disease and network with the Australian experts. Overall working on this chapter was a rewarding experience.

Impact

This was the first time that this work has been done in a population setting for hospitalisations and procedures with OM. This has also not been done separately for Aboriginal and non-Aboriginal children.

This work is timely as the WA Child Ear Health Strategy is currently out for consultation and these data can be included in the next draft. The Australian Recommendations for clinical Care Guidelines are also being updated so hopefully this work can be included to help expand the knowledge base, particularly for the information about the burden of hospitalisations among Aboriginal children.

I had the opportunity to present these data at the Otitis Media of Australia National Conference 2015 (OMOz) as an oral presentation (**Appendix 4**). In addition to OMOz, I also presented this work at the Telethon Kids Institute Scientific Retreat 2016.

Abstract

Introduction

Otitis media is one of the most common infectious diseases affecting children, being responsible for the highest level of antibiotic prescribing and surgical procedures, mainly myringotomy with ventilation tube insertion (MVTI). Approximately two-thirds of children in Australia will have at least one episode of OM by the time they reach their first birthday. While Aboriginal children are more likely to experience earlier and more severe disease than their non-Aboriginal peers, there is little information about rates for hospitalisations with otitis media and related procedures. Using a population birth cohort of all children born in Western Australia between 1996 and 2012 extracted from the Birth and Death Register and the Midwives Notification System linked to hospitalisation data, I described the age-specific rates of OM hospitalisations and MVTI by age, Aboriginal status, region of birth (metropolitan, rural and remote) and Socio Economic Index for Area. I also looked at the trends for OM-diagnoses prior to and after the introduction of the pneumococcal vaccine. I also explored the maternal and infant risk factors for hospitalisation with an OM diagnosis or a MVTI among non-Aboriginal and Aboriginal children.

Methods

I used the International Classification of Disease Australian Modification codes to identify hospital admissions with relevant OM diagnoses and procedures. To calculate hospitalisation rates for OM and OM-related procedures, I used a person-time-at-risk (PTAR) incorporating the date of birth, death and the end of the study, 31 December 2012. I present rates by age group, region of birth and Aboriginal status per 1000 child years.

Maternal and infant risk factors were available from the linked datasets. I built a negative binomial regression model to calculate the risk of an OM diagnosis in children <2 years or MVTI in children <5 years, adjusted for all other risk factors in the model.

Results

Children who were born outside of major cities had the highest rates of OM-related hospitalisations while children born in major cities had the highest MVTI procedure rates. Similarly, children who lived in the most disadvantaged neighbourhoods had the highest rates of OM-related hospitalisation but the lowest rates of MVTIs.

Overall, the hospitalisation rate for OM among non-Aboriginal children <15 years born in metropolitan area was 1.82 per 1000 child years. The hospitalisation rate for Aboriginal children was 8.82 per 1000 child years. Overall, the hospitalisation rate for MVTI among non-Aboriginal children <15 years born in metropolitan area was 12.91 per 1000 child-years compared with 10.43 per 1000 child years for Aboriginal children. Overall the rates of OM hospitalisations for both non-Aboriginal and Aboriginal children declined from 1996 to 2012, however the rates were ten times higher for Aboriginal children and remained so throughout the study.

Non-Aboriginal children who were born to teenage mothers aged <20 years had almost three times the rate of OM hospitalisations compared with children whose mothers were aged ≥35 years (IRR 2.87, 95%CI: 2.05-4.01). Spending any time in the NICU was also associated with a higher rate of OM hospitalisations, IRR 1.61 95%CI 1.25,2.07 for ≥4 days. Having an elective caesarean was associated with increased risk of hospitalisation for OM (IRR 1.35, 95%CI: 1.10-1.65). The OM admission rate for Aboriginal children living in very remote parts of the state was four times higher than those living in major cities (IRR 4.54, 95%CI: 3.48,5.93). Spending ≥4 days in the NICU was also associated with OM hospitalisations (IRR 2.24, 95%CI: 1.67,3.02), as it was for non-Aboriginal children.

Conclusions

Hospitalisation rates with an OM-related diagnosis among both non-Aboriginal and Aboriginal children have declined since 1996. Aboriginal children at the end of the study still experienced higher rates of hospitalisation with OM. Conversely, they had fewer MVTI, a procedure that helps to improve OM and related sequelae while improving hearing quality. These results should be used to influence policy makers to make decisions that help to improve the ear and hearing outcomes for all Australian children, particularly those who suffer the greatest burden of hospitalisations.

1.0 Background

1.1 Introduction

Otitis media (OM) is an infection of the middle ear distinguished by inflammation of the tympanic membrane (ear drum) and the space behind it (**Figure 1**). It is one of the most common infectious diseases affecting children.[1,2] Approximately two-thirds of children in Australia will have at least one episode of OM by the time they reach their first birthday.[3] Incidence is most common between 18-24 months of age.[4] In the United States (US) city of Boston, over 90% of children are reported to have an OM episode before they turn two years.[5] OM is responsible for the highest level of antibiotic prescribing[1,5-7] leading to increased antibiotic resistance[8] and surgery in infants and young children, commonly myringotomy with ventilation tube insertion (MVTI), adenoidectomy or adenotonsillectomy.[1] Children who experience an early episode of OM are more likely to have frequent and more serious disease as they get older.[1,2]

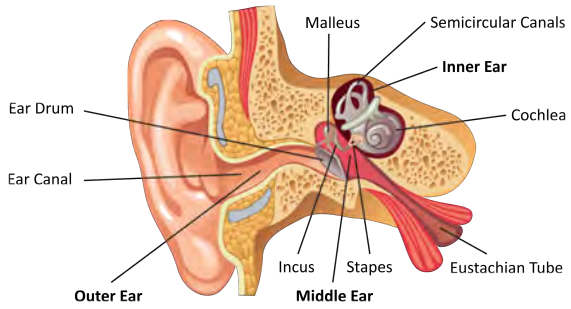

Figure 1. Anatomy of the ear[10]

Box 1. List of terms used in this chapter[9]

Otitis media (OM) – General term for all kinds of middle ear infection.

Acute otitis media (AOM) – presence of fluid behind the eardrum with at least one of bulging eardrum, red eardrum, recent discharge of pus, fever, ear pain or irritability. Can be with or without perforation.

Chronic suppurative otitis media (CSOM) – perforated ear drum with persistent discharge for more than six weeks.

Otitis media with effusion (OME) – also known as glue ear, middle ear fluid without symptoms of suppurative infection.

Untreated acute otitis media (AOM) can lead to a more serious condition called chronic suppurative OM (CSOM). CSOM is marked by a steady discharge of fluid through a perforated tympanic membrane lasting more than five weeks and which may not heal.[11] This can lead to chronic hearing loss which affects speech and language development and can lead to educational disadvantage.[12,13] In 2004, the World Health Organization (WHO) estimated that between 65 and 330 million people suffer from CSOM globally. Approximately 60% of these suffer significant hearing loss and approximately 28,000 people die each year from CSOM complications.[14] The most common cause of

death is brain abscess[15] followed by mastoiditis.[14] More recently, the WHO has recognised CSOM in an expanded group of neglected conditions.[16]

Globally, children in resource poor contexts (particularly within high income countries)[17] have the highest burden of AOM in the world. Among children aged 1-4 years, the areas with the highest incidence rates for AOM are Oceania (114.98%), Central (143.87%) and West (154.12%) Sub-Saharan Africa, indicating that children in this age group experience more than one episode of AOM during a 12-month period.[18] The high burden in Aboriginal Australians is described below in section 1.2. Alaskan native children <5 years of age attended primary care for OM-related illness more than three times as often as children in the general US population, 181.2 vs. 62.7 visits per 100 children per year.[19] Native Americans made approximately 80 visits per 100 children.[19] OM is endemic among many northern Canadian Aboriginal communities with rates 40 times higher than those in urban Canadian communities.[20]

A list of terminology used in this chapter can be found in **Box 1**.

1.2 Otitis Media in Australia

Australian Aboriginal and/or Torres Strait Islander children (hereafter referred to as Aboriginal as only 0.07% of the Western Australian population identify as Torres Strait Islander[21]) have some of the highest rates of OM in the world.[22] In a cross-sectional study of Australian Aboriginal children in Northern and Central Australian communities, 91% showed evidence of any OM, 76% had history of AOM and 44% had a history of perforation.[23] In 2003 it was estimated that there were 1,174,267 cases of OM in Australia, 68% of which occurred in children 0-14 years.[24]

The cost to treat OM in Australia is high in terms of consultations, antibiotics and procedures. Data from the *Bettering the Evaluation and Care of Health* (BEACH) study was used to estimate OM in primary care. The BEACH study is a cluster survey of primary healthcare consultations that has been ongoing since 1998.[25] Using these data researchers estimated that between 1998 and 2006, 7.3 per 100 consultations and 9.8 per 100 consultations for non-Aboriginal and Aboriginal visits to primary care providers were for OM-related illness.[26] The estimated number of patient encounters managed between April 2011 and March 2015 with an OM diagnosis were 1.07 million in children <15 years,

an increase of approximately 10% from the four year period April 2003 to March 2007.[27] The cost to treat OM in Australian children <5 years was estimated to be between $52m and $129m in 2008.[28] Antibiotics for OM-related primary care visits were prescribed in 80% of visits[27] and made up 10% of the total medications prescribed.[28]

1.3 Microbiology of otitis media and vaccination

The primary otopathogens associated with nearly all of AOM are *Streptococcus pneumoniae,* non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*.[2,29] In Australia, the heptavalent pneumococcal conjugate vaccine (7vPCV) was introduced and funded in 2001 for targeted groups with the highest risk for invasive pneumococcal disease including Aboriginal children and other children with certain medical risk factors. This was for a primary three-dose schedule. In 2005 the program was expanded universally for all children with a catch-up for those up to age 2 years.[30] Since the widespread use of the 7vPCV in Australia, there has been a reduction in the 7vPCV serotypes and an increase in non-vaccine serotypes recovered from middle ear fluid.[31]

In 2009 Jardine *et. al*. conducted an ecologic study to measure the effect of the 7vPCV on the frequency of MVTI in Australia between 1998-2007. They showed a decline in the rates of MVTI hospitalisation after the routine use of 7vPCV vaccines in some age groups.[32] In Western Australia (WA) others also reported decreasing rates of MVTI in children born between 1980 and 2004 using administrative data, however not related to 7vPCV.[33]

1.4 Myringotomy with ventilation tube insertion

A myringotomy involves a surgical incision into the tympanic membrane for the purpose of relieving pressure or to drain fluid build-up in the middle ear.[34] If left, the fluid can cause OM and hearing loss. The incision often closes within a few days so an otolaryngologist (ENT) surgeon will often insert a tympanostomy or ventilation tube (grommets) into the eardrum to keep it open and allow the build-up to drain, without having to do another incision.[35] The tube is extruded naturally by the body.[36] Those that are not extruded can be removed by the surgeon.

1.5 Research aims

Despite the cost and incidence of OM, there is very little information available that describes the burden of OM-related hospitalisations in the general Australian population[3] and no information about OM-related hospitalisations comparing non-Aboriginal and Aboriginal children. We wanted to better understand the burden in terms of hospitalisations for OM in the population over time and investigate maternal and infant risk factors for OM diagnoses and procedures in the early years of life. Due to the availability of linked administrative data in WA, we were able to investigate the patterns and trends of OM hospitalisations and procedures using a total population birth cohort of children born between 1996 and 2012. Our aims were to:

- describe the overall rates of OM and MVTI hospitalisations by age, Aboriginal status, region of birth (metropolitan, rural and remote) and Socio Economic Index for Area (SEIFA), a composite of variables from the Census to rank areas of Australia according to relative advantage and disadvantage[37] (described in more detail in section 2.7.2).
- describe the temporal trends for OM hospitalisation and MVTI for non-Aboriginal and Aboriginal children over the period of the study (1996-2012).
- explore the maternal and infant risk factors for hospitalisation with an OM diagnosis in children <2 years or an MVTI in children <5 years separately for non-Aboriginal and Aboriginal children over the period of the study (1996-2012).

2.0 METHODS

2.1 Setting and Population

Western Australia (WA) is Australia's largest state covering one third of the landmass of the continent. WA is sparsely populated with only 2.5 million residents, 1.9 million of whom live in and around the metropolitan Perth region.[38] The state is divided into nine public health regions. Two health regions comprise the Perth metropolitan area, while the other seven make up the WA Country Health Service (WACHS). These are the Kimberley, Pilbara, Midwest, Goldfields, Wheatbelt, South

West and Great Southern. These regions can further be combined into three subcategories for relative remoteness.

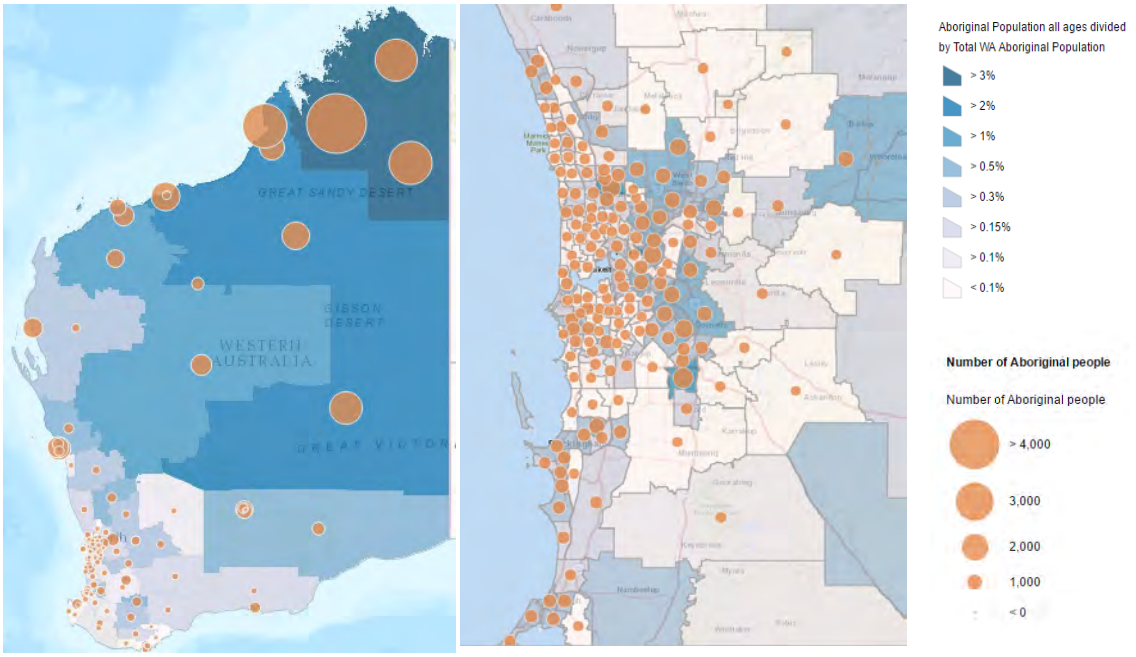

Figure 2. Map of Western Australia and Perth metropolitan region with highlighted areas indicating proportion of Aboriginal population and total number of Aboriginal residents. (Map courtesy of Rebecca Seth, Telethon Kids Institute. Data from ABS)

The Perth and surrounding area make up the metropolitan area; the Midwest, Wheatbelt, South West and Great Southern are categorised as rural; and the Kimberley, Pilbara and Goldfields are categorised as remote. Four percent of the population in WA identify as Aboriginal,[21] however a greater proportion of Aboriginal people reside outside of the capital. The Kimberley and Pilbara, the two most northern regions, have the highest proportion of residents who are Aboriginal. Kimberley residents who are Aboriginal make up 43% of the region and 18% of the state's Aboriginal population while in the Pilbara Aboriginal residents make up 16% of the region and 11% of the state, respectively (**Figure 2**).[39] Approximately 44% of Aboriginal and 80% of non-Aboriginal Western Australian's live in the metropolitan area.[21,38]

2.2 Data linkage in Western Australia

Data linkage is the process of bringing together records collected from two or more sources that relate to the same person.[40] The Western Australia Data Linkage System (WADLS) has been linking health data since the 1970s and uses a best practice protocol[41] to link routinely collected data from several core government datasets. Data are available for the whole WA population giving way to conduct whole of population analytical studies following ethical approval.

2.3 Datasets used in this analysis

2.3.1 Midwives' Notification System

The Midwives' Notification System (MNS) collects maternal and birth information from midwives about all births they attend in WA providing the infant is at least 20 weeks in gestational age or weighs at least 400 grams if the gestational age is not known. This system has been operational since 1975 and collects information on approximately 99% of births occurring in WA. Data providers include public and private hospital maternity services, publically funded homebirth services, private practice midwives, and any other health service first to provide care to a woman who has given birth.[42]

2.3.2 Birth and Death Registers

The Birth register contains records of all births and the Death Register contains records of all deaths registered in WA. The Birth Register contains information about the mother, father and baby. The Death Register includes coded cause of death data.

2.3.3 Hospital Morbidity Data Collection

The Hospital Morbidity Data Collection (HMDC) is the largest data collection managed by WA Health. Records in this system have been collected since 1970. This dataset contains all separation records from all public and private hospitalisations in WA. These include public acute hospitals, public psychiatric hospitals, private acute hospitals (licensed by WA Health), private psychiatric hospitals (licensed by WA Health) and private day surgeries (licensed by WA Health).[43]

2.4 *Data used in the current study*

This study is part of a larger, total population-based retrospective cohort study investigating the pathogen-specific burden of respiratory infections in children. Data used for the present study, *i.e.* study of hospitalisation for OM and related procedures, were extracted from the HMDC, Birth and Death Register and Midwives' Notification System for all 469,589 children born in WA between 1996 and 2012 (**Figure 3**). Analyses for the present study were restricted to children who were aged under 15 years at the time of their OM related hospitalisation. Data cleaning and coding were completed using SPSS v23.

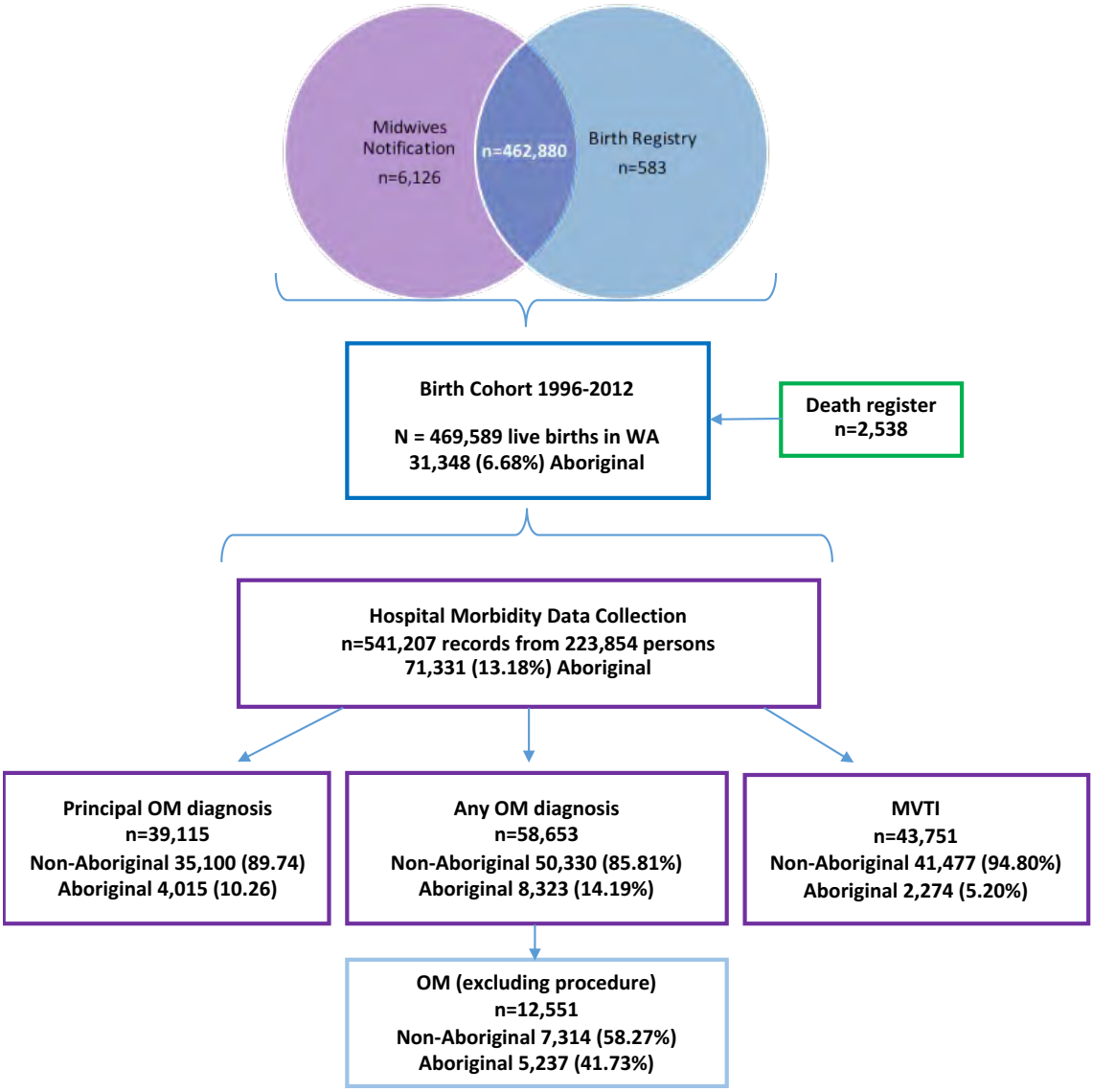

Figure 3. Flow chart of all data available from the datasets used in this study, includes all children *(< 18 years at time of admission to hospital)* born between 1996 and 2012

2.5 *Aboriginal status*

Aboriginal status in administrative datasets is often affected by inaccurate, missing or inconsistent data.[44] The datasets used in this study contain an Indigenous status flag that was derived using the methods from the *Getting Our Story Right* project.[44-46] These methods, jointly developed by the Australian Bureau of Statistics, WADLS and Telethon Kids Institute, involve a series of algorithms to code Aboriginal status from variables in all the available datasets held by WADLS. Then in datasets with observations for the same individual, the flag is attached. These methods have been used successfully by others.[47,48] The result is greatly improved data quality with more accurate Aboriginal representation.[44] The result was complete Aboriginal status ascertainment in the linked dataset.

2.6 *Data Coding*

I used the International Classification of Disease (ICD) Australian Modification (AM)[49] codes (hereafter all ICD-AM codes will be referred to as ICD) to identify hospital admissions with relevant OM diagnoses and procedures. ICD coding is performed by trained clinical coders based on discharge summaries that are completed by treating doctors (usually junior medical staff). We used the principal diagnosis and up to 20 additional diagnosis codes to identify admissions of interest. A principal diagnosis code is the code related to the condition that required the most care during the hospitalisation. The additional diagnoses were other diagnoses that also required care. For example, a patient with a principal diagnosis of suppurative otitis media or tonsillitis could have an additional diagnosis of perforation. Likewise, a principal procedure and a possible 20 additional procedure variables were available. In 1999, three years into data collection for this birth cohort study, the ICD codes changed from ICD ninth version (ICD 9) to tenth version (ICD 10). We obtained both ICD 9 and ICD 10 codes for each condition of interest and extracted diagnosis and procedure data to create new variables. OM was assessed by reviewing principal OM diagnosis, any mention OM diagnosis, that is principal and/or any additional diagnosis field, and MVTI procedures. Throughout this chapter OM refers to any mention OM unless otherwise stated. In our dataset, MVTI made up 97.95% of all

of these procedures and 98.25% in children aged <5 years. We included all of these in the analysis. Hereafter we refer to myringotomy with or without ventilation tube insertion broadly as MVTI.

A full list of ICD codes can be found in **Appendix 1**. As these are separation data, only hospital stays that include both an admission and discharge during the study period are included in this analysis. Hereafter separation, hospitalisation, or admission will be referred to synonymously.

Inter-hospital transfers were combined to avoid double counting of admissions. Admissions for OM that occurred within 14 days of a previous admission for OM were considered part of the same illness episode and were grouped together. All hospital procedures were included even if a new or repeat procedures was conducted in succession in order to retain possible complications resulting from the procedure.

2.7 Statistical Methods

To calculate hospitalisation rates for OM and OM-related procedures, a person time at risk (PTAR) algorithm was calculated using the date of birth, death and the end of the study, 31 December 2012. Hospitalisation rates were expressed per 1000 child-years. We then calculated age-specific rates for principal and OM diagnoses, which included both principal and all related additional diagnoses (hereafter referred to as any OM) as well as procedures and rates of non-procedural OM, that is OM-related diagnosis where a procedure was not performed. Finally we calculated hospitalisation rates for MVTI. For MVTI we applied a three year moving average to smooth out annual variations, as a result we do not report rates for the first and last year of the study. All analyses were conducted separately for Aboriginal and non-Aboriginal children and by region of birth. Incidence rate ratios (IRR) were used to compare rates of Aboriginal and non-Aboriginal children for an OM diagnosis or procedure. We used the following age groups in the analysis: <6, 6-11, 12-17, 18-23 months and 2, 3-4, 5-9, 10-14 years. Children aged >14 years at time of hospital admission were not included in these analyses. Some variables in the dataset had missing observations. In analyses where a variable had missing information, the number of observations with missing information were presented in the footnotes of the applicable tables but were not included in that analysis.

2.7.1 Interrupted time series analysis of trends prior to and after the introduction of the 7vPCV

To determine whether there was an effect on hospitalisation rates following the introduction of the 7vPCV, I conducted an interrupted time series analysis using log-linear modelling. First, a negative binomial regression model was fitted to obtain coefficients for the reference time period, that is the time prior to 7vPCV use (*i.e.* 2001 for Aboriginal children and 2005 for non-Aboriginal children) and for the time period after 7vPCV use. We used a negative binomial regression model in view of over-dispersion due to the fact that the data were not normally distributed. To estimate the annual change for each group, the regression coefficients were exponentiated and multiplied by 100 (to represent the annual percentage change). A significant result from the negative binomial regression model (*i.e.* a p-value of < 0.05) indicated a statistically significant difference in the trend, per year compared to no 7vPCV use. For age groups where the trend for the time period prior to and after 7vPCV use was significantly different, we plotted a graph showing the relative increase or decrease using a logarithmic scale.

2.7.2 Risk factors

The following risk factors were available from the Midwives' Notification System and Birth Register: sex, gestational age (≤28, 29-32, 33-36, ≥37 weeks), maternal age at birth (<20, 20-24, 25-29, 30-34, ≥35 years), number of siblings, maternal smoking during pregnancy (yes/no), maternal asthma during pregnancy (yes/no), season of birth (spring, summer, autumn, winter), mode of delivery (vaginal, instrumental, elective caesarean, emergency caesarean), days in neonatal intensive care unit (NICU) (0, 1-3, ≥4), percentage of optimal birthweight (POBW), SEIFA, and Accessibility/Remoteness Index of Australia (ARIA).

An elective caesarean was defined as a planned procedure occurring before the onset of labour and rupture of membranes, without an intervention to induce labour. POBW, a measure that accounts for gestational duration, gender, maternal age, maternal height and parity[50] was used rather than birthweight alone as an indication of age-specific appropriateness of foetal growth. POBW was grouped as low <85%, normal 85-114%, or high ≥115%.

We used the SEIFA to measure relative advantage and disadvantage. There are four indices of SEIFA, each focusing on a different aspect of socioeconomic disadvantage from variables in the Census data. The SEIFA was developed by the Australian Bureau of Statistics (ABS) using information about low income, low educational attainment, unemployment and having jobs in unskilled professions as a measure for advantage and disadvantage.[37] We used the advantage and disadvantage index as it was the only one that did not derive values from Aboriginal status because we wanted to stratify our analysis by Aboriginal status. The ARIA is an Australian Government Department of Health sponsored tool that uses accessibility by road to health services as a measure to classify remoteness across the country. The ARIA has five major classifications (major cities, inner regional, outer regional, remote or very remote).[51]

Maternal and infant risk factors were calculated for each child by running a negative binomial regression model where the outcome was a) number of principal OM diagnoses in children <2 years and b) number of admissions with any OM (without procedure) in children <2 years because we wanted to explore OM hospitalisations alone as procedures will often have an OM diagnosis code, and lastly c) number of MVTI in children <5 years **(Figure 3)**. The risk factors were included in the model as predictor variables with time-at-risk as the exposure option in the model. Time-at-risk was calculated as the time from the child's date of birth to the end of the study, 31 December 2012, death, or time from birth to the censored age (<2 or <5 years), whichever came first. We conducted a univariate analysis exploring each risk factor. Finally, we conducted a multivariable analysis and retained all of the covariates from the univariate analysis in the full model as potential confounders or effect modifiers. All risk factors were reported with incidence rate ratios (IRR) and 95% confidence intervals (CIs) and calculated separately for non-Aboriginal and Aboriginal children. We repeated this analysis for each separate model.

We reported 95% confidence intervals (CI) where appropriate. Any analysis with an observation of <5 values in any cell was reported as <5. Results were considered significant if $\alpha<0.05$. These data analyses were completed using Stata 14.1 (Stata Corp, College Station, TX).

2.8 Ethics Approval

Ethical approval for this work was granted by the Department of Health Western Australia Human Research Ethics Committee (Projects 2011/78 and 2012/56), the Western Australian Aboriginal Health Ethics Committee (Ref no. 437) and the Australian National University Human Research Ethics Committee (Protocol: 2016/451).

3.0 RESULTS

3.1 Description of birth cohort

Our birth cohort consisted of 469,589 children born between January 1996 and December 2012. Of these, 31,348 (6.68%) were Aboriginal and 240,237 (51.16%) were boys. Singleton births accounted for 455,689 (97.04%) of the cohort and 2,538 (0.54%) children had died by 2012.

3.2 Overall OM Rates

There were a total of 541,207 hospital admissions in WA from 223,854 children (aged <18 years), 71,331 (13.18%) of the admissions were for Aboriginal children. Of these, 5,709/469,869 (1.22%) admissions were from non-Aboriginal and 639/71,338 (0.90%) admissions for Aboriginal children aged ≥15 years at time of admission and not included in these analyses. Among the 534,859 hospital admissions by children aged <15 years, we identified 38,881 (7.27%) of the admissions were coded with a principal OM diagnosis, 35,261/38,881 (90.69%) of which also had an OM-related procedure recorded at the same admission.

There were 58,597 (10.96%) records with OM diagnoses which included admissions where an OM-related procedure was also performed.

Overall, non-procedural OM admissions accounted for 12,468 (21.27%) of these, that is an OM-related admission where no OM-related procedure was also performed during that admission.

There were a total of 48,712 OM-related procedures performed, 43,737 (89.79%) were for a MVTI. Some children had records for more than one hospitalisation. A summary of the admissions by children <15 years of age who were hospitalised with OM can be found in **Table 1**. Hospitalisation with a non-procedural OM admission occurred in 7,258/464,160 (1.56%) non-Aboriginal admissions and 5,210/70,699 (7.37%) of Aboriginal admissions among children aged <15 years.

There were 174 readmissions with an OM-related diagnosis within 14 days of the first and 11 children with a third admission within two weeks of the second. These were not included in the analysis.

Table 1. Distribution of admissions by children under age 15 years with a principal diagnosis of OM, OM (excluding procedure) or a MVTI between 1996 and 2012

non-Aboriginal children			
Type of admission	**Principal diagnosis of OM**	**OM (excluding procedure)**	**MVTI**
Total no. of separations	**34,909**	**7,258**	**41,465**
Sex			
male, n (%)	21,272 (60.98)	4,351 (59.95)	25,314 (61.05)
female, n (%)	13,637 (39.02)	2,907 (40.05)	16,151 (38.95)
Age, years			
mean	3.29	1.82	3.21
median	3	1	3
standard deviation	2.56	2.20	2.26
No. of separations/child			
mean (range)	1.55 (1 to 17)	1.30 (1 to 37)	1.48 (1 to 10)
Aboriginal children			
Type of Admission	**Principal diagnosis of OM**	**OM (excluding procedure)**	**MVTI**
Total no of separations	**3,972**	**5,210**	**2,272**
sex			
male	2,217 (55.94)	2,916 (55.97)	1.296 (57.04)
female	1,755 (44.06)	2,294 (44.03)	976 (42.96)
age, years			
mean	4.36	1.60	4.42
median	4	1	4
standard deviation	3.44	2.23	2.86
No. of separations/child			
mean (range)	1.53 (1 to 12)	1.87 (1 to 19)	1.37 (1 to 8)

Abbreviations; OM, otitis media; MVTI, myringotomy with ventilation tube insertion

3.3 Age-specific rates of OM-related hospitalisations (excluding procedure)

The region and age-specific rates of OM are presented in **Table 2**. The admission rates for non-Aboriginal children 0-4 years were significantly higher if they were born in a rural or remote part of the state. Aboriginal children of all ages had higher admission rates for OM if they were born in a rural or remote part of the state, compared with those children born in the metropolitan area. The hospitalisation rate increased with greater relative remoteness. The hospitalisation rate for Aboriginal children aged 0-5 months born in a remote part of the state was 15 times higher than that of non-Aboriginal children.

The hospitalisation rate for OM was higher among Aboriginal children regardless of where they were born. Overall, the hospitalisation rate for OM in non-Aboriginal children <15 years was 1.82 for

metropolitan-born, 2.94 for rural-born and 3.18 per 1000 child-years for remote-born children. The OM-related hospitalisation rates for Aboriginal children was 8.82 for metropolitan-born, 16.10 for rural-born and 34.04 per 1000 child-years for remote-born children (**Table 2**).

Table 2. Rates of hospital admission for an OM diagnosis (excluding procedures) in a Western Australian birth cohort 1996-2012, by Aboriginal status and region of birth*

	Non-Aboriginal			Aboriginal			IRR (95% CI)
Age	No.	Rate†	Regional IRR	No	Rate†	Regional IRR	Aboriginal : non-Aboriginal
0-5 months							
Metropolitan	281	1.70	Reference	80	14.59	Reference	**8.60 (6.63,11.06)**
Rural	124	3.58	**2.11 (1.69,2.61)**	98	27.14	**1.86 (1.37,2.53)**	**7.59 (5.76,9.97)**
Remote	62	4.49	**2.65 (1.98,3.50)**	414	67.69	**4.64 (3.64,5.97)**	**15.08 (11.52,20.03)**
6-11 months							
Metropolitan	880	5.53	Reference	191	36.30	Reference	**6.57 (5.59,7.69)**
Rural	368	10.96	**1.98 (1.75,2.24)**	210	60.28	**1.66 (1.36,2.03)**	**5.50 (4.62,6.53)**
Remote	167	12.51	**2.26 (1.91,2.67)**	887	150.03	**4.13 (3.53,4.86)**	**11.99 (10.15,14.24)**
12-17 months							
Metropolitan	1048	6.85	Reference	154	30.40	Reference	**4.44 (3.72,5.26)**
Rural	355	10.92	**1.59 (1.41,1.80)**	181	53.69	**1.77 (1.42,2.20)**	**4.92 (4.09,5.90)**
Remote	196	15.17	**2.22 (1.89,2.58)**	692	120.96	**3.98 (3.34,4.77)**	**7.97 (6.79,9.39)**
18-23 months							
Metropolitan	686	4.67	Reference	96	19.63	Reference	**4.21 (3.36,5.22)**
Rural	218	6.93	**1.49 (1.27,1.73)**	109	33.46	**1.70 (1.28,2.27)**	**4.83 (3.80,6.10)**
Remote	109	8.68	**1.86 (1.51,2.28)**	424	76.63	**3.90 (3.12,4.92)**	**8.62 (6.97,10.74)**
2 years							
Metropolitan	711	2.57	Reference	90	9.73	Reference	**3.78 (3.00,4.72)**
Rural	263	4.40	**1.71 (1.48,1.98)**	131	21.26	**2.18 (1.66,2.89)**	**4.83 (3.88,5.97)**
Remote	94	3.96	**1.54 (1.23,1.91)**	426	40.62	**4.18 (3.32,5.30)**	**10.26 (8.19,12.97)**
3-4 years							
Metropolitan	631	1.30	Reference	74	4.52	Reference	**3.47 (2.69,4.42)**
Rural	217	2.04	**1.56 (1.33,1.82)**	121	11.08	**2.45 (1.82,3.32)**	**5.44 (4.32,6.82)**
Remote	74	1.74	**1.34 (1.04,4.70)**	328	17.53	**3.87 (3.00,5.06)**	**10.05 (7.79,13.11)**

5-9 years							
Metropolitan	448	0.53	Reference	70	2.46	Reference	**4.64 (3.55,5.98)**
Rural	154	0.80	**1.51 (1.25,1.82)**	74	3.90	**1.58 (1.13,2.23)**	**4.87 (3.64,6.47)**
Remote	44	0.56	1.06 (0.76,1.45)	245	7.23	**2.94 (2.24,3.89)**	**12.85 (9.29,18.13)**
10-14 years							
Metropolitan	92	0.23	Reference	18	1.40	Reference	**5.98 (3.40,9.99)**
Rural	19	0.20	0.86 (0.50,1.43)	16	1.86	1.33 (0.64,2.77)	**9.24 (4.44,18.96)**
Remote	<5	0.10	0.43 (0.12,1.15)	56	3.58	**2.56 (1.48,4.63)**	**35.29 (13.04,134.01)**
Total							
Metropolitan	4777	1.82	Reference	773	8.82	Reference	**4.85 (4.49,5.23)**
Rural	1718	2.94	**1.61 (1.53,1.70)**	940	16.10	**1.83 (1.66,2.01)**	**5.48 (5.06,5.94)**
Remote	750	3.18	**1.74 (1.61,1.88)**	3472	34.04	**3.86 (3.57,4.18)**	**10.71 (10.36,11.09)**

Abbreviations: OM, otitis media; Regional IRR, relative risk of outcome based on region; IRR, incidence rate ratio comparing Aboriginal to non-Aboriginal; 95% CI, 95% confidence interval.

*38 records with incomplete region of birth were excluded; 13 non-Aboriginal and 25 Aboriginal children.

†Rate per 1000 child years

3.4 Rates of hospitalisation by SEIFA

3.4.1 Rates of hospitalisation for OM (excluding procedure) by SEIFA in children <2 years at the time of hospitalisation

Non-Aboriginal children in the most disadvantaged SEIFA quintile had the highest rates of OM-related hospitalisations (9.37 per 1000 child-years). The rates reduced with each step on the SEIFA quintile to a low of 2.50 per 1000 child-years in the most advantaged SEIFA quintile. Among Aboriginal children the trends for OM hospitalisations remained high across all quintiles, however the highest was in the most disadvantaged SEIFA group, 64.41 per 1000 child years (**Table 3**). The rates of OM-related hospitalisation among Aboriginal children in the most disadvantaged SEIFA quintile were nearly seven times higher than non-Aboriginal children. The disproportionate rates of hospitalisation between children rose with each step on the SEIFA quintile with rates in Aboriginal children 18 times higher than those in their non-Aboriginal peers in the least disadvantaged SEIFA quintile (IRR 18.22, 95%CI, 9.48,32.12).

3.4.2 Rates of hospitalisation for MVTI by SEIFA in children <5 years at time of hospitalisation

Non-Aboriginal children whose parents were the least disadvantaged had the highest rates of MVTI, despite having the lowest overall OM-related hospitalisation rate. The rates of admissions for MVTI increased with each additional step (Table 4). Aboriginal children who were hospitalised for a MVTI also experienced higher rates with each step on the SEIFA quintile, the same as non-Aboriginal children.

Rates for Aboriginal children hospitalised for a MVTI were generally lower and half that of non-Aboriginal children in the most disadvantaged SEIFA quintile (IRR 0.52 95%CI 0.46,0.59).

Table 3. Rates of hospitalisation with OM (excluding procedures) among children <2 years at the time of admission by SEIFA quintiles of disadvantage and Aboriginal status

SEIFA quintile group	Non-Aboriginal		Aboriginal		IRR
	Total	Rate Per 1000 child years	Total	Rate Per 1000 child years	Aboriginal : non-Aboriginal children
0-10%	578	9.37	1068	64.41	**6.88 (6.21,7.62)**
(most disadvantaged)					
11-25%	886	7.52	485	39.10	**5.19 (4.64,5.81)**
26-75%	1995	5.16	790	44.13	**8.55 (7.86,9.28)**
76-90%	481	3.87	57	33.41	**8.64 (6.45,11.39)**
91-100%	150	2.50	13	45.46	**18.22 (9.48,32.12)**
(least disadvantaged)					

Abbreviations: OM, otitis media; SEIFA, socioeconomic index for area; IRR, incidence rate ratio

Table 4. Rates of hospitalisation with a MVTI among children <5 years at the time of admission, by SEIFA quintiles of disadvantage and Aboriginal status

SEIFA quintile group	Non-Aboriginal		Aboriginal		IRR
	Total	Rate Per 1000 child years	Total	Rate Per 1000 child years	Aboriginal : non-Aboriginal children
0-10%	1959	14.04	339	9.11	**0.65(0.58,0.73)**
(most disadvantaged)					
11-25%	4005	15.28	270	9.88	**0.65 (0.57,0.73)**
26-75%	14,486	16.89	429	10.62	**0.63 (0.57,0.69)**
76-90%	5351	19.65	49	13.46	**0.69 (0.51,0.91)**
91-100%	2863	21.38	9	14.62	0.68 (0.31,1.30)
(least disadvantaged)					

Abbreviations: MVTI, myringotomy with or without ventilation tube insertion; SEIFA, socioeconomic index for area; IRR, incidence rate ratio

3.5 Temporal trends for OM associated hospitalisations

From 1996 to 2012, the overall OM admission rate for an OM diagnosis (excluding procedures) across all age groups was 2.07/1000 (95%CI 2.03,2.12) child years for non-Aboriginal and 20.29/1,000 (95%CI 19.74,20.84) child years for Aboriginal children. Aboriginal children had higher point estimates than non-Aboriginal children for every age group across every year and were hospitalised younger than their non-Aboriginal peers. There was a decline in the admission rate for OM diagnoses over time for both groups of children. This was also true when admissions that included a procedure were excluded (**Figure 4** & **Figure 5**) and when including only the first admission (data not shown).

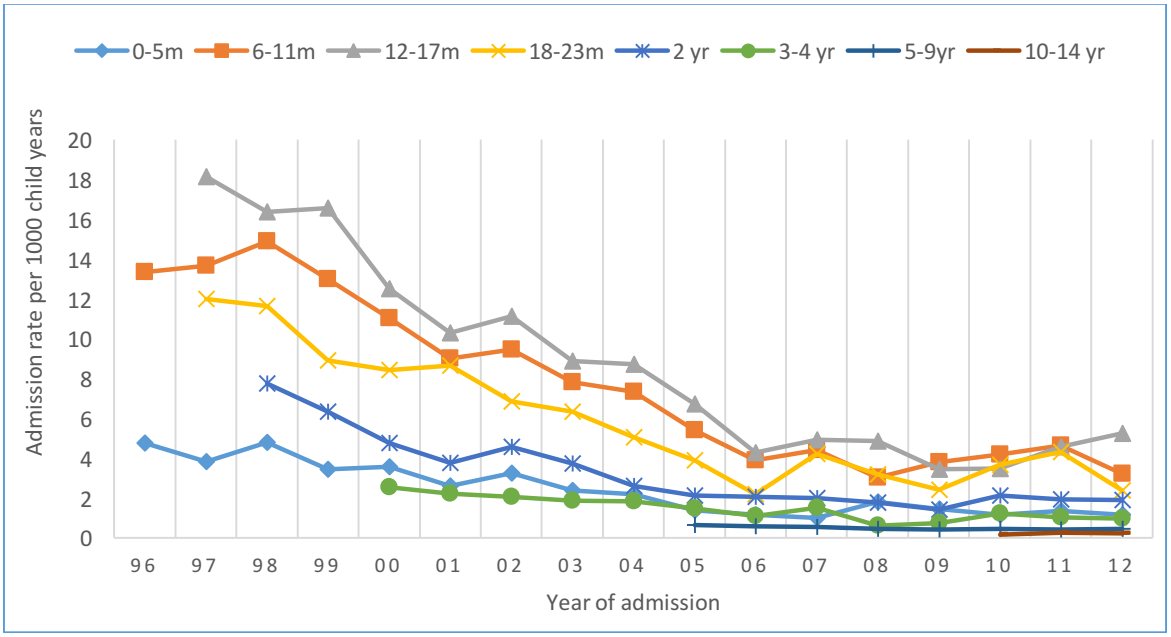

Figure 4. Hospital admission rate with non-procedural OM per 1000 child years for non-Aboriginal children born in WA between 1996 and 2012

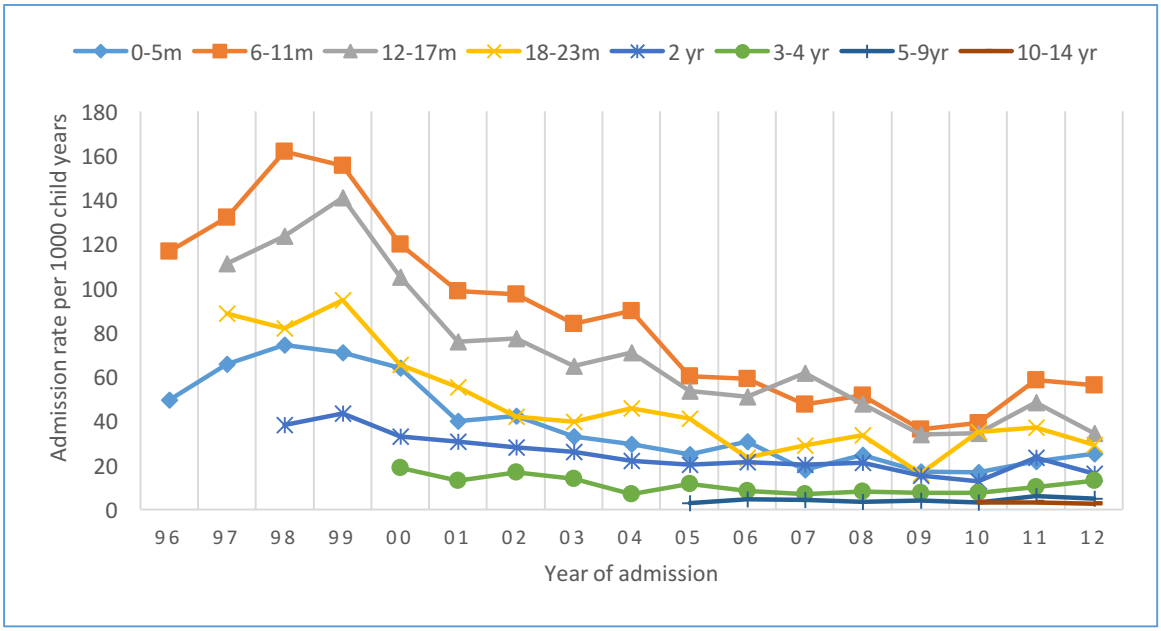

Figure 5. Hospital admission rate with non-procedural OM per 1000 child years for Aboriginal children born in WA between 1996 and 2012

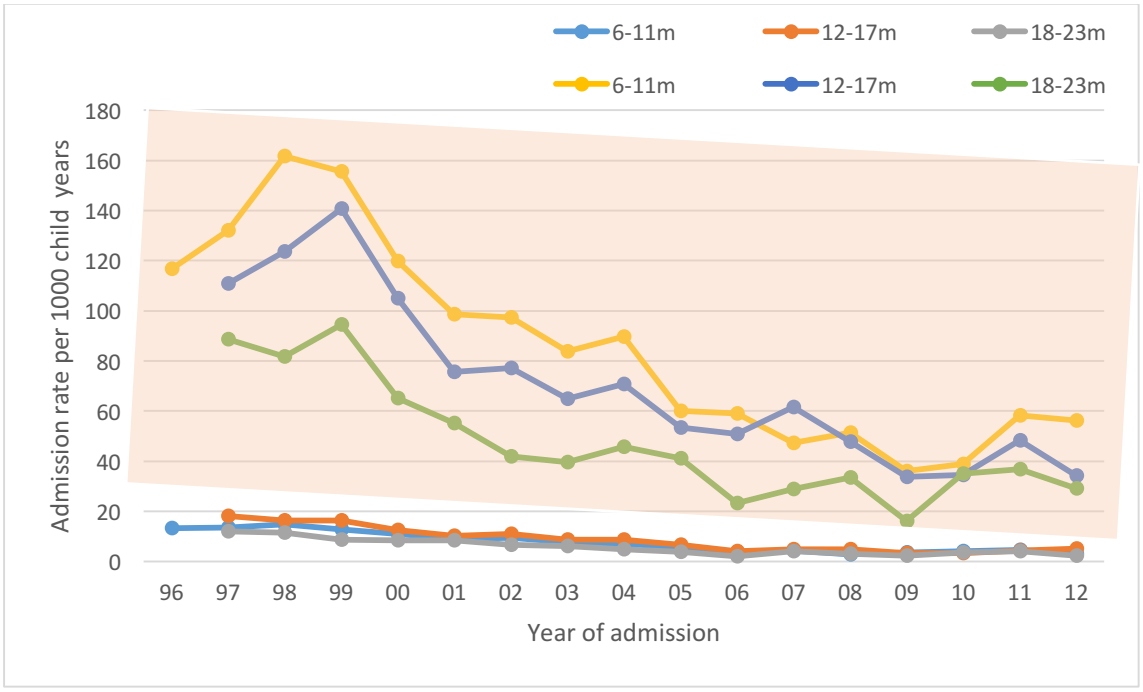

Figure 6. Non-procedural OM hospitalisation comparing non-Aboriginal (not shaded) with Aboriginal children (shaded) who were between 6 and 23 months of age

The highest hospitalisation rate for non-Aboriginal children was among those aged 12-17 months peaking at 14.90/1000 child years in 1998. The highest hospitalisation rate for Aboriginal children was among those aged 6-11 months, 161.76 per 1000 child years in 1998. Hospitalisation rates declined over time to a low of 5.27/1000 child years for non-Aboriginal children and 56.21/1000 child

years for Aboriginal children in 2012 respectively. While there was variation across the years, the OM hospitalisation rate among Aboriginal children in 1996 and 2012 was 10 times higher than that of non-Aboriginal children in the younger age groups with the highest hospitalisation rates (**Figure 6**).

3.6 Interrupted time series

I conducted analyses using interrupted time trend models to test whether there was a difference in the log linear time trend relative to the introduction of the 7vPCV in each population. The 7vPCV was introduced for Aboriginal children in 2001 and universally for all children in 2005.

There was a declining trend in OM hospitalisation for both non-Aboriginal and Aboriginal children that began before the 7vPCV use (Figures 4&5). There was a significant change in the trend for non-Aboriginal children aged 6-11 months corresponding to the introduction of 7vPCV (**Figure 7**). This meant that the decline in the incidence of OM hospitalisation was significantly greater after the introduction of the 7vPCV. The change in the trend was not statistically significant in other age groups.

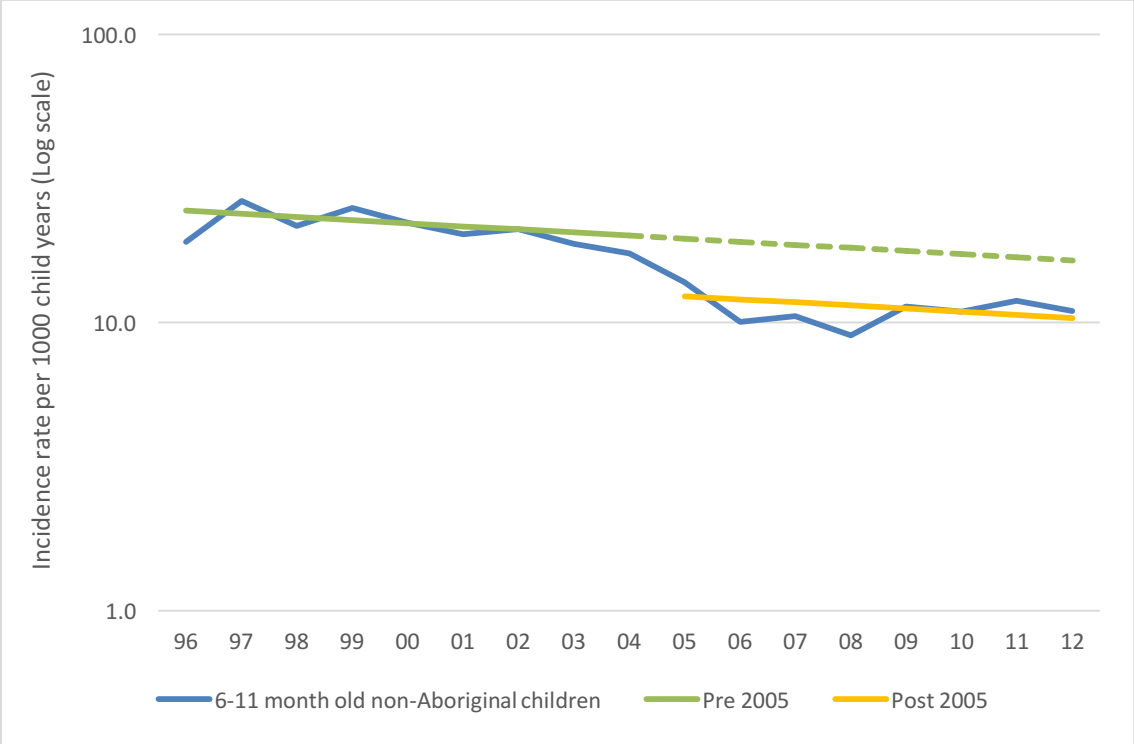

Figure 7. Temporal trends for non-Aboriginal children aged 6-11 months, pre- and post-PCV introduction for non-Aboriginal children in 2005

3.7 Temporal trends for MVTI associated hospitalisations

Of 541,207 records, there were 48,767 OM-related procedures between 1996 and 2012, 43,751 (89.71%) of which were MVTI. Of all children having a MVTI, 32,008 (73.16%) had a principal diagnosis of OM. This increased to 42,395 (96.90%) when including any diagnosis of OM. Of all children in the cohort, the principal diagnoses of the 1,356 (3.10%) who had a MVTI but did not have a principal OM-related diagnosis are presented in **Table 5** with the principal diagnosis recorded.

Table 5. Principal diagnosis recorded when a MVTI was performed without a diagnosis of OM for all children in the birth cohort

Principal Diagnosis	**n (%)** **N = 1,356**
Chronic diseases of the adenoids and/or tonsils	519 (38.27)
Sleep apnoea	246 (18.14)
Ear disorder (not middle ear)	417 (30.75)
Other respiratory illnesses	56 (4.13)
Other illnesses not indicated above	118 (8.70)

3.7.1 Age-specific rates of MVTI related hospitalisations

The region and age-specific hospital admission rates for MVTI are presented in **Table 6**. All children regardless of age or Aboriginal status had higher admission rates for a MVTI procedure if they born in the metropolitan region. Hospitalisation rates were higher in Aboriginal children <6 months, however the number of procedures contributing to the rate was very small. Compared with non-Aboriginal children, Aboriginal children aged 5-14 years had higher rates of hospitalisation, particularly in rural and remote parts of the state. Hospitalisation with MVTI was four times higher among Aboriginal vs. non-Aboriginal children 10-14 year olds born in a remote part of the state (IRR 4.16, 95%CI 2.72,6.43).

The highest MVTI-related hospitalisation rate for non-Aboriginal children was among 18-23 month olds, 27.42 per 1000 child years. The highest rate for Aboriginal children was among 2 year olds, 16.54 per 1000 child years. Even in this age group with the highest rate, the Aboriginal children still had less

MVTI-related hospitalisations per 1000 child years than non-Aboriginal children (IRR 0.74, 95%CI 0.62,0.86).

Table 6. Rates for hospital admission with a MVTI (per 1000 child years) in a Western Australian birth cohort 1996-2012, by Aboriginal status and region of birth*

	Non-Aboriginal			Aboriginal			IRR (95% CI)
Age	No.	Rate	Regional IRR	No.	Rate	Regional IRR	Aboriginal : non-Aboriginal
0-5 months							
Metropolitan	96	0.58	Reference	7	1.28	Reference	2.20 (0.86,4.72)
Rural	10	0.29	**0.50 (0.23,0.96)**	<5	1.11	0.43 (0.04,2.28)	1.92 (0.20,9.01)
Remote	<5	0.29	0.50 (0.13,1.32)	<5	0.33	0.26 (0.03,135)	1.12 (0.10,7.88)
6-11 months							
Metropolitan	1,620	10.18	Reference	34	6.46	Reference	**0.63 (0.43,0.89)**
Rural	204	6.08	**0.60 (0.51,0.69)**	19	5.45	0.84 (0.45,1.52)	0.89 (0.53,1.44)
Remote	78	5.84	**0.57 (0.45,0.72)**	25	4.23	0.65 (0.37,1.13)	0.72 (0.44,1.15)
12-17 months							
Metropolitan	3,957	25.85	Reference	51	10.07	Reference	**0.39 (0.29,0.51)**
Rural	473	14.55	**0.56 (0.51,0.62)**	37	10.98	1.09 (0.69,1.70)	0.75 (0.52,1.06)
Remote	164	12.70	**0.49 (0.42,0.57)**	33	5.77	**0.57 (0.36,0.91)**	**0.46 (0.30,0.66)**
18-23 months							
Metropolitan	4,032	27.42	Reference	79	16.16	Reference	**0.59 (0.47,0.74)**
Rural	528	16.79	**0.61 (0.56,0.67)**	42	12.89	0.80 (0.54,1.17)	0.77 (0.55,1.05)
Remote	200	16.32	**0.60 (0.51,0.69)**	42	7.59	**0.47 (0.32,0.69)**	**0.47 (0.33,0.65)**
2 years							
Metropolitan	6,213	22.47	Reference	153	16.54	Reference	**0.74 (0.62,0.86)**
Rural	976	16.34	**0.73 (0.68,0.78)**	85	13.79	0.83 (0.63,1.09)	0.84 (0.67,1.05)
Remote	301	12.67	**0.56 (0.50,0.63)**	88	8.39	**0.51 (0.39,0.66)**	**0.66 (0.52,0.84)**
3-4 years							
Metropolitan	9,589	19.81	Reference	251	15.34	Reference	**0.77 (0.68,0.88)**
Rural	1,648	15.46	**0.78 (0.74,0.82)**	142	13.00	0.85 (0.68,1.05)	0.84 (0.70,1.00)
Remote	555	13.07	**0.66 (0.60,0.72)**	171	9.14	**0.60 (0.49,0.73)**	**0.69 (0.59,0.83)**

5-9 years							
Metropolitan	7,889	9.35	Reference	294	10.34	Reference	1.11 (0.98,1.24)
Rural	1,708	8.88	0.95 (0.90,1.00)	220	11.60	1.12 (0.94,1.34)	**1.31 (1.13,1.50)**
Remote	560	7.17	**0.77 (0.70,0.84)**	348	10.28	0.99 (0.85,1.16)	**1.43 (1.25,1.64)**
10-14 years							
Metropolitan	462	1.17	Reference	45	3.49	Reference	**2.98 (2.14,4.05)**
Rural	108	1.15	0.98 (0.79,1.21)	27	3.14	0.90 (0.54,1.48)	**2.74 (1.73,4.21)**
Remote	37	0.94	0.80 (0.56,1.12)	61	3.90	1.12 (0.75,1.68)	**4.16 (2.72,6.43)**
Total for all children aged 0-14 years							
Metropolitan	33,867	12.91	Reference	914	10.43	Reference	**0.81 (0.76,0.86)**
Rural	5,658	9.67	0.75 (0.73,0.77)	574	9.83	**0.94 (0.85,1.05)**	1.02 (0.93,1.12)
Remote	1,899	8.04	0.62 (0.59,0.65)	772	7.57	**0.74 (0.66,0.80)**	0.94 (0.86,1.02)

Abbreviations: OM, otitis media; Regional IRR, relative risk of outcome based on region; IRR, incidence rate ratio comparing Aboriginal to non-Aboriginal; 95% CI, 95% confidence interval.

*67 records with incomplete region of birth were excluded; 53 non-Aboriginal and 14 Aboriginal children.

The overall separation rate for MVTI was 12.02 per 1000 (11.91,12.14)) child years for non-Aboriginal and 9.11 per 1000 (8.74,9.50) child years for Aboriginal children respectively. This was highest for those born in metropolitan Perth for non-Aboriginal children 12-17 months with a rate of 31.26 per 1000 child years in 1998 declining to 24.12 per 1000 child years in 2011 (**Figure 8**).

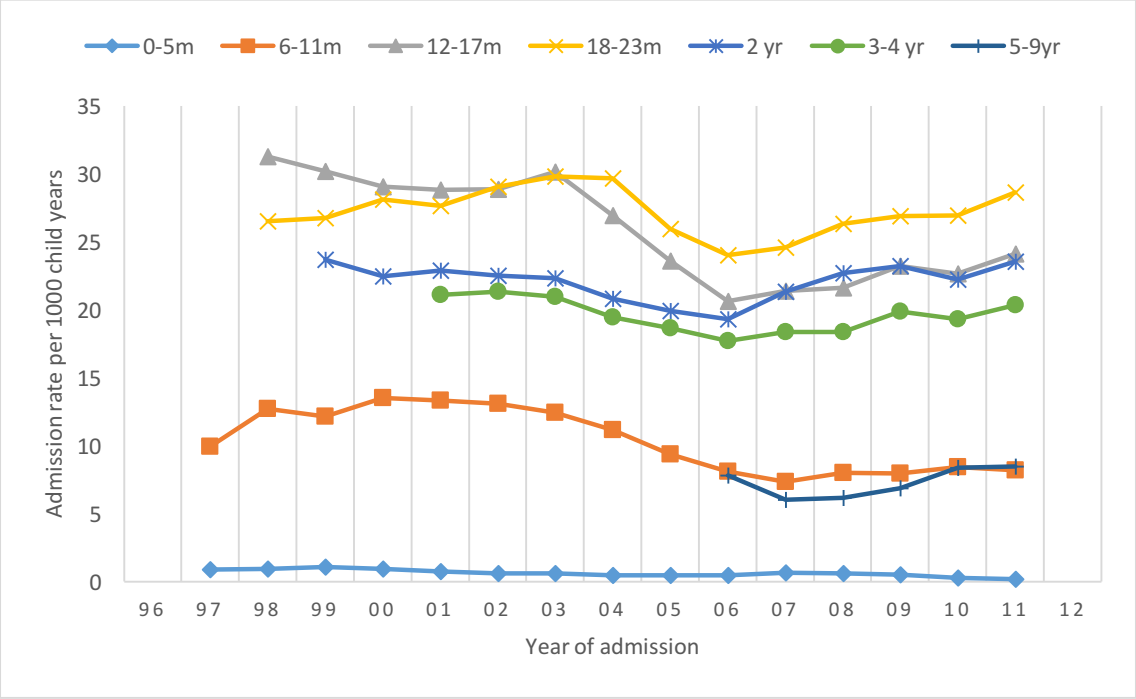

Figure 8. Hospital admission rates for MVTI among non-Aboriginal children born in metropolitan Perth (3 year moving average)

While there was fluctuation across the years, the highest rate was among Aboriginal children aged 18-23 months. The peak was 25.14 per 1000 child years in 2001 reducing to 14.86 per 1000 child years in 2011 (**Figure 9**).

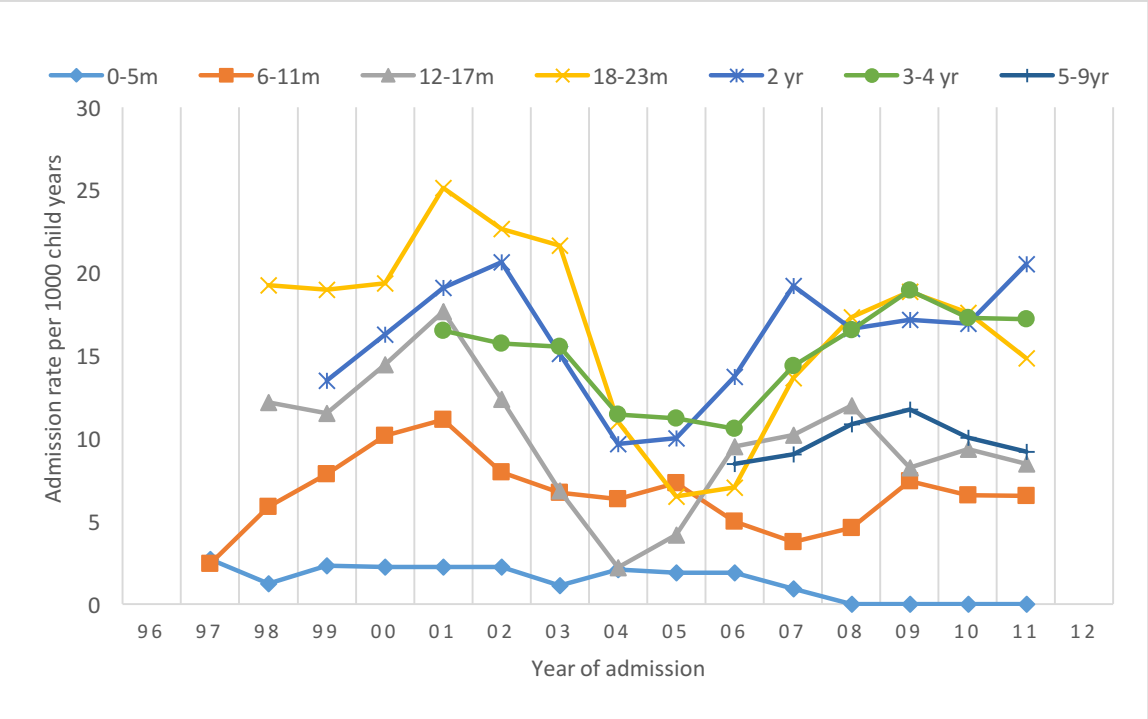

Figure 9. Hospital admission rates for MVTI among Aboriginal children born in metropolitan Perth (3 year moving average)

There was an increase in MVTI performed on children who were born in remote parts of the state from 2007 yet the procedure rates were still higher among non-Aboriginal children (**Figure 10** & **Figure 11**).

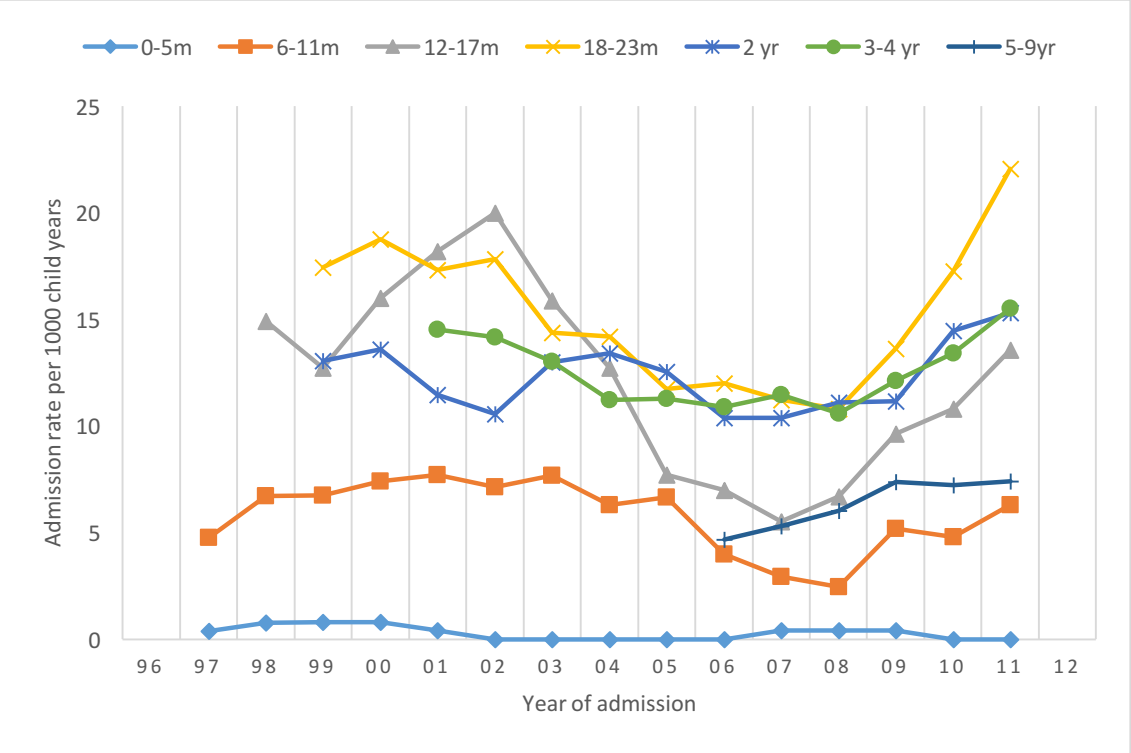

Figure 10. Hospital admission rates for MVTI among non-Aboriginal children born in remote Western Australia (3 year moving average)

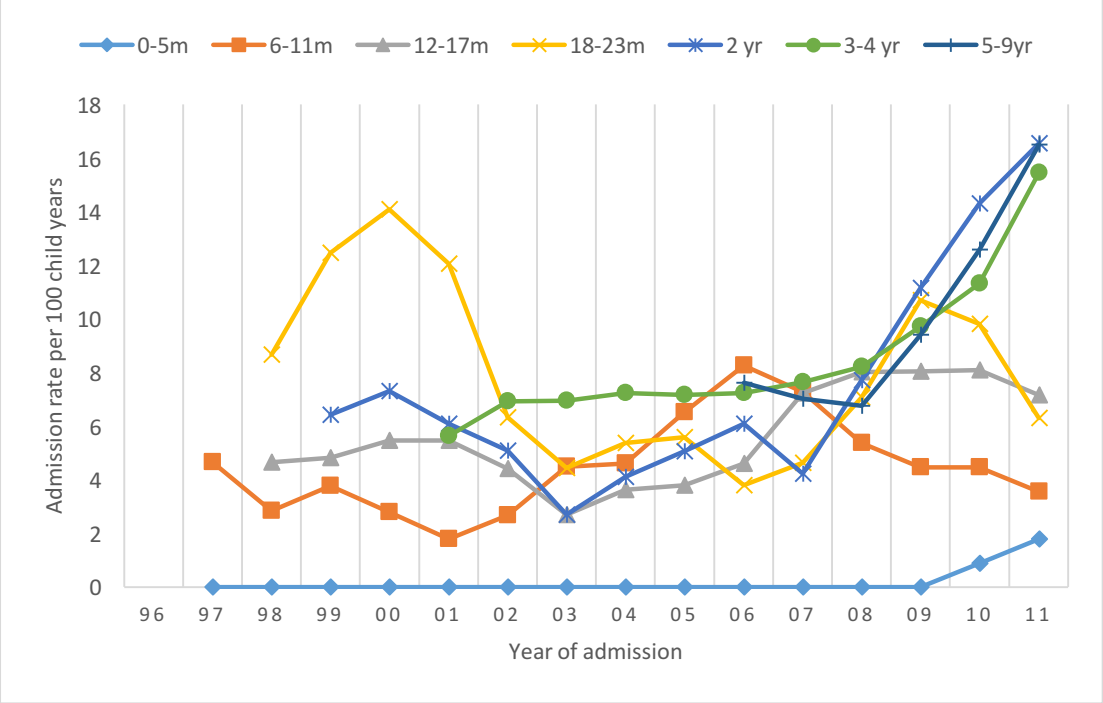

Figure 11. Hospital admission rates for MVTI among Aboriginal children born in remote Western Australia (3 year moving average)

Of all hospitalisations for non-Aboriginal children with a MVTI, 63% were at metropolitan private hospitals (data not shown) while only 7% of Aboriginal children had a MVTI at a metropolitan private hospital. The number of hospitalisations for MVTI by hospital and Aboriginal status is summarised in **Table 7.**

Table 7. MVTI by hospital type, region of birth and Aboriginal status for children <15 years

	Non-Aboriginal				Aboriginal		
	Region of birth				Region of birth		
	Metro n=33,858 n(%)	**Rural n=5,655 n(%)**	**Remote n=1,899 n(%)**		**Metro n=914 n(%)**	**Rural n=574 n(%)**	**Remote n=770 n(%)**
Tertiary n=5,108	4,399 (12.99)	508 (8.98)	201 (10.58)	**Tertiary** n=602	328 (35.89)	164 (28.57)	110 (14.29)
Public Metro n=6,399	5,917 (17.48)	305 (5.39)	117 (6.16)	**Public Metro** n=496	390 (42.67)	71 (12.37)	35 (4.55)
Rural Public/Private n=3,820	474 (1.40)	2,850 (50.40)	496 (26.12)	**Rural Public/Private** n=1,002	73 (7.99)	318 (55.40)	611 (79.35)
Private Metro n=26,145	23,068 (68.13)	1,992 (35.23)	1,085 (57.14)	**Private Metro** n=158	123 (13.46)	21 (3.66)	14 (1.82)

Abbreviations: MVTI, myringotomy with ventilation tube insertion
Percentages may not equal 100% due to rounding.
53 non-Aboriginal and 14 Aboriginal variables were not included due to missing residence at birth data.

3.8 Risk factor analysis

3.8.1 Otitis media where no procedure was performed

A total of 6,735 children aged under two years contributed 8,166 admissions with an OM diagnosis. Of those, 2,549 (37.85%) were Aboriginal children (data not shown). Both non-Aboriginal and Aboriginal children with an OM hospitalisation were significantly more likely to be boys, to spend time in the NICU or to be born outside major cities (**Table 8**).

Using multivariable analysis to adjust for all known risk factors, we found that non-Aboriginal children who were born to teenage mothers had almost three times the rate of OM hospitalisations compared with non-Aboriginal children whose mothers were aged ≥35 years (IRR 2.87, 95%CI: 2.05-4.01). Spending any time in the NICU was also associated with a higher rate of OM hospitalisations, highest when spending ≥4 days in the NICU (IRR 1.61 95%CI 1.25,2.07). Having an elective caesarean was associated with increased risk of hospitalisation for OM (IRR 1.35, 95%CI: 1.10-1.65) (**Table 8**) as it was for principal OM diagnosis (not included here, table for principal diagnosis risk factors can be found in **Appendix 2**).

Aboriginal children living in very remote parts of the state had higher admission rates for OM than those living in major cities (IRR 4.54, 95%CI: 3.48,5.93). Spending ≥4 days in the NICU was also associated (IRR 2.24, 95%CI: 1.67,3.02), as it was for non-Aboriginal children.

When restricting the analysis to principal diagnosis only, many of the risk factors showed similar results with the exception of those affected by MVTI; namely ARIA and SEIFA (**Appendix 3**).

Table 8. Risk factors for repeated hospitalisations with a diagnosis of otitis media (excluding procedures) among non-Aboriginal children aged <2 years at the time of admission

Risk Factor		IRR (95% CI)	
	n*	Univariate	Multivariable
Gender			
Female	1,661	Reference	
Male	2,525	**1.47 (1.38,1.57)**	**1.57 (1.36,1.81)**
Gestational age			
≥37 weeks	3,659	Reference	
33-36 weeks	393	**1.56 (1.40,1.74)**	**1.40 (1.11,1.77)**
29-32 weeks	79	**2.17 (1.70,2.78)**	**1.93 (1.32,2.83)**
≤28 weeks	51	**3.52 (2.56,4.84)**	**2.73 (1.70,4.38)**
Percent optimal birthweight			
Normal 85-114%	3,001	Reference	
Low <85%	551	**1.26 (1.14,1.38)**	1.05 (0.87,1.27)
High ≥115%	364	1.03 (0.92,1.15)	1.04 (0.82,1.31)
No. of siblings			
0	1,606	Reference	
1	1,460	**1.12 (1.04,1.21)**	**1.32 (1.11,1.57)**
2	669	**1.28 (1.17,1.40)**	**1.51 (1.21,1.89)**
≥3	417	**1.54 (1.37,1.72)**	**1.77 (1.37,2.30)**
Multiple birth			
Singleton	4,021	Reference	
Twins	150	**1.23 (1.04,1.47)**	0.86 (0.64,1.16)
≥3	11	**2.97 (1.48,5.95)**	1.69 (0.70,4.11)
Season of birth			
Spring	1,050	Reference	
Summer	1,059	1.07 (0.98,1.17)	1.03 (0.85,1.25)
Autumn	1,076	1.02 (0.94,1.12)	0.95 (0.78,1.16)
Winter	1,001	0.95 (0.87,1.04)	0.92 (0.76,1.12)
Days in NICU			
0	1,256	Reference	
1-3 days	185	1.06 (0.90-1.24)	**1.43 (1.16,1.76)**
≥4 days	280	**1.68 (1.46-1.93)**	**1.61 (1.25,2.07)**
Mode of delivery			
Vaginal	2,353	Reference	
Instrumental	501	**0.81 (0.73-0.89)**	1.03 (0.81,1.31)
Elective caesarean	739	0.97 (0.89-1.06)	**1.35 (1.10,1.65)**
Emergency caesarean	589	0.99 (0.90-1.09)	1.16 (0.96,1.40)
Smoking during pregnancy			
No	2,599	Reference	
Yes	770	**1.73 (1.59-1.88)**	**1.29 (1.08,1.54)**
Asthma during pregnancy			
No	3,701	Reference	
Yes	481	**1.26 (1.15-1.40)**	1.20 (0.98,1.48)
Maternal age			
≥35 years	580	Reference	
30-34 years	1,102	1.14 (1.02-1.26)	1.06 (0.85,1.33)
25-29 years	1,368	**1.60 (1.44-1.76)**	**1.54 (1.24,1.93)**
20-24 years	849	**2.00 (1.80-2.23)**	**2.00 (1.57,2.56)**
<20 years	283	**2.55 (2.20-2.96)**	**2.87 (2.05-4.01)**

SEIFA Index of disadvantage			
0-10% (most disadvantaged)	515	**3.68 (3.05-4.43)**	**2.03 (1.36,3.04)**
11-25%	779	**2.90 (2.43-3.47)**	**1.94 (1.33,2.83)**
26-75%	1,871	**1.99 (1.68-2.36)**	1.23 (0.85,1.76)
76-90%	465	**1.47 (1.22-1.77)**	1.37 (0.92,2.03)
91-100% (least disadvantaged	150	Reference	
Accessibility/Remoteness index of Australia			
Very Remote	90	**2.14 (1.69-2.70)**	**2.57 (1.50,4.43)**
Remote	314	**2.29 (2.01-2.61)**	**1.98 (1.37,2.87)**
Outer regional	638	**2.23 (2.03-2.45)**	**1.37 (1.03,1.82)**
Inner regional	565	**1.43 (1.30-1.58)**	1.07 (0.85,1.34)
Major cities	2,331	Reference	

Abbreviations: IRR, incidence rate ratio; 95% CI, 95% confidence interval; NICU, neonatal intensive care unit; SEIFA, socio economic index for area

Bold type denotes statistical significance at $\alpha<0.05$

*The sum of the observations in each risk factor group may not equal due to missing values

Table 9. Risk factors for repeated hospitalisation with a diagnosis of otitis media among Aboriginal children aged <2 years

Risk Factor		IRR (95% CI)	
	n*	Univariate	Multivariate
Gender			
Female	1,120	Reference	
Male	1,429	**1.25 (1.14,1.36)**	**1.32 (1.08,1.61)**
Gestational age			
≥37 weeks	2,048	Reference	
33-36 weeks	355	1.48 (1.31,1.69)	0.90 (0.68,1.20)
29-32 weeks	89	**2.04 (1.57,2.66)**	1.19 (0.76,1.85)
≤28 weeks	51	**2.21 (1.31,1.69)**	**1.94 (1.11,3.39)**
Percent optimal birthweight			
Normal 85-114%	1,427	Reference	
Low <85%	749	**1.54 (1.40,1.72)**	1.04 (0.83,1.31)
High ≥115%	157	1.07 (0.89,1.29)	0.73 (0.50,1.08)
No. of siblings			
0	698	Reference	
1	599	1.07 (0.95,1.21)	1.26 (0.93,1.72)
2	469	**1.20 (1.05,1.37)**	**1.63 (1.15,2.30)**
≥3	777	**1.21 (1.08,1.35)**	**1.75 (1.24,2.47)**
Multiple birth			
Singleton	2,461	Reference	
Twins	80	**1.74 (1.34,2.25)**	**1.62 (1.12,2.37)**
≥3	<5	n.a†	n.a†
Season of birth			
Spring	561	Reference	
Summer	651	**1.17 (1.03,1.32)**	**1.54 (1.16,2.05)**
Autumn	682	**1.15 (1.01,1.30)**	1.18 (0.88,1.59)
Winter	655	1.12 (0.99,1.27)	1.40 (1.04,1.86)
Days in NICU			
0	628	Reference	
1-3 days	107	**1.37 (1.10,1.72)**	**1.47 (1.08,2.00)**
≥4 days	278	**2.09 (1.76,2.48)**	**2.24 (1.67,3.02)**
Mode of delivery			
Vaginal	1,785	Reference	
Instrumental	167	1.08 (0.91,1.29)	1.21 (0.80,1.82)
Elective caesarean	201	0.96 (0.81,1.13)	1.19 (0.84,1.68)
Emergency caesarean	390	**1.18 (1.04,1.34)**	1.16 (0.90,1.49)
Smoking during pregnancy			
No	920	Reference	
Yes	1,193	**1.35 (1.23,1.49)**	1.09 (0.89,1.33)
Asthma during pregnancy			
No	2,353	Reference	
Yes	190	0.74 (0.63,0.87)	1.02 (0.75,1.38)
Maternal age			
≥35 years	157	Reference	
30-34 years	332	1.12 (0.90,1.38)	1.10 (0.73,1.65)
25-29 years	629	1.19 (0.98,1.46)	1.14 (0.78,1.66)
20-24 years	774	1.09 (0.90,1.32)	1.01 (0.67,1.52)
<20 years	651	**1.25 (1.03,1.52)**	1.39 (0.88,2.20)

SEIFA Index of disadvantage			
0-10% (most disadvantaged)	778	1.46 (0.73,2.91)	1.22 (0.31,4.76)
11-25%	396	0.86 (0.43,1.74)	0.83 (0.21,3.26)
26-75%	583	1.00 (0.50,1.98)	0.96 (0.25,3.76)
76-90%	43	0.72 (0.34,1.53)	0.72 (0.17,3.13)
91-100% (least disadvantaged	12	Reference	
Accessibility/Remoteness index of Australia			
Very Remote	913	**5.68 (4.99,6.47)**	**4.54 (3.48,5.93)**
Remote	418	**2.42 (2.09,2.79)**	**2.15 (1.59,2.92)**
Outer regional	335	**2.06 (1.77,2.40)**	**1.49 (1.07,2.07)**
Inner regional	92	**1.30 (1.03,1.63)**	0.94 (0.61,1.45)
Major cities	362	Reference	

Abbreviations: IRR, incidence rate ratio; 95% CI, 95% confidence interval; NICU, neonatal intensive care unit; SEIFA, socio economic index for area

Bold type denotes statistical significance at $\alpha<0.05$

*The sum of the observations in each risk factor group may not be equal due to missing values

†Too few observations

3.9 MVTI

A total of 25,324 children aged under five years contributed 33,125 MVTI in all WA hospitals (both public and private) between 1996 and 2012. Of these 1,316 (3.4%) were performed on Aboriginal children. Overall, children who were hospitalised for a MVTI were more likely to be boys (6.49%, 95%CI 6.10,6.88) than female (4.24%, 95%CI 3.84,4.64).

The MVTI admission rate for Non-Aboriginal children was almost twice as high if they spent any time in the NICU (1-3 days IRR 1.93, ≥4 days IRR 2.11). They had nearly twice the rate of hospitalisation if they were born ≤28 week's gestation than if being born at ≥37 weeks, IRR 1.86 (1.47,2.34). Their admission rates were also higher if they had one sibling, were born in winter, were born by elective caesarean, or had an older mother (**Table 10**).

The admission rate for MVTI was 3.5 time higher among Aboriginal children born premature, that is, ≤28 weeks' gestation compared with those who were born at ≥37 weeks, IRR 3.46, (95%CI 1.90,6.29). There was also an association between MVTI hospitalisation and spending ≥4 days in the NICU (IRR 1.67, 95%CI 1.18,2.37), or being born in a major city (IRR 1.65, 95%CI 1.08,2.52).

Table 10. Risk factors for repeated hospitalisation with MVTI among non-Aboriginal children aged <5 years

Risk Factor		IRR (95% CI)	
	n*	Univariate	Multivariate
Gender			
Female	9,291	Reference	
Male	14,936	**1.56 (1.52,1.60)**	**1.61 (1.52,1.71)**
Gestational age			
≥37 weeks	21,596	Reference	
33-36 weeks	2,036	**1.38 (1.31,1.46)**	1.11 (1.00,1.28)
29-32 weeks	363	**1.83 (1.62,2.07)**	**1.41 (1.18,1.69)**
≤28 weeks	221	**2.62 (2.20,3.12)**	**1.86 (1.47,2.34)**
Percent optimal birthweight			
Normal 85-114%	17,171	Reference	
Low <85%	2,608	**1.08 (1.03,1.13)**	1.03 (0.95,1.33)
High ≥115%	2,344	**1.17 (1.11,1.22)**	1.16 (1.05,1.28)
No. of siblings			
0	9,926	Reference	
1	9,579	**1.22 (1.18,1.26)**	**1.24 (1.15,1.33)**
2	3,396	1.01 (0.97,1.06)	1.07 (0.97,1.18)
≥3	1,315	0.76 (0.71,0.81)	0.81 (0.71,0.92)
Multiple birth			
Singleton	23,333	Reference	
Twins	858	**1.29 (1.20,1.39)**	0.99 (0.87,1.13)
≥3	25	1.21 (0.78,1.87)	0.56 (0.32,0.99)
Season of birth			
Spring	5,856	Reference	
Summer	6,088	**1.06 (1.02,1.10)**	1.07 (0.99,1.17)
Autumn	6,260	1.04 (0.98,1.08)	1.06 (0.98,1.15)
Winter	6,023	1.03 (0.98,1.07)	1.12 (1.04,1.22)
Days in NICU			
0	6,044	Reference	
1-3 days	1,262	**1.61 (1.50,1.72)**	**1.93 (1.78,2.10)**
≥4 days	1,511	**2.01 (1.89,2.15)**	**2.11 (1.90,2.35)**
Mode of delivery			
Vaginal	11,854	Reference	
Instrumental	3,425	**1.10 (1.06,1.15)**	0.93 (0.85,1.03)
Elective caesarean	5,207	**1.41 (1.36,1.46)**	**1.27 (1.16,1.38)**
Emergency caesarean	3,730	**1.25 (1.20,1.30)**	1.05 (0.97,1.14)
Smoking during pregnancy			
No	18,195	Reference	
Yes	3,079	0.96 (0.92,1.00)	1.06 (0.97,1.16)
Asthma during pregnancy			
No	21,437		
Yes	2,779	**1.23 (1.17,1.28)**	**1.34 (1.22,1.46)**
Maternal age			
≥35 years	4,557	**1.41 (1.29,1.53)**	**1.30 (1.08,1.55)**
30-34 years	8,461	**1.61 (1.47,1.75)**	**1.42 (1.20,1.69)**
25-29 years	7,352	**1.53 (1.41,1.67)**	**1.40 (1.18,1.67)**
20-24 years	3,160	**1.24 (1.13,1.35)**	**1.28 (1.07,1.52)**
<20 years	686	Reference	

SEIFA Index of disadvantage			
0-10%	1,558	Reference	
11-25%	3,132	1.07 (1.00,1.14)	**1.16 (1.02,1.32)**
26-75%	11,498	**1.18 (1.11,1.24)**	1.13 (1.00,1.27)
76-90%	4,218	**1.33 (1.25,1.42)**	**1.26 (1.11,1.45)**
91-100%	2,223	**1.51 (1.40,1.62)**	**1.34 (1.14,1.57)**
Accessibility/Remoteness index of Australia			
Very Remote	223	**1.20 (1.02,1.41**)	1.38 (0.92,2.07)
Remote	597	Reference	
Outer regional	1,511	**1.12 (1.02,1.24)**	1.03 (0.77,1.38)
Inner regional	2,607	**1.49 (1.36,1.64)**	**1.51 (1.17,1.95)**
Major cities	18,358	**1.76 (1.62,1.91)**	**1.61 (1.26,2.04)**

Abbreviations: IRR, incidence rate ratio; 95% CI, 95% confidence interval; NICU, neonatal intensive care unit; SEIFA, socio economic index for area

Bold type denotes statistical significance at $\alpha<0.05$

*The sum of the observations in each risk factor group may not be equal due to missing values

Table 11. Risk factors for repeated hospitalisation with MVTI among Aboriginal children aged 5 years

Risk Factor		IRR (95% CI)	
	n*	Univariate	Multivariate
Gender			
Female	437	Reference	
Male	660	**1.47 (1.29,1.67)**	**1.39 (1.12,1.73)**
Gestational age			
≥37 weeks	877	Reference	
33-36 weeks	141	**1.29 (1.06,1.56)**	1.11 (0.80,1.53)
29-32 weeks	32	**1.78 (1.22,2.60)**	1.38 (0.82,2.34)
≤28 weeks	42	**4.75 (3.14,7.18)**	**3.46 (1.90,6.29)**
Percent optimal birthweight			
Normal 85-114%	661	Reference	
Low <85%	262	1.14 (0.98,1.34)	1.07 (0.83,1.38)
High ≥115%	86	**1.31 (1.03,1.68**)	1.00 (0.67,1.48)
No. of siblings			
0	323	Reference	
1	278	1.08 (0.91,1.28)	1.03 (0.75,1.41)
2	192	1.00 (0.83,1.21)	1.03 (0.71,1.48)
≥3	299	0.99 (0.84,1.17)	0.89 (0.62,1.28)
Multiple birth			
Singleton	1,050	Reference	
Twins	39	1.71 (1.20,2.45)	0.99 (0.60,1.63)
≥3	<5	4.70 (0.73,30.30)	4.83 (0.66,35.26)
Season of birth			
Spring	260	Reference	
Summer	298	1.06 (0.88,1.27)	1.01 (0.74,1.38)
Autumn	275	0.96 (0.80,1.14)	1.03 (0.75,1.40)
Winter	264	0.99 (0.82,1.18)	1.18 (0.87,1.60)
Days in NICU			
0	355	Reference	
1-3 days	60	**1.40 (1.06,1.86)**	1.36 (0.97,1.91)
≥4 days	146	**2.03 (1.64,2.52)**	**1.67 (1.18,2.37)**
Mode of delivery			
Vaginal	740	Reference	
Instrumental	80	1.16 (0.91,1.49)	0.99 (0.63,1.57)
Elective caesarean	97	1.17 (0.93,1.47)	1.03 (0.70,1.52)
Emergency caesarean	175	**1.35 (1.13,1.61)**	1.04 (0.78,1.38)
Smoking during pregnancy			
No	522	Reference	
Yes	438	0.82 (0.71,0.94)	0.77 (0.62,0.97)
Asthma during pregnancy			
No	954	Reference	
Yes	138	**1.48 (1.22,1.80)**	1.24 (0.92,1.68)
Maternal age			
≥35 years	89	**1.51 (1.16,1.97)**	**1.77 (1.10,2.86)**
30-34 years	160	**1.34 (1.08,1.66)**	1.47 (0.96,2.25)
25-29 years	289	**1.28 (1.06,1.55)**	1.24 (0.85,1.82)
20-24 years	333	1.05 (0.88,1.26)	1.07 (0.77,1.50)
<20 years	221	Reference	

SEIFA Index of disadvantage*			
0-10%	296	0.73 (0.52,1.05)	1.14 (0.61,2.11)
11-25%	249	0.79 (0.55,1.14)	1.06 (0.57,1.96)
26-75%	349	0.87 (0.61,1.24)	1.37 (0.74,2.49)
76-90%	40	Reference	
91-100%	7	1.09 (0.46,2.61)	1.48 (0.38,5.71)
Accessibility/Remoteness index of Australia			
Very Remote	148	1.02 (0.80,1.29)	1.54 (0.91,2.61)
Remote	141	Reference	
Outer regional	175	**1.41 (1.12,1.78)**	1.52 (0.90,2.57)
Inner regional	89	**1.56 (1.17,2.08)**	1.49 (0.84,2.62)
Major cities	456	**1.73 (1.42,2.11)**	**1.65 (1.08,2.52)**

Abbreviations: IRR, incidence rate ratio; 95% CI, 95% confidence interval; NICU, neonatal intensive care unit; SEIFA, socio economic index for area

*bold denotes statistical significance at $\alpha<0.05$

*The sum of the observations in each risk factor group may not be equal due to missing values

4.0 Discussion

4.1 Overall OM hospitalisations

To our knowledge, this was the first time that the burden of otitis media in terms of hospital admissions, procedures and maternal and infant risk factors have been reported for children in a total population. A summary of the key findings of this work can be found in **Box 2**.

Box 2. Key findings

- There has been a reduction in hospitalisations with OM over the period of this study.
- The rate of hospitalisation with OM was ten times higher among Aboriginal children and the gap did not change over the course of the study.
- Children who were born outside of major cities had the highest rates of OM-related hospitalisations while children born in major cities had the highest MVTI procedure rates.
- Children who lived in the most disadvantaged neighbourhoods had the highest rates of OM-related hospitalisation but the lowest rates of MVTIs.
- The maternal and infant risk factors associated with being hospitalised for OM were being male, being born premature, being born outside major cities and spending time in the NICU.
- Elective caesarean was independently associated with both OM and MVTI hospitalisations among non-Aboriginal children.

4.2 Overall hospitalisations with OM diagnosis

I found that the burden of hospital admissions for OM has declined since 1998 for all Western Australian children. A possibility for the observed reduction over time could be that there was less severe disease or that there was better treatment in the community, *i.e.* prior to requiring hospitalisation. Notably Aboriginal children aged 5 to 15 years had higher rates of hospitalisation for MVTI compared with non-Aboriginal children which could mean that they are not getting the treatment that they need when they are younger and are having more serious disease which is getting treated in this older age group. This is probably due to increased surveillance in schools through the identifying of disease that was previously unascertained. It could also be the result of recurrent OM that progressively got more serious over time and required surgical intervention. It has been reported that children who get OM early in life are more likely to have more serious disease as they get older[1,2] and we have shown that Aboriginal children were hospitalised at a younger age than non-Aboriginal children in this cohort, consistent with what others

have found, that Aboriginal children experience OM earlier in life compared with their non-Aboriginal peers.[23,26,53-55] While I did not evaluate this in the current study, another possibility could be that children were having more MVTI with adjunctive surgery such as adenoidectomy or adenotonsillectomy. This has been shown in this population to help reduce the chances of a second MVTI operation, with the greatest benefit from adjunctive adenotonsillectomy at first MVTI, which corresponded to a reduction of 42%.[56]

The hospitalisation rates for Aboriginal children were ten times higher than they were for non-Aboriginal children and that disparity remained throughout the years of the study. I also found that the decline in MVTI reported previously[33] was not sustained in some age groups. I also noted a dip between 2004 and 2006 in the current study. Fluctuations in MVTI rates have been shown previously.[57] The reasons for this are unknown but could be the result of changes in service, resourcing or availability of ENT surgeons. It may also be possible that there was a short effect caused by the introduction of 7vPCV until serotype or pathogen replacement occurred. There was a notable increase in the MVTI hospitalisation rates for children born in remote parts of the state from 2005 onwards. The increase we observed could reflect increased trips to remote parts of the state by ENT surgeons or other ear screening services such as the Earbus Program.[58] While it is possible that some of these children may have travelled to the metropolitan area to have their operation because of the availability of private surgical options, this is less likely as most will have stayed in their region of residence.

I demonstrated in this analysis that the burden for OM-related hospitalisations was highest among children born in remote parts of the state. This has been reported previously in the Northern Territory (NT). Residents living in these areas can be isolated and access to health services can be challenging.[59] It could be that disease progressed prior to seeking care and thus required hospitalisation or the greater prevalence of risk factors such as overcrowding or smoking in the household.[60,61] Hospitals in regional centres often do not have full time specialist services and ENT surgeons are primarily located in major cities.[62] Fortunately in recent years there has been an increase in the operations performed on children born in remote parts of the state. This likely reflects the increased provision of visiting ENT services to rural and remote locations but may also reflect a change in the epidemiology of ear disease, *e.g.* more closed disease. In recent years there has been a move toward OME among urban Aboriginal children and this has

also been observed in remote areas but at a slower pace. This is likely to reflect improvement in risk factors and may also be due to improvements in primary care. Where there is intensive management of ears there is a corresponding decrease of CSOM and an increase in OME (personal communication, Harvey Coates, ENT surgeon).

4.3 Socioeconomic indicator (SEIFA)

My finding that children in the most disadvantaged SEIFA group experienced the highest rates of OM-related hospitalisation is interesting though not surprising. In a group of 2,253 infants in Pittsburgh, those whose parents were in the lowest socioeconomic group had higher cumulative proportion of days with OME compared with those in the highest economic group.[5] Another US study, that compared two phases of the National Health and Nutrition Examination Survey, found that children below poverty status had the highest increase in prevalence of early onset OM and repeated OM compared with affluent children.[63] This further demonstrates the disparity between the most and least advantaged. In this study it was the most advantaged that had the lowest OM hospitalisation rates but the highest rates of MVTI. This disparity was also observed between non-Aboriginal and Aboriginal children hospitalised for a MVTI in New South Wales[64] and in WA.[33]

4.4 Interrupted time series

In the current study there were declining trends in rates of OM-related hospitalisations before and after the introduction of the 7vPCV. I was unable to determine whether the declining rates were associated with the 7vPCV introduction because we did not have individual vaccination data. I conducted an ecologic analysis and while most age groups demonstrated declines before and after the 7vPCV introduction in Australia, particularly in younger children, only one represented a statistically significant step down trend. The reduction in OM resulting from vaccination with PCV has been shown by others in different settings. Using individually linked vaccination information, the frequency of physician claims for OM after widespread use of PCV in Quebec Canada declined by 13% in the three years post implementation.[65] In Tennessee and New York Poehling *et. al.* used an ecological study design and reported a decline in outpatient, ED and hospitalisations for OM in Tennessee, associated with PCV introduction. However, in New York the decline was only for outpatient and ED visits, there appeared to

be no change in hospitalisations.[66] When comparing rates of MVTI in the same population, there was a decline in both states after the introduction of PCV in those states.[67] Results from the Finnish Otitis Media Vaccine Trial showed that the number of OM episodes, as measured by clinic follow-up, decreased by 6% (95%CI -4,16) in PCV recipients compared with a control group.[68] Finally in the Kaiser Permanente randomised controlled trial in Northern California, PCV was associated with an 8% (95% CI 5,10) reduction in OM visits and 24% (95%CI 12,35) reduction in MVTI.[69]

4.5 Risk Factors

These results may be helpful for understanding the relative contribution of OM risk factors to hospitalisation rates with OM and related procedures. They can be used to support the design of interventions aimed at reducing the burden of OM hospitalisations by focusing them where they can derive the most benefit.

In the current study, non-Aboriginal children had an increased risk for all OM-related hospitalisation if born by elective caesarean when compared with a vaginal birth. OM related hospitalisation was also associated with being born by elective caesarean for Aboriginal children but the result was not statistically significant. Possibly due to a smaller proportion of Aboriginal mothers having this procedure (8.06% of Aboriginal mothers vs. 17.26% of non-Aboriginal mothers).

An association between elective caesarean and increased risk of respiratory illnesses has been previously reported.[70-75] In a population-based study, the authors found that elective caesarean increased the risk and severity of hospitalisation for respiratory syncytial virus[73] and diseases associated with immune function[75] in children. While rare, authors in Chicago using computerised retrospective record review noted a five times higher risk of persistent pulmonary hypertension in infants born by elective caesarean compared with infants born vaginally.[74] In both a systematic review and cohort study, elective caesarean increased the morbidity of respiratory illness (*e.g.* respiratory distress syndrome, transitory tachypnea of the newborn and persistent pulmonary hypertension) compared with vaginal delivery, with the risk increasing further with lower gestational age.[70,71] Our team has also shown previously a 1.5 increased odds of an acute lower respiratory illness hospitalisation by age two years among children born by elective caesarean.[72] The reasons for this association are not well established. One hypothesis is that differential acquisition of

microbiota in the infant might influence the risk for respiratory illness. The gastrointestinal tract of a foetus is sterile. During the birthing process via normal vaginal delivery the neonate's gut is colonised with bacteria from maternal vaginal and intestinal microbiota.[76] This process may be important in postnatal development of the immune system.[77] A caesarean delivery removes this direct contact with maternal intestinal microbiota. Ongoing studies to test this hypothesis among children who suffer from OM and OM-related hospitalisations may be able to confirm this.

Spending time in the NICU was also a risk associated with OM-related hospitalisation in children <2 years and MVTI in children <5 years for both non-Aboriginal and Aboriginal children even when we controlled for prematurity. There is a scarcity of data in this area. However, a study of 926 infants in Greece showed a 1.64 greater odds of acute OM among children who were admitted to a NICU, although the result was not significant in the multivariable analysis.[78] Others demonstrated a trend toward a higher odds of chronic OME for infants who had a NICU stay, specifically if they were intubated. The authors hypothesised that it could have been the result of mucosal damage in the nasopharynx that increased the odds of chronic OM.[79] While I had information in the dataset about NICU stays, I did not have information about whether the child was intubated so I was unable to explore the role of neonatal ventilator assisted breathing and OM. The possible reasons for this higher OM admission rate are multifactorial and could include use of antibiotics in the neonatal period affecting the infant nasopharyngeal microbiome.[80] The position in the NICU bed may also affect the shape of the premature infant's head or possibly nasogastric tube feeding that could damage the nasopharynx which would predispose the infant to infection leading to OM (personal communication, Francis Lannigan). There may also be other confounders that I was unaware of and therefore unable to control for that may have led to an effect.

Consistent with the age-specific admission rates for OM, the risk factor analysis also showed that being born in a remote part of the state was associated with higher OM diagnoses at hospital separation for both non-Aboriginal and Aboriginal children compared with being born in a metropolitan hospital, the incidence rate increased as remoteness increased, IRR 2.57 (CI 1.50,4.43) (**Table 8**) for non-Aboriginal and IRR 4.54 (CI 3.48,5.93) for Aboriginal children respectively (**Table 9**). This is consistent with *The*

Western Australia Aboriginal Child Health survey report which shows the prevalence of children with recurring OM is higher in more extreme settings. In addition, those who live in remote settings have less access to healthcare than those who do not.[59]

I found the inverse was true for MVTI. Birth in a metropolitan location was significantly associated with a MVTI (IRR 1.61 among non-Aboriginal and IRR 1.65 among Aboriginal children). This is consistent with higher reported MVTI rates in metropolitan hospitals in New South Wales.[64] This finding is not surprising. I have shown that the greatest proportion of procedures were performed in private metropolitan hospitals (60.20%) and when combined with all metropolitan hospitals, rose to 88.95% (**Table 7**). This highlights the discordance between loci of highest rates of hospitalisation for acute disease and availability of surgery. In a project exploring ear health service availability in Aboriginal Medical Services (AMS) around the country, practitioners in rural or remote AMSs were asked about the frequency of OM they treat and about the frequency of specialist services to their clinic. These practitioners reported managing a higher load of OM cases and reported fewer specialist health services (*e.g.* audiology, ENT surgery and hearing aids) than practitioners in metropolitan AMSs,[62] thus corroborating our results.

While I was not able to assess this in the current study, it would be interesting to determine whether higher private hospital use helps to relieve the pressure on the public system or whether it shifts the specialist services out of the public system. The former would help free up surgical lists in public hospitals for those who have the highest rates of OM-related hospitalisations while the latter would extend wait times and make it more difficult for those parents without the means to pay for it to get early treatment.

Non-Aboriginal children in the most disadvantaged SEIFA group had the highest rates of OM hospitalisation yet had lowest rates of MVTI. This dichotomy highlights the disproportionate provision of services to more advantaged families when the greatest burden is among families that are economically disadvantaged. This is unchanged from what was reported previously in WA.[33]

4.6 Strengths and limitations

The greatest strength of this study was the ability to investigate OM hospitalisations in a large, unselected total population cohort which allowed accurate measurement of rates, increased statistical power and

reduced selection bias associated with participant selection. In Australia, MVTIs are only performed in hospitals on inpatients. This allowed us to ascertain all such procedures within the birth cohort.

It is well known that OM is most often diagnosed and treated in primary care not hospitals. Our datasets do not include primary care data. We don't believe this was a limitation as it was not our intended aim, however it is important to understand when interpreting these data. It is likely that the OM-related hospitalisations that we report here represent the 'tip of the iceberg' of all OM diagnoses and are likely to sit at the severe or chronic end of the clinical spectrum.

It is possible that there may have also been variability in coding practices over the duration of this study. There was a change from ICD9 to ICD10 that could have meant a delay in entering diagnostic information while the technology was updated. There were also changes in the coding whereby ICD10 included more detailed and specific diagnoses compared with ICD9. During this period WA did not have activity-based funding which may have meant less scrutiny in coding and may have led to an under-ascertainment of the outcomes. However, clinical coding follows a standardised training protocol throughout Australia. It would therefore be plausible that inter-hospital variability would be minor across all hospitals in WA.[72]

Aboriginal status is often underestimated in administrative data.[81-83] Using the ABS Indigenous flag from the 'getting our story right' project, greatly increased the sensitivity of Aboriginal status across all datasets.

The hospital dataset that we used contained only records of children born in WA. We do not believe this affected our analyses however, these data will not accurately reflect the total burden of OM on the hospital system. Our study was intended as a birth cohort and therefore only included WA born children. However, to confirm that our cohort represented the majority of hospitalised children, we contacted the HMDC data custodian to obtain the crude number of hospitalisations for two given years for comparison. Our overall hospitalisations represented >90% of all hospitalisations for all children aged <6 years in WA (HMDC Data Custodian, personal communication).

4.7 Policy implications

Quantifying the burden of OM related hospitalisations and procedures can provide evidence for policy and funding decisions aimed at reducing the burden in the population. The results from these analyses should be used to guide public health interventions where they are most relevant and likely to derive the most benefit. For example, providing information about elective caesarean and prematurity. Incorporating information that include risks for OM as a part of antenatal care, especially among young mothers. The results of this study demonstrate who need services and the discordance between those who need and for whom they are available. These results can also be used to feed into the WA Ear Health Strategy that is currently being revised.[84]

4.8 Future work

While it was not possible to include all analyses in this chapter, other research questions that are planned include:

- Has adjunctive adenoidectomy and/or adenotonsillectomy and MVTI helped decrease the mean number of OM related hospitalisations?
- Evaluate previous finding that adjunctive adenoidectomy and/or adenotonsillectomy and MVTI reduced the risk of subsequent MVTI surgery to determine if it has been sustained.
- What is the age at which the greatest benefit could be realised for the above mentioned adjunctive procedures?
- Using individually linked vaccination information, what was the effect of 7vPCV vaccination on reducing OM hospitalisations and procedures in non-Aboriginal and Aboriginal children?

4.9 Conclusions

Hospitalisation rates for both non-Aboriginal and Aboriginal children have declined over the years of this analysis. Aboriginal children still experience a higher proportion of hospitalisation with an OM-related diagnosis. Conversely, they had fewer MVTI a procedure that helps to improve OM and related sequelae while improving hearing quality. These results should be used to influence policy makers to make

decisions that help to improve the ear and hearing outcomes for all Australian children, particularly those who suffer the greatest burden of disease.

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Appendix 1. International Classification of Diseases (ICD) Australian Modification (AM) coding used in this analysis

Diagnosis Codes		
ICD 10	ICD 9	Description
H65	381	Non-Suppurative OM
H66	382	Suppurative and unspecified OM
H67	382	OM in diseases classified elsewhere
H70	383	Mastoiditis and related conditions
H71	385	Cholesteatoma tympani
H72	384	Perforation of the tympanic membrane
H73	384	Other disease of tympanic membrane
H74	385	Other disease of middle ear & mastoid
H75	385	Other disease of middle ear & mastoid classified elsewhere
H83	386	Labyrinthine fistula
H90	389	Conductive and sensorineural hearing loss
H92.1-2	388	Otorrhoea & Otorrhagia
H95	383	Postprocedural disorders of ear and mastoid, not classified elsewhere
Procedure Codes		
41650-00,01, 41629-00	20.1	EUA-Exam procedures on eardrum or middle ear
41626-00,01, 41632-00,01	20.01, 20.0, 20.09	Myringotomy any
41533-00,02	20.23	Atticotomy

30075-29, 41635-00, 41644-00	20.59	Excision procedures on eardrum or middle ear
41635-01, 41527-00, 41530-00, 41533-01	19.4	Myringoplasty
90112-00	19.9	Other repair of eardrum or middle ear
41542-00, 41536-00,01, 41638-00,01	19.4-6, 52-55, 20.5, 20.51	Reconstruction procedures on eardrum or middle ear (myringoplasty with ossicular chain reconstruction, tympanoplasty I-IV),
41539-00		Ossicular chain reconstruction
90115-00		Other procedures on ossicles of ear
41557-03		Incision of mastoid
41545-00, 41557-00,01, 41548-00, 41564-00, 41564-01	20.04, 20.41-42,49	Mastoidectomy
41551-00, 41560-00, 41560-01		Repair procedures on mastoid or temporal bone
41554-00, 41563-00, 41563-01		Reconstruction procedures on mastoid or temporal bone
41566-00,01,02	20.92	Revision procedures on mastoid or temporal bone
90116-00		Other procedures on mastoid or temporal bone
41789-00,01	28.2-3	Tonsillectomy with/without adenoidectomy
41801-00	28.6	Adenoidectomy without tonsillectomy

Appendix 2. Risk factors for repeated hospitalisation with principal otitis media diagnosis among non-Aboriginal children under 2 years

Risk Factors	IRR (95% CI)	
	Univariate	Multivariable
Gender		
Female	Reference	
Male	1.6 (1.5,1.6)	1.69 (1.54,1.84)
Gestational age		
≥37 weeks	Reference	
33-36 weeks	1.3 (1.2,1.4)	1.12 (0.96,1.30)
29-32 weeks	1.5 (1.2,1.7)	1.37 (1.06,1.76)
≤28 weeks	1.8 (1.4,2.3)	1.29 (0.91,1.82)
Percent optimal birthweight		
Normal 85-114%	Reference	
Low <85%	1.01 (0.95,1.08)	0.99 (0.88,1.12)
High ≥115%	1.16 (1.08,1.24)	1.15 (1.00,1.31)
No. of siblings		
0	Reference	
1	1.43 (1.37,1.50)	1.46 (1.31,1.62)
2	1.27 (1.20,1.35)	1.25 (1.08,1.43)
≥3	1.00 (0.92,1.09)	1.00 (0.84,1.21)
Multiple birth		
Singleton	Reference	
Twins	1.11 (0.99,1.25)	0.93 (0.77,1.12)
≥3	1.11 (0.59,2.09)	0.67 (0.30,1.48)
Season of birth		
Spring	Reference	
Summer	1.04 (0.98,1.10)	0.96 (0.86,1.09)
Autumn	0.98 (0.93,1.04)	0.96 (0.85,1.08)
Winter	0.97 (0.92,1.03)	1.01 (0.89,1.13)
Days in neonatal ICU		
0	Reference	
1-3 days	1.37 (1.24,1.51)	1.59 (1.41,1.80)
≥4 days	1.62 (1.48,1.78)	1.81 (1.55,2.10)
Mode of delivery		
Vaginal	Reference	
Instrumental	1.00 (0.94,1.06)	0.97 (0.84,1.12)
Elective caesarean	1.36 (1.29,1.43)	1.29 (1.14,1.45)
Emergency caesarean	1.15 (1.08,1.22)	1.07 (0.95,1.21)
Smoking during pregnancy		
No	Reference	
Yes	0.93 (0.88,0.99)	0.96 (0.85,1.10)
Asthma during pregnancy		
No	Reference	
Yes	1.26 (1.19,1.35)	1.34 (1.18,1.53)
Maternal age		
≥35 years	Reference	
30-34 years	1.16 (1.09,1.22)	1.09 (0.97,1.23)
25-29 years	1.07 (1.02,1.22)	1.05 (0.92,1.19)

20-24 years	0.83 (0.64,0.82)	0.96 (0.82,1.13)
<20 years	0.73 (0.64,0.82)	0.95 (0.73,1.23)
SEIFA Index of disadvantage		
0-10% (most disadvantaged)	Reference	
11-25%	1.07 (0.97,1.17)	1.04 (0.86,1.26)
26-75%	1.16 (1.07,1.27)	0.96 (0.81,1.13)
76-90%	1.38 (1.27,1.52)	1.19 (0.98,1.44)
91-100% (least disadvantaged)	1.59 (1.44,1.76)	1.28 (1.03,1.59)
Accessibility/Remoteness index of Australia		
Very Remote		1.39 (0.8-2.37)
Remote		1.07 (0.70,1.64)
Outer regional	Reference	
Inner regional		1.31 (0.99,1.75)
Major cities		1.56 (1.22,2.01)

Abbreviations: IRR, incidence rate ratio; 95% CI, 95% confidence interval; ICU, intensive care unit; SEIFA, socio economic index for area **Bold** type indicates statistical significance at $\alpha<0.05$

Appendix 3. Risk factors for repeated hospitalisation with principal otitis media diagnosis among Aboriginal children under 2 years

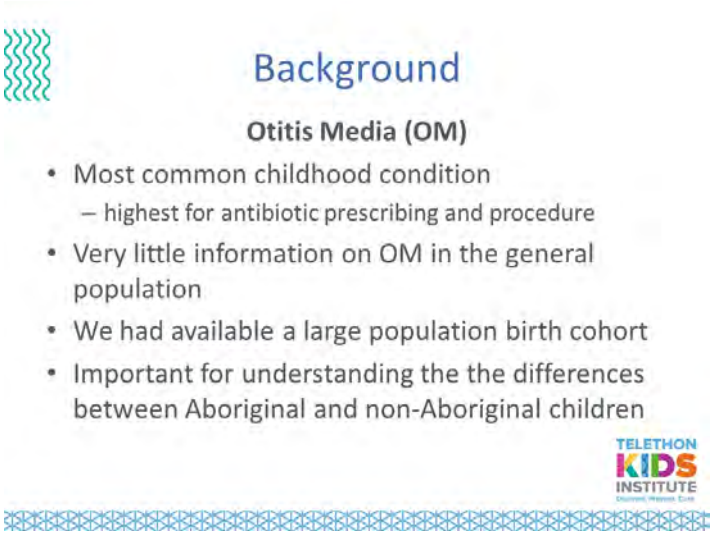
Risk Factors	IRR (95% CI)	
	Univariate	Multivariate
Gender		
Female	Reference	
Male	1.5 (1.3,1.7)	1.50 (1.16,1.95)
Gestational age		
≥37 weeks	Reference	
33-36 weeks	1.4 (1.1,1.6)	0.91 (0.65,1.26)
29-32 weeks	1.7 (1.2,2.5)	0.88 (0.51,1.52)
≤28 weeks	2.9 (1.9,4.5)	1.96 (1.09,3.52)
Percent optimal birthweight		
Normal 85-114%	Reference	
Low <85%	1.24 (1.06,1.44)	1.04 (0.78,1.40)
High ≥115%	0.93 (0.70,1.22)	0.64 (0.38,1.07)
No. of siblings		
0	Reference	
1	1.01 (0.84,1.20)	1.31 (0.89,1.94)
2	0.99 (0.82,1.20)	1.11 (0.70,1.76)
≥3	1.02 (0.87,1.21)	1.25 (0.81,1.94)
Multiple birth		
Singleton	Reference	
Twins	1.90 (1.36,2.66)	1.80 (1.15,2.83)
≥3	5.55 (1.16,26.54)	5.26 (0.89,30.97)
Season of birth		
Spring	Reference	
Summer	1.04 (0.86,1.25)	1.09 (0.77,1.55)
Autumn	1.05 (0.88,1.26)	0.81 (0.56,1.18)
Winter	1.09 (0.91,1.31)	1.04 (0.72,1.49)
Days in neonatal ICU		
0	Reference	
1-3 days	1.25 (0.91,1.72)	1.43 (0.95,2.16)
≥4 days	2.10 (1.68,2.63)	2.06 (1.40,3.04)
Mode of delivery		
Vaginal	Reference	
Instrumental	1.12 (0.88,1.44)	1.25 (0.74,2.11)
Elective caesarean	0.99 (0.78,1.26)	1.15 (0.74,1.78)
Emergency caesarean	1.14 (0.95,1.37)	1.00 (0.72,1.38)
Smoking during pregnancy		
No	Reference	
Yes	1.12 (0.98,1.29)	0.89 (0.68,1.15)
Asthma during pregnancy		
No	Reference	
Yes	1.13 (0.92,1.40)	1.01 (0.69,1.49)
Maternal age		
≥35 years	Reference	
30-34 years	1.07 (0.79,1.45)	1.15 (0.69,1.93)
25-29 years	1.11 (0.83,1.47)	1.24 (0.76,2.00)
20-24 years	0.99 (0.75,1.31)	0.76 (0.45,1.28)

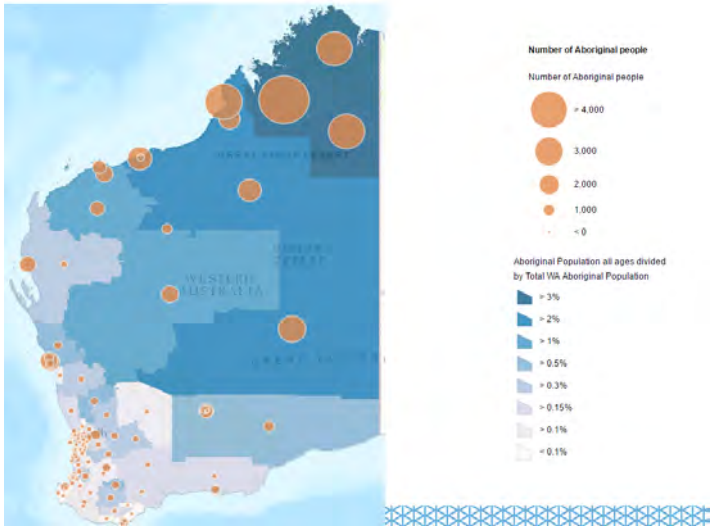
<20 years	1.10 (0.83,1.46)	0.90 (0.50,1.62)
SEIFA Index of disadvantage		
0-10% (most disadvantaged)	1.25 (0.84,1.91)	1.28 (0.59,2.76)
11-25%	1.05 (0.69,1.62)	1.05 (0.49,2.29)
26-75%	1.01 (0.66,1.54)	1.26 (0.59,2.69)
76-90%	Reference	
91-100% (least disadvantaged)	1.38 (0.53,3.59)	2.89 (0.69,12.14)
Accessibility/Remoteness index of Australia		
Very Remote	2.41 (2.00,2.91)	2.58 (1.80,3.68)
Remote	1.49 (1.20,1.84)	1.19 (0.76,1.86)
Outer regional	1.65 (1.33,2.04)	1.58 (1.05,2.37)
Inner regional	1.40 (1.04,1.89)	1.28 (0.77,2.10)
Major cities	Reference	

Abbreviations: IRR, incidence rate ratio; 95% CI, 95% confidence interval; ICU, intensive care unit; SEIFA, socio economic index for area

Bold type indicates statistical significance at $\alpha<0.05$

Appendix 4. Slides from OMOz 2016 oral presentation in Newcastle NSW



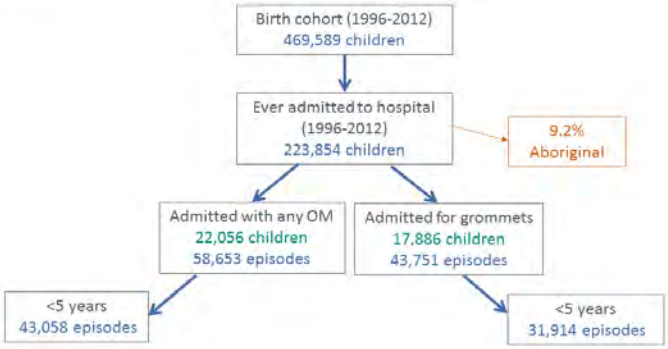


Aims

- Describe the hospitalisation and procedure rates for OM over time
- Explore the maternal and infant risk factors for OM

Any OM hospitalisation

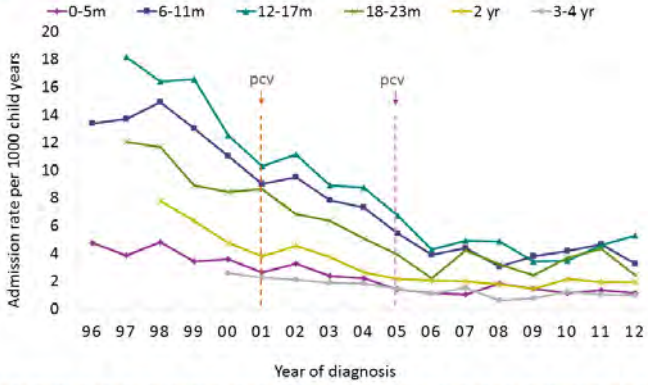
Cohort flow chart (HMDS)



Any OM hospitalisation

	Aboriginal n = 8,323	Non-Aboriginal n = 50,330
Sex		
Male	56%	61%
Age, mean years (range)	3.0 (0-16)	3.2 (0-16)
Mean no of repeat admissions by child	1.4	1.3
Place of hospitalisation		
Metropolitan Perth	23%	80%
Rural	20%	15%
Remote	57%	5%

Non-Aboriginal children admitted for any OM diagnosis (1996-2012)



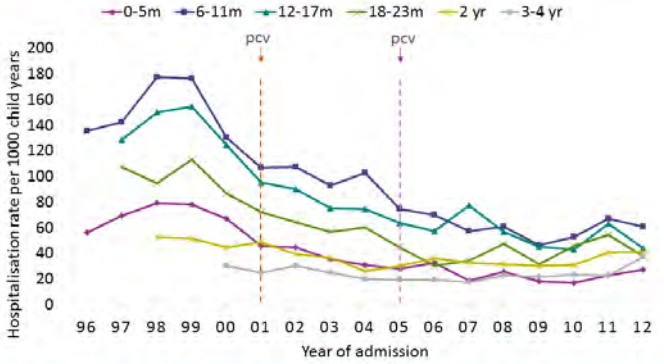
Summary of OM admissions

Peak incidence

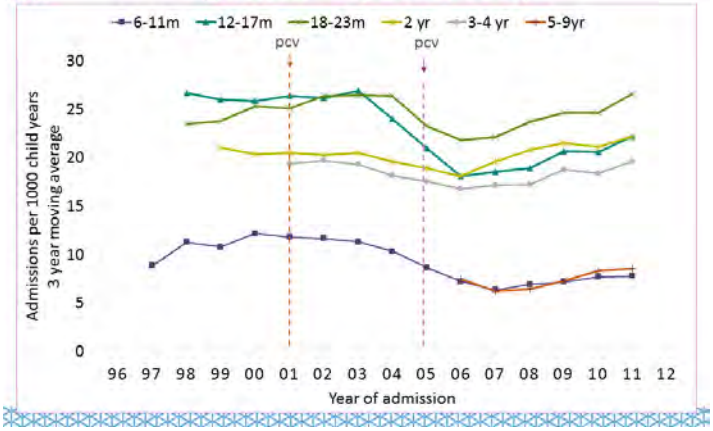
- Non-Aboriginal children
  - 12-17 month age group
    - 18.1 per 1000 child years in 1997 decreased to 5.3 per 1000 child years in 2012
- Aboriginal children
  - Burden younger in 6-11 month age group
    - 177.7 per 1000 child years in 1998 decreased to 60.4 per 1000 child years in 2012
- For both groups hospitalisation rates decreased over time

TELETHON KIDS INSTITUTE

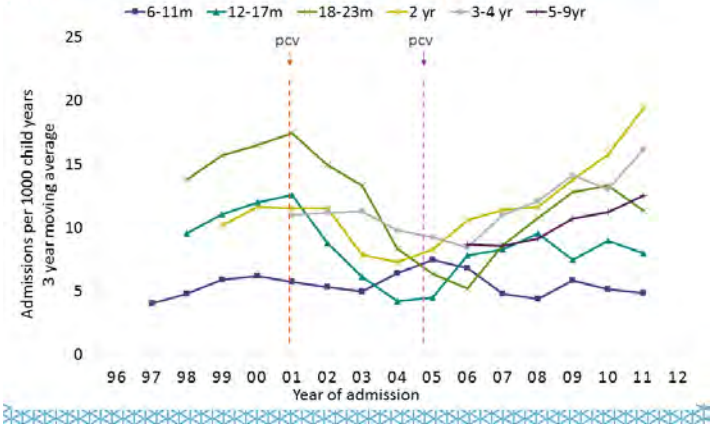
Aboriginal children admitted for any OM diagnosis (1996-2012)



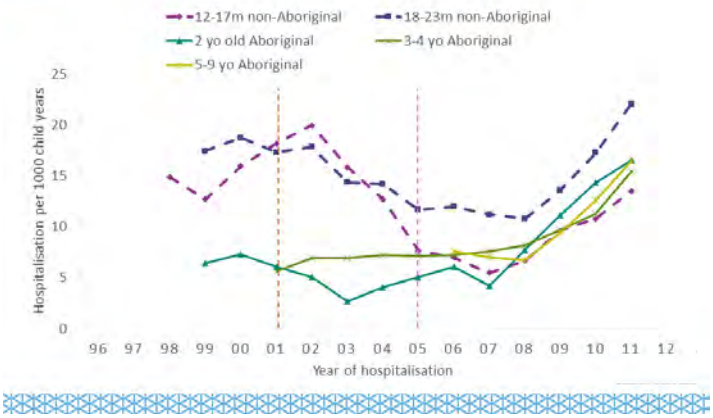
Non-Aboriginal children admitted for grommets (1996-2012)



Aboriginal children admitted for grommets (1996-2012)



Children admitted to remote hospitals for grommets (1996-2012)



Grommet procedures summary

- Non-Aboriginal children more likely to be hospitalised for grommets despite Aboriginal children having a higher burden
- The incidence of hospitalisations for grommet insertion has increased in some age groups from about 2004-2006, particularly in remote hospitals

Risk of OM

	Non-Aboriginal		Aboriginal	
	IRR (95%CI)	PAF %	IRR (95%CI)	PAF %
Sex Male	1.6 (1.4,1.8)		1.3 (1.1,1.6)	
Prematurity ≤28 weeks	2.7 (1.7,4.4)	63%	1.9 (1.11,3.39)	48%
Days in NICU				
1-4 days	1.4 (1.2,1.8)	30%	1.5 (1.1,2.0)	32%
≥4 days	1.6 (1.3,2.1)	38%	2.2 (1.7,3.0)	55%
Elective caesarean	1.4 (1.1,1.7)	26%	1.2 (0.84,1.68)	-
Location of birth Remote part of state	2.6 (1.5,4.4)	61%	4.5 (3.5,5.9)	78%

Risk factors

- We examined the following risk factors:
  - Sex
  - Gestational age (≤28, 29-32, 33-36, ≥37 weeks)
  - Percentage of optimal birthweight
  - Number of live siblings
  - Multiple birth (twins, triplets)
  - Season of birth
  - Days spent in the neonatal intensive care unit (NICU) at birth
  - Mode of delivery (vaginal, instrumental, elective or emergency caesarean)
  - Mother smoked during pregnancy
  - Mother had asthma during pregnancy
  - Maternal age (<20, 20-24, 25-29, 30-34, ≥35 years)
  - Socio Economic Index For Area (SEIFA)
  - Remoteness Index
    - (major cities, inner, outer-regional, remote, very remote)

Limitations

- These data do not include primary care where highest proportion of OM managed.

Strengths

- Large, representative total population dataset reduces bias
- Likely generalisable across jurisdictions
- Better representation of Aboriginal status with the ABS Indigenous variable
- PAFs can help guide interventions where they are likely to have the most benefit

Conclusions

- Decreasing OM hospitalisation trends over time
- Remote areas have highest burden of OM hospitalisations
- Highest proportion of grommets performed in major cities – however recent increase for both Aboriginal and non-Aboriginal children in remote areas
  - Better outreach services to remote areas
- Elective caesarean associated with increased risk of all OM-hospitalisations

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Conclusions

- Living in remote areas greatly increases risk for OM-hospitalisation, more so among Aboriginal children
- While not evaluated here, lower observed rates could be the result of other oropharyngeal surgery in younger children

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Thank you!

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Appendix 5. Plain language summary of this work

Middle ear infection, also known as otitis media, is a condition in which the area behind the ear drum becomes swollen and infected. This is very common in young children but can also occur in older children and adults. Many children get antibiotics that help with the pain and reduce the swelling. If that doesn't work or if the infection continues, a specialist surgeon can operate and put grommets into the eardrum which help drain the fluid that is causing the pressure and pain. Some other symptoms seen in young children include pulling at the ears, irritability, difficulty sleeping or liquid dripping out from the ear. Unfortunately if it is not treated it can get worse and cause hearing problems or even deafness.

We had hospital admission information from 469,589 children born in Western Australia between 1996 and 2012. We also had the information that is collected by the midwife at the time of birth; for example birthweight, whether the child was premature, whether the mother had asthma or smoked while pregnant, age of the parents, home postcode and so on. This dataset did not have any names or identifying information, only basic demographic details and the reason for any hospitalisations or procedures.

We wanted to see how many children went to hospital for middle ear infection and how often grommets were put in. We also wanted to see if there were any differences between boys and girls, Aboriginal and non-Aboriginal children, children who live in major cities compared with those who live outside of major cities, and by socioeconomic status. Finally we wanted to look at any possible risk factors for middle ear infection.

We did this research because the information may help us know how to take better care of children with middle ear infection to reduce how often children get it. It could also help us to know where the biggest need is so that we can help those children. This plan was reviewed by an ethics committee to make sure that it followed ethical guidelines and that any information about individuals was confidential.

There were 58,653 records with middle ear disease. There were 43,751 records with grommets over the period 1996-2012.

We found that children who were Aboriginal and/or Torres Strait Islander were 10 times more likely to go to hospital for middle ear infection than non-Aboriginal children. Despite this, non-Aboriginal

children were more likely to have a procedure than Aboriginal children. This was the same for children born in low socioeconomic neighbourhoods. Boys were more likely to be hospitalised for middle ear disease than girls. Children who were born in a rural or remote parts of the state were more likely to be hospitalised when compared with children born in the city. For example, Aboriginal children aged 0-5 months were four times as likely to be hospitalised if they were born in a remote part of the state than if they were born in the city.

Aboriginal children have a high likelihood of hospitalisation for middle ear disease in all levels of socioeconomic neighbourhoods but less likely to have grommets despite where they live.

The risk factors that we found for middle ear disease were being a boy, spending time in the newborn special care unit and living in a rural or remote part of the state. This was the same for all children. Non-Aboriginal children born to teenage mothers or being born by an elective caesarean section had a higher chance of being hospitalised for middle ear disease.

Being born in a remote part of the state and having higher middle ear disease was also reported in the Northern Territory. One reason for this could be that residents are isolated from health services and hospitals or clinics in those regions often do not have specialists. Boys were also more likely to suffer from middle ear infection than girls, this has also been reported in other countries. We were also not the first to demonstrate that middle ear infection is a disease of poverty. Others have also. Children who are the poorest have the most disease but are the least likely to have grommets.

We hope that this research helps in the development of policies and strategies designed to help the children who are at highest risk and who need early interventions the most.

An evaluation of SmartVax: an active vaccine safety monitoring tool for collection of adverse event following immunisation data

List of abbreviations

ACIR	Australian Childhood Immunisation Register
ACSOM	Advisory Committee on the Safety of Medicines
ACSOV	Advisory Committee on the Safety of Vaccines
ADEC	Australian Drug Evaluation Committee
ADRAC	Adverse Drug Reaction Advisory Committee
AEFI	adverse event following immunisation
ATAGI	Australian Technical Advisory Group on Immunisation
CDC	Centers for Disease Control and Prevention
CDCD	Communicable Disease Control Directorate
CALD	Culturally and linguistically diverse
ED	Emergency Department
ELS	extensive limb swelling
GP	General Practitioner
HREC	Human Research Ethics Committee
IQR	interquartile range
MAE	Masters of Applied Epidemiology
MMR	Measles Mumps Rubella
MMRV	Measles Mumps Rubella Varicella
NCIRS	National Centre for Immunisation Research & Surveillance

NIP	National Immunisation Program
PHAA	Public Health Association of Australia
QIV	quadravalent influenza vaccine
SAE	serious adverse event
SAFEVIC	Surveillance of Adverse Events Following Vaccination in the Community
SMS	short message service
STARRS	Stimulated Telephone Assisted Rapid Safety Surveillance
TGA	Therapeutic Goods Administration
TIV	trivalent influenza vaccine
US	United States
WA	Western Australia
WAVSS	Western Australia Vaccine Safety Surveillance System

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Prologue

I evaluated SmartVax, a novel and rapidly expanding tool used for the surveillance of adverse events following immunisation (AEFI). The system commenced operation at a single pilot general practice at the end of 2011 and had just begun to be rolled out to other sites in Western Australia (WA) when I started the Masters of Philosophy in Applied Epidemiology (MAE) at the start of 2015. WA Department of Health (WA Health) had been supporting the system because of its potential as a state and national AEFI surveillance system since 2012. I was tasked with day-to-day management of the data that were received by WA Health from SmartVax. During my MAE work at WA Health, I completed a retrospective analysis of the data from the pilot general practice with 44 months of longitudinal data. In addition to this, the other activities of my day-to-day work included:

- writing an application for a competitive grant to help fund the growth and development of the system; the grant was submitted to the Telethon-Perth Children's Hospital Research Fund, unfortunately it was not successful;
- writing and submitting an ethics application to the WA Health and Aboriginal human research ethics committees, the purpose of which was to obtain ethics approval to analyse de-identified data from all participating SmartVax sites, all were approved;
- compiling and submitting weekly influenza surveillance data to AusVaxSafety at the National Centre for Immunisation Research & Surveillance (NCIRS), who conduct national AEFI surveillance following influenza vaccination in children (6 months to 5 years) on behalf of the Commonwealth Government, Immunisation Branch. As part of this work the AusVaxSafety team published a peer-reviewed report which highlighted surveillance results of the 2015 influenza season of which I am a co-author (Appendix 1).

SmartVax evolved organically out of the desire of a local general practitioner (Dr. Alan Leeb) to provide real-time vaccine safety information at his practice following the increased incidence of febrile convulsions experienced by children receiving the 2010 Fluvax® vaccine. WA Health recognised the potential of SmartVax and it was later recognised by the NCIRS as a valuable resource providing

vaccine safety information. I spent much of the first year of my MAE working with SmartVax. This involved cleaning and analysing data, writing the paper, contributing to the ongoing work of AusVaxSafety and successfully obtaining ethics approval from two ethics committees in WA. I was then able to share those approvals with the NCIRS which in turn helped them to get timely ethics approval at other ethics committees in other jurisdictions of Australia. The result of this work has been setting the platform for reliable, streamlined vaccine safety surveillance that has extended far beyond WA and is now active throughout Australia. Since my involvement with SmartVax began, the system has experienced ongoing expansion with the aim of increasing the number of sites and participants contributing data.

When I began, it was too early for the system to benefit from a full evaluation because it was still growing and changing. It did not make sense to 'draw the line in the sand' and end up submitting a list of outdated recommendations. Considering that, I have set up this chapter as follows. The chapter begins with a peer-reviewed publication for which I was the first author, *Continuous active surveillance of adverse events following immunisation using SMS technology.* This is the result of the retrospective analysis that I did of SmartVax data at the first/pilot site and is related to this evaluation. This published paper in Vaccine gives an overview of the system and analyses data outputs for children aged <5 years from 2011 to 2015. Although the publication is not a full evaluation, I have included it first to provide context and a brief system description that includes summarised surveillance data. The publication is followed by the formal evaluation of SmartVax as a public health tool contributing data for AEFI surveillance.

In the formal evaluation I describe the background, system operation and attributes; however, it is written to include work that has been done while I have been a MAE scholar. So, again, rather than provide a list of things that should be done, I have instead highlighted how the system has developed and finish with a list of final recommendations as at October 2016.

Lessons learned

I found it a challenge attempting to conduct an evaluation of a surveillance tool that looks different each month because it continues to evolve with modifications being made very frequently to keep up with growing demand. SmartVax is a surveillance tool, not a surveillance system, and adapting the CDC guidelines (which are set up for traditional infectious diseases surveillance systems) was difficult.

Public health impact

During my MAE, the landscape of active AEFI surveillance in Australia has been rapidly changing. This is in part due to my involvement in the SmartVax tool and ability to link it in to national programs in order to streamline and provide in real-time, data on vaccine safety. This is now the aim of AEFI surveillance, but has changed dramatically in the two years from a passive system to an emerging active surveillance system.

This evaluation provides background on the SmartVax tool, how it operates and how it complements the passive vaccine safety surveillance system. I highlight that active surveillance of AEFI now plays an integral part in vaccine safety monitoring in Australia. Most importantly, using SmartVax provides information that could allow public health officials to react quickly if there is a spike in serious AEFIs with confidence in the reported signals being timely and representative.

Information from this evaluation will be shared with AusVaxSafety to be used in the preparation of the annual surveillance report to the Australian Government Department of Health. The evaluation will also be shared with the SmartVax developers and WA Health for review.

My work fed back to Alan to improve what was a novel system that now functions in all states and territories. My knowledge of the tool helped inform AusVaxSafety surveillance at a pivotal time when it was coming to rely on SmartVax as the predominant active surveillance tool. I contributed to the discussions surrounding the development of AusVaxSafety as a national, novel surveillance system. I also collaborated with vaccine safety experts to expand AusVaxSafety and my intimate understanding of the SmartVax system was a key part of this.

I presented different aspects of this work as oral presentations at three conferences:

- the 2016 European Society of Pediatric Infectious Diseases conference in Brighton, UK,
- the 2016 Council of State and Territorial Epidemiologists in Anchorage, Alaska, and
- the 2016 National Immunisation Conference in Brisbane Australia

and completed a peer-reviewed publication as first author and collaborated on an AusVaxSafety publication.

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Continuous active surveillance of adverse events following immunisation using SMS technology

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ABSTRACT

Introduction: On-going post-licensure surveillance of adverse events following immunisation (AEFI) is critical to detecting and responding to potentially serious adverse events in a timely manner. SmartVax is a vaccine safety monitoring tool that uses automated data extraction from existing practice management software and short message service (SMS) technology to follow-up vaccinees in real-time. We report on childhood vaccine safety surveillance using SmartVax at a medical practice in Perth, Western Australia.
Methods: Parents of all children under age five years who were vaccinated according to the Australian National Immunisation Schedule between November 2011 and June 2015 were sent an SMS three days post administration to enquire whether the child had experienced a suspected vaccine reaction. Affirmative replies triggered a follow-up SMS requesting details of the reaction(s) via a link to a survey that could be completed using a smartphone or the web. Rates of reported AEFI including fever, headache, fatigue, rash, vomiting, diarrhoea, rigours, seizures, and local reactions were calculated by vaccination time point.
Results: Overall, 239 (8.2%; 95% CI 7.2–9.2%) possible vaccine reactions were reported for 2897 vaccination visits over the 44 month time period. The proportion of children experiencing a possible AEFI, mostly local reactions, was significantly greater following administration of diphtheria–tetanus–pertussis–poliomyelitis vaccine at 4 years of age (77/441; 17.5%; 95% CI 13.9–21.0%) compared to the vaccinations given at 2–18 months ($p < 0.001$). Across all time points, local reactions and fatigue were the most frequently reported AEFI.
Conclusion: Automated SMS-based reporting can facilitate sustainable, real-time, monitoring of adverse reactions and contribute to early identification of potential vaccine safety issues.

1. Introduction

Post-marketing surveillance of vaccines is critical to identify potential safety issues [1,2] as quickly as possible, so that changes in practice can occur in a timely manner. Important policy responses to safety signals identified through post-marketing surveillance include the withdrawal of the first rotavirus vaccine because of increased rates of intussusception [3,4] and a contraindication for administering one brand of influenza vaccine to children less than 5 years of age due to the increased risk of severe febrile reactions [5].

Ongoing monitoring is also important for maintaining public confidence in the safety of vaccines. While pre-licensure safety studies are critical, they can be limited by relatively small sample sizes, may not reflect use of the vaccine outside the clinical trial setting (e.g. use with other vaccines or in alternate patient cohorts), and do not capture changes to the vaccine that may occur after licensure (e.g. annual strain changes in the influenza vaccine) [1,2,6]. Post-marketing vaccine safety surveillance is therefore important, however current mechanisms are mostly passive and may be unfavourably affected by underreporting, reporting biases, and the lack of accurate denominators for determining rates [7,8]. To help address the limitations of passive surveillance, routine, active vaccine safety monitoring has recently been established in the United States [9,10]. Here we describe ongoing efforts to

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develop a system for active post-marketing vaccine safety surveillance in Australia. SmartVax is a vaccine safety monitoring tool that uses automated data extraction from provider-based electronic patient records and short message service (SMS) technology to follow-up vaccinees in real-time. This report describes how SmartVax was used to establish reactogenicity profiles for paediatric vaccine combinations and assess the impact of changes to the childhood immunisation schedule.

2. Methods

2.1. Setting

In Australia, more than 70% of vaccinations are given by general practitioners (GPs) [9]. SmartVax has been used at a single GP medical practice in metropolitan Perth, the capital of Western Australia (WA), since 2011. The practice has approximately ten full-time practitioners, 21,000 active patients, and administers approximately 2000 paediatric vaccinations each year. Details on operational aspects of the SmartVax system have been previously described [11]. In brief, parents or guardians of vaccinated children (hereafter patients) were explained the risks and benefits of vaccination prior to consenting, as per routine clinic practice. Patients were informed that they would be contacted by SMS in three days. Those who preferred not to be contacted by SMS could opt-out of SMS communication by advising their provider; no patients declined participation. Each weekday the SmartVax tool extracted vaccination data from the practice's commercially available management software. SMS text messages were sent to patients three days post-vaccination to query whether they had experienced any perceived reactions following their vaccination. The SMS read, "*Thank you for caring to have a vaccination. We would like to know if there were any reactions. Kindly reply Y or N only*." Affirmative replies to this query were followed up by two additional SMSs, the first to ascertain whether the reported adverse event was medically attended and the second with a link to a survey that could be completed on a smartphone to obtain details of the nature, duration and severity of the possible AEFI (Supplementary material). All SMS replies received from patients were automatically written back into the tool database. Medically attended reactions were automatically sent to the correspondence inbox of the practice software where they were entered into the electronic patient record.

Patients who indicated they had experienced a reaction but did not reply to the survey request, as well as those who did not respond to the first SMS, were telephoned by a practice nurse or doctor.

Ethics approval for analysis of AEFI data from SmartVax was received by the WA Department of Health Human Research Ethics Committee.

2.2. Participants

All children under five years of age who received one or more vaccines recommended in the Australian Childhood Immunisation Schedule [12] at 2, 4, 6, 12, 18 and/or 48 months between 9 November 2011 and 9 June 2015 were included in this analysis. Since SmartVax is intended to be an SMS/Smartphone-based system, the responses of those who did not reply by SMS but were subsequently reached by telephone were not included in the primary analysis. However, a secondary analysis compared the age, sex and reactions reported using SMS/Smartphones and those who required follow-up by voice telephone call.

2.3. Outcome measures

Possible AEFI were defined as a patient's affirmative reply to the first SMS. Patients reporting a possible AEFI were then asked if they sought medical attention and whether they experienced any of the following symptoms: fever, headache, fatigue, rash, vomiting, diarrhoea, rigours, seizures, and local reactions (pain or swelling at the injection site). A serious adverse event (SAE) was defined using the US Vaccine Adverse Events Reporting System criteria; an event where the patient experienced a health-risk, a life-threatening illness, was hospitalised, had a permanent disability, or died [7].

2.4. Statistical analysis

The response rate was defined as the proportion of patients who responded to the clinic's SMS with a reply SMS. Patients who provided an incorrect or disconnected mobile number or did not answer after three attempted phone calls were classified as uncontactable. Duplicate observations and SMS replies that were unrelated to the vaccination event (e.g. "wrong number" or "stop and get milk on your way home") were removed prior to analysis.

The proportion of patients reporting each clinical symptom, or possible AEFI, at each time point on the vaccination schedule was defined as the number of patients reporting the symptom divided by the total number of vaccinations given for that age time point $\times 100$.

We compared proportions of possible AEFI by year for each time point to determine if there were differences in reports by year. On 1 July 2013, measles–mumps–rubella–varicella (MMRV) vaccine replaced the varicella-only vaccine dose at 18 months and the dose of MMR vaccine at four years of age was removed on the national immunisation schedule. We report the proportion of reported reactions at 18 months of age prior to and after this change using a two-sample test of proportions assuming equal variances.

We also looked at individual patients to calculate SMS response times; this sub-analysis was restricted to the first vaccination visit only so each patient would contribute equally. In addition we determined whether individuals who had more than one visit, and who reported a possible AEFI after their first visit, were more likely to report a possible AEFI at a subsequent visit.

Finally, we compared demographic characteristics of those who did not reply by SMS to determine whether they were different to all those who did reply by SMS (i.e. voice telephone only respondents and those who were uncontactable).

Data were analysed using Stata 14 (Stata Corp., College Station, TX). Descriptive data are presented as proportions with 95% confidence intervals (CI). Logistic regression was used with reaction (Y/N) as the dependent variable, sex and scheduled time point as independent variables. Subsequent logistic regression was used with each reaction type (fever, local reaction, fatigue, etc.) as the dependent variable. Results were considered significant at $\alpha < 0.05$.

3. Results

Between November 2011 and June 2015, 1667 patients who were aged five years or under had a total of 3922 vaccination visits. Post-visit SMSs were sent to 3906/3922 (99.6%) of these patients and 2897/3906 (74.2%) SMS replies were received. Of the 1009/3906 (25.8%) patients sent an SMS who did not reply to the initial SMS, 284/1009 (28.1%) were reached through follow-up telephone calls. Post-vaccination information on possible reactions was unavailable for the remaining 725/3906 (18.6%) vaccination visits.

There was no significant difference in age, sex or reporting of possible AEFI between those patients who replied to the initial SMS and those who provided information only after being telephoned (Table 1); there was also no significant difference in terms of age, sex and number of vaccination visits between patients who were uncontactable and those who replied by SMS (Table 2). The final dataset for primary analysis included a total of 2897 SMS replies

Table 1
Comparison of patients who replied to the SmartVax SMS and those who did not reply but were contacted by telephone.

	Replied to SMS (n = 2898)	Telephoned (n = 284)	p value
Mean age, months (median [IQR])	14.6 (9 [4–18])	17.0 (12 [4–19])	0.28
Sex, female *N* (%; 95% CI)	1359 (46.9; 44.2–49.6)	133 (46.8; 38.3–55.3)	0.98
Any reaction *N* (%; 95% CI)	239 (8.3; 4.8–11.8)	27 (9.5; 1.6–20.6)	0.83

Abbreviations: IQR, Interquartile Range; SMS, short message service; 95% CI, 95% confidence interval.

Table 2
Comparison of demographic characteristics of individual patients who responded to SMS and those who did not respond.

	Replied to SMS (n = 1216)	Unable to be contacted (n = 725)	p value
Age, months mean	18.1	16.7	0.10[a]
Median [IQR]	6 [2–48]	12 [4–19]	
Gender			
Female *n* (%)	564 (46.4)	342 (47.2)	0.82
Male *n* (%)	652 (53.6)	383 (52.8)	0.80
No. of vaccination visits, mean	2.1	2.2	0.78[a]
Median [IQR]	2 [1–3]	2 [1–3]	

[a] Compared using an independent t-test with equal variances.

from 1216 unique patients, of whom 564/1216 (46.4%) were female. Of the patients with ethnicity recorded, approximately 1% were identified as Aboriginal and/or Torres Strait Islander. The mean number of visits per patient was 1.8 (range 1–6).

Responses to the first SMS were prompt: 988/1216 (81.3%) individual patients replied within 2 h. Of those responding within 2 h, 602/988 (60.9%) responded within 10 min after the outgoing SMS was sent. A significantly higher proportion of people who reported "no" to any reaction responded within 2 h 896/1216 (82.2%) compared with those who reported "yes" 92/1216 (73.0%), Pearson's chi-square $p = 0.03$.

3.1. Reported reactions

Overall, 239 (8.2%; 95% CI 7.2–9.2) possible vaccine reactions were reported for all 2897 vaccination visits over the 44 month time period. The most frequently reported reactions were local reactions (2.5%; 95% CI 2.0–3.2) and fatigue (2.1%; 95% CI 1.6–2.7) across all time points. Local reactions were higher at the 48-month time point (8.6%, 95% CI 6.0–11.2). The odds of a patient having a local reaction at the 48-month scheduled time point was nine times that of the two-month time point (OR 9.2, 95% CI 3.6–23.6) (Table 3). The results were similar when other time points were used as the reference. Frequency of fever was 2.5%, 95% CI 1.0–4.0 (11/441) at the 48-month time point but ranged between 0.6% and 1.2% for all other time points. There were a total of 20 GP or after-hours doctor visits and two reported visits to an emergency department (Table 4).

There was no significant difference between the proportion of possible AEFI reported before and after the change from varicella as a single antigen to MMRV at 18 months, i.e. 8.9% vs. 5.9% respectively, $p = 0.24$ (Table 5).

Table 3
Patient reported local reactions using SmartVax at each scheduled vaccination time point at a general practice in Perth, Western Australia 2011–2015.

Vaccination time point	Odds ratio	95% confidence interval
2 months	[1] Reference	[1] Reference
4 months	1.1	0.31–3.7
6 months	2.3	0.82–6.7
12 months	1.2	0.36–3.9
18 months	1.4	0.45–4.6
48 months	9.2	3.6–23.7

When assessing proportions of reported AEFI by year (2012–2014) using each time point on the schedule we found no significant differences across years for any vaccination time points (Fig. 1).

One possible serious adverse reaction, a seizure, was reported, however at medical follow-up the patient denied having had a seizure and suggested an accidental affirmative response.

Of 130 individual patients who reported a possible AEFI at their first visit, 68 were age-eligible to attend a subsequent vaccination visit during the period of our study (i.e. 48-month time point excluded). Of these patients, 54/68 (79.4%) were documented to have returned for one or more subsequent vaccinations. Rate of reactions reported at a subsequent visit was significantly higher among those who reported at reaction at their first visit 17/54 (31.5%, 95% CI 19.1–43.9) vs. those who did not report a reaction at their first visit, 71/847 (8.4%, 95% CI 6.5–10.3).

4. Discussion

Our report on a novel vaccine safety surveillance system that uses automatically-generated SMS to actively monitor AEFI in children has three important findings: first, the participation rate by parents is high (>70%); second, the responses are timely (81% reply within 2 h); third, the program is sustainable with high rates of participation over time.

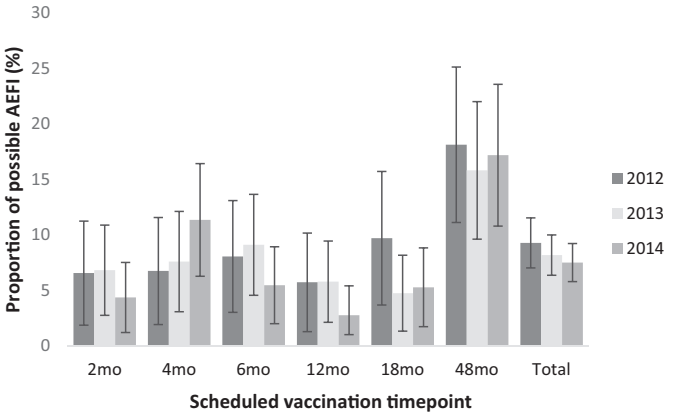

Fig. 1. Proportion of patients reporting a possible AEFI using SMS by year and vaccination time point with error bars indicating 95% confidence intervals. *Abbreviations*: AEFI, adverse events following immunisation; SMS, short message service.

Table 4
Parental reports of possible AEFI by vaccination time point using SmartVax, a SMS adverse events monitoring system in General Practice.

	2 months (n = 494)	4 months (n = 459)	6 months (n = 515)	12 months (n = 505)	18 months (n = 483)	48 months (n = 441)	Total[b] (n = 2897)
Scheduled vaccinations (vaccinations administered concomitantly)	Diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, haemophilus influenza type b, pneumococcal and rotavirus	Diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, haemophilus influenza type b, pneumococcal and rotavirus	Diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, haemophilus influenza type b, pneumococcal and Rotavirus	Measles, mumps, rubella, haemophilus influenza type b and meningococcal C	Before 1 July 2013 Varicella After 1 July 2013 Measles, mumps, rubella and varicella	Diphtheria, tetanus, pertussis and poliomyelitis	
Any reaction[a] *N* (%, 95% CI)	29 (5.9, 3.8–8.0)	37 (8.1, 5.6–10.6)	39 (7.6, 5.3–9.9)	24 (4.8, 2.9–6.6)	33 (6.8, 4.6–9.1)	77 (17.5, 13.9–21.0)	239 (8.2, 7.2–9.2)
Fever ≥38 °C	5 (1.0)	4 (0.9)	3 (0.6)	6 (1.2)	3 (0.6)	11 (2.5)	32 (1.1)
Headache	0	0	0	0	0	2 (0.5)	2 (0.1)
Fatigue	12 (2.4)	8 (1.7)	11 (2.1)	11 (2.2)	1 (0.2)	13 (2.0)	60 (2.1)
Rash	0	1 (0.2)	1 (0.2)	3 (0.6)	3 (0.6)	1 (0.2)	9 (0.3)
Vomiting	3 (0.6)	2 (0.4)	4 (0.8)	2 (0.4)	4 (0.8)	3 (0.7)	18 (0.6)
Diarrhoea	8 (1.6)	3 (0.7)	6 (1.2)	3 (0.6)	0	2 (0.5)	22 (0.8)
Rigours	0	0	0	0	0	0	–
Seizure	0	1 (0.2)	0	0	0	0	1 (0.03)
Local reaction	5 (1.0)	5 (1.1)	12 (2.3)	6 (1.2)	7 (1.5)	38 (8.6)	73 (2.5)
Attended GP or after hours service	3 (0.6)	4 (0.9)	0	5 (1.0)	2 (0.4)	6 (1.4)	20 (0.7)
Attended an emergency department	0	0	1 (0.2)	0	1 (0.2)	0	2 (0.06)

Abbreviations: AEFI, adverse events following immunisation; SMS, short message service text message; 95% CI, 95% confidence interval; GP, general practitioner.
n = number of SMS responses received per scheduled vaccination.

[a] "Any reaction" refers to a patient responding by SMS to, "Thank you for caring to have a vaccination. We would like to know if there were any reactions. Kindly reply Y or N only."

[b] Total reactions may not equal the sum of individual symptoms reported as patients were allowed to report multiple symptoms.

The overall rate of possible AEFI of 8.3% was within the range of AEFI reported from passive surveillance [13]. The most common reported reactions, i.e. local (2.5%) and fatigue (2.1%) were below rates reported in the Australian Immunisation Handbook (handbook) [12] and other sources [13]. At each vaccination time point, the proportions of possible adverse events observed in our study were below those reported in the United States [14]. Thus it appears using SMS technology has made it possible to actively solicit information in near real-time without leading to an over-estimation of AEFI.

Although reactogenicity of individual antigens could not be calculated because the majority of vaccines are combination vaccines, we were able to establish profiles of these vaccine combinations given at each time point.

We identified that the proportion of reactions reported at the 48 month time point may be higher than that for vaccinations administered at younger ages, and this finding is consistent with data collected by the state's passive AEFI monitoring program, the WA Vaccine Safety Surveillance System [15]. Also consistent with our finding, an increased incidence of reactions following booster doses of acellular pertussis-containing vaccines have been reported in a Cochrane review of clinical trials [16] and post-marketing surveillance of 4–6 year olds receiving their fifth dose in Canada [17].

Reassuringly, we found no evidence that changing the immunisation schedule from varicella as a single antigen to MMRV affected reactogenicity experienced at the 18 month time point. Our finding of no increased reaction after MMRV is consistent with others who demonstrated the same for the first dose of MMRV [18,19].

Adjustments to the childhood immunisation schedule or changes in the lots of vaccine distributed do occur. Having a pre-existing system that can quickly and efficiently assess a change's impact on reactogenicity may be useful to regulatory authorities and providers.

Our findings on rates of specific reactions should be interpreted in context. Although they describe possible adverse events that occurred following vaccination, they do not necessarily prove that the events were caused by the vaccination. Some reported adverse reactions can be the result of coincidence with the timing of the vaccination and not causally-linked [16]. Even so, the rates of possible reactions reported via SmartVax in this analysis are generally reassuring as they do not exceed rates from previous published studies using different methodologies.

We were not able to ascertain why patients were more likely to report a possible AEFI at a subsequent visit if they reported a possible AEFI at their first visit. It could be that these patients were more likely to experience a substantive reaction after vaccination and report it, or alternatively, that they had, on average,

Table 5
Parental reported proportions of AEFI before and after MMR booster and varicella vaccination schedule changes in July 2013.

	Prior to 1 July 2013 *N* (%) 95% CI	After 1 July 2013 *N* (%) 95% CI	*p* value[a]
18 months Varicella-only (n = 158)	16 (8.9) 4.5–13.3		0.24
18 months Measles, mumps, rubella, varicella (n = 272)		17 (5.9) 3.1–8.7	

[a] Using a two-sample test of proportions.

a lower threshold for reporting post-vaccination symptomatology than other patients.

The fact that there was no significant difference in the proportion of patients reporting reactions between those who replied by SMS or who were followed-up by telephone in our study implies that relying only on responses that are received by SMS and smartphone survey are likely to be representative of the broader patient population. Follow-up telephone calls to non-responders are resource intensive and removing this arm of the program would substantially reduce the staff time required to actively monitor AEFI [11]. Bexelius and colleagues found similar results to ours when they compared SMS with telephone interviews in collecting data about influenza vaccinations from a random sample of the Swedish population registry and found no significant difference between the data obtained by SMS and that obtained by telephone interview [20].

The need to individually follow-up some patients is inevitable; for example, a person who replies affirmatively to the SMS asking about whether their reaction was medically attended may fail to complete the smartphone/web survey. The system only collects self-reported reaction information, it does not evaluate it.

In our assessment, using automated data extraction and SMS/smartphone surveys to actively monitor vaccinees has the potential to make major contributions to vaccine safety surveillance, particularly in countries lacking programs like the Vaccine Safety Datalink in the United States [21]. To help realise this potential in Australia, there have been several enhancements to the SmartVax program since the data in this report were collected. First, the number of practices participating in SmartVax has been expanded. At present there are more than 90 practices which include government and hospital immunisation clinics using SmartVax; increasing the number of vaccinations under surveillance means that any significant deviations from established rates of AEFI will be able to be detected more quickly. Second, SmartVax has been configured to aggregate de-identified patient data across practices so it can be regularly reviewed by vaccine safety professionals. Third, there is flexibility in the timing of when the system sends an SMS, depending on which vaccine was administered; this flexibility should enable SmartVax to actively survey vaccinees about potential reactions other than reactogenicity. For example, it would likely be more meaningful to inquire about fever and rash 7–10 days post-vaccination for patients receiving MMR/V vaccines. Last, in order to ensure the program remains sustainable as it grows in scope, we are examining the concept of tiered-reporting, i.e. having all participating practices report details for every medically attended possible AEFI, but a smaller number routinely supplying information on those events not serious enough in the patients mind to necessitate medical attention. Future research can focus on how this system can be used to quickly assemble adverse event profiles for newly released vaccine lots and assess differences across vaccine brands to evaluate the impact of recommended changes to the timing of vaccine doses. Further work will evaluate the extent to which these enhancements make SmartVax capable of contributing to robust, national AEFI surveillance.

5. Conclusions

We described a system for active post-marketing vaccine safety surveillance in Western Australia that demonstrated our ability to establish reactogenicity profiles for paediatric vaccine combinations at a practice and assess the impact of changes to the childhood immunisation schedule on reported rates of AEFI. Automated SMS-based reporting can facilitate sustainable, real-time, monitoring of adverse reactions and contribute to early identification of potential vaccine safety issues.

Acknowledgements

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Authors' contributions: DWW, SAW and PVE designed the study. DWW reviewed the literature, conducted the statistical analyses, analysed the data and wrote the initial draft of the manuscript. SAW and PVE supervised the analysis and assisted with writing the manuscript. AL collected and assisted with the interpretation of the data. All authors contributed by making critical revisions to the manuscript and all have approved the final article. *Conflicts of interest statement:* DWW, SAW, and PVE have no conflict of interest to disclose. AL is a co-developer of the SmartVax system. SmartVax is a registered trademark but is not commercially available nor is it under copyright. If this software were to be licensed and sold commercially, he may derive financial benefit. *Funding:* This work was supported by the Western Australia Department of Health.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.05.015.

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Abstract

On-going post-licensure surveillance of adverse events following immunisation (AEFI) is critical to detecting and responding to potentially serious adverse events in a timely manner. SmartVax is a vaccine safety monitoring tool that uses automated data extraction from existing immunisation provider management software and short message service (SMS) technology for follow-up of vaccinees in near real time. I describe SmartVax and provide background on it and on AEFI surveillance in Australia more broadly, and evaluate the tool against public health surveillance system attributes. I also incorporate record review and the results of vaccine administrator interviews and provide a list of recommendations for improving the operational capacity of the tool as an AEFI surveillance system. The scope of this evaluation is limited to the functionality of the system in Western Australia (WA).

SmartVax was viewed as a useful tool by providers and patients. Providers believe it improves the service that they already provide to their patients. In addition, it provides useable AEFI surveillance data.

SmartVax now has a track record of providing useful and sustained data for the national AEFI surveillance of two important immunisations (influenza and pertussis). It will have even greater utility once new vaccines are included for routine monitoring.

2.0 Introduction

On-going post-licensure surveillance of adverse events following immunisation (AEFI) is critical to detecting and responding to potentially serious adverse events in a timely manner.[1] SmartVax is a vaccine safety monitoring tool that uses automated data extraction from existing immunisation provider management software and short message service (SMS) technology for following up vaccinees in near real-time. SmartVax was developed by a general practitioner (GP) in 2011, with WA Department of Health (WA Health) providing financial and in kind support for the system since 2012. The feasibility of using SMS technology to follow up vaccinees was evaluated previously.[2] This evaluation aimed to:

1. Describe SmartVax and its day-to-day functionality; and
2. Evaluate the attributes of the SmartVax tool as a public health surveillance system.

The evaluation was intended to inform the usefulness of the tool in contributing data for the active surveillance of AEFI. Here I will describe the system and its day-to-day functionality. While the system has grown to include immunisation providers nationally, the scope of this evaluation is limited to the functionality of the system in WA. The evaluation has been completed using the CDC Guidelines for the Evaluation of Surveillance Systems criteria as a guide.[3] Given the novelty and growth of this tool, I highlight where the system has been modified during the course of this evaluation.

3.0 Background

3.1 Adverse events following immunisation

AEFI are defined as any untoward medical occurrence following an immunisation which could be causal or temporal.[4] A causal event is one that is associated with the vaccination[5] or by its handling or administration.[6] A temporal event is one that is associated with the vaccine in time only, which could be perceived as causal but is only coincidental.[7] To establish whether a vaccination was responsible for an adverse event a clinical evaluation is required. The Therapeutic Goods Administration (TGA) has assigned a level of causality for AEFI; they are, 'certain', 'probable' and 'possible' and refer to the

likelihood that a vaccine was actually associated with an AEFI in the vaccinee.[6] While the overall responsibility of vaccine safety surveillance in Australia lies with the TGA, there is regular sharing of safety information between the TGA and state and territory health authorities.

3.2 The events that led to active AEFI surveillance in WA

3.2.1 Influenza vaccination in WA

The government of WA has funded trivalent influenza vaccination (TIV) to children aged 6 months to four years since 2008, following the deaths of three preschool aged children from influenza in 2007.[8] As a result, 45% of children <5 years in WA were vaccinated against influenza in 2008-2009.[9]

The 2009 global H1N109 pandemic resulted in high awareness in the community for influenza vaccination and improved vaccination coverage. Attempts were made to vaccinate as many as possible against the new strain that emerged in 2009. In 2010, there was expected high uptake of vaccine.

In 2010, the TIV vaccination program began on the 19th of March. Following this there was an unexpected increase in the incidence of febrile convulsions in children following the administration of TIV reported from the week of 4 April 2010. A range of reactions were detected and reported by astute clinicians in the state's Emergency Departments and not through AEFI surveillance.[10] After an investigation into the febrile convulsions, the program was suspended for children <5 years of age on 22 April 2010 in WA and the next day in all of Australia. An investigation was completed to determine the source of the febrile convulsions.[8] A single brand, Fluvax® and Fluvax Jr® (Seqirus, Parkville Australia) (marketed as Afluria® in the United States of America (US) and Enzira® in the United Kingdom[11]), was found to be associated with the increased febrile convulsions.[11] Further investigation attributed this to the manufacturer's use of the detergent taurodeoxycholate as the virus-splitting agent[12] which led to a partially-split and reactogenic vaccine.[13]

All Fluvax® products were contraindicated in children <5 years and the childhood influenza vaccination program in Australia was reinstated (with other TIV products recommended for children) on 30 July 2010 after investigations by the TGA were completed.[14] Subsequently federal and state reviews were conducted which identified critical gaps in Australia's passive vaccine safety surveillance

system. Key recommendations included ongoing monitoring of vaccination programs, development of a web-based mechanism to record vaccination details and real-time AEFI surveillance system to provide more robust and timely information on AEFIs in a timeframe that is acceptable to the public and public health decision makers.[10,14] Despite the reinstatement of the program, vaccination rates in WA for children <5 years receiving influenza vaccination dropped to only 7% in 2011-2012[9] and have remained low. In all subsequent seasons. These events have had dramatic and sustained impact on influenza vaccine uptake in WA. No other states have introduced a program for children <5 years.[15]

3.2.2 Development of SmartVax

The events in 2010 prompted Dr. Alan Leeb, a GP and principal of the Illawarra Medical Centre in WA to conduct a telephone survey of parents or carers of all children who received the TIV in the preceding two months at his general practice. To his surprise, parents or carers reported that 101/337 (30%) of their children experienced a reaction including eight hospital attendances and three febrile convulsions (www.smartvax.com.au). This prompted him to establish a vaccine safety monitoring system for all vaccinations given at his practice to follow-up patients using short message service (SMS) technology. By having this information, he believed he could provide better patient care by informing his patients of possible reactions (even minor ones) and alert relevant health authorities if the frequency of reactions increased. In November 2011, he partnered with a software developer to design an AEFI tool that is known today as SmartVax. The operation of the tool is described in detail in section 4.3. In short, a SMS message is sent to vaccinees approximately three days after receipt of any vaccination enquiring whether they had any reactions.

After the events of 2010, Dr. Leeb met with WA Health to express his interest in developing an active surveillance tool. They designed a study to follow up adults at his practice to compare the odds of having a reaction for those receiving Fluvax® TIV and those receiving Influvac® TIV (BGP Products, Macquarie Park NSW Australia). The results showed that adults receiving the Fluvax® TIV (n= 156) were four times more likely to have local reactions than adults receiving Influvac® (127) (adjusted odds ratio 4.13, 95%CI 1.29—13.24).[16] WA Health began helping Illawarra Medical Centre to support the development of SmartVax from 2012. The system has been refined and automated over time and by

the middle of 2014 it was made available to general practices and immunisation providers across the country at no cost. Although the system evolved out of a need for responding to TIVs, it was designed to monitor all vaccines given to children and adults.

3.2.3 SMS technology

Using a SMS platform for vaccine safety surveillance is sustainable as a growing number of people own mobile phones in Australia. In 2015 the World Bank reported that the number of mobile cellular subscriptions per 100 people in Australia was 133.[17] In fact smartphone ownership has grown nationally and globally. In 2014, Deloitte, a global consulting firm, conducted a Media Consumer Survey and found 81% of Australians owned a smartphone, a 21% increase over the previous three years.[18] With a growing number of people with smartphones, the utility of using this technology for vaccine safety follow-up has merit.

3.3 The safety of vaccines

To monitor vaccine safety, pre-licensure clinical trials are carried out by vaccine manufacturers to test the safety, tolerability and efficacy of vaccines.[19-21] Clinical trial phases, sample sizes and the purpose of each phase are summarised in **Table 1**.

Table 1. Pre-licensure clinical trial testing of vaccines by manufacturers[4]

Clinical Trial Phase	Sample Size (per group)	Purpose
Phase I	10	Tolerability and safety
Phase II*	100-300	Dose response curve; safety data, increased understanding of the tolerability and safety indices.
Phase III	500-4000 or more	Efficacy

*Phase II and Phase III clinical trials may sometimes be divided into phases a and b where IIa evaluates short term safety and IIb confirms efficacy and therapeutic dose range, for example.

While pre-licensure safety studies are critical, they can be limited by relatively small sample sizes, may not reflect use of the vaccine outside of the clinical trial setting (*e.g.* use with other vaccines or in alternate patient cohorts), are unlikely to be powered to detect rare adverse events,[4,19] and do not capture changes to the vaccine that may occur after licensure (*e.g.* annual strain or production changes

in the influenza vaccine).[19,22,23] Detecting AEFI in a 'real-world' environment requires post-marketing surveillance data.[24] However, current mechanisms are mostly passive and could be unfavourably affected by underreporting, reporting biases, and the lack of accurate denominators for determining rates.[21,25,26] Furthermore, if a possible AEFI is identified by the passive surveillance system, it can take a long time before the risk is evaluated by relevant authorities.[27]

3.4 The history of surveillance of adverse events following immunisation in Australia

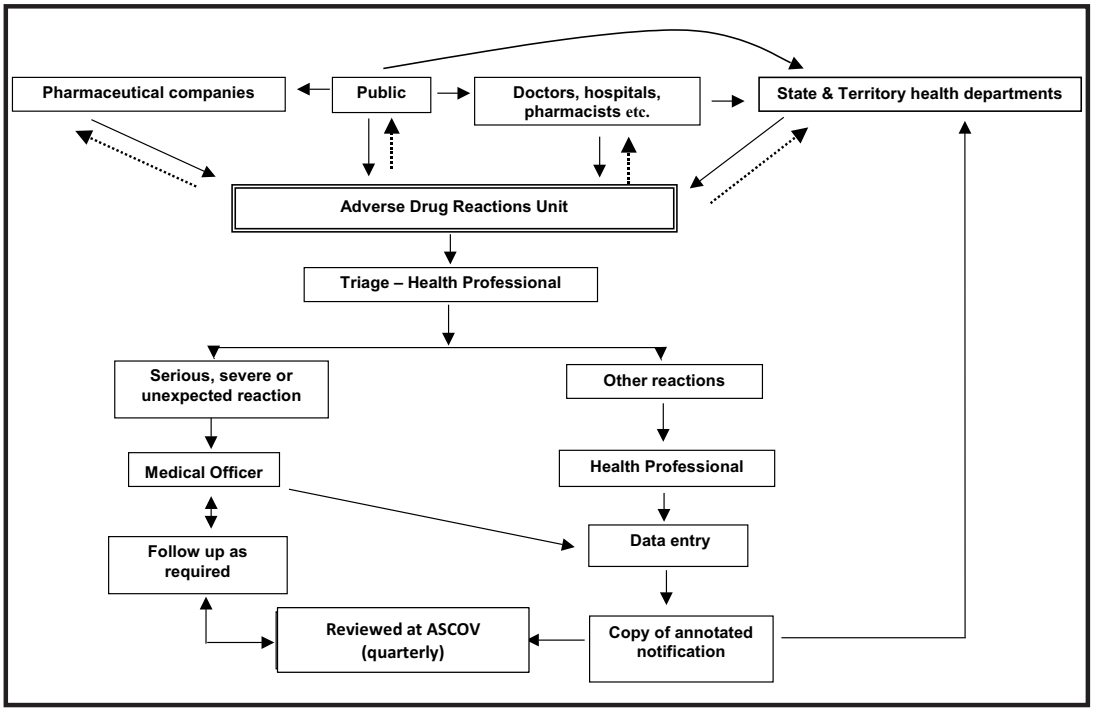
The history of vaccine safety surveillance in Australia began in 1964 with the establishment of the Australian Drug Evaluation Committee (ADEC); a sub-section of the TGA. A sub-committee responsible to report to the ADEC met for the first time in May 1970. This group was called the Adverse Drug Reaction Advisory Committee (ADRAC).[28] ADRAC was replaced by the Advisory Committee on the Safety of Medicines (ACSOM) in 2010[29] and in 2013 by the Advisory Committee on the Safety of Vaccines (ASCOV), which continues today.[30]

In 1968, 70% of suspected AEFI reports to the TGA came from doctors, 20% from hospitals and 7% from industry.[28] Today, reporting of AEFI to the Health Department has been established in all states and territories in Australia with the exception of Tasmania where they still report directly to the TGA.[31] Suspected AEFI reports are now more broadly received from multiple sources including state and territory health departments responsible for immunisation, vaccine manufacturers, general practitioners and the general public.[32]

In addition, two states have developed enhanced passive surveillance systems; Victoria's Surveillance of Adverse Events Following Vaccination in the Community (SAFEVIC)[33] and the Western Australia Vaccine Safety Surveillance (WAVSS) system.[34] SAFEVIC enhances surveillance by integrating passive surveillance with clinical services to investigate possible AEFI that occur.[35]

The Database of Adverse Event Notifications, managed by the TGA, contains reports of safety issues from drugs or medical devices and is received from a range of sources. It is publically available on the TGA website.[36] A flow chart illustrating the passive reporting of AEFI in Australia can be found in **Figure 1**.

Passive systems have limitations. They are susceptible to underreporting.[6] They lack comparator information about vaccinees who do not have or report a reaction, or those who are not vaccinated[37] (people who are not vaccinated may be different to those who are and/or those who report a reaction). Passive systems can also be slow.



Arrows indicate the directions of information transfer. Dotted lines indicate acknowledgment of receipt of an AEFI notification by the Adverse Drug Reactions Unit. All notifications are reviewed by the Adverse Drug Reactions Advisory Committee which meets at six-weekly intervals.

Figure 1. Flow chart of Australia's passive adverse events following immunisation. Figure reproduced by permission from the author[6]

3.4.1 WAVSS

The WAVSS system in WA arose from recommendations in the Stokes Review[10] and commenced operation in March 2011.[38] WAVSS employs a fulltime nurse whose responsibility it is to triage all events and alert clinicians to the need for review in the clinics that operate at the Princess Margaret Hospital for children (PMH) and Sir Charles Gairdner Hospital (SCGH). The WAVSS nurse position is supported by clinicians at PMH, SCGH and the CDCD. Other responsibilities of the nurse are to field telephone calls from the public about perceived AEFI, follow-up possible adverse events reported through the online portal and enter data into the system. Reports can be generated in order to review vaccine safety and data from WAVSS is reported to the TGA.

3.5 Surveillance of adverse events following immunisation internationally

To help address the limitations of passive surveillance, routine, active vaccine safety monitoring has been established in other countries.[39-41] The Vaccine Safety Datalink Project (VSD) commenced in the US in 1990 at sentinel sites across the country. It uses longitudinal data on millions of patients receiving routine vaccinations at a diverse network of sentinel sites to provide near real-time vaccine safety surveillance information. Data are prospectively collected, linked using a standardised protocol for analysis, and are updated weekly. They contain vaccination information, hospitalisations, clinic and emergency department visits, health plan enrolment as well as vaccinee demographic characteristics.[41,42] Public health authorities use these data to detect predefined AEFI signals in near real time,[40] make policy decisions and provide assurance to the public.[43] The Canadian Immunization Monitoring Program, ACTive (IMPACT) commenced in 1993 and is set up at 12 tertiary paediatric hospitals across Canada. Nurses are employed to search for possible AEFI and forward reports to local public health authorities for follow up and assessment.[39,44]

3.6 Public health importance of AEFI surveillance

Some reactions are expected as part of the reactogenicity profile of vaccines and can be relatively minor in severity. Such minor reactions following vaccination include local reactions (pain or tenderness at the injection site), low-grade fever and fatigue.[45] **Figure 2** shows AEFI reported across different age groups from passive surveillance Australia-wide between 2000 and 2008. Injection site reactions and fever are the highest of all those reported.[46]

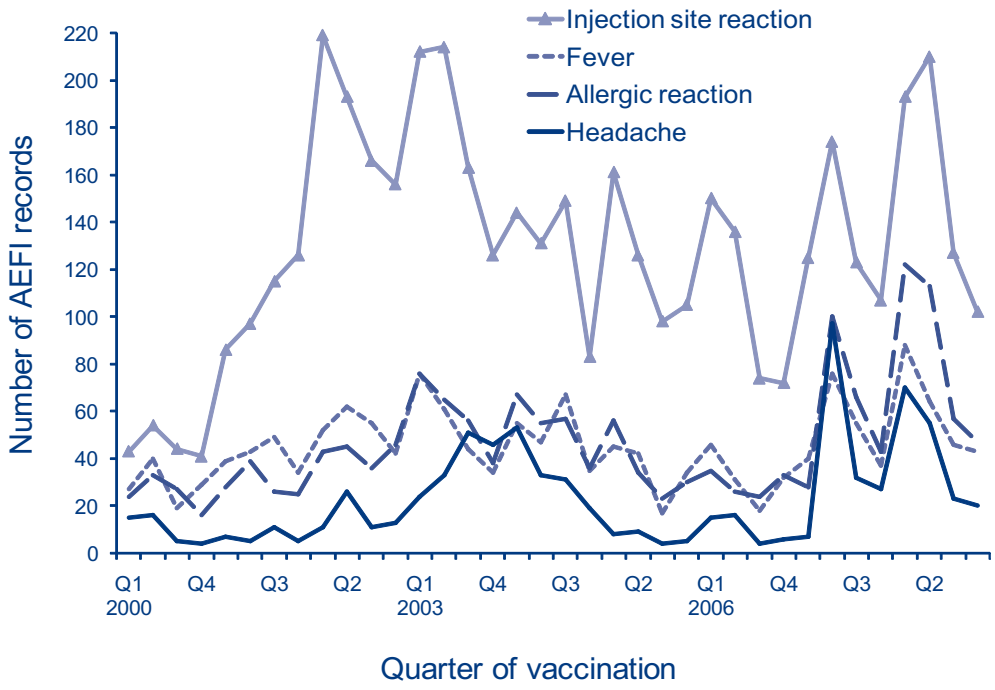


Figure 2. Frequency of adverse events following immunisation from the Australian adverse drug reaction database between 2000 and 2008. Figure reproduced by permission from the author[46]

Serious but rare AEFI can also occur. Some examples of these are listed in **Table 2** with their global incidence and vaccine associations.

3.7 Vaccine Hesitancy

As a result of the success of vaccination programs and elimination or near-elimination of vaccine preventable diseases (VPD), some diseases are no longer seen as a threat by the public. The new threat in the vaccine safety arena is vaccine hesitancy. Some people are now more concerned about the potential adverse effects of vaccines than the diseases they are meant to prevent.[19] Some parents are swayed by controversial and well-publicised concerns that have resulted in recent declines in vaccine uptake in many Western countries.[47,48] However, routine and ongoing surveillance of AEFI can help give assurance to the public about the safety of vaccines. This is accomplished by making safety information publically available and by countering anti-vaccination messages that are in the public domain with well-collected, rigorous vaccine safety data. Active surveillance of AEFI may also provide reassurance to the public that these vaccinations are being monitored for safety.

Table 2. Potential adverse events following immunisation that are uncommon or rare and their incidence globally

AEFI	Incidence	Vaccine association
Febrile convulsions	450 in 1,000,000 doses	MMR, MMRV, co-administration of 13vPCV with TIV[49]
Brachial neuritis	50-100 in 1,000,000 doses in adults	Tetanus toxoid-containing vaccines[31]
Intussusception	60 in 1,000,000 doses	Rotavirus vaccine[50]
Anaphylaxis	2.6 in 1,000,000 doses 1 in 1,100,000 doses	4vHPV,[51] Hepatitis B[51,52]
Hypotonic-hyporesponsive episode (HHE)	32 in 1,000,000 doses	DTPa-containing vaccine given to children aged <1 year[53]
Guillain-Barré syndrome (GBS)	<1 in 1,000,000 doses	TIV[54]

Abbreviations: AEFI, adverse events following immunisation; 13vPCV, 13 valent pneumococcal conjugate vaccine; TIV, trivalent influenza vaccine; 4vHPV, 4-valent human papilloma virus; MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; DTPa, diphtheria-tetanus-acellular pertussis

3.8 Rationale for the evaluation

SmartVax has the potential to address some of the limitations of passive surveillance. SmartVax allows more timely reporting of possible reactions, increased reporting across all levels of severity, increased reporting from adults and, for comparison, results compared with vaccinees who did not have a reaction. Active monitoring by SmartVax may also help provide information that addresses vaccine hesitancy.

At October 2016, SmartVax had been rolled out to over 105 immunisation providers comprised of general practices, travel vaccination clinics, public, council and hospital immunisation clinics (hereafter referred to as providers) in all states and territories. AEFI reporting to AusVaxSafety by SmartVax had also expanded from childhood influenza vaccination to year-round surveillance of all pertussis-containing booster doses for children aged <7 years (detailed in section 4.9). With this in mind, I conducted this evaluation of the SmartVax tool to help identify any gaps that would limit the strength, practicality and usefulness of the tool for further expansion and greater influence on vaccine safety surveillance in Australia. I accomplished this by record review using SmartVax data and interviewing representatives from 13 providers. These providers were from a convenience sample. The SmartVax administrator emailed users to ask if any would be willing to participate in a short survey about the tool. The details of those who replied were forwarded to me and I subsequently contacted

them to set up a time to do the interview by phone, two provider representatives preferred to do it on paper and email me the results. I also talked to two users of SmartVax data to ascertain the quality of the data.

4.0 Describe the system

4.1 Purpose

The purpose of SmartVax is to detect an increase in post-immunisation reactions (a 'signal'), using the medical attendance flag (described in section 4.3.3). Secondary aims agree to determine the proportion of reactions by vaccine, age and vaccination time point and evaluate changes to the childhood vaccination schedule as these are implemented. This is accomplished by collecting safety information directly from vaccinees in near real time. However, neither the purpose nor system objectives are currently documented.

Safety data collected by SmartVax are also a potential source of safety information that can be used in strategies to improve vaccine uptake, establish safety profiles and answer research questions about vaccinations in Australia. Safety profiles that are collected and updated by Australian providers can then be used by public health authorities to compare with AEFI published rates internationally. While the secondary purposes of the system are useful, they are not the focus of this evaluation.

4.2 Stakeholders

SmartVax aims to serve a number of stakeholders who consist of data users, data custodians and software managers. Data users use SmartVax data to do analyses aimed at 1) detecting a possible vaccine-related signal, 2) establishing rates either in the context of public health surveillance or possibly for research purposes. Data providers (immunisation providers) collect data through routine vaccination from which SmartVax extracts and aggregates. Software managers are those who own the SmartVax software licence (**Figure 3**).

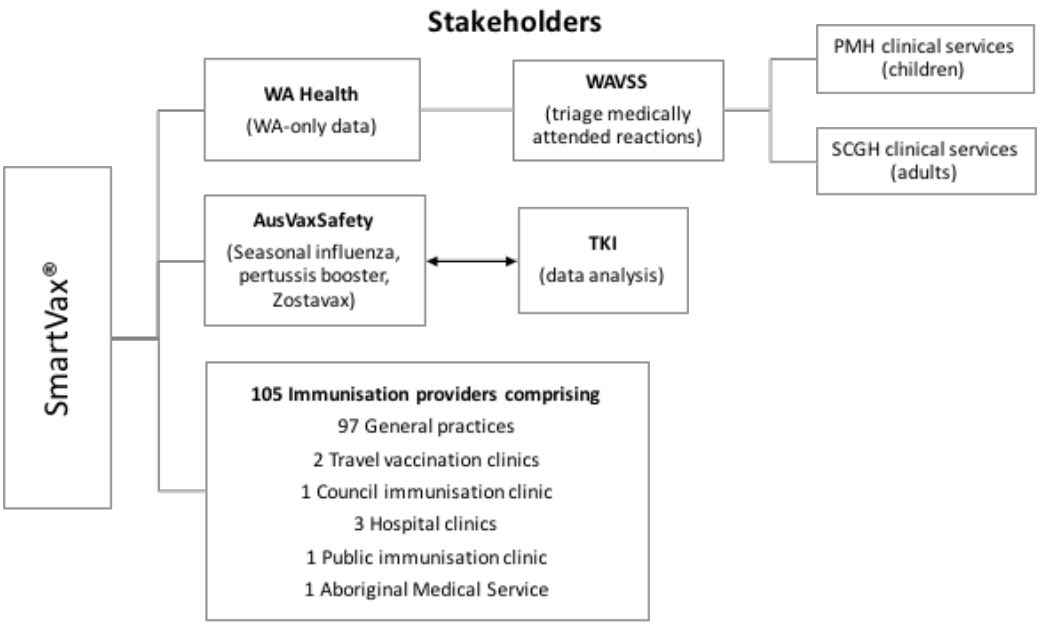


Figure 3. SmartVax stakeholders

AusVaxSafety is an enhanced surveillance system run by the National Centre for Immunisation Research & Surveillance (NCIRS) and is described in detail in section 4.9.1.

SmartVax is supported financially by WA Health, AusVaxSafety and the Illawarra Medical Centre.

4.3 Operation

4.3.1 SmartVax description

Vaccination information is extracted from immunisation provider's commercially available software and SMSs are sent to vaccinees. Responses are written back into the SmartVax tool. The system is compatible with the Best Practice, Medical Director, MedTech32, WINVaccs, and ImPS. Best Practice and Medical Director are used by the vast majority of GPs in Australia. WINVaccs and ImPS are programs used specifically by immunisation providers other than general practices. Since this evaluation began, two additional practice software packages were added: Zedmed and Practix.

It is standard practice by GPs in Australia for vaccination information to be entered by the health professional in the medical record of the patient. Each weekday, SmartVax extracts recent vaccination records and sends the first SMS three days later (and up to five days as SmartVax only runs on weekdays). The first SMS asks vaccinees or parents of minor vaccinees (hereafter referred to synonymously as vaccinees) whether they experienced a reaction following their immunisation. They are prompted to reply with 'Y' or 'N' only. If vaccinees respond 'N' to the first SMS they receive no further messages for that vaccination visit. Affirmative replies receive two follow-up SMSs. One asks whether the reaction was medically attended (SMS2) and the other (SMS3) links to a short survey that can be completed on a smartphone (**Figure 4**). SMS3 is sent to all vaccinees who respond affirmatively to SMS1, regardless of whether they respond to SMS2. SmartVax runs automatically – extracting immunisation data from the clinical software, initiating text messages to vaccinees and transferring de-identified, aggregated weekly data.

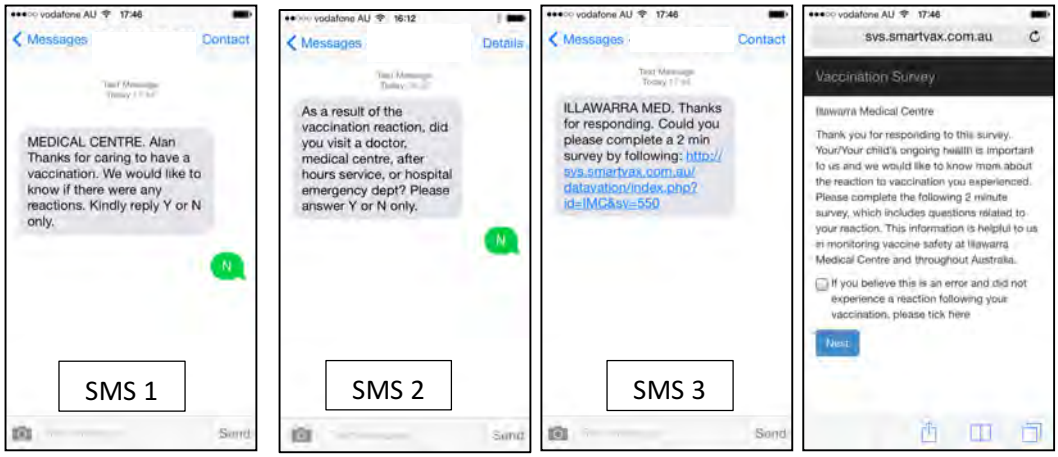


Figure 4. Screenshots detailing the three short message service (SMS) messages and introduction to the vaccination survey as seen by vaccinees after receiving a vaccination at a participating immunisation provider using the SmartVax vaccine safety monitoring tool
Images are the property of SmartVax® (www.smartvax.com.au/about-smartvax.html)

During early stages of SmartVax operation, the developers became aware that some vaccinees who were users of the mobile phone carrier Vodafone were not receiving SMSs. This prompted a move to a different bulk SMS company and the result was improved receipt of messages for vaccinees using all mobile carriers in Australia.

From time to time there are non-standard responses, for example, "just a fever, not much. Thank you very much for asking," "sorry, I meant NO not yes," or "wrong number." This can be updated manually in the tool. Many of the vaccination administrators I spoke with said that they go into the tool and modify those errors when they get their daily report. Other non-standard replies can be dealt with at the data analysis stage.

4.3.2 Central database

Early on in my involvement with SmartVax, it was identified that some of the processes for transferring data were not sustainable. At that time, the system administrator would manually forward emails with de-identified data spreadsheets from providers to WA Health each week. In discussion with others, I identified this as a limitation that was not sustainable as the system grew. During the course of this evaluation a better solution was discussed and actioned. It involved removing the email component and setting up the system to communicate directly with a database stored on a server. This change added flexibility and stability to the data extraction process. From early in 2016, aggregated

data were written directly to the central database that was housed at a secure data management company in Perth. This further automated the data transfer process.

4.3.3 Medical attendance flag

When a vaccinee indicates by responding 'Y' to SMS2, that they attended a general practice, after-hours service or emergency department following their vaccination, it is flagged in the system. This medically attended reaction is used as a proxy for a possible severe AEFI and the medical attendance flag is a prompt for further investigation, despite the fact that the reaction may not be associated with the vaccine. The medical attendance flag may provide better sensitivity for a possible severe AEFI than any individual symptom or combination of symptoms. With consent from the vaccination providers, medically attended reactions for vaccinations that occurred in WA, are automatically sent daily to WA Health for follow up. These data are fully identifiable and include all survey data that was completed. They are medically assessed as possible vaccine-related reactions and sent to the WAVSS nurse for follow-up as required. This process has been implemented during the course of this evaluation and greatly improves consistent follow-up across all WA SmartVax sites. Reactions that are determined to be associated with vaccination are entered into WAVSS and reported to the TGA. A record of medically attended AEFI are also sent to the relevant provider's inbox in the clinical software for follow-up.[55] There is still room for improvement, as some vaccine administrators who were interviewed revealed that they did not follow-up patients. Instead they used SmartVax to provide vaccination data from their patients for [WA Health] to monitor. This represented a minority of the small number of providers interviewed. This is a discrepancy between use of the tool by providers to complete the loop for public health surveillance versus use of the tool to provide best patient care to their individual patients.

4.3.4 Survey

The third and final SMS is a 2 minute survey which can either be completed on a smartphone or the link can be copied into an internet browser for completion. This is illustrated in **Figure 4**. Once the vaccinee chooses 'next', a screen with a list of symptoms is presented for the vaccinee to select, as appropriate (**Figure 5**).

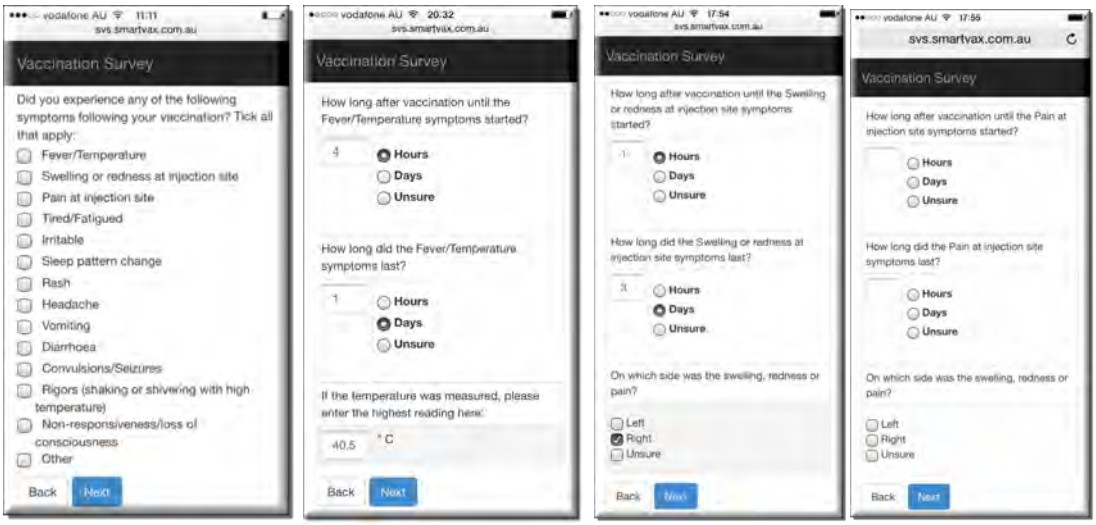


Figure 5. Screenshot with a choice of symptoms, followed by screens requesting details relating to time and duration

The number of screens presented to the vaccinee depends on the number of symptoms they have selected. For each symptom, the patient is asked about the time of onset in respect to the vaccination and duration of the possible reaction.

- For fever, the patient is also asked about the highest recorded temperature.
- For swelling, the patient is asked about which side the reaction was on.

Vaccinees who do not have a smartphone can still reply to the first and second SMS. However, for completion of the survey they need to copy the link into a web browser as it is not compatible on devices that are not smartphones. While the feature works, it is unknown whether any vaccinees fill in the survey using the web-based method.

4.3.5 Data flow

Each Monday, de-identified data from SmartVax are aggregated and automatically transferred from each practice to the central database. This process has been streamlined since I started the MAE program, as at that time the data were sent weekly by email. The data flow as it developed in the context of this evaluation is illustrated in **Figure 6** and has been updated to reflect the change to storing data on a central database (section 4.3.2). Medically attended reports are sent within 24 hours giving vaccinees time to fill in the survey. All available information is included if completed. These emails contain patient identifying details to aid in follow-up if required. Reports with local data at each provider, can be generated at any time from the main interface of SmartVax installed at the provider (**Figure 7**). These reports contain information about the AEFI of the patient and can be presented in the form of tables or charts. Providers can also modify information, *e.g.* correct mobile phone numbers, in the SmartVax tool interface.

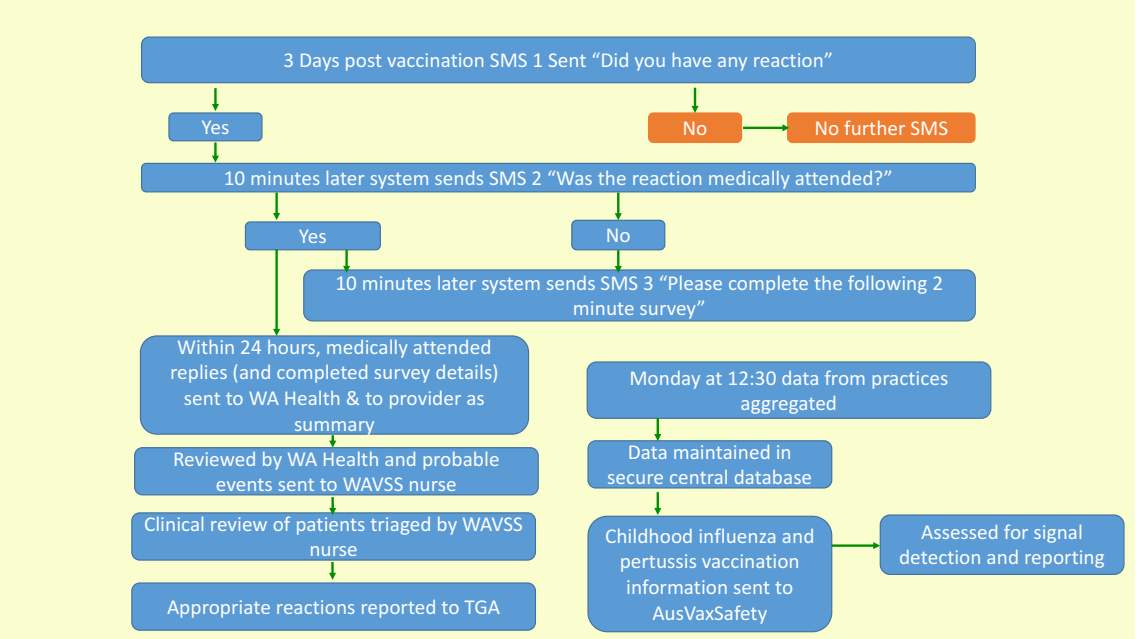


Figure 6. Flow of SmartVax Data

4.4 Security and confidentiality

All de-identified vaccination data from SmartVax are aggregated at the practice and securely stored on the central server within a secure, password-protected environment. Access to this server is only by authorised personnel. In 2015 this included me, the MAE scholar.

4.5 Variables and Data

A unique patient number remains as a variable which facilitates the cleaning and analysis of the data.

Other variables include the following:

Demographic information: sex, age at vaccination (in months), Aboriginal status, postcode

Vaccination information: date of vaccination, type (scheduled, travel, other), name and brand of vaccine, batch number, other vaccines given concomitantly

SMS information: SMS sent date and time, SMS reply received data and time, Response to SMS (free text), reaction (yes/no), medically attended (yes/no)

Reaction information: Full list of symptoms with time and duration, medical attendance flag

While this list is not exhaustive, it is an example of the types of variables present in the data.

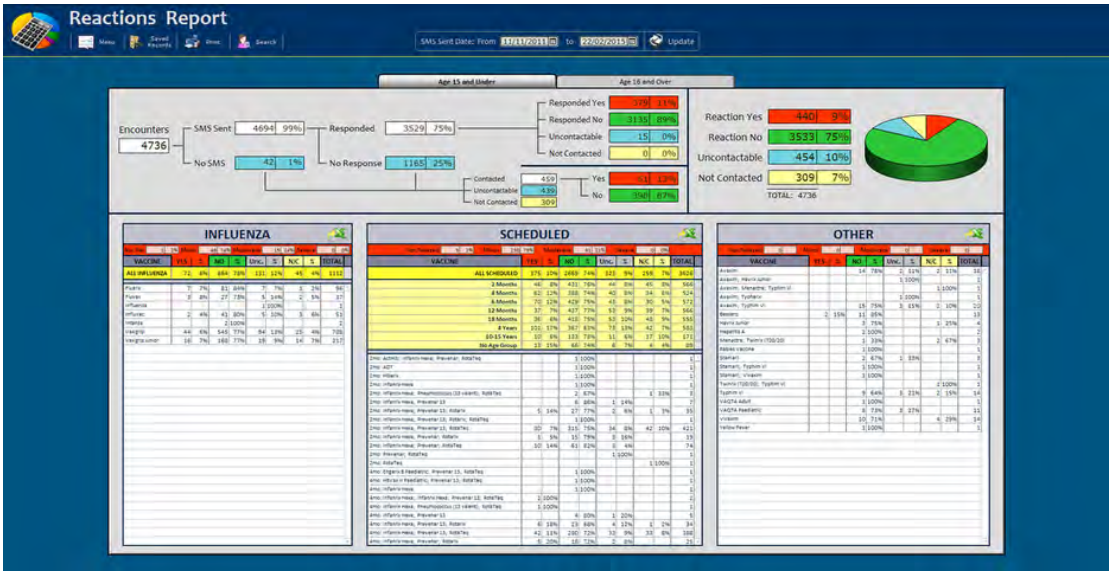


Figure 7. Screenshot of the SmartVax report

4.6 Data cleaning and analysis

4.6.1 The challenges of data cleaning

When I began, several individual emails were sent to WA Health every week (increasing in number as participating providers increased), each with an attached excel spreadsheet. I combined the data from each spreadsheet for the week into a single spreadsheet. When a modification was made to the tool whereby additional variables were extracted, modifications had to be made to the 'master' spreadsheet. For example, when the pregnancy-related variables were collected, extra columns needed to be added to the older spreadsheets that did not have those variables to ensure that the columns were aligned and the overall data were not compromised.

During the data cleaning process, duplicate records were removed, missing data were addressed by using special statistical coding techniques so that missing values could be counted but were not included in the analysis.

4.6.2 Data analysis

I wrote Stata code called syntax to assist in cleaning the data. I saved it in a special file to use on future datasets, for convenience. This file could also be modified as required. Certain variables in the dataset appeared as free text fields, known as "string" variables. Those fields were not useful in the analysis process as "strings" are needed to be converted into numeric variables.

For example, the variable 'scheduled vaccination details', had the names of all the vaccines given at the vaccination visit. If, for example, those were Infanrix Hexa, Pneumococcal conjugate (13vPCV) and Rotateq, special syntax could be used to extract each of those from the list to a new, binary (0,1) variable as in the example in **Table 3**.

The variables infhex, pcv13, rotateq, mmr, mmrv are new variables generated from the Scheduled vaccination details field.

Table 3. Example of how variables are created using SmartVax data

Id	Scheduled vaccination details	infhex	pcv13	rotateq	mmr	mmrv
101	Infanrix Hexa; Pneumococcal conjugate (13vPCV); Rotateq	1	1	1	0	0
102	Infanrix Hexa; MMR, Rotateq	1	0	1	1	0
103	MMRV	0	0	0	0	1

4.7 System administrator

SmartVax was co-developed by Ian Peters, a software developer and owner of DataVation. Ian has extensive experience in development and management of extraction and aggregation tools used in healthcare. At the start of this evaluation, Ian was the sole administrator of the software system. He managed the rollout to practices, program modifications and upgrades. He also provided technical support as needed and held the historical and technical knowledge of the SmartVax platform. Since then others have been trained to support Ian and help provide administrative support and technical assistance.

4.8 Signal detection

At the start of this evaluation there were no procedures in place defining who was responsible for monitoring the medical attendance flagged data on a daily basis or other data arriving weekly. Although retrospective analysis could occur for establishing rates and reactogenicity, this was not sufficient for signal detection. Suspected AEFI reports were reviewed by WA Health but there was no standardised protocol for the process of data review or follow up. This has since changed. Medically attended events are now monitored daily and applicable AEFI are sent to WAVSS for follow-up.

4.9 Collaboration with AusVaxSafety

4.9.1 Background

AusVaxSafety is a surveillance collaborative led by the National Centre for Immunisation, Research and Surveillance (NCIRS), funded by the Australian Government, Department of Health. Vaccine safety experts, state and territory public health officers, general practitioners and representatives from children's hospitals across Australia make up a national project group that provide advice and feedback. AusVaxSafety uses data from three collaborating systems to monitor for adverse events

following influenza vaccination, during the influenza season, in children from six months to <5 years.[56] The system was expanded in 2016 to include monitoring of potential AEFI in children receiving a fifth pertussis-containing vaccine dose at 18 months of age, a change to the childhood immunisation schedule. In addition to SmartVax, the other data contributors include Vaxtracker[57] and Stimulated Telephone Assisted Rapid Safety Surveillance (STARSS).[58]

Vaxtracker is a web-based surveillance system based at the Hunter New England Area Health Service in New South Wales that follows up vaccinees receiving influenza vaccination at providers in New South Wales (NSW), Victoria (VIC), and the Northern Territory (NT). The system allows vaccinees or parents of paediatric influenza patients to complete a web-based survey.[57] STARSS is an ongoing NHMRC-funded system. It is a randomised controlled interventional study examining different reporting options including web, SMS, and computer assisted telephone interview for all vaccines and AEFI. Some data are shared with AusVaxSafety. STARSS is managed by researchers at the University of Adelaide and began in September 2015 and the trial is scheduled to be completed in 2017.[58]

4.9.2 WA AusVaxSafety SmartVax data and reporting

During the 2015 influenza season, I sent SmartVax AEFI data on a weekly basis to the NCIRS where national influenza AEFI surveillance was collated. The data included basic demographic characteristics of vaccinees, date of vaccination, whether vaccinees replied to the SMS, whether they indicated that they had a reaction, and details of the type of reaction. If the vaccinee indicated that they had sought medical attention after the vaccination, details of patient follow up were also included. Analysis of data for signal detection used fast initial response cumulative sum (FIR CUSUM) and Bayesian statistical methods,[59,60] and were completed by statisticians at the Telethon Kids Institute. The FIR CUSUM is a statistical method used to rapidly detect small changes to the mean where no baseline exists. Bayesian methods use prior probabilities as the baseline then incorporate new information as it accumulates to estimate the probability of a signal and is updated with each addition of new data.

The results were updated weekly and available on the NCIRS website for anyone to access.[61] A weekly report was sent to the national project group and state and territory health departments. An end of

season final report was delivered to the Australian Government Department of Health and a summary was also published in a peer-reviewed article (**Appendix 1**).[56]

5.0 SmartVax system attributes

This section focuses on the analysis of the attributes of SmartVax as a public health surveillance system; each attribute is addressed in the sections that follow.

5.1 Simplicity

The simplicity of the system should be demonstrated by its structural simplicity and ease of operation.[3]

SmartVax software is straightforward and operates 'behind the scenes' with little interaction required by the immunisation provider. Once the software tool is set up, it runs automatically. Each weekday, it extracts vaccination information and sends SMSs at pre-programmed times, usually at 12:30 PM on the third day post vaccination administration or up to five days if it falls over a weekend; the tool only runs on weekdays. In addition to a valid mobile phone number recorded in the mobile phone field, only routine entry of vaccination-related data in the patient's medical record in the provider software is required for SmartVax to extract this information and send the SMS. This includes brand, batch, expiration date of vaccine, location of administration (*e.g.* Right Arm, Left Thigh, etc), and type of vaccine (scheduled NIP vaccine, travel vaccinations, seasonal influenza, etc). It is a simple add-on program to data that the practice is already entering routinely. Vaccine administrators indicated that SmartVax was easy to have at their practice/clinic and that the workload required was manageable, often citing that it "runs on its own."

SmartVax is simple for vaccinees to use, demonstrated by their response rates and comments that they make to their providers.

Using the data extracted by SmartVax to establish a possible vaccine safety signal was not as straightforward early on as it is today. There have been a number of improvements and modifications that have been made during the course of this evaluation. Improved reporting has also occurred such that medically attended events are now reviewed daily by WA Health.

5.2 Flexibility

A flexible system is one that can be easily adapted as needs and operating conditions change.[3] SmartVax is flexible. This was demonstrated during the course of this evaluation through several modifications that were made to accurately collect the new data. For example, there were some changes to the vaccination program in WA which meant changes to the SmartVax software to enable collection of the new data. These changes were related to pertussis vaccination in pregnancy and childhood pertussis vaccinations.

From April 2015, WA Health began funding pertussis vaccination for women in their third trimester of pregnancy (between 28-32 weeks gestation). This timing was ideal for maximum antibody transfer to the foetus to provide protection of the newborn child until they become old enough to be vaccinated themselves.[62-64] To assess possible AEFI associated with the pregnancy dose, two further variables were added to the SmartVax extraction tool by the administrator; whether the patient was pregnant (yes/no) and number of weeks' gestation (numeric).

The second change occurred at the end of 2015. SmartVax began providing vaccine safety surveillance data to the NCIRS on the fifth pertussis-containing vaccine dose that was added to the childhood immunisation schedule for vaccine safety surveillance. In preparation for contributing data, a new survey question had to be added that accurately measured the outcome, extensive limb swelling (ELS), in the context of the booster.

Related to simplicity, flexibility is also demonstrated by the ease with which SmartVax can be rolled out to new providers using different practice management software. In 2014 the few providers that were enrolled used Best Practice software. As of 3 November 2016, the SmartVax software was being used by 105 providers nationally; 39 (37.1%), are located in WA. The tool has been modified to incorporate multiple additional provider management software packages.

Many vaccines today are polyvalent (containing multiple strains or serotypes *e.g.* pneumococcal conjugate vaccine) or combination vaccines (contain multiple antigens in a single injection *e.g.* measles-mumps-rubella vaccine). Currently it is not possible to determine which strain or antigen was

responsible for the possible AEFI when combinations are given and when the reaction is systemic. If it is a local reaction, the software has been recently updated to collect information on the site of administration of each vaccine, making it possible to determine which vaccine or combination may have been responsible.

5.2.1 Flexibility of system upgrades

Modifications are made by the system administrator as needed. The time it takes to make a modification depends on its complexity but can take from a few hours to a few days to complete. After that, a new version of the SmartVax software can be downloaded by the provider. The new version has a new number, similar to when other types of software are upgraded. This number (*e.g.* 1.1.A5) is also included as a variable in the data which makes it easy to identify which software version each provider is using.

The software upgrade is initiated by the system administrator. An upgrade message appears on the provider's interface requesting that the software be upgraded to the newest version. Users manually select to upgrade, download the upgrade, follow the screen prompts, and install. Once installed the system must be restarted and data from previous versions are automatically imported into the new version. This only takes a few minutes to complete. Sites that do not complete the upgrade are contacted by the system administrator to initiate the upgrade. It is possible that some sites will be using an old version of the software and key information in the extraction could be missing. These providers are easily identified with the version number variable. While straightforward, some providers do not open the tool which means they would not see the message. These providers can be followed up by telephone to upgrade the tool, as needed.

5.3 Data Quality

Data quality is a composite measure of completeness and validity of the data recorded by the system.[3]

Using record review, data quality was evaluated by examining the completeness of the data, specifically the number of SMSs sent, number of replies received and missing data from all WA data collected during the 2015 calendar year from the SmartVax tool. The proportion of vaccinees who indicated

that they had a reaction, the proportion that replied to the follow-up messages and whether they completed the survey was recorded.

As highlighted in the previous flexibility section, early in the analysis of SmartVax data, it became evident that some important information about local reactions was missing. Details reported by vaccinees about potential swelling or rash were recorded as was information about where it occurred (*e.g.* which arm and for what duration), however there were no data about which vaccine was administered to which site (R Arm, L thigh, etc). This was relevant as vaccines are often given concomitantly and this made it easier to establish the possible connection with a vaccine.

5.3.1 Completeness

The results of the completeness analysis showed that in the 2015 calendar year 53,583 initial SMSs were sent for 56,703 (94.4%) vaccination encounters, indicating that a valid mobile phone number was recorded in the mobile phone field for 94.4% of encounters. There were 40,746 (76.0%) replies received. Of those who replied 'yes' to the first SMS, 3,909 (88.9%) replied to the second SMS and 2,405 (54.7%) went on to fill in the survey details. Each SMS represents a vaccination visit and overall totals include potential multiple visits by the same patient (**Figure 8**).

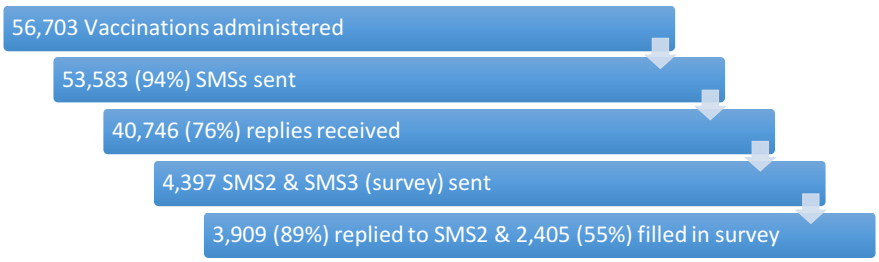


Figure 8. Results of SmartVax completeness analysis, WA 2015

At the pilot general practice using SmartVax between November 2011 and June 2015, 1,667 vaccinees aged five years or under had a total of 3,922 vaccination visits. Post-visit SMSs were sent to 3,906 (99.6%) of these vaccinees and 2,897 (74.2%) SMS replies were received.[55] Key data variables from all SmartVax providers in 2015 were checked for missing values and the results are in **Table 4**. Most variables were complete or near complete with the exception of Aboriginal status. Unfortunately,

Aboriginal status is often underreported in health data.[65] The mobile phone field was incorrect in 5.6% of records. Human entry errors like this were also a frustration raised during interviews with vaccine administrators. It was reassuring that the key vaccination-related variables were close to 100% complete.

Table 4. Completeness of selected SmartVax data variables from all Western Australian providers contributing data in 2015

	Completeness %	Missing data n (%)
Patient ID	100%	0
Provider name	100%	0
Aboriginal Status	67.6%	18,362 (32.4)
Gender	99.7%	190 (0.34)
Vaccination Date	100%	0
Vaccination type	99.9%	79 (0.14)
Batch No	99.9%	79 (0.14)
Age	100%	2
Postcode	99.6%	213 (0.38)
Valid mobile phone no.	94.4%	3,165 (5.6)

During an interview with someone who uses SmartVax data, I confirmed that it can take a lot of time to clean the data in preparation for analysis. For a new AEFI surveillance program it can take a week of full-time work preparing a 'do file' of Stata syntax. After this 'do file' is set up, however, updated data can be added and analysed without the need to rewrite the syntax. After this initial step the process is greatly improved and can be done quickly. While it takes time to do this for SmartVax data, it is not dissimilar to other public health datasets.

5.3.2 Validity

Assessing the validity of the data was difficult given that it is self-reported. Despite this, all medically attended reactions are assessed and possible reactions are triaged by the WAVSS nurse and those requiring medical review are referred as a check on validity of the response. To accurately test the validity of the reported data beyond this, further investigation would be required. For example, conducting interviews with clinicians as a final step to ascertain whether the event was vaccine-related or by applying the Brighton criteria.

5.4 Sensitivity

Sensitivity refers to the proportion of all cases that the system detects as well as the system's ability to detect epidemics.[3]

Sensitivity can also be viewed as the ability of the system to monitor changes in the number of reported events over time. The sensitivity of data from SmartVax is influenced by whether a suspected reaction is related to the vaccine and whether the vaccinee who experienced the reaction replies. If there was increased reporting the sensitivity must be high to detect a signal. SmartVax is a quick response tool and intentionally collects all reaction information from all vaccinees, therefore sensitivity of data is high. With SmartVax data, proportions of symptoms can be examined and compared with those reported elsewhere. However, sensitivity at the population level may not be as high as SmartVax only captures data from providers that use the tool. For example, if distribution of a new or bad batch of vaccine that caused reactions occurred in an area where no SmartVax sites existed, the tool could not capture those data and would limit the tool from detecting the signal.

5.5 Acceptability

Acceptability is demonstrated through willingness to participate in the system.[3]

Response rates can be used as a proxy for vaccinees acceptability of the system in addition to feedback given to their provider. Approximately 76% of vaccinees replied to the first SMS (was there a reaction?). Of those with a reaction, 89% replied to the second message (was it medically attended?) and 55% of vaccinees with a reaction went on to fill in the survey. Providers have reported that vaccinees do not object to being followed up by their provider and appreciate the service. During my interviews, responses to the question, "have patients given any feedback on being followed up by SmartVax?" included:

> "it's great to see surgeries keeping up with technology to make it easier for us"
>
> "it's (SmartVax) really good and why wouldn't others want a service like this"

or general comments thanking the provider for the follow up and for caring. The only complaints from providers were not related to the tool but to human error, *e.g.* recording of the incorrect mobile

number. Conversely, at one large immunisation clinic, the manager said that some patients were suspicious on receiving the SMS and called to ask if anything was wrong with the vaccine. This manager said that more training of nurse immunisers would be required, explaining further that they might not be explaining the SmartVax follow-up process with patients. The manager said that there were some new staff members. This same provider provides school immunisations and their staff advise students that their parent/guardian should expect a SMS to ask if they had any reactions, but admitted that students' often do not advise their parents. Our interview prompted the manager to add "SMS follow-up" to the consent form for the next school year.

Of all (n=13) providers that I talked to, 10 responded to the comment, "All staff who vaccinate know about SmartVax and are happy to participate," with "strongly agree or agree." One thought that staff were "vaguely aware" and the other that there were some new staff in the clinic and would not know about SmartVax yet.

Although it is not known whether any WA providers would have declined enrolment because not all were approached, those that were invited all started using the tool. None have stopped using it after enrolling. Most see it as an automatic technology that "runs in the background" while providing a valuable service to their clients.

It is clear that while some providers are actively involved with the tool and following-up patients who report a reaction, others see themselves as contributing to the broader monitoring of vaccine safety (*e.g.* "the Department of Health") and that if there was a signal, they would be notified.

5.6 Representativeness

Representativeness refers to how well the system accurately describes an event over time as well as how those events are distributed in the population by person and place.[3]

The advantage of SmartVax is that it solicits responses from all vaccinees with a valid mobile phone number and therefore the results include all types of AEFI, whether serious or not. SmartVax only excludes those who do not have a valid mobile phone number or who have opted out of SMS communication with their provider. In discussing this with providers, there had been very few patients

who had opted out. One Practice Manager said that the only patients at the general practice who opted out did so because of their frequent attendance at the practice, advising that if they had a reaction they would, "tell you at my next visit." The result is that SmartVax data have details about location and demographics of the vaccinees reporting a reaction as well as details for those who do not report, enabling comparison.

The results comparing those who responded to the SMS and those who did not are in **Table 5**. Age and sex were very similar between those who replied and those who did not. Aboriginal and/or Torres Strait Islander patients were less likely to reply than non-Aboriginal vaccinees, however this variable was not always recorded. Their representation in SmartVax data is well below that of the state population proportion of 4%.

While this evaluation was intended to only examine providers in WA, the nationwide coverage of SmartVax sites does add to its overall representativeness. At the time of writing, the total number of sites by state was 42 sites in WA, 36 in QLD, 12 in NSW, 5 in VIC, 3 in TAS, 5 in SA, 1 in ACT and 1 in NT.

Table 5. Demographic comparison of vaccinees who replied to SmartVax SMS at all Western Australian providers and those who did not reply

	Number of vaccinations recorded (n=56,893) SMSs sent (n=53,720)	Participants who replied to SMS (n=40,213)	Those who did not reply, un-contactable (n=14,854)
Age, years			
mean (range)	22.5 (0-99)	22.5 (0-99)	21.72 (0-98)
median [IQR]	13 [1.1-38]	13 [1-38]	14 [1.5-32]
mode (years)	13	13	13
Sex			
Female, n (%)	29,921 (52.59)	20,736 (53.55)	7,444 (50.27)
Male, n (%)	26,777 (47.07)	17,986 (46.45)	7,365 (49.73)
Aboriginal status			
Missing Aboriginal	1,002 (1.77)	436 (1.12)	541 (3.64)
data, n (%)	18,427 (32.39)	13,259 (34.12)	4,417 (29.73)

Abbreviations: IQR, interquartile range

All messages from SmartVax are in English which may not access some culturally and linguistically diverse communities (CALD) in WA. At the 2011 census, 15% of the Western Australian population spoke a language other than English at home, a 3% increase from the 2006 census, many of these people reported speaking English 'not well' or 'not at all'.[66] A total of 98,201 more people speaking a language other than English at home was reported between 2006 and 2011. The language with the greatest change was Mandarin Chinese, 11,511/98,201 additional people (12%).[67] This could be a limitation of the tool if vaccinees in CALD groups are somehow different to vaccinees in other groups.

5.6.1 AEFI over time

AEFI trends over time are assessed for vaccinations under surveillance by AusVaxSafety. This is done weekly using statistical methods that are described in section 4.9.2. WA Health is also able to assess trends over time using different variables. This is not done routinely as the purpose for WA Health is to detect a safety signal. Monitoring of changes in reaction reporting over time can be completed, as in the example in **Figure 9**. This was calculated using all "Y" replies and could also be done by symptom, age or vaccine. This was a snapshot of only one year of data using cumulative sum. I assessed trends retrospectively for the pilot general practice and the results over three years of paediatric vaccinations are presented in the publication in section 1.0.

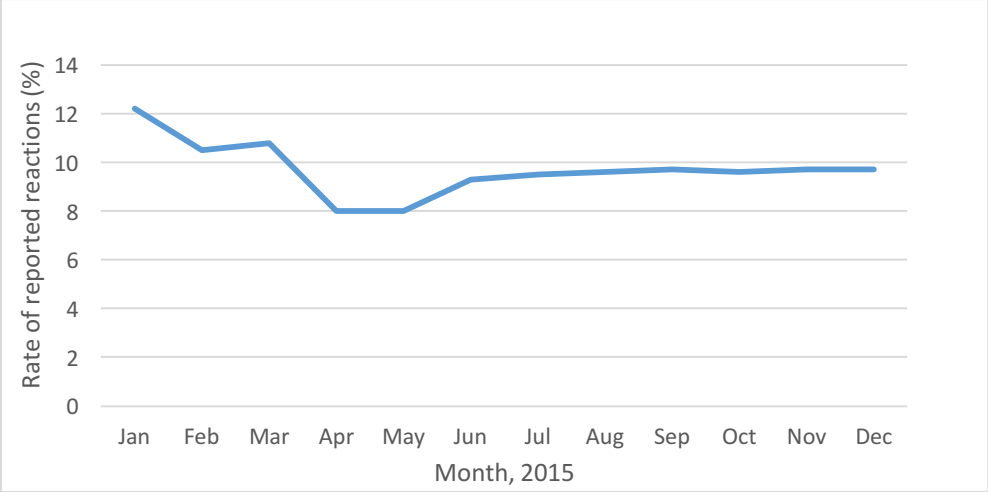


Figure 9. Rate of reported reactions by month using the cumulative sum, all ages and all vaccinations at all Western Australia SmartVax providers

5.6.2 AEFI by place

When considering representativeness in terms of place, in WA the majority of providers are located in the metropolitan area, but not all. Some providers are located in regional general practice surgeries but none in remote parts of the state. SmartVax sites in other states incorporate regional and remote areas. It would improve the representativeness of the results if SmartVax could also collect data in remote parts of WA and particularly locations that service Aboriginal Western Australians. Establishing SmartVax in Aboriginal Community Controlled Health Services or in Community Health Services serving remote communities would help to collect data from Aboriginal vaccinees.

5.7 Timeliness

Timeliness reflects the speed between steps in the system.[3]

Using record review of all WA SmartVax data received, the system was assessed for timeliness of response to SMS1 and SMS2. The time that it took to respond to an SMS asking if there was a reaction was also reported.

5.7.1 Timeliness of response to the first and second SMSs

Of the 53,720 vaccinees that were sent a SMS in WA during the 2015 evaluation period, 38,865 (72.4%) replied to the first SMS. Of those who replied, 30,717 (79.0%) did so within the first two hours and 15,241 (39.2%) were within the first 10 minutes.

5.7.2 Timeliness between receipt of aggregated data and possible AEFI signal detection

Medically attended reaction reports are received daily at WA Health and are reviewed by a medical practitioner at WA Health. Medically attended reactions suspected to be vaccine-related are forwarded to the WAVSS nurse for follow-up. This is done each weekday. If there were a signal, the time to detect this would be minimal.

5.8 Usefulness

SmartVax data have been used by providers, AusVaxSafety and the WA Health in vaccine safety surveillance. Providers are able to see in near real-time the responses of vaccinees through their report

function (**Figure 7**), however some providers do not use all of the functionality of the tool and may not use that function.

As described earlier, SmartVax data are used by AusVaxSafety for the surveillance of seasonal influenza and pertussis-containing vaccines in children for reporting to the Australian Government Department of Health. Use of SmartVax data in the context of national vaccine surveillance may provide better opportunities for detecting a signal because they are combined with data from other systems (described in section 4.9). Collecting data from states and territories outside of WA also provides better generalisability of the results for reporting or predicting vaccine safety events.

SmartVax reaction data that were reported from the pilot general practice from 2011-2015 showed an increased odds of a local reaction at the fourth pertussis-containing vaccine time point on the childhood immunisation schedule.[55] This is consistent with reports made to the state's passive system,[68] data from the published literature[69] and when 2015 data from all SmartVax sites are combined. The tool was modified to include specific survey data related to ELS to help further ascertain the type of symptomatology reported.

SmartVax is a useful tool for contributing to AEFI surveillance in Western Australia. It complements the passive system by adding active follow-up with potentially immediate responses (provided that vaccinees continue to reply to SMSs). Providers like it because it helps to provide better care for their patients. Vaccinees like that their vaccination is being followed up by the provider. Some patients have told their provider that it helps give them confidence in the safety of vaccination. All of this helps promote vaccine safety in Australia.

5.9 Resources for operation

There are substantial costs required to operate SmartVax, yet it is not clear exactly how much. The tool has been provided at no charge to interested immunisation providers with the costs of setting it up and sending SMSs absorbed by Dr Alan Leeb. WA Health has provided additional funds to help support the system development and growth since 2012. From 2015 AusVaxSafety provided financial support for the influenza season surveillance activities. At the end of 2015, AusVaxSafety entered into a

contractual agreement with SmartVax with ongoing funds for development and running costs. This agreement was modified for inclusion of Zostavax® surveillance data from November 2016 and expanded influenza and NIP surveillance from 2017. The amount provided to SmartVax is not public information. WA Health provides in-kind support for assessing medically attended reactions, data analysis and WAVSS reporting as part of routine AEFI surveillance.

5.10 Overall governance

Robust governance of the SmartVax tool has not been formally established. While I have been involved, there have been attempts to establish a governance structure around the tool with a group of professionals from different backgrounds and organisations to provide oversight and ensure safe and efficient operation. The tool has arisen in General Practice through the entrepreneurship and vision of a local GP, not an official Health Department program. Governance is needed but determining the best fit for this has been complex. In particular, SmartVax still needs to establish the formal steps to follow if a signal were detected, how to manage serious AEFI, how to escalate suspected signals to the Minister of Health or equivalent body. Fortunately, since the roll out of SmartVax there has not been a similar high level AEFI signal such as was reported in 2010 with FluVax®. However, with new additions to the immunisation schedule (18-month pertussis booster, Zostavax®, quadrivalent influenza vaccine) it is not known when the next signal might arise and governance over the use of the tool is needed to minimise risk. It is the opinion of this reviewer that a signal could be managed in WA with the appropriate investment in leadership and governance from WA Health. However, with SmartVax now collecting data in all states and territories, it seems more appropriate to have governance established at the national level in one of the national bodies.

6.0 Conclusions and recommendations

6.1 Conclusions

SmartVax is a novel tool for the surveillance of AEFI. It has the potential for real-time collection of AEFI information, to detect a possible safety signal if there is one. Its operation is largely automatic and can be modified to suit different provider types (*e.g.* general practice, hospital, government immunisation centre). The tool is flexible in being able to accommodate new variables or vaccines.

Providers find it useful and report that their patients appreciate the follow-up. No patients have reported to providers that the number of messages sent to them by SmartVax was excessive. The only patients that opted out were ones that attended the provider frequently or elderly patients who did not use the technology. The tool is easily modifiable if there are changes to vaccines or variables under surveillance.

SmartVax naturally evolved by persistence from a good idea to a tool that is now used nationally to actively collect AEFI data in real-time, with real-time adaptations as opportunities arise.

While there are some recommendations that could help to improve the overall package, SmartVax goes beyond the capacity of the passive system by using SMS technology to rapidly detect a possible safety signal. During the course of my involvement, there were no alarming safety signals detected, however the tool is well positioned to do this if needed.

Aboriginal Australians, receive some different vaccine products than non-Aboriginal Australians. It is important to have good representation from this group in the data. This is reflected in the recommendations.

Many of the limitations of the passive system are overcome by the ability of SmartVax to actively follow up vaccinees. This fulfils two of the key recommendations in the Stokes Review[10] that followed the events of 2010, that more is needed such as:

> *A web-based mechanism to record the number of vaccinations, including batch number and product name, to provide real-time data, including the denominator over the program duration,* and
>
> *A surveillance system to provide ongoing monitoring of vaccination programs.*

The ability of SmartVax to adapt to changes was demonstrated by the modifications undertaken as the system expanded, *i.e.* to operate with several different management software packages, the addition of national pertussis surveillance, and the continued and sustained growth both within and outside of WA. The change from an email platform to automatic de-identified data storage in a central database

has provided added security of data while reducing the possibility of human error related to merging multiple files.

Finally, the coverage of SmartVax continues to grow as new sites are added and continues to be more useful as new vaccines come under surveillance (Zostavax® will be added on 1 November 2016 with the Shingles program for 70-79 year olds as well as all influenza vaccinations to commence in 2017 and for select NIP vaccines to begin in 2017). With this, the geographical scope and generalisability will be expanded. SmartVax will be well placed for further enhancements to be able to provide national AEFI surveillance for all vaccines.

6.2 Recommendations

- Recommend documenting the objectives of SmartVax. Each user could then be provided with these objectives and future evaluations can then assess appropriate attributes against them.

- Governance should be clearly outlined, documented and implemented. As the system has evolved from the brainchild of an outstanding GP, to a nationally useful active surveillance tool, governance at the national level is essential to outline responsibility, ownership and to manage medicolegal issues if they arise. Governance can provide oversight for SmartVax as it is positioned for continued expansion. Given its national position in vaccine safety surveillance and multitude of stakeholders, strong governance will be critical to its success.

- Provide training to all SmartVax providers. It became evident during this evaluation that not all providers are aware of or know how to use all of the features of the tool which provides the ability to view reports, response rates and reactions reported. While some may choose not to use those features, all should have a standardised training. (relates to usefulness)

- Aboriginal and/or Torres Strait Islander representation in the system is below the state average. Some vaccinations that are recommended for Aboriginal Australians are different from vaccinations recommended to other Australians. Monitoring of these vaccines is important to ongoing vaccine safety among this population. Expansion to sites in areas where Aboriginal and/or Torres Strait Islander residents live is recommended. This should include

expanding the number of Aboriginal Community Controlled Health Services or vaccination clinics in communities with high proportions of Aboriginal and/or Torres Strait Islander residents. (relates to representativeness)

- Data should be used to establish baseline vaccine profiles by type and brand of vaccine using data from all sites.

- A SmartVax report was sent to participating providers once in 2016. Some providers have suggested that the resource was good and that they would like to see it more frequently. Regular reporting, *e.g.* quarterly, to participating providers is recommended. (relates to acceptability)

- A national evaluation of SmartVax should be carried out once the system has completed its expansion.

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Rapid communications

Real-time safety surveillance of seasonal influenza vaccines in children, Australia, 2015

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Increased febrile reactions in Australian children from one influenza vaccine brand in 2010 diminished confidence in influenza immunisation, highlighting the need for improved vaccine safety surveillance. *AusVaxSafety*, a national vaccine safety surveillance system collected adverse events in young children for 2015 influenza vaccine brands in real time through parent/carer reports via SMS/email. Weekly cumulative data on 3,340 children demonstrated low rates of fever (4.4%) and medical attendance (1.1%). Fever was more frequent with concomitant vaccination.

In 2014, a multi-jurisdictional national system, *AusVaxSafety,* was established to undertake enhanced influenza vaccine safety surveillance and report real-time adverse events in children aged six months to four years. This collaborative system was funded by the Australian Government Department of Health. Surveillance (n = 782 children) demonstrated the safety of 2014 seasonal influenza vaccines in a matter of weeks, although most children received one vaccine brand (Vaxigrip, Sanofi Pasteur; 86.2%; n = 674 children) [1,2]. Expansion of the programme in 2015 to incorporate a new data management platform and more participating general practice (GP) sites (GPs provide more than 70% of vaccines given nationally [3]) has enabled reporting of the safety of 2015 southern hemisphere trivalent influenza vaccines for thousands of children receiving multiple manufacturers' vaccines. Here we report the results of our surveillance conducted during the 2015 Australian influenza season.

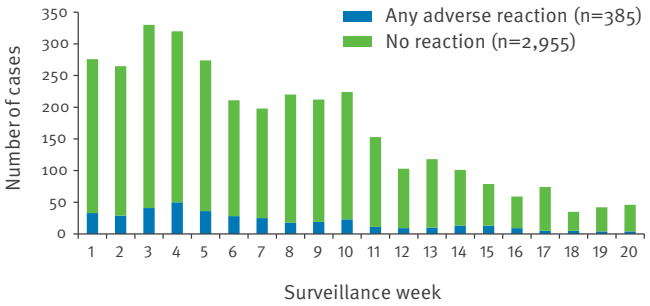
The *AusVaxSafety* vaccine safety surveillance system

In Australia (population 23 million [4]), influenza vaccination is funded under the National Immunisation Program for children aged six months to four years who have medical conditions pre-disposing them to complications and/or for Indigenous children. Only one state, Western Australia (WA), has funded influenza vaccination for this age group since 2008.

For the purposes of *AusVaxSafety* surveillance, children aged six months to four years receiving seasonal influenza vaccine from participating GP sites (n = 54), hospitals (n = 6), public clinics (n = 2) and primary healthcare providers such as Aboriginal Medical Services (n = 7) in four states (New South Wales (NSW), Victoria, South Australia and WA) were eligible for inclusion. Parent/carer-reported adverse events in children were solicited within three days of vaccination using two computer-based data management platforms, Vaxtracker [5] and SmartVax [6]. Both systems sent automated SMS messages (and/or emails for Vaxtracker) and received parent/carer-completed questionnaire responses via reply SMS with a URL link to smartphone survey (SmartVax)

Figure

AusVaxSafety participants with and without post-vaccine reaction, by week of vaccination, and cumulative percentage of participants, Australia, 1 April–31 August 2015 (n = 3,340)



Surveillance Week 1 included all participants vaccinated prior to the official rollout of the influenza vaccine for the 2015 season (20 April 2015) and captured children vaccinated from 1 to 19 April 2015. After that, each surveillance week consisted of seven days, with Week 2 including 20–26 April, etc. Week 20 included eight days (24–31 August 2015).

or web-based survey (Vaxtracker). Demographic details were obtained, as well as information regarding vaccine brand, medical conditions, concomitant vaccines, reactions and healthcare consultations required after vaccination (including follow-up visit to a GP, emergency department (ED) or hospitalisation).

Serious adverse events (SAE) were categorised according to predefined criteria, which included any untoward medical event that resulted in death, was life-threatening or required hospitalisation [7]. We also included seizures requiring medical attendance (ED and/or hospitalisation) as medically important events. SAEs were reported to state/territory health departments and the Therapeutic Goods Administration as required by legislation. For this report, data were compiled from 1 April through 31 August 2015 and cumulative data reported to health authorities weekly. After week 4 of surveillance, progressive results were periodically made publically available online and shared via immunisation provider networks.

For rapid signal detection, fast initial response cumulative summation (FIR CUSUM) and Bayesian methods [8,9] were employed weekly to estimate the probability that any potential safety signal was true or false based on predetermined expected and threshold rates of two objective outcome measures (fever and medical advice/attendance sought) in relation to the number of reports received. Expected and threshold rates were set according to previous surveillance results and published studies. For fever, the expected rate was 6% and the threshold rate for triggering a signal was 13% [5,10-12].

Results

Approximately 75% of the 4,441 parents/carers invited agreed to participate, resulting in 3,340 post-vaccination reports (Figure). The majority of parent/carers responded within two hours of being queried. Descriptive details of participants are presented in Table 1.

Weekly analysis using FIR CUSUM and Bayesian methods (conducted 1 April through 5 July 2015) did not demonstrate a safety signal at any time. After the third week of surveillance (n = 877 cumulative reports), fever rates remained less frequent than 5% each week and medical advice/attendance rates remained lower than 2%.

Parent/carer-reported fever was recorded by 4.4% (n = 148); medical advice/attendance was sought by 1.1% (n = 35). Details on reactions and medical advice/attendance sought are included in Table 2.

Of the 35 children who received medical advice/attendance, 23 reported fever. Five children experienced seizures, four of whom had a history of seizures (three: underlying neurological conditions; one: previous febrile seizures). The fifth seizure case occurred in a child diagnosed with a febrile viral illness. Only three of the children with seizures sought medical attendance and were thus classified as having SAEs; all attended an ED only. One additional SAE was recorded in a child hospitalised with an influenza-like illness and fever. Two of the four children experiencing an SAE had received Vaxigrip, one had received Fluarix and the other received Influvac. All reported improvement within days.

No significant difference was identified between children who had received one of the two most commonly used vaccine brands, Vaxigrip or Fluarix, and who experienced fever or sought medical advice/attendance. All other brands had been administered in insufficient numbers to reliably report on differences (Table 3). Children receiving other vaccines concomitantly were significantly more likely to experience fever (60/687; 8.7%) than those who did not (87/2,618; 3.3%) (p = 0.000). There was no difference between children with and without an underlying condition regarding fever (29/400 (7.3%) vs 56/721 (7.8%)) or medical advice/attendance sought (9/400 (2.3%) vs 17/721 (2.4%)).

Discussion

Our novel system of active, prospective vaccine safety surveillance, *AusVaxSafety,* has demonstrated in real time that 2015 southern hemisphere influenza vaccines registered for use in young Australian children were safe and well-tolerated. Adverse event rates reported by parents/carers remained low and within expected ranges throughout the surveillance period. The fever rate was lower than the pooled estimate (6.7%) in a recent systematic review of randomised control trials of children aged six to 35 months receiving the first dose of a trivalent influenza [12].

Table 1

Demographic details of *AusVaxSafety* participants, Australia, 1 April–31 August 2015 (n = 3,340)

Variable	Response	Number	Percentage
Median age (range)	23.0 months (6.0–59.9)		
Sex [a]	Male	1,781/3,314	53.7%
Ethnicity [b]	Indigenous	119/2,519	4.7%
Underlying medical condition [c]	Yes	400/1,121	35.7%
Concomitant vaccine(s) received [d]	Yes	687/3,305	20.8%

[a] Sex unknown for 26 of 3,340 participants.

[b] Ethnicity unknown for 821 of 3,340 participants.

[c] Underlying medical condition not available for 2,219 of 3,340 participants (SmartVax data management system does not currently collect this variable).

[d] Data on whether concomitant vaccine was received unknown for 35 of 3,340 participants.

Table 2

Adverse events reported by 2015 *AusVaxSafety* participants within three days of vaccination, Australia, 1 April–31 August 2015 (n = 3,340)

Adverse event		Number	Percentage
Any adverse event		385/3,340	11.5%
Fever		148/3,340	4.4%
Seizure [a]		5/3,340	0.2%
Injection site reaction		67/3,340	2.0%
Vomiting/abdominal pain		41/3,340	1.2%
Rash		36/3,340	1.1%
Participants who sought any medical advice and/or required any medical attendance		35/3,340	1.1%
Highest medical advice and/or attendance reported	Participants attending a medical facility for consultation with a general practitioner or other medical practitioner	23/3,340	0.7%
	Participants telephoning a medical facility or a medically staffed helpline for advice	4/3,340	0.1%
	Participants presenting to an emergency department (not admitted) [a]	6/3,340	0.2%
	Participants hospitalised [b]	2/3,340	0.1%

[a] Of the five children with seizures reported, three presented to an emergency department and were thus classified as having a serious adverse event.

[b] One child was hospitalised with an unrelated condition not deemed a serious adverse event. The other hospitalised child had an influenza-like illness.

Active, prospective vaccine safety surveillance is superior to traditional post-marketing vaccine safety surveillance which typically relies on passive reporting. In Australia, SMS technology has also been used to study vaccine reactions among healthcare workers and pregnant women [13,14]. One study in the United States also used SMS follow-up of parents, detecting increased fever rates in children who had concomitantly received trivalent influenza vaccine and 13-valent pneumococcal vaccine compared with those who received each vaccine alone [15]. Similarly, we reported an increased (although low) rate of fever when influenza vaccine was administered together with other vaccines. This was also associated with a significantly higher likelihood of seeking medical advice and warrants further investigation.

Because large volumes of influenza vaccine are distributed annually within short, defined periods, active surveillance provides the opportunity to gain early, reliable assessments of the safety profiles of new vaccines. As the number of available influenza vaccines increases, obtaining timely safety data becomes more important, particularly as strain composition may vary from season to season. In 2010 in Australia, an unexpected increase in febrile reactions following receipt of influenza vaccination in young children led to a three month suspension of all national paediatric influenza immunisation programmes [16]. Epidemiological and laboratory studies linked these reactions to one manufacturer's vaccine (Fluvax or Afluria, bioCSL) which is no longer registered for use in young children [16,17]; however, confidence in all influenza vaccines was negatively impacted [18,19]. In response to these safety concerns which have resulted in low uptake of

Table 3

Details of influenza vaccines administered to *AusVaxSafety* participants, Australia, 1 April–31 August 2015 (n = 3,340)

Brand[a] (manufacturer)	Vaccine type	Number of vaccines administered (n = 3,336)		Number of participants with fever by brand		Number of participants who sought medical advice/attendance by brand	
		n	%	n/N	%	n/N	%
Vaxigrip (Sanofi-Pasteur)	Trivalent	3,075	92.2	133/3,075[c]	4.3%	28/3,075[d]	0.9%
Fluarix (GlaxoSmithKline)	Trivalent	189	5.7	9/189	4.8	4/189	2.1
Influvac (BGP Products)	Trivalent	47	1.4	5/47	NR	2/47	NR
Agrippal (Novartis Vaccines and Diagnostics)	Trivalent	11	0.3	0/11	NR	0/11	NR
FluQuadri[b] (Sanofi Pasteur)	Quadrivalent	14	0.4	1/14	NR	1/14	NR

NR: not relevant.

[a] Brand unknown for four participants.

[b] All administered vaccines except for FluQuadri were trivalent. Quadrivalent vaccines (FluQuadri/ FluQuadri Junior and Fluarix Tetra (GlaxoSmithKline)) were available for use for the first time in Australia in 2015 but were not funded under the National Immunisation Program.

[c] p = 0.775 for rates of fever among those who received Vaxigrip (4.3%) compared with those who received Fluarix (4.8%) calculated using Pearson's chi-square test.

[d] p = 0.102 for rates of medical advice/attendance sought among those who received Vaxigrip (0.9%) compared with those who received Fluarix (2.1%) calculated using Fisher's exact test.

seasonal influenza vaccines in children, *AusVaxSafety* surveillance data have been able to provide reassuring results.

Data obtained from parental reporting should be interpreted with care. Consequently, *AusVaxSafety* reports on outcomes which are the most objective: fever and medical advice/attendance sought within three days of vaccination. Although these provide less precision than results obtained in more formal follow-up such as clinical trials, this is unlikely to reduce our system's sensitivity for detecting SAEs, of which medical advice/attendance sought can be considered a good proxy. This was demonstrated in the epidemiological investigation of the 2010 increase in febrile reactions [16].

An advantage of our system is its potential adaptability for monitoring new vaccines, such as live attenuated influenza vaccine, although this is not yet available in the southern hemisphere. Another advantage is its ability to provide rapid real-time feedback to inform programme rollout and vaccine promotion. In addition, *AusVaxSafety*'s flexibility may be valuable in situations where vaccine safety data are limited, such as for pandemic vaccines. The timeliness of our results also makes them valuable beyond Australia; our data may be of interest to counterparts in the northern hemisphere preparing for 2015/16 vaccination using vaccines comprised of the strains administered in the 2015 southern hemisphere season.

Our system, which is able to report adverse events within days of vaccination, is as near to real time as possible. Such timeliness is feasible thanks to the strong collaboration with parents/carers and providers and the use of SMS technology for reporting reactions. We anticipate being able improve our system by including more participants in future years. To our knowledge, *AusVaxSafety* is the only active influenza vaccine safety surveillance system for young children analysing and reporting data on a weekly basis, allowing safety deliberations on vaccines within mere weeks of influenza vaccination commencing. Our ability to provide early and reliable safety profiles of seasonal influenza vaccines for children is likely to improve public confidence and vaccine uptake, which we will continue to assess.

AusVaxSafety 2015 surveillance team

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at our participating hospitals, clinics and general practices, as well as the parents/carers of children who participated in and supported 2015 *AusVaxSafety* surveillance.

Conflict of interest

None declared.

Authors' contributions

AP served as *AusVaxSafety* surveillance coordinator for 2015, drafted the manuscript, and conducted data analysis and interpretation of results. PC contributed to the design and implementation of the *AusVaxSafety* surveillance system, served as coordinator/recruiter of the Hunter New England area surveillance sites, reviewed and contributed to the manuscript draft. AL contributed to the design and implementation of the *AusVaxSafety* surveillance system, recruited general practice site participants, reviewed and contributed to the manuscript draft. AR contributed to the design and implementation of the *AusVaxSafety* surveillance system, served as a coordinator of the Western Australia surveillance sites, conducted data collection and analysis, and reviewed and contributed to the manuscript draft. DW served as a coordinator of the Western Australia surveillance sites, conducted data collection and analysis, and reviewed and contributed to the manuscript draft. TS contributed to the design and implementation of the *AusVaxSafety* surveillance system, conducted data analysis, and reviewed the manuscript draft. CB contributed to the design and implementation of the *AusVaxSafety* surveillance system and reviewed and contributed to the draft manuscript. NC contributed to the design and implementation of the *AusVaxSafety* surveillance system and reviewed and contributed to the draft manuscript. KM contributed to the design, implementation and coordination of the *AusVaxSafety* surveillance system, and drafted the manuscript.

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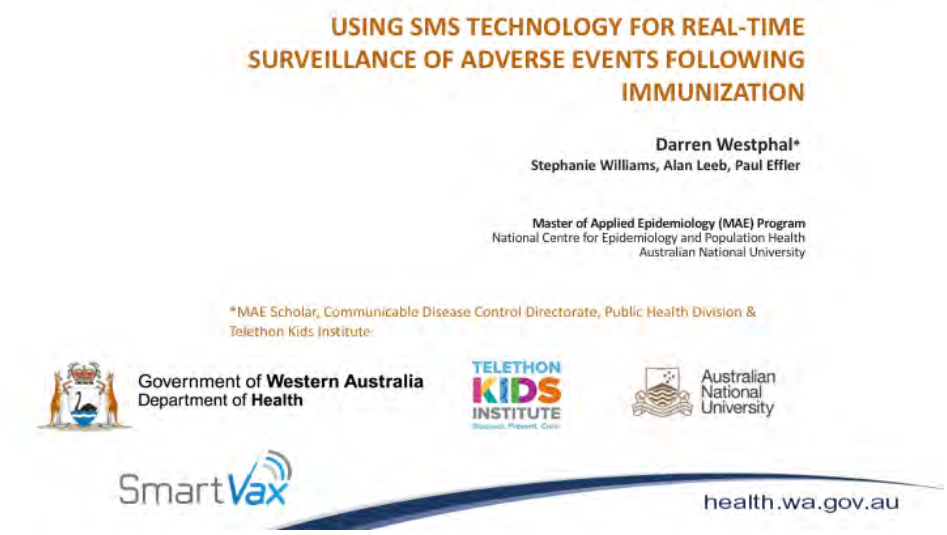
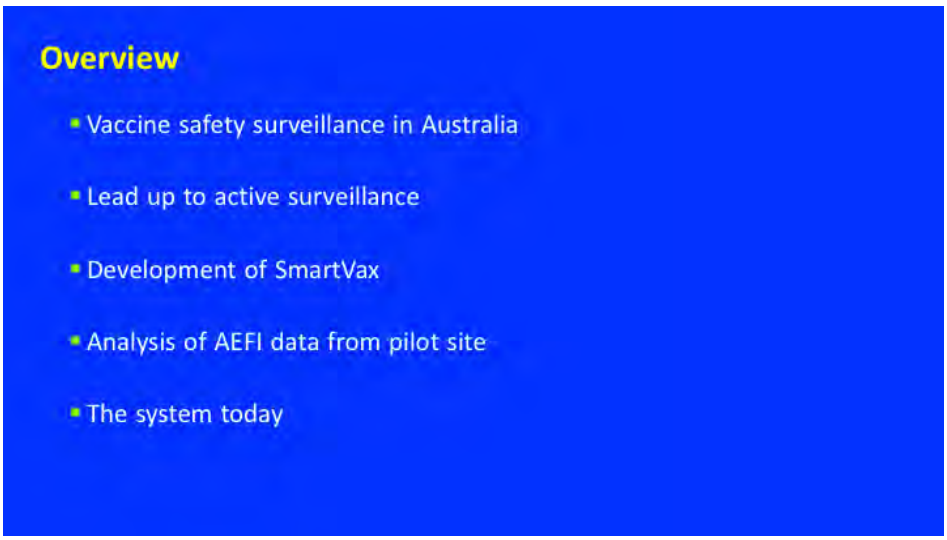
Appendix 2. Slides presented at the Council of State and Territorial Epidemiologists conference in Anchorage, Alaska





What happened

- Three child deaths in 2007 with confirmed Influenza
- In 2008 Western Australia began offering free flu vaccine to children 6 months to 5 years of age
- 2008 - 2009 - 60,000 doses of TIV given in children
- CSL – Fluvax (Afluria in the USA) and Sanofi – Vaxigrip

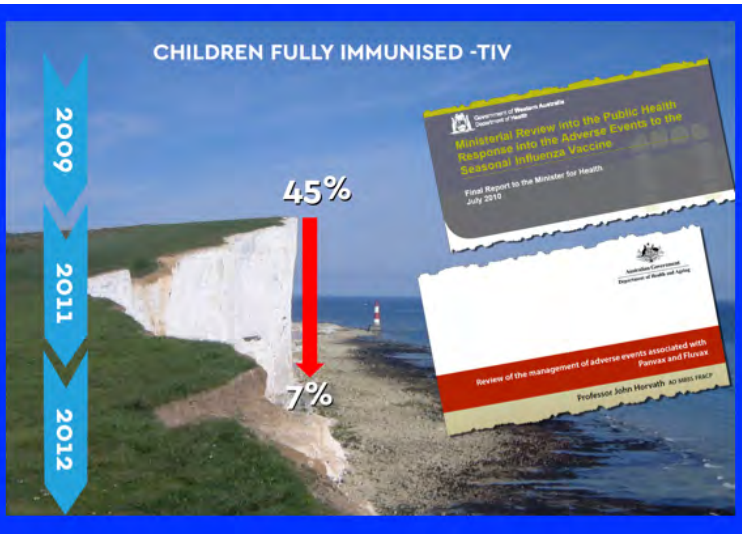

Flu kills three young children

Contraindication of TIV in children < 5


Flu vaccination ban goes national after fever, convulsions in children

Chris Thomson
April 23, 2010

Comments 39



Development of Active AEFI Surveillance

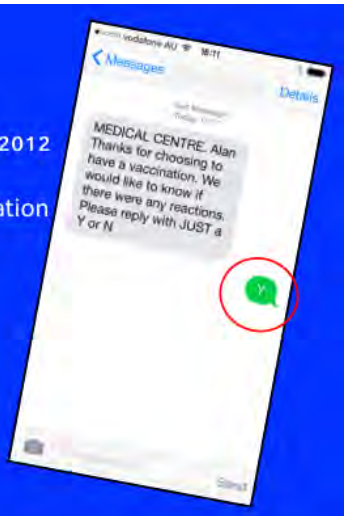
Aims of this study

- Assess response rates to SMS/acceptability of the system
- Measure the rate of reported reactions in children by vaccination time point
- Determine whether those reporting a reaction at the first visit were likely to report again
- Assess reactions before and after MMR added to the NIP at 18 months in July 2013

Age/School Year	Disease	Vaccine brand
Birth (must be given within 7 days of birth)	Hepatitis B	H-B-Vax II Paediatric
6-8 weeks	Diphtheria, Tetanus, Pertussis, Hepatitis B, Poliomyelitis and Hib Pneumococcal Rotavirus (ORAL use only) (Latest to be given at 12.9 weeks of age)	Infanrix hexa Prevenar 13 RotaTeq
4 months	Diphtheria, Tetanus, Pertussis, Hepatitis B, Poliomyelitis and Haemophilus influenzae type b Pneumococcal Rotavirus (ORAL use only) (Latest to be given at 32.9 weeks of age) [1] Allow for minimum interval of 4 weeks between doses.	Infanrix hexa Prevenar 13 RotaTeq
6 months	Diphtheria, Tetanus, Pertussis, Hepatitis B[2], Poliomyelitis and Haemophilus influenzae type b Pneumococcal Rotavirus (ORAL use only) (Latest to be given at 32.9 weeks)	Infanrix hexa Prevenar 13 RotaTeq
12 months	Measles, Mumps, Rubella Haemophilus influenzae type b and Meningococcal C	Priorix or MMR II Menitorix
18 months	Measles, Mumps, Rubella, Varicella[7] Diphtheria, Tetanus, Pertussis	Priorix-Tetra or ProQuad Infanrix, Tripacel
4 years (Vaccines can be administered from 3.5 years)	Diphtheria, Tetanus, Pertussis, Poliomyelitis Measles, Mumps, Rubella (only for children who have not already received 2 doses of MMR containing vaccine)	Quadracel or Infanrix IPV Priorix or MMR II

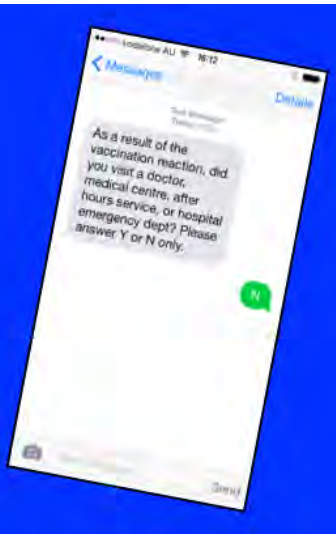
Collection of AEFI Data

- Data collection between November 2011 - June 2012
- Parents of children receiving a scheduled vaccination were sent a text message three days later
- Affirmative replies triggered two further text messages



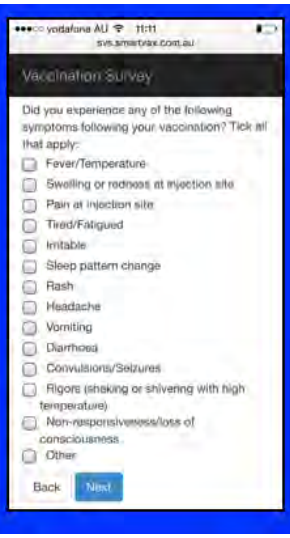
Collection of AEFI Data

- 1st asking whether it was medically attended
- 2nd contained a link to an online survey



Collection of AEFI Data

- Survey asks for details of suspected AEFI

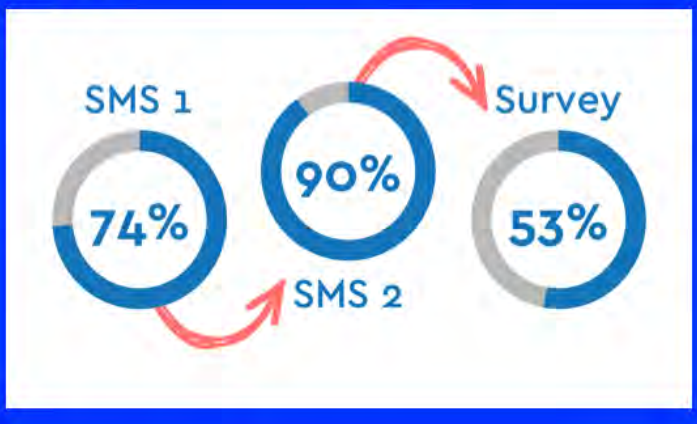


PLAY MOVIE

Analysis of AEFI data

- Proportions of suspected reactions at each time point on the childhood vaccination schedule reported
- Response rates to first SMS calculated
- Those who didn't reply were telephoned
- Compared characteristics of those who replied and those who didn't

Response Rate



Timeliness

- Timeliness: 81% within 2 hours

Comparison of SMS vs Telephone

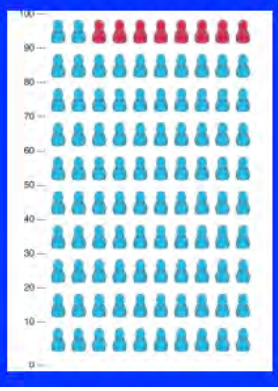
	Replied to SMS n=2,898	Telephoned n=284	P Value
Mean age, months (median)	14.6 (9)	17.0 (12)	0.28
Sex, Female N (%)	1,359 (47%)	133 (47%)	0.98
Any reaction N (%)	239 (8%)	27 (9%)	0.83

Comparison of SMS Responders and Non-responders

	Replied to SMS (n=1,216)	Unable to be contacted (n=725)	P Value
Age, months mean	18.1	16.7	0.10
Gender			
Female n (%)	564 (46.4)	342 (47.2)	0.82
Male n (%)	652 (53.6)	383 (52.8)	0.80
No. of visits, mean	2.1	2.2	0.78

Overall Reactions

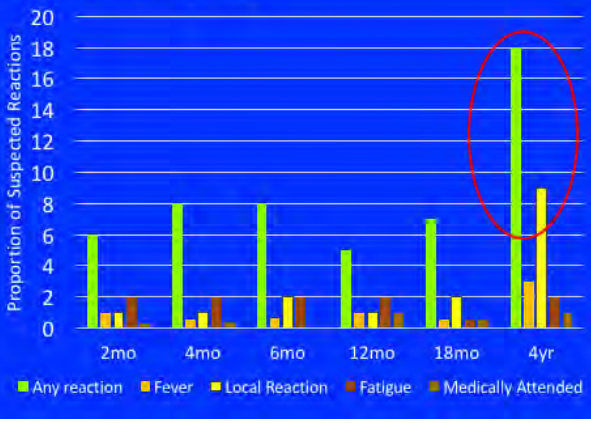
- 1,216 patients reporting 2,897 vaccination events
- 92% NO reactions overall
- 239 "Yes" replies
- Local reactions (3%) & fatigue (2%) most common



Overall Reactions

- Reactions at 4 year time point 9 times higher compared with 2 month
  - OR 9, 95% CI 4-24

Reporting Suspected AEFI



Evaluation of Schedule Change

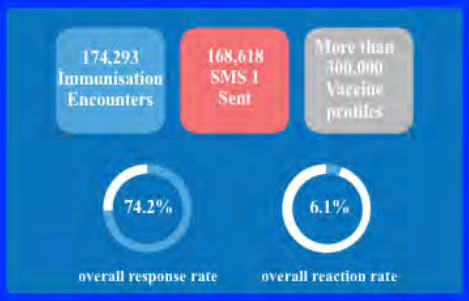
	Prior to 1 July 2013 N (%) 95% CI	After 1 July 2013 N (%) 95% CI	P Value[a]
18 months Varicella-only (n=158)	16 (8.9) 4.5—13.3		0.24
18 months Measles, Mumps, Rubella, Varicella (n=272)		17 (5.9) 3.1—8.7	

Limitations

- Collected reaction information at a single time point (i.e. 3 days post vaccination)
- The system collects self-reported reaction information, it doesn't evaluate it
- Very small numbers
- Single medical practice - generalisability

System today

System today



Conclusions

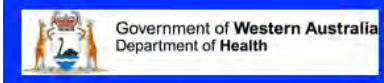
- Acceptable with 74% response rate, >80% within 2 hours
- Rates of reported reactions calculated in children by vaccination time point
- Similar results between responders vs non-responders
- Although not assessed here, this technology could be applied to other safety follow up in children

Vaccine

Continuous active surveillance of adverse events following immunisation using SMS technology

Darren W. Westphal, Stephanie A. Williams, Alan Leeb, Paul V. Effler

Thank you



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Teaching exercises

Prologue

As part of the MAE requirements, scholars present a lessons from the field (LFF) to their colleagues and teach a lesson to the first year MAEs during courseblock.

Lesson from the field

My lesson from the field stemmed from my epidemiological project; A matched case-control study, using administrative data for controls, to ascertain vaccine effectiveness during a mumps outbreak (Chapter 2). I thought the process would be a good 'lesson' to walk through with my colleagues but also an opportunity to get insight from my colleagues about some of the challenges using this method, and more broadly about the outbreak.

I presented my LFF during courseblock which, in hindsight, was a great way to do it. It meant being face-to-face with my colleagues and talking through the LFF together. The other advantage of doing it at courseblock was that we had nothing else in our diary and could continue the conversation as long as people were happy to do so. I sent out the LFF two weeks prior and asked my fellow scholars to bring their responses to the meeting rather than sending them ahead of time.

The LFF generated a great discussion about the matched case-control method but more broadly about why the mumps outbreak was affecting Aboriginal people more than non-Aboriginal people.

Teaching of the first years

This exercise was a collaborative effort involving a group of three MAE scholars working together to come up with a teaching topic and plan of execution. We communicated by email and teleconference to put together our lesson on confounding, a topic that we initially found confusing. We wanted it to be useful for the first years and set the foundation for understanding it when they came across it in their work. We were also aware that they had a confounding lecture during the courseblock and wanted to make sure that it wasn't redundant. With our lesson in the afternoon of the final day of

courseblock, we began with a skit then a short interactive lecture. The lesson plan and skit script is attached following the LFF.

Lesson from the field:

A matched case-control study to ascertain vaccine effectiveness during a mumps outbreak

Learning objectives:

By the end of this exercise you will be able to:

- Define the difference between vaccine efficacy and vaccine effectiveness
- Discuss the advantages and disadvantages of matching in case-control studies
- Calculate VE from an odds ratio generated from a regression model
- Discuss limitations of different control selection techniques

Scenerio

You have been working at the State Public Health unit for a few weeks and you've heard that there is a mumps outbreak in the remote areas of the state. Your supervisor suggests that this might be a good outbreak for your MAE and you are happy to take it on. You had a sense that it could go on for a few months but actually goes on for much longer than you thought and case numbers continued to increase.

In collaboration with your supervisor you decide to do a matched case-control study to establish vaccine effectiveness of the measles-mumps-rubella (MMR) vaccine. The reason for doing this is that the vaccine doesn't appear to be performing in this population, with most cases being fully vaccinated. Using this rigorous method you hope that it will provide robust epidemiological data that can then pave the way for further research studies in an effort to find out why the vaccine may not be performing.

You learn that the National Centre for Immunisation Research and Surveillance (NCIRS) hold a de-identified Australian Childhood Immunization Register (ACIR). The ACIR is a population-based register with records for all children of citizens and permanent residents enrolled in Australia's publically-funded health system. Approximately 99% of children aged 12 months are enrolled in the ACIR, regardless of their vaccination status.[1] You contact NCIRS to ask about collaborating and use of the database to match your cases with the de-identified controls from the database. All goes well and they are happy to help.

1. To start, what is the difference between vaccine efficacy and vaccine effectiveness?

2. What variables would you choose to match on (see Appendix 1)? Briefly explain why.

3. Is this the right study design for this type of study? Why, why not?

Read the following excerpts from *Field Epidemiology* by Michael Gregg about matching (let me know if you don't have the book).

- Sources of Controls, chapter 8, page 146-148.
- Sampling Methods for Selecting Controls, "pair matching" bottom of page 148-149
- Size of Control Group, page 150.
- Matching in Case Control Studies, chapter 10, p. 228-231.

4. What are some advantages and disadvantages of matching?

5. What is overmatching, what is the result when this happens?

In collaboration with your supervisor and the NCIRS, you decide to match on two variables, they are:

a. Age, using date of birth ±30 days, and
b. Location, matching broadly by region. Large town cases are restricted to controls from large towns, rural cases are restricted to rural control matches.

6. Why do you think the epidemiologist matched on these variables? Are there any potential problems with those variables?

7. How do these variables align with the variables you chose in Q.2? If you chose different variables, defend that decision.

You send your de-identified case list and matching is done. The spreadsheet is returned to you with all of your cases and varying number of controls:

- One case has 3 controls
- One case has 7 controls
- The rest all have 13 or more controls

You're not sure what to do with the list and wonder if you can have a different number of controls for each case or if it needs to be standardised across the list. You remember reading that 1:1 matching is about 50% efficient and 1:4 about 80% with a diminishing return beyond 5-10 controls.[2]

For reference (reading of these is optional): Breslow and Day[2] (1980) provide guidance on case-control study designs and analysis that is very useful. A table of contents can be found here: http://www.iarc.fr/en/publications/pdfs-online/stat/sp32/. This is a good reference to keep in your portfolio.

Chapter 5: Classical Methods of Analysis of Matched Data and
Chapter 7: Conditional Logistic Regression for Matched Sets are particularly useful for this exercise.

The epidemiologist decides to match 11 controls to each case, losing the two cases with 3 and 7 controls.

8. What are some possible reasons that the epidemiologist matched such a large number of controls to each case if there isn't much added value? What would you have done?

You receive the dataset and begin to clean the data in preparation for your analysis. See the data dictionary in Appendix 1.

9. What statistical test(s)might you use and why.

You put in this code and get the following output:

```
. clogit status i.dose, group(id) or

Iteration 0:   log likelihood = -356.49747
Iteration 1:   log likelihood = -356.49643
Iteration 2:   log likelihood = -356.49643

Conditional (fixed-effects) logistic regression

                                                Number of obs     =      1,728
                                                LR chi2(2)        =       2.66
                                                Prob > chi2       =     0.2644
Log likelihood = -356.49643                     Pseudo R2         =     0.0037

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        dose |
          1  |   1.667518   1.190286     0.72   0.474     .4116018      6.7556
          2  |   2.228318   1.343601     1.33   0.184     .6834886     7.26479
------------------------------------------------------------------------------
```

10. What does the output tell you, what is the VE? What happens to VE when the odds ratio is greater than 1? What might cause this?

You prepare a table of results, Table 1.

11. Look at the table and describe briefly what messages you might take from it? What might some of the limitations be?

12. When thinking about VE, what might be the cause of this result in this population?

Appendix 1. Data Dictionary

Variable Name	Explanation	Recorded
id	Unique identification	Numeric, continuous
vax_1	date of MMR1	date, missing=.
vax_2	date of MMR2	date, missing=.
vax_3	date of MMR3	date, missing=.
dob	date of birth	date
onsetdate	date of onset	date
sex	gender	numeric, dichotomous Male, Female, missing=.
atsi	identify as Aboriginal or Torres Strait Islander	numeric, categorical missing=.
postcode		numeric
district	public health region of residence	numeric Kimberley Broome Esperance Geraldton Goldfields Kalgoorlie Karratha Midwest Perth Pilbara Hedland Wheatbelt
status	case/control	numeric, dichotomous
age		numeric, continuous
ysld	years since last vaccination	numeric, categorical 0-5, 6-9, 10+
bdose	time between first and second dose	numeric, continuous

Appendix 2. Table of results

Comparison of Vaccine Effectiveness of MMR Vaccine During a Mumps Outbreak in Western Australia 2015, Using a Matched Case-Control Study and the Screening Method

Estimated VE Model	Cases, No. (n=144)	Controls, No. (n= 1,584)	VE, % (95% CI) Matched Design
	No. (%)	No, (%)	
No. of Doses			
0	3 (2.1)	69 (4.4)	1 [Reference]
1	7 (4.9)	98 (6.2)	-66.8% (-575.6 – 58.8)
2	134 (93.1)	1,417 (89.5)	-122.8% (-626.5 – 31.7)
At least 1 dose	141 (97.9)	1,515 (95.6)	-118.8% (-613.0 – 32.9)

Abbreviations: VE, vaccine effectiveness; 95% CI, 95% confidence interval

1. Hull BP, Deeks SL, McIntyre PB. The Australian Childhood Immunisation Register-A model for universal immunisation registers? *Vaccine* 2009; **27**(37): 5054-60.
2. Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ* 1980; (32): 5-338.

Lesson Plan for teaching exercise

Topic	*WHAT WE WANT YOU TO KNOW ABOUT CONFOUNDING*
Date and Time	Friday 4 March 2016 1330-1355 (approx.)
Presenters	Darren Westphal Samantha Siripol Amy Burroughs Alex Marmor
Learning Objectives	*By the end of the session, participants will be able to:* • *define the relationship between a confounder and an outcome* • *differentiate a "red herring" from a confounder* • *apply this understanding to examples*
Ways of assessing if objectives have been achieved	Pre-test (informal): asking students what they know before the lesson Post-test: interactive quiz Teaching evaluation: electronic/paper survey
Materials	Skit ☐ narrator's script ☐ corpse ☐ knife ☐ fake blood ☐ police badge ☐ handcuffs ☐ notebook Lectures ☐ computer and projector for powerpoint Interactive Quiz ☐ headbands with names for exposures and outcomes (eg "Murder victim", "secretary", "co-worker", "birth defects", "Zika Virus", "insecticide") ☐ large laminated labels for participants to assign: "outcome", "confounder", "true relationship", "spurious relationship"

OUTLINE

Timing (approx.)	Key Points	Instructional Technique	Presenter
1330-1340	• Participants drawn outside to the garden by a blood-curdling scream • Actors act silently while Narrator describes how a secretary was found red-handed at the scene of her husband's murder	Attention-grabbing skit	All
1340-1343	Why is confounding so…confounding? • explain the aims of the session • present the learning objectives	Lecture	Sam
1343-1346	What is confounding? • A quick recap asking participants to recall what they learnt from the morning's lecture on confounding	Lecture/group discussion	Amy
1346-1350	Zika example • confounding explained using the "waterpipes" approach	Lecture	Darren
1350-1355	Assessment of learning objectives • Characters from skit return with names on their heads • Participants are asked to apply the labels to the characters and their relationships • If there's time, participants can apply the labels to the other examples presented • Allow time for questions • Distribute teaching assessment survey (although this may be integrated with other groups at the end of the afternoon)	Interactive Quiz	All

Skit Script

Location: Area outside Balmain Crescent cottage

Cast:

Narrator (Darren)

David Smith (Amy)

Mary Brown (Alex)

DCI Shoe-leather (Sam)

Peter Green (MAE volunteer TBC)

PART 1 (Pre-lecture)

<David Smith is lying dead on the ground, covered in blood>

<Mary Brown is kneeled next to David, also covered in blood, holding a knife, hysterical>

Narrator (Darren):

<Runs into classroom>

"Someone's been killed, there's a dead body on the ground!!!"

<Wait for class to get out onto the grass to see David's body and Mary kneeling over with the knife, crying>

Narrator (Darren):

"You are all looking at the dead body of NCEPH senior academic, David Smith"

"Another NCEPH staff member, Mary Brown, is kneeled over him, covered in blood and with a knife in her hand"

<DCI Shoe-leather enters the scene with clipboard in hand, handcuffs Mary and starts to photograph scene>

<Peter Green enters scene just after DCI Shoe-leather arrives and tries to console Mary>

<MARY TOO HYSTERICAL TO TALK>

< DCI SHOE-LEATHER INTERVIEWS PETER INSTEAD>

<DCI SHOE-LEATHER AND PETER MIME A CONVERSATION>

NARRATOR (DARREN):

"DCI SHOE-LEATHER HAS ARRIVED QUICKLY ON THE SCENE TO INVESTIGATE DAVID'S MURDER"

"ALSO ARRIVING AT THE SCENE IS DAVID'S OLD FRIEND AND NCEPH COLLEAGUE, PETER GREEN"

"MARY IS TOO HYSTERICAL TO BE QUESTIONED AT THE MOMENT SO DCI SHOE-LEATHER INSTEAD ASKS PETER SOME QUESTIONS"

"PETER REVEALS TO DCI SHOE-LEATHER THAT DAVID HAS BEEN INVOLVED IN A SCANDALOUS AFFAIR WITH MARY, PETER'S SECRETARY. IT'S HIS GUESS THAT MARY HAS ONLY JUST FOUND OUT THAT DAVID HAS A WIFE AND GOT HER REVENGE"

"ON THE FACE OF IT, THE EVIDENCE AGAINST MARY AS DAVID'S MURDERER IS VERY CONVINCING"

"HOWEVER, THERE ARE MORE SECRETS TO THIS CASE WHICH WILL BE REVEALED IN DUE COURSE…"

PART 2 (POST-LECTURE, AS PART OF INTERACTIVE QUIZ)

Narrator (Darren):

"There is strong evidence to suggest that Mary is David's murderer"

"However, on closer investigation, DCI Shoe-leather made some startling discoveries"

"After Mary had calmed down, she told DCI Shoe-leather that she had never met David before. She only came across David's body because Peter had asked her earlier that day to meet her at that time and location. She was caught with the knife in her hand while trying to revive him"

"Mary never knew David, let alone had an affair with him"

"With her keen investigative skills, DCI Shoe-leather got to the bottom of the mystery: Peter was jealous of David's recent promotion to a position he had been coveting for years"

"Out of frustration he murdered David and framed Mary by making up the story of the affair"

"Peter was present on campus and could not provide an alibi"

"The apparently strong case against Mary is greatly reduced when you remove the malicious influence of Peter"

"Peter was confounding the relationship between Mary and David"

"The confounder, Peter, was actually the murderer, and Mary was a red herring"

Teaching feedback

Question / Person	1	2	3	4	5	6	7	8	9	10	11	Total	Average
Content	5	5	5	4	5	4	4	4	4	4	4	48	4.4
Instructor presentation	4	5	5	5	5	5	5	4	5	4	4	51	4.6
Methods	5	5	5	5	5	5	5	4	5	4	4	52	4.7
Learnt something new	5	5	5	4	5	4	4	4	4	5	3	48	4.4
Engagement	5	5	5		5	5	5	4	4	4	4	46	4.6
Asking questions	4	5	5	4	5	5	5	4	5	4	5	51	4.6

Additional comments

Enjoyed the balance between interactive and didactic learning

Thought the session was fun no need to improve

All sessions very well run - to the point and clear!

The case study/skit with the murder victim was great! Loved the pipes example as well

Session was great. Don't be afraid to go out into deeper detail though, I think we would have coped

No, it was pretty good. Oh, actually we really liked hearing about your projects and more info on these would be super.

Short and sweet

Explained well, thorough

Perhaps some more examples, and ones that are a bit trickier to define, in case we come across such thing

2015-2016 MAE Cohort

Anthony Draper, Jana Lai, Craig Thompson, Johanna Dups, Tambri Housen, Paul Dutton

Amy Burroughs, Tanyth DeGooyer, Alex Marmor, Darren Westphal

Cecilia Xu, Alicia Arnott, Samantha Siripol