Applied Epidemiology of Vaccine Preventable Diseases and Outbreaks in New South Wales

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My thesis submitted for the degree of Master of Philosophy

The Australian National University

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Master of Philosophy (Applied Epidemiology)

MAE Program

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NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE

1.1 Originality Statement

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material that have been accepted for the award of any other degree or diploma at Australian National University or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked with at the National Centre for Immunisation Research and Surveillance (NCIRS) or Western Sydney Public Health Unit (WSPHU) or Communicable Diseases Branch (CDB), NSW Health is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation or linguistic expression is acknowledged.

Signed: .....

Date: Tuesday 11 July 2017

Science should be based on…

"try today and be less wrong tomorrow"

rather than

"be right at all times and if you are even momentarily wrong…..
than death to you"

Rufus Hound
The Infinite Monkey Cage Podcast
05 July 2016

1.2 Acknowledgements

This bound volume is a result of field work and on-the-job training that would not have been achievable without the guidance and support of some very special people.

Firstly, huge thanks go to each of my field supervisors at the National Centre for Immunisation Research and Surveillance (NCIRS): Helen Quinn, Frank Beard and Aditi Dey. With their encouragement, patience and remarkable expertise in the field of vaccine preventable diseases, I feel that I have grown as an epidemiologist during my MAE journey. I feel very honoured to have been offered this awesome opportunity at NCIRS and have done my best to fill the shoes of MAE'ers before me. To be immersed in the NCIRS work environment is truly an honour - an experience that I will never forget. I have enjoyed being a part of this passionate and productive team; a team that goes well above and beyond of what is expected of them each and every day. I thank you, Helen, Frank and Aditi for the last two years.

I would like to also thank my 'revolving' team of academic supervisors at ANU: Emily Fearnley, Kerri Viney and Katrina Roper. Emily was academic supervisor #1 for the first year of the MAE. Kerri followed as academic supervisor #2 while Emily was on maternity leave. Then, to my surprise, both Emily and Kerri departed from the MAE program in September 2016. This is when academic supervisor #3, Katrina took hold of the reins and got me through the pointy end of the MAE. I would like to thank Emily, Kerri and Katrina for all of their help during 2015 and 2016. I am truly appreciative for their guidance, expertise and patience during the roller-coaster that is the MAE. Thank you.

> *…….however, after re-reading what I just wrote, I am not too sure if I should take the revolving team of academic supervisors personally????*
> *hummmm…….. was it something I said or did?*

I would also like to thank Martyn Kirk and the National Centre for Epidemiology and Population Health (NCEPH) for this truly awesome opportunity. The MAE is a great program, one that I have found challenging, fulfilling and rewarding.

I would like to thank the MAE15 Cohort, for the great times during the course blocks in Canberra. Special big thanks go to Alicia and Tambo. Sessions under the tree helped to clear the mind, focus our thoughts and reflect on the day that had just been! I also have a new appreciation for '*people without lights*'….you know who you are ☺

Other people that I would like to thank include Peter McIntyre (NCIRS), Kristine Macartney (NCIRS), Alexis Pillsbury (NCIRS), Sanjay Jayasinghe (NCRIS), Shopna Bag (WSPHU), Kirsty Hope (NSW Health), Paula Spokes (NSW Health), Nick Rose (NSW Health) and Vicky Sheppeard (NSW Health). A big thanks you to all of you.

Huge thanks goes to my wife Eileen and son Ash. Your unconditional support and understanding (yet again) had allowed me to complete this mammoth task on time. I know that I have written this before (at the completion of my PhD three years ago), and I am writing it again……..but I mean it this time!

Never Again!!!!!

In completing of this bound volume, I dedicate it to my daughter, Ivy Rose (11 July, 2016). Your arrival into this world was an experience that has trumped my MAE journey. Exhilaration, anxiety, trepidation, and a big helping of happiness; this was the mixture of emotions that I experiences as I delivered you personally in our bedroom while on the phone to '000' and waiting for the ambulance to arrive. This experience has helped enormously to manage the ups and downs of the MAE during its last few months.

Mind you …….the bottle of champagne from Kristine Macartney also helped to calm the nerves ☺

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Chapter 1

An overview of my MAE experience

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1.3 Overview

In fulfilling the requirements for the Master of Philosophy (Applied Epidemiology), this bound volume represents work completed at:

a) National Centre for Immunisation Research and Surveillance (NCIRS),

b) Western Sydney Public Health Unit (WSPHU), and

c) Communicable Diseases Branch (CDB), NSW Health.

The National Centre for Immunisation Research and Surveillance (NCIRS) is located within the Kids Research Institute (KRI) at Westmead Children's Hospital. It is somewhat hidden away from the children's hospital, and no easier to navigate internally once you find the building on your first day. During my two years there, I was part of the Coverage, Evaluation and Surveillance (CES) Program Stream, which met monthly to discuss achievements and deliverables of the group. As an active member, I was encouraged to keep the group up to date on my progress throughout my MAE journey.

The Western Sydney Public Health Unit (WSPHU) is located at Cumberland Hospital adjacent to Westmead Children's Hospital. I spent two weeks at the PHU, observing and assisting wherever possible. I helped with a measles outbreak, including contract tracing, interviewing people, maintaining clinical line lists, informing high-risk people of a measles-clinic and assisting medical staff during the running of the measles-clinic. During this emergency response, all high-risk people (including pregnant mothers and newborn babies) were contacted and provided with appropriate prophylaxis to prevent illness. During my time there, I was also very fortunate to lead a *Salmonella* outbreak investigation (Chapter 3).

The Communicable Diseases Branch (CDB) is located in the Ministry of Health building in North Sydney. I spent almost four months there conducting the epidemiological investigation (Chapter 4). During my time at the CDB, I attended staff meetings, afternoon debriefs, surveillance meetings and an in-house emergency response workshop. I was also very fortunate to be funded to attend

the OzFoodNet whole genome workshop in Melbourne. I also assisted with two *Legionella* outbreaks, where I helped to maintain line-lists and the Sit-Rep, and attended the afternoon meetings, where I was asked to take, transcribe and distribute minutes of meeting from time to time. I truly enjoyed my experience at the CDB, NSW Health.

1.4 Summary of my public health experience

1.4.1 Analysis of a public health dataset (Chapter 2)

In November 2005, hepatitis A vaccine was funded under the Australian National Immunisation Program for Indigenous children aged 12-24 months in the targeted jurisdictions of Queensland, South Australia, Western Australia and the Northern Territory. I reviewed the epidemiology of hepatitis A from 2000-2014 using data from the Australian National Notifiable Diseases Surveillance System, the National Hospital Morbidity Database, and Australian Bureau of Statistics causes-of-death data. Overall, the national hepatitis A immunisation program has had a significant impact in the targeted population with relatively modest vaccine coverage, with evidence of substantial herd protection effects.

1.4.2 Outbreak Investigation (Chapter 3)

During May 2015, an increase in *Salmonella* Agona cases was reported from western Sydney, Australia. I present the public health actions used to investigate and control this increase. A descriptive case-series investigation was conducted. Six outbreak cases were identified; all had consumed cooked tuna sushi rolls purchased within a western Sydney shopping complex. Onset of illness for outbreak cases occurred between 7 April and 24 May 2015. *Salmonella* was isolated from food samples collected from the implicated premise and a prohibition order issued. No further cases were identified following this action. In addition, this outbreak investigation also demonstrated genomics-enhanced public health action, where whole genome sequencing significantly enhanced the resolution of the epidemiological investigation.

1.4.3 Epidemiological investigation (Chapter 4)

Among adults, pneumococcal pneumonia causes significant mortality and morbidity. While the funding of polysaccharide pneumococcal vaccines have reduced the incidence of invasive pneumococcal disease (IPD) in older people, uncertainty remains regarding their effectiveness against reducing the hospitalisation rate due to community acquired pneumonia. In this study I use linked-data to document that approximately one in seven hospital admissions coded for pneumococcal pneumonia in older people of NSW were due to invasive pneumococcal disease. The remaining six hospital admissions were presumptive non-invasive pneumococcal pneumonia cases. I also documented significant declines in the rate and severity of hospitalisations over time due to presumptive non-invasive pneumococcal pneumonia. The pneumococcal polysaccharide vaccine that was used for adults has not been consistently shown to be effective against non-invasive pneumococcal pneumonia hospitalisations, while the conjugate vaccine used in the children program has provided substantial indirect protection against IPD to adults. The results presented here could impact on cost-effectiveness of pneumococcal vaccine programs in Australia.

1.4.4 Evaluation of a surveillance system (Chapter 5)

The AusVaxSafety enhanced active surveillance system was established in 2014 and has two main functions. Firstly, to gather near real-time data of AEFI following seasonal influenza vaccination of children aged between six months and five; secondly, to collate, interpret and disseminate these results in near real-time to stakeholders and the public. AusVaxSafety was evaluated to assess the usefulness of the information collected; identify strengths and limitations; and provide feedback to stakeholders regarding recommendations to the system. During the 2015 influenza season, the AusVaxSafety successfully demonstrated, in real-time, that influenza vaccines registered for used in children aged six months to five years were safe, well tolerated, and that the AEFIs experienced were within expected ranges.

1.5 Oral presentations

1. Sources of Infant Pertussis Infection in the United States; NCIRS Journal Club, October 2015.
2. Impact of the national targeted hepatitis A immunisation program in Australia: 2000-2014. Public Health Association of Australia (PHAA) 15th National Immunisation Conference. Brisbane June, 2016
3. NSW Invasive Pneumococcal Disease (IPD) Linkage Study….early findings: NCIRS Inaugural i-BESIG Meeting, August 2016.
4. Evaluation of AusVaxSafety sentinel active SMS-based surveillance system following the 2015 influenza season. NCIRS Academic Meeting, October 2016.

1.6 Additional Courses

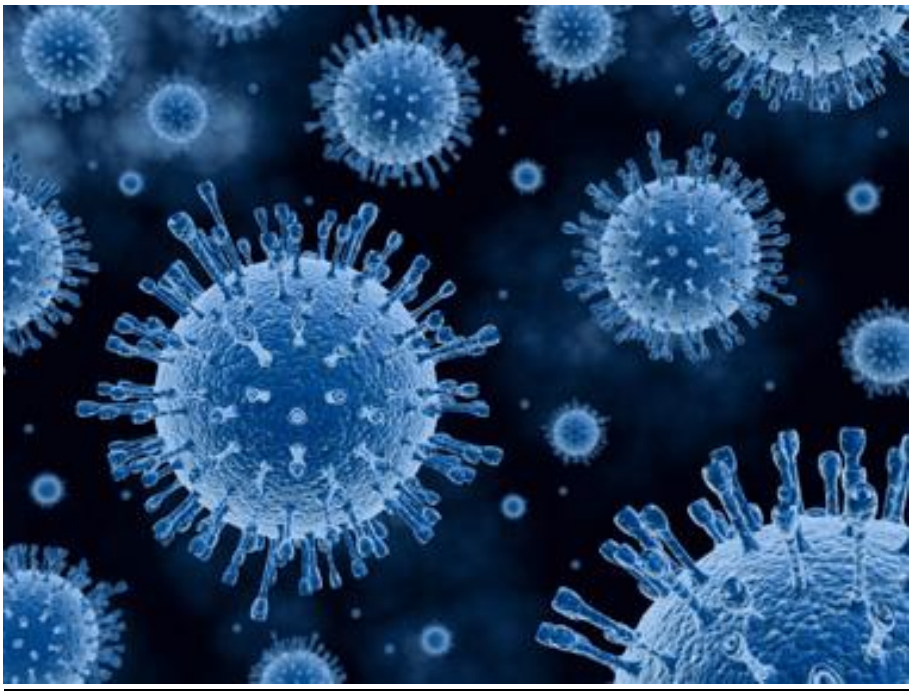
5. Managing Big Data in Health Research (PHCM9521). University of NSW, Summer Semester 2015-2016.
6. Vaccines in Public Health Workshop 2016. NCIRS, August/September 2016.

1.7 Publications in peer reviewed journals

7. Craig Thompson, Aditi Dey, Emily Fearnley, Benjamin Polkinghorne, Frank Beard. Impact of the national targeted Hepatitis A immunisation program in Australia: 2000-2014. *Vaccine* 2017; 35: 170-176.
8. Craig Thompson, Qinning Wang, Shopna Bag, Neil Franklin, Craig Shadbolt, Peter Howard, Emily Fearnley, Helen E Quinn, Vitali Sintchenko, Kirsty Hope. Epidemiology and whole genome sequencing of an ongoing point-source *Salmonella* Agona outbreak associated with sushi consumption in western Sydney, Australia 2015. *Epidemiol Infect* 2017; 145: 2062-2071.

Chapter 2

Impact of the national targeted hepatitis A immunisation program in Australia: 2000-2014



Source : www.goodtrips.org

(*Accessed 20 November 2016*)

Chapter 2 Contents

2.1 List of Tables

2.2 List of Figures

2.3 Prologue

2.3.1 Background

As I write this, I am taken back to my first day as an MAE scholar. Four hours after arriving at the National Centre for Immunisation Research and Surveillance (NCIRS), I was asked to attend an emergency Communicable Diseases Network Australia (CDNA) teleconference that had been organised to discuss the outbreak of hepatitis A and frozen berries. After the two hour teleconference, I remember thinking that I was going to have to increase my treading of water in order to keep my head above the waterline. It also became obvious that the MAE was the right direction for me and I was going to enjoy this new educational path as an epidemiologist-in-training.

2.3.2 My role

I was the principal investigator and analyst for this chapter. I was responsible for liaising with Ms Han Wang (statistician and data manager at NCIRS) to obtain access to the datasets and supporting data dictionaries. I cleaned the data, merged data and conducted all of the analyses. I conducted the literature review for this chapter, generated all tables and figures, liaised with co-authors during preparation of the manuscript to *'Vaccine'*, formatted the manuscript for the target journal, submitted the manuscript as lead-author and drafted the responses to peer-reviewers.

2.3.3 Lessons learned

Before starting this project at NCIRS, I was very fortunate to have had some experience conducting a major data analysis project during my PhD candidature. However, this data analysis was my first introduction to Stata. Throughout this project I learned many valuable skills including data cleaning, creating and validating variables, cross-tabulation, and conducting descriptive analyses and incidence rate ratios. I now have a much better understanding of count data and Poisson analyses.

I learned how to properly document a data analysis project, especially when using multiple datasets. This approach included completing an analysis plan, writing and annotating do-files, and maintaining log files in Stata so that detailed records were kept throughout. At the completion of this analysis, I definitely have a much better understanding of Stata and how to write syntax, with these new skills transferable to my new career as an epidemiologist.

Furthermore, I now have a much better understanding of hepatitis A disease, its epidemiology in Australia, and the benefits of the targeted immunisation program upon the Indigenous people of Australia.

2.3.4 Public Health impact

This impact evaluation of the hepatitis A vaccination program in Australia is an important review of a highly effective targeted program. Due to an excessive burden of disease in Indigenous people, hepatitis A vaccine became funded under the Australian National Immunisation Program (NIP) for all Indigenous children aged 12 to 24 months residing in Queensland, South Australia, Western Australia and the Northern Territory during November, 2005. Historically, targeted vaccine programs in Australia have somewhat failed to deliver the desired results. For example, the initial strategy for hepatitis B vaccination was a program targeting infants born to chronic carrier mothers; however, this was expanded to universal vaccination for all infants from 2000. Here I present a good news story that demonstrates that a targeted vaccination program can work, with evidence of the significant impact that the hepatitis A immunisation program has had in the Indigenous population of Australia.

Originally this report was to complement the Australian vaccine preventable disease epidemiological review series published in Communicable Diseases Intelligence (CDI). However, as the manuscript developed, it became obvious that the results were of public health significance, in particular to the Indigenous people of Australia, and for the success of a targeted vaccine program; it was agreed that we should target a higher impact journal with a wider target audience, such as ‘*Vaccine*’.

Since this refocus of target journals, the results have been formatted and submitted for peer-review at '*Vaccine*.' Minor comments from the peer-review have been received, addressed and resubmitted. This manuscript has been accepted for publication and is currently in press.

In addition, results of this data analysis were presented at the recent Public Health Association of Australia (PHAA) 15th National Immunisation Conference, held in Brisbane 7-9 June, 2016 (Appendix 2.1). Together, the presentation at PHAA and publication will make this data more accessible to those who rely on current information, including policy makers of the hepatitis A vaccine schedule in Australia.

2.3.5 Acknowledgements

Emily Fearnley, Frank Beard and Aditi Dey took the lead supervisory roles during this project. I am very grateful to Benjamin Polkinghorne at the Australian Government Department of Health, Helen Quinn and Peter McIntyre at NCIRS and Katrina Roper and Kerri Viney at ANU for their technical guidance, thoughtful review and feedback during the development of this chapter and the manuscript to '*Vaccine*'.

2.4 Abstract

In November 2005, hepatitis A vaccine was funded under the Australian National Immunisation Program for Aboriginal and Torres Strait Islander (Indigenous) children aged 12-24 months in the targeted jurisdictions of Queensland, South Australia, Western Australia and the Northern Territory.

I reviewed the epidemiology of hepatitis A from 2000-2014 using data from the Australian National Notifiable Diseases Surveillance System, the National Hospital Morbidity Database, and Australian Bureau of Statistics causes-of-death data. The impact of the national hepatitis A immunisation program was assessed by comparison of pre-vaccine (2000-2005) and post-vaccine time periods (2006-2014), by age group, Indigenous status and jurisdiction using incidence rate ratios (IRR) per 100,000 population and 95% confidence intervals (CI).

The national pre-vaccine notification rate in Indigenous people was four times higher than the non-Indigenous rate, and declined from 8.41 per 100,000 (95% CI 5.03 – 11.79) pre-vaccine to 0.85 per 100,000 (95% CI 0.00 – 1.99) post-vaccine, becoming similar to the non-Indigenous rate. Notification and hospitalisation rates in Indigenous children aged <five years from targeted jurisdictions declined in the post-vaccine period when compared to the pre-vaccine period (notifications: IRR = 0.07; 95% CI 0.04 – 0.13; hospitalisations: IRR = 0.04; 95% CI 0.01 – 0.16). Notification rates also declined in Indigenous people aged five to 19 (IRR = 0.08; 95% CI 0.05 – 0.13) and 20 to 49 years (IRR = 0.06; 95% CI 0.02 – 0.15) in targeted jurisdictions. For non-Indigenous people from targeted jurisdictions, notification rates decreased significantly in children aged <five years (IRR 0.47; 95% CI 0.31 – 0.71), and significantly more overall (IRR = 0.43; 95% CI 0.39 – 0.47) compared to non-Indigenous people from non-targeted jurisdictions (IRR = 0.60; 95% CI 0.56 – 0.64).

The national hepatitis A immunisation program, with relatively modest vaccine coverage, has achieved a significant impact in the targeted population with evidence suggestive of substantial herd protection effects.

2.5 Acronyms

ABS	Australian Bureau of Statistics
ACT	Australian Capital Territory
CDNA	Communicable Diseases Network Australia
CI	Confidence Intervals
ICD-10-AM	International Statistical Classification of Disease and Related Health Problems, 10th Revision, Australian Modification
IRR	Incidence Rate Ratios
NCIRS	National Centre for Immunisation Research and Surveillance
NHMD	National Hospital Morbidity Database
NIP	National Immunisation Program
NNDSS	National Notifiable Diseases Surveillance System
NSW	New South Wales
NT	Northern Territory
QLD	Queensland
SA	South Australia
TAS	Tasmania
USA	United States of America
VIC	Victoria
WA	Western Australia

2.6 Introduction

Hepatitis A causes significant morbidity globally, affecting approximately 120 million people annually[1], with the incidence of disease usually inversely correlated with level of sanitation and access to safe drinking water.[2-4] With improved sanitation and living conditions in Australia, the annual notification rate of hepatitis A has declined from 123 notifications per 100,000 population in 1961 to 1 per 100,000 population in 2014.[5,6] A number of person-to-person and foodborne outbreaks of hepatitis A have occurred in Australia over the past twenty years, including very large outbreaks associated with raw oysters (1997) and semi-dried tomatoes (2009).[7-15]

Hepatitis A vaccine was first registered for use in Australia in 1994 and has since been recommended for high-risk groups.[16] In response to an increasing number of hepatitis A cases and the death of three Aboriginal and Torres Strait Islander (henceforth referred to as Indigenous) children in north Queensland, a hepatitis A immunisation program commenced in February 1999 for all Indigenous children in this region. North Queensland has a population of approximately 600,000 people, of which 1.2% are Indigenous children aged under five years.[17,18] Two doses of hepatitis A vaccine were scheduled at 18 and 24 months of age, and catch-up vaccination recommended for children less than six years of age.[16,17] Following implementation of the north Queensland program, a rapid decline in hepatitis A notifications was reported in the Indigenous and non-Indigenous populations.[17]

In November 2005, hepatitis A vaccine was funded under the Australian National Immunisation Program (NIP) for all Indigenous children aged 12 to 24 months residing in four of the eight states and territories of Australia, namely Queensland, South Australia, Western Australia and the Northern Territory, due to a high risk of acquiring hepatitis A and resulting hospitalisation.[16] Two doses were originally scheduled at 12 months and 18 months of age in the Northern Territory and Western Australia, and at 18 and 24 months of age in Queensland and South Australia, changing to 12 and 18 months of age in all four jurisdictions in July 2013.[16,19] Over the period 2006 to 2010, decreases in hepatitis A notifications in the Indigenous Australian population was reported.[20] These

decreases in targeted jurisdictions occurred in the context of relatively modest hepatitis A vaccination coverage in Indigenous children before 36 months of age, with two-dose coverage increasing from 31% in 2007 to 60% in 2013, and one-dose coverage at 71% during 2013.[19,20]

The aim of this study was to review the epidemiology of hepatitis A in Australia from 2000 to 2014, focusing on the impact of the national hepatitis A immunisation program on both the directly targeted population (Indigenous children in the targeted jurisdictions) and broader herd protection effects Australia-wide.

2.7 Methods

2.7.1 Study design and study period

I undertook a descriptive epidemiological study with comparison of notifications and hospitalisations in the period before (2000 to 2005) and after (2006 to 2014) the introduction of the targeted hepatitis A immunisation program in Australia.

2.7.2 Data sources

Notifications

Confirmed and probable cases of hepatitis A are notifiable to the National Notifiable Diseases Surveillance System (NNDSS) under the public health legislation of each jurisdiction.[21] A confirmed case of hepatitis A requires either laboratory definitive evidence (detection of hepatitis A virus by nucleic acid testing [added to the confirmed case definition in January 2013]); or laboratory suggestive evidence (detection of hepatitis A-specific immunoglobulin M antibodies in the absence of recent vaccination [moved from definitive evidence to suggestive evidence in January 2013]) plus clinical evidence; or laboratory suggestive evidence plus epidemiological evidence (contact between two people involving a plausible mode of transmission at a time when one of them is likely to be infectious and the other has an illness that started within 15 to 50 days after this contact and at least one case in the chain of epidemiologically linked cases is laboratory confirmed).[22] A probable case requires clinical evidence plus epidemiological evidence.[22]

For this analysis, notification data included all confirmed and probable cases of hepatitis A from the NNDSS with an onset date between 1 January 2000 and 31 December 2014. For cases with no recorded onset date, I used the earliest recorded date among the fields of date of specimen, date of notification, and date when the notification was received. Variables extracted comprised onset date, age, sex, jurisdiction of residence, Indigenous status, place of acquisition, whether died from disease, and vaccination status. The analysis of the ‘place of

acquisition' data field was restricted to the years 2010 to 2014, where data completeness was 80% or greater.

Hospitalisations

The National Hospital Morbidity Database (NHMD) is an administrative database maintained by the Australian Institute of Health and Welfare. Private and public hospital discharge summaries are used to capture data relating to administrative, demographic and clinical information on patients hospitalised in Australia.[21] Using the International Statistical Classification of Disease and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) code B15 (hepatitis A), all eligible hospital admissions coded as hepatitis A (either as the principal or other diagnosis) and with an admission date between 1 January 2000 and 31 December 2013 (latest data available) were included in this analysis.

Variables extracted comprised primary or other diagnosis, date of admission, age, sex, jurisdictions of residence, Indigenous status, length of stay (bed days) and mode of separation from hospital. Jurisdiction of residence and age specific hospitalisation data were only available between 1 January 2000 and 30 June 2012.

Mortality

Mortality data related to hepatitis A were obtained from the NNDSS, NHMD and the Australian Bureau of Statistics (ABS). ABS causes of death data included in this analysis were deaths due to hepatitis A (ICD-10: code B15) as the primary underlying cause, for deaths registered between 2007 and 2011 (latest data available).

Population estimates

National, jurisdictional, age-specific and Indigenous-specific mid-year estimates of resident population sizes were obtained from the ABS.[23]

2.7.3 Data analysis

I compared notification and hospitalisation rates for two time periods, i.e. before the introduction of the hepatitis A targeted immunisation program (pre-vaccine 2000-2005) and after (post-vaccine 2006-latest available data), and for targeted (Queensland, South Australia, Western Australia and the Northern Territory) and non-targeted (New South Wales, Victoria, Tasmania and the Australian Capital Territory) jurisdictions. In this analysis, missing Indigenous data was included in the 'non-Indigenous and others' category, which will be referred to as 'non-Indigenous' for the rest of the chapter.

Notification and hospitalisation rates were calculated using ABS population estimates as the denominator and are presented as age-specific, jurisdiction-specific, or Indigenous-specific subpopulation rates per 100,000 population. Descriptive statistics included median age (and range) and average length of hospital stay. Place of acquisition for Indigenous and non-Indigenous people was compared and tested for significance using a Fisher's exact test. Age-specific incidence rate ratios (IRR), 95% confidence intervals (95% CI) and p-values were calculated for Indigenous and non-Indigenous populations at the national level, and for targeted and non-targeted jurisdictions, assuming a Poisson distribution. If the 95% CI for any age-specific or total IRR did not overlap with the corresponding comparison group, this was considered evidence of a difference beyond that expected from random variation. Analyses were conducted using STATA software (version 13.1; StataCorp, College Station, Texas USA).

Geo-mapping of hepatitis A notifications during the pre-vaccine (2000-2005) and post-vaccine (2006-2014) time periods were created using ArcGIS Online (2016; http://www.arcgis.com/home/index.html; Esri, Redlands CA, USA). Notifications were plotted using the post codes of residence variable; data points were included if they represented a cluster of three or more cases.

Ethical approval was not required as de-identified non-reidentifiable data collected in the course of routine public health surveillance was used for the analysis.

2.8 Results

2.8.1 Overarching trends

A total of 5,096 hepatitis A notifications were recorded in the NNDSS between January 2000 and December 2014, of which 5,004 (98%) were confirmed and 92 (2%) were probable cases. The overall national notification rate declined from 4.25 per 100,000 in 2000 to 0.97 per 100,000 in 2014, with a nadir of 0.65 per 100,000 in 2011. The national notification rate in Indigenous people declined from 8.41 per 100,000 (95% CI 5.03 – 11.79) during the pre-vaccine period to 0.85 per 100,000 (95% CI -0.28 – 1.98) during the post-vaccine period, while the notification rate in non-Indigenous people declined from 2.24 per 100,000 (95% CI 1.22 – 3.25) pre-vaccine to 1.17 per 100,000 (95% CI 0.71 – 1.63) post-vaccine.

In the NHMD, 3,398 hospitalisations with a diagnosis that included hepatitis A were recorded between January 2000 and December 2013. The overall national hospitalisation rate declined from 2.31 per 100,000 in 2000 to 0.89 per 100,000 in 2013, with a nadir of 0.53 per 100,000 in 2012. The national hospitalisation rate in Indigenous people declined from 4.23 per 100,000 (95% CI 3.52 – 4.94) during the pre-vaccine period to 1.09 per 100,000 (95% CI 0.46 – 1.73) during the post-vaccine period, while the hospitalisation rate in non-Indigenous people declined from 1.45 per 100,000 (95% CI 0.95 – 1.96) pre-vaccine to 0.87 per 100,000 (95% CI 0.62 – 1.13) post-vaccine. Of the 3,398 hospitalisations, 1,781 (52%) had hepatitis A identified as the primary diagnosis, with a median length of stay of three days for these 1,781 hospitalisations (range: one – 55 days).

Eight deaths (age range five – ≥ 65 years) were recorded by the ABS between 2007 and 2011 with hepatitis A as the primary underlying cause (data available for post-vaccine period only); six of these deaths were of people aged ≥ 65 years. Fewer deaths were recorded in the other data sources; NNDSS (2000 to 2014) and NHMD (2000 to 2013) captured five deaths each. Matching of deaths between data sources was not possible using the data fields available.

2.8.2 Age and sex distribution

The median age of notified and hospitalised hepatitis A cases in Australia was similar between the pre-vaccine (notifications: 28 years, range 0 – 93; hospitalisations: 41 years, range 0 – 93) and post –vaccine periods (notifications: 27 years, range 0 – 97; hospitalisations: 41 years, range 0 – 97). Overall, 6.9% of notified and 2.7% of hospitalised cases were aged less than five years. The average male to female notification ratio was 1.61:1 (range 1.16:1 - 2.54:1) in the pre-vaccine period, and 1.21:1 (range 0.95:1 - 1.47:1) in the post-vaccine period.

2.8.3 Indigenous status

Between 2000 and 2014, 6% (326/5096) of people notified with hepatitis A were recorded as Indigenous, 77% (3895/5096) as non-Indigenous and 17% (875/5096) as unknown or missing Indigenous status. Completeness of this data field was higher for the targeted jurisdictions (87% complete; 1803/2073) than non-targeted jurisdictions (80% complete; 2418/3023). Of people hospitalised with hepatitis A between 2000 and 2013, 6% (196/3398) were recorded as Indigenous, 92% (3137/3398) as non-Indigenous and 2% (62/3398) as unknown or missing Indigenous status. Between January 2000 and June 2012, completeness of this data field was slightly higher for the non-targeted jurisdictions (99% complete; 1877/1899) than targeted jurisdictions (97% complete; 1118/1158).

2.8.4 Vaccination status

Of all notifications (N= 5096), 13 (0.3%) were reported as fully vaccinated (three during the pre-vaccine period and ten during the post-vaccine period), 36 (0.7%) as partially vaccinated (four during the pre-vaccine period and 32 during the post-vaccine period), and 5047 (99%) were of unknown vaccination status (where unknown vaccination status included 'missing' and 'not vaccinated' data).

2.8.5 Place of acquisition

Of the 882 notifications with a recorded place of acquisition between 2010 and 2014, 72% (638/882; annual range 56% - 87%) were acquired overseas. Common places of overseas acquisition included the Oceania region (15.2% [134/882]), southern-east Asia (17.1% [151/882]) and southern-central Asia (21.3% [188/882]). The proportion of hepatitis A notifications acquired overseas was significantly higher in non-Indigenous people (73%; 636/874) than in Indigenous people (25%; 2/8) ($p>0.05$).

2.8.6 Jurisdiction

Targeted jurisdictions (Queensland, Northern Territory, South Australia and Western Australia)

In the targeted jurisdictions, notifications dropped from 411 in 2000 (rate 2.2 per 100,000) to 73 in 2014 (0.3 per 100,000), and hospitalisations from 188 in 2000 (1.0 per 100,000) to 24 during the first half of 2012 (0.1 per 100,000). Prior to the introduction of the national hepatitis A immunisation program Indigenous people residing within targeted jurisdictions had an 11.6 times higher notification rate (13.85 vs. 1.19 per 100,000) and a 3.9 times higher hospitalisation rate (6.20 vs. 1.61 per 100,000) of hepatitis A than Indigenous people residing within non-targeted jurisdictions (Table 2.1).

The notification rate in Indigenous people residing within targeted jurisdictions declined by 93% overall (IRR = 0.07; 95% CI 0.05 – 0.10) in the post-vaccine period. Age-specific declines were also identified; 93% for the less than five years age group (IRR = 0.07; 95% CI 0.04 – 0.13), 92% for the five to 19 years age group (IRR = 0.08; 95% CI 0.05 – 0.13) and 94% for the 20-49 years age group (IRR = 0.06; 95% CI 0.02 – 0.15). The overall notification rate in non-Indigenous people declined by 57% (IRR = 0.43; 95% CI 0.39 – 0.47), and by 51% for the less than five years age group (IRR = 0.49; 95% CI 0.33– 0.73) (Table 2.1).

Hospitalisations in Indigenous people declined by 82% overall (IRR = 0.18; 95% CI 0.12 – 0.27). Age-specific declines were also identified; 96% for the less than five years age group (IRR = 0.04; 95% CI 0.01 – 0.16), 82% for the five to 19

years age group (IRR = 0.18; 95% CI 0.09 – 0.40) and 63% for the 20-49 years age group (IRR = 0.37; 95% CI 0.20 – 0.66). In non-Indigenous people the overall hospitalisation rate declined by 46% (IRR = 0.54; 95% CI 0.48 – 0.62) (Table 2.1).

The largest decreases in notification and hospitalisation rates were in the Northern Territory (88% and 86%, respectively) and Western Australia (70% and 64%, respectively) (Figure 2.2). The geo-mapped decrease of notifications is depicted in Figure 2.3.

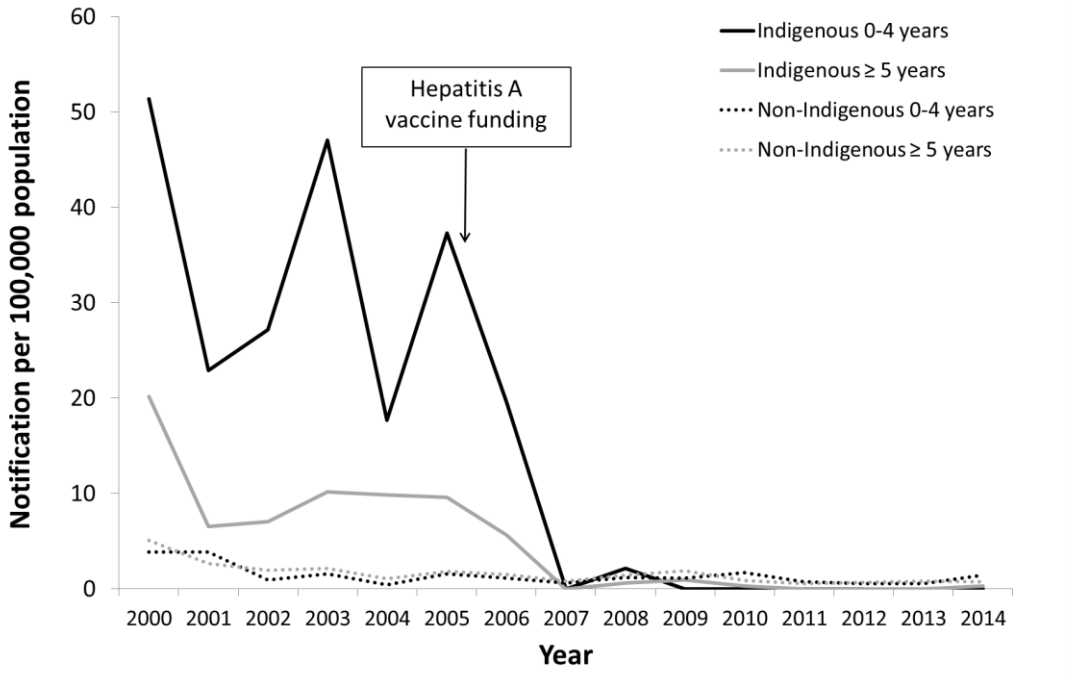
Non-targeted jurisdictions (New South Wales, Victoria, Tasmania and the Australian Capital Territory)

Notifications in Indigenous people residing in non-targeted jurisdictions declined by 53% (IRR = 0.47; 95% CI 0.23 – 0.95) in the post-vaccine period. An age-specific decline of 68% was identified for the five to 19 years age group (IRR = 0.32; 95% CI 0.11 – 0.95), while there were no notifications in children aged less than five years during the entire study period. Notifications in non-Indigenous people declined by 40% (IRR = 0.60; 95% CI 0.56 – 0.64). No significant reduction was identified in the non-Indigenous less than five years age group (IRR = 0.96; 95% CI 0.69 – 1.33) (Table 2.1).

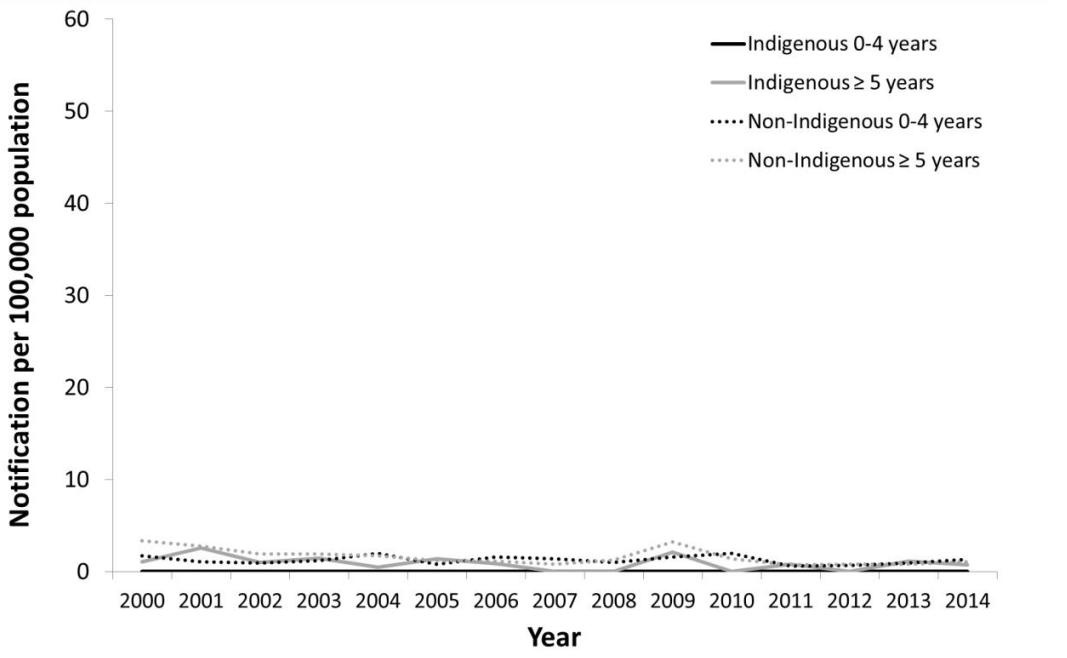
Hospitalisations in Indigenous people declined by 30%, however, this was not statistically significant (IRR = 0.70; 95% CI 0.38 – 1.27). Hospitalisations in non-Indigenous people declined by 33% (IRR = 0.67; 95% CI 0.61 – 0.73) (Table 2.1).

Figure 2.1: Targeted and non-targeted hepatitis A notification* and hospitalisation# rates of Australia, by Indigenous status, age group and year

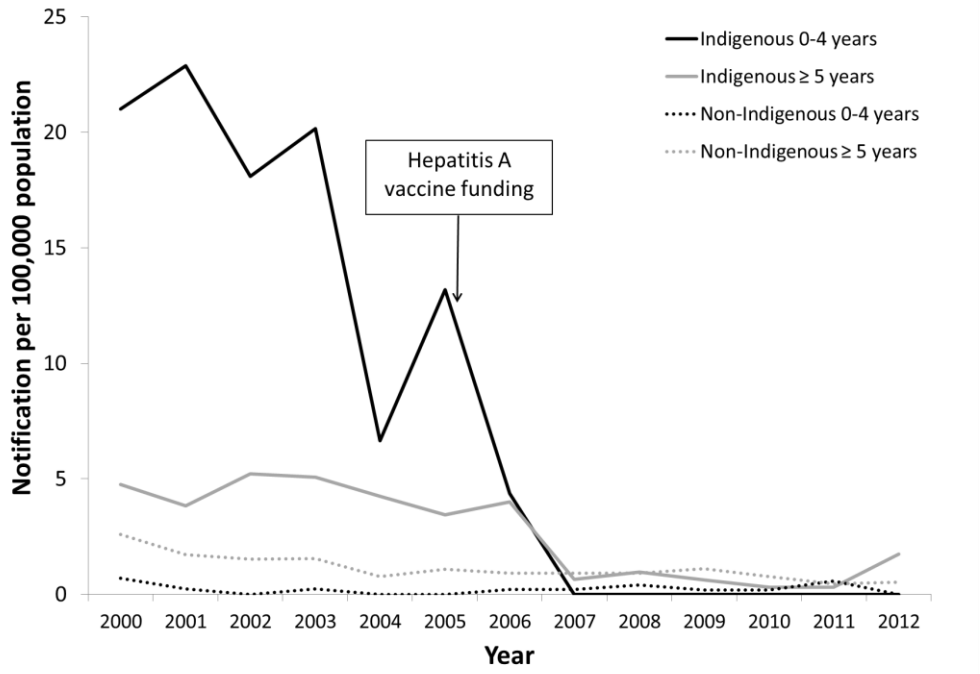
(continue on next page)



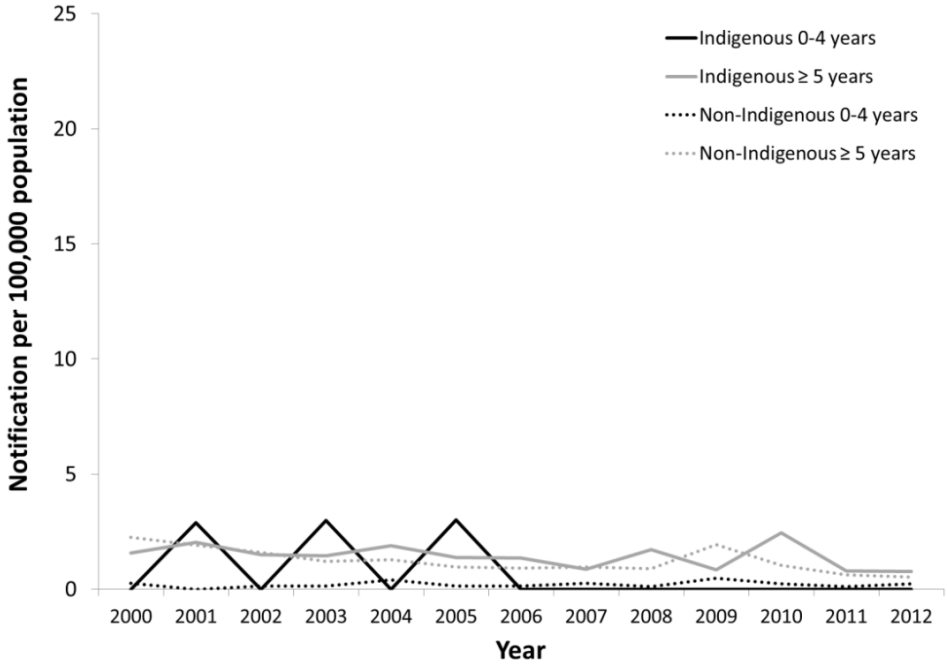
a) Notification rates for targeted jurisdictions^



b) Notification rates for non-targeted jurisdictions~



c) Hospitalisation rates for targeted jurisdictions^



d) Hospitalisation rates for non-targeted jurisdictions~

**Notifications: January 2000 - December 2014*

 # Hospitalisations: January 2000 - June 2012

^ *Targeted jurisdictions: Queensland, South Australia, Western Australia and the Northern Territory*

~ Non-targeted jurisdictions: New South Wales, Victoria, Tasmania and the Australian Capital Territory

Table 2.1: Hepatitis A notifications and hospitalisations, by age group, Indigenous status and pre-/post- vaccine period, Australia, 2000 – 2014; rates, counts and incidence rate ratios (95% CI)

a) Targeted jurisdictions: Queensland, South Australia, Western Australia and the Northern Territory

		Pre-vaccine (2000-2005)		Post-vaccine *		Incidence Rate Ratio[#]	
	Age group (years)	Non-Indigenous^ (N)	Indigenous^ (N)	Non-Indigenous^ (N)	Indigenous^ (N)	Non-Indigenous (95% CI)	Indigenous (95% CI)
Notifications	<5	2.09 (55)	33.91 (90)	0.99 (46)	2.41 (10)	**0.49 (0.33-0.73)**	**0.07 (0.04-0.13)**
	5-19	2.24 (194)	18.37 (120)	1.33 (185)	1.46 (16)	**0.59 (0.48-0.73)**	**0.08 (0.05-0.13)**
	20-49	3.30 (604)	6.13 (48)	1.30 (404)	0.38 (5)	**0.39 (0.35-0.45)**	**0.06 (0.02-0.15)**
	50-64	1.63 (116)	2.36 (3)	0.66 (88)	0.81 (2)	**0.41 (0.31-0.54)**	0.29 (0.05-1.73)
	≥65	1.01 (52)	0.00 (0)	0.35 (33)	0.98 (1)	**0.34 (0.22-0.52)**	–
	Total	2.44 (1021)	13.85 (261)	1.04 (756)	1.08 (34)	**0.43 (0.39-0.47)**	**0.07 (0.05-0.10)**
Hospitalisations	<5	0.19 (5)	16.99 (45)	0.26 (9)	0.62 (2)	1.45 (0.49-4.33)	**0.04 (0.01-0.16)**
	5-19	0.54 (47)	5.26 (35)	0.43 (44)	1.04 (8)	0.82 (0.54-1.23)	**0.18 (0.09-0.40)**
	20-49	1.95 (359)	4.51 (35)	0.89 (200)	1.72 (16)	**0.46 (0.39-0.55)**	**0.37 (0.20-0.66)**
	50-64	1.53 (108)	1.54 (2)	0.88 (87)	0.00 (0)	**0.61 (0.46-0.81)**	–
	≥65	1.76 (91)	0.00 (0)	0.94 (65)	0.00 (0)	**0.55 (0.40-0.76)**	–
	Total	1.45 (610)	6.20 (117)	0.77 (405)	1.15 (26)	**0.54 (0.48-0.62)**	**0.18 (0.12-0.27)**

b) Non-targeted jurisdictions: New South Wales, Victoria, Tasmania and the Australian Capital Territory

		Pre-vaccination (2000-2005)		Post-vaccination *		Incidence Rate Ratio[#]	
	Age group (years)	Non-Indigenous^ (N)	Indigenous^ (N)	Non-Indigenous^ (N)	Indigenous^ (N)	Non-Indigenous (95% CI)	Indigenous (95% CI)
Notifications	<5	1.21 (55)	0.00 (0)	1.23 (92)	0.00 (0)	0.96 (0.69-1.33)	–
	5-19	2.21 (319)	1.96 (10)	1.79 (393)	0.57 (5)	**0.81 (0.70-0.94)**	**0.32 (0.11-0.95)**
	20-49	2.89 (907)	1.09 (6)	1.43 (720)	0.70 (7)	**0.50 (0.46-0.56)**	0.67 (0.23-1.99)
	50-64	1.12 (133)	0.00 (0)	0.77 (164)	0.86 (2)	**0.69 (0.55-0.87)**	–
	≥65	1.07 (102)	2.07 (1)	0.64 (107)	0.00 (0)	**0.59 (0.45-0.78)**	–
	Total	2.12 (1516)	1.19 (17)	1.25 (1476)	0.55 (14)	**0.60 (0.56-0.64)**	**0.47 (0.23-0.95)**
Hospitalisations	<5	0.18 (8)	1.48 (3)	0.23 (12)	0.00 (0)	1.28 (0.52-3.14)	–
	5-19	0.53 (77)	0.81 (4)	0.61 (99)	0.28 (1)	1.18 (0.87-1.58)	0.20 (0.02-1.80)
	20-49	1.79 (562)	2.50 (14)	1.01 (383)	2.08 (15)	**0.60 (0.52-0.68)**	0.88 (0.42-1.82)
	50-64	1.56 (185)	0.90 (1)	1.15(177)	1.99 (4)	**0.76 (0.62-0.93)**	2.67 (0.30-23.88)
	≥65	2.22 (211)	2.34 (1)	1.19 (142)	0.00 (0)	**0.54 (0.44-0.67)**	–
	Total	1.45 (1043)	1.61 (23)	0.94 (813)	1.10 (20)	**0.67 (0.61-0.73)**	0.70 (0.38-1.27)

**Post-vaccine period- Notifications: January 2006- December 2014; Hospitalisations: January 2006- June 2012*

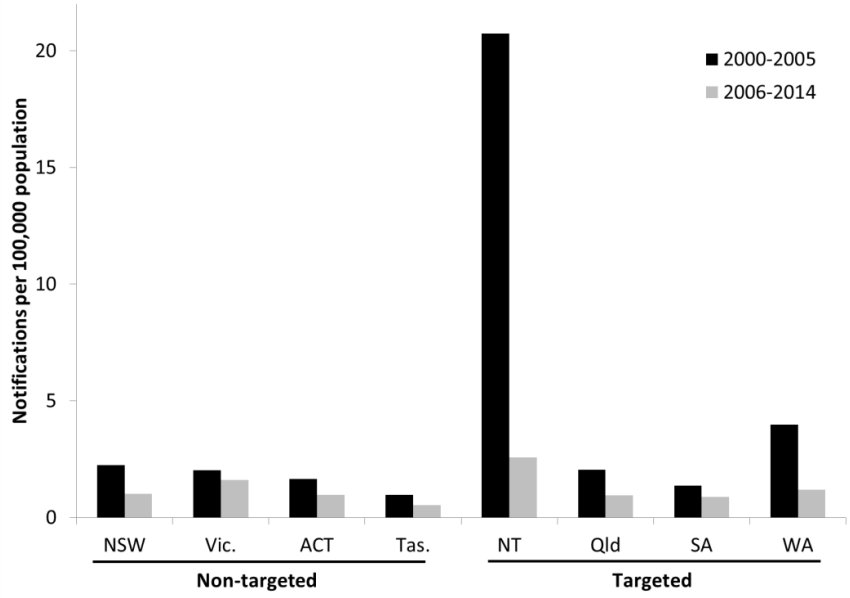
 # Comparison of pre- and post-vaccine periods

^ average annual rate per 100,000 total population

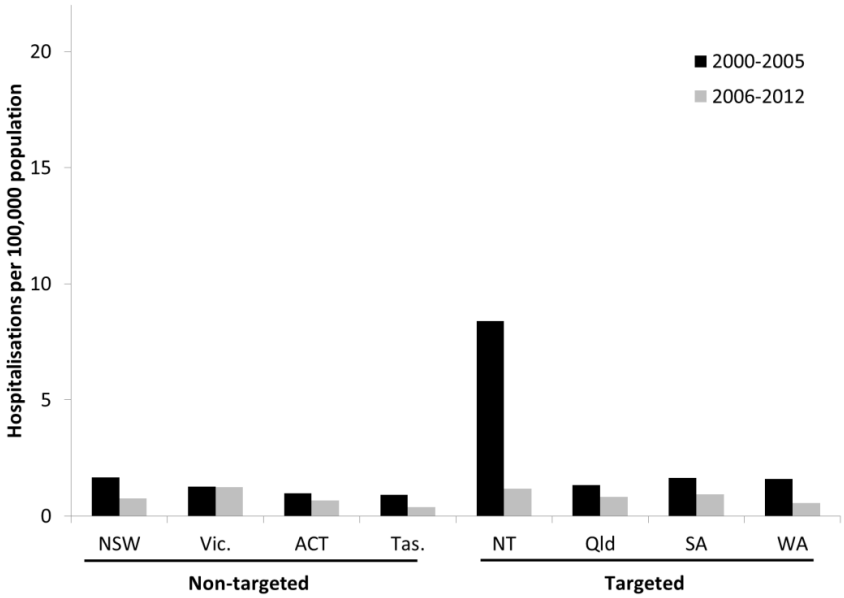
N= number of cases

***bold** IRR denote significant reductions (p-value < 0.05)*

Figure 2.2: Hepatitis A notification and hospitalisation rates by jurisdiction, and pre-/post- vaccine period, Australia, 2000 to 2014



a) Notification rates in pre-vaccine period 2000-2005 and post vaccine period 2006-2014

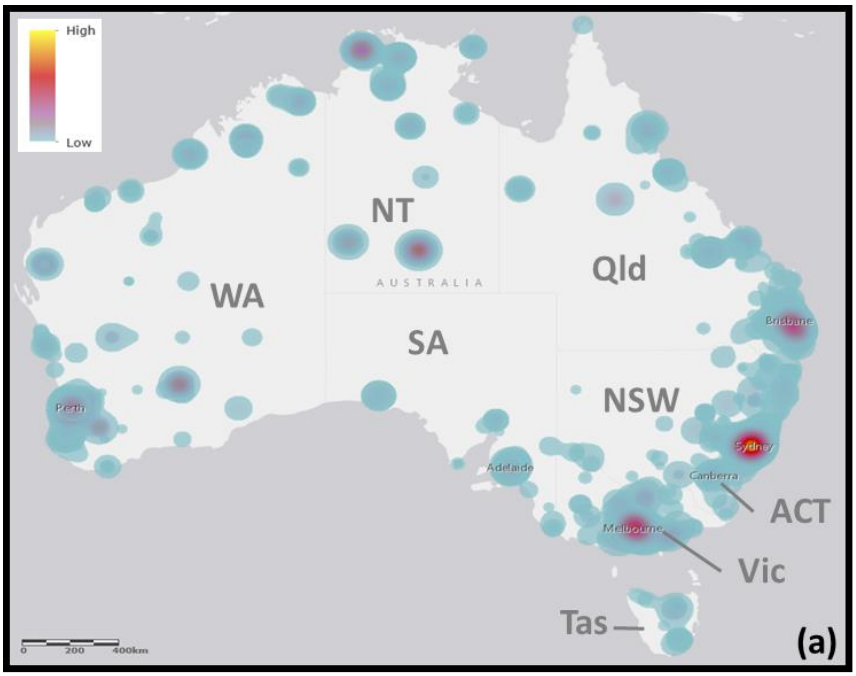


b) Hospitalisation rates in pre-vaccine period 2000-2005 and post vaccine period 2006-2012

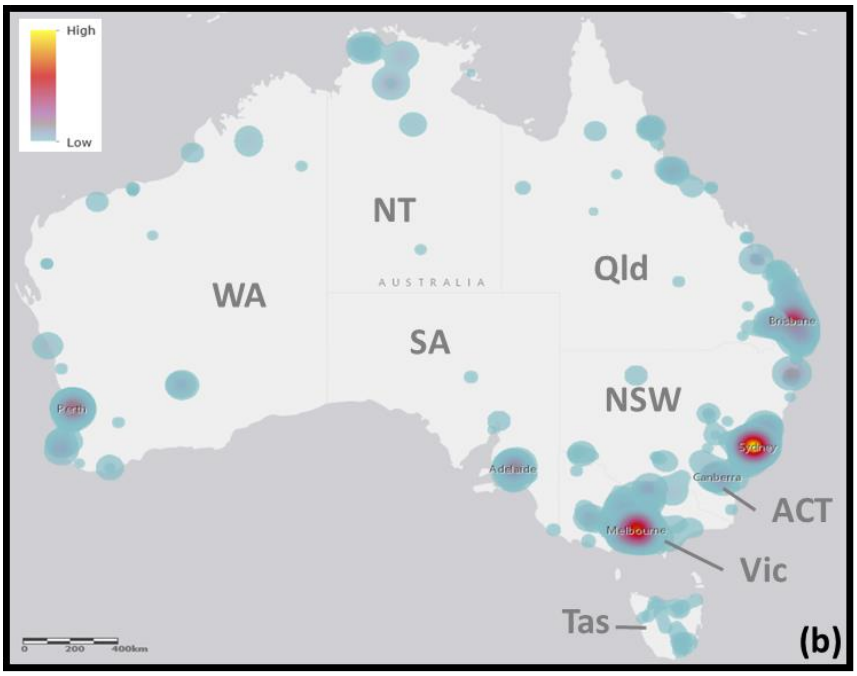
Non-targeted: NSW- New South Wales; VIC.- Victoria; ACT- Australian Capital Territory; TAS- Tasmania

Targeted: NT- Northern Territory; QLD- Queensland; SA- South Australia; WA- Western Australia

Figure 2.3: Geo-mapping of hepatitis A notifications in Australia using post codes of residence



a) Notifications in pre-vaccine period 2000-2005



b) Notifications in post vaccine period 2006-2014

Non-targeted: NSW- New South Wales; VIC.- Victoria; ACT- Australian Capital Territory; TAS- Tasmania

Targeted: NT- Northern Territory; QLD- Queensland; SA- South Australia; WA- Western Australia

Cluster point represented by three of more cases

2.9 Discussion

Significant declines in hepatitis A notification and hospitalisation rates (93% and 96%, respectively) between the pre- and post-vaccine periods were observed in the population directly targeted by the national hepatitis A immunisation program in Australia, that being Indigenous children aged less than five years residing in targeted jurisdictions. The program also appears to have provided substantial herd protection to both the Indigenous and non-Indigenous populations aged five to 49 years within targeted jurisdictions. Notification rates declined in the post-vaccine period by 92% for the five to 19 years Indigenous age group, and by 94% for the 20 to 49 years age group, compared to 68% and 33%, respectively, in non-targeted jurisdictions, with the decrease being significantly different to the non-targeted jurisdictions for the latter age group. In non-Indigenous people, the notification rate in targeted jurisdictions decreased by 51% for children aged less than five years, and by 57% overall, with the overall decrease being significantly different to the overall decrease in non-targeted jurisdictions.

These decreases in targeted jurisdictions occurred in the context of relatively modest hepatitis A vaccination coverage in Indigenous children.[24,25] Young children play a key role in the transmission of hepatitis A to other children and adults, as they are usually asymptomatic (or only mildly symptomatic) and have lower levels of personal hygiene.[17,18,26] Significant, albeit lower, decreases in hepatitis A notifications were also observed between the pre- and post-vaccine periods in both Indigenous and non-Indigenous populations in non-targeted jurisdictions (53% and 40%, respectively). These decreases may also be partly attributable to the targeted national immunisation program given the extensive population movement of Indigenous people between states and territories of Australia.[27]

The national targeted hepatitis A immunisation program appears to have been highly effective at reducing the incidence of disease in Australia. However, the descriptive nature of this study makes it difficult to quantify the exact contribution of this program. Of note, the funding of a hepatitis A immunisation program in north Queensland from 1999 (with estimated two-dose coverage of 77% in the Indigenous birth cohort for the year 2000[17]) may have led to an underestimation

of the true impact of the national targeted program. Other factors, including the targeted immunisation of high-risk groups (such as travellers to hepatitis A endemic areas, and people with an increased risk of exposure to hepatitis A based on their occupation or lifestyle) as recommended in the Australian Immunisation Handbook[16], may also have contributed to the declines Australia-wide. However, available information indicates that hepatitis A vaccination coverage of adults in high-risk groups such as travellers to hepatitis A endemic areas, although recommended since 1994, is relatively low.[28,29]

More general limitations of this data are that hepatitis A notifications may underestimate true incidence, particularly in young children, and may be influenced by changes in case definition, diagnostic and public health follow-up practices over time and across jurisdictions. In particular, the national hepatitis A case definition was amended in January 2013, changing the definitive laboratory evidence required to confirm a case from serology to the more specific nucleic acid testing, and changing serology to laboratory suggestive evidence requiring clinical or epidemiological evidence to confirm a case. False positive IgMs occur with serology, particularly in the elderly population and in the presence of other infectious agents. Therefore, the test should only be performed in patients with a clinical picture of hepatitis A. The impact of the amended case definition on notification data is unclear but could mean that during the final years of this investigation we could have overestimated the impact of the targeted vaccination program, with fewer cases (i.e. fewer false positive cases) included in the analysis resulting from a more specific case definition.

Hospitalisation data can be influenced by access to hospital care, changes in admission practices and coding error. Also, given that only 52% of cases have hepatitis A identified as the primary diagnosis, we could have overestimated hospitalisation by using all diagnostic fields coded for hepatitis A, as we cannot be as sure about the actual contribution of hepatitis A to that hospitalisation. The accuracy of hospital coding could be significantly improved by the linking of hospitalisation data with the notification dataset, as core data in the NNDSS dataset would help to clarify the case status (with the importance of this methodology discussed further in Chapter 4). As recommended by the Australian Institute of Health and Welfare, all hospitalisation data were included for analyses

of Indigenous status.[30] However, data relating to Indigenous status from the non-targeted jurisdictions should be interpreted with caution, as weighted completeness for Indigenous identification in public hospitals during 2011-12 was below the level considered acceptable (80%) in Tasmania, the Australian Capital Territory, and Victoria.[30]

Declines in hepatitis A in indigenous populations following targeted childhood immunisation programs have also been reported in the United States of America (USA), although without clear evidence of broader herd protection impacts on the non-indigenous population.[31-34] However Indigenous Australians make up a greater proportion (2.4%) of the Australian population than Native Americans and Alaskan Natives do in the USA (0.9%).[33,35] Substantial herd protection effects arising from universal childhood hepatitis A immunisation programs have been documented in Israel, Argentina and the USA, with the USA introducing a national universal program in 2006 following evidence of substantially higher decreases in incidence in states with universal programs already in place.[36-40] However, targeted hepatitis A vaccination programs have generally been estimated to be more cost-effective in lower incidence settings than universal programs.[41] The World Health Organization recommends mass vaccination programs in countries moving from high to intermediate hepatitis A endemicity, but targeted programs in countries with low endemicity.[1] The USA is the only low endemicity country of similarly high income to Australia that has introduced a universal childhood program. As of 2011, the hepatitis A notification rate in the USA was similar to that reported in Australia (0.4 and 0.6 per 100,000, respectively) despite reasonable vaccination coverage in the USA among children aged 19-35 months (78-87% one-dose coverage and 50-57% two dose coverage in 2011).[42]

In most Western European countries hepatitis A incidence has also declined to below 1.0 per 100,000, in the context of immunisation programs targeting only individuals at high risk.[43] Universal routine vaccination of children has been associated with increased age of infection, and hence risk of more severe disease.[44,45] In the context of the targeted Australian immunisation program there was no observed change in the median age of notified and hospitalised cases between pre- and post-vaccine periods.

The relatively low hepatitis A seroprevalence in the Australian population (approximately 55% in persons aged less than 70 years, from Victoria during 2008 [46]) leaves a large pool of susceptible individuals. Non-immune individuals in Australia, and other developed countries, remain at risk of hepatitis A, particularly when they travel to endemic countries and during foodborne outbreaks linked to the global food economy, such as those which occurred in Australia in 2009, associated with imported semi-dried tomatoes,[9] in the USA in 2013, associated with imported pomegranate arils,[37,47] and in Europe, Australia and New Zealand, associated with raw and frozen berries.[7,48-51] The majority of hepatitis A cases (ranging from 56% to 87% between 2010 and 2014) in Australia now acquire their infection while travelling to endemic countries. Increasing hepatitis A vaccine coverage among travellers will reduce the risk of importation and subsequent secondary spread. However, this has proven difficult to achieve in Australia and further research is needed to inform effective strategies.[28,29] Foodborne outbreaks are also difficult to prevent, even with rigorous food safety standards in place, due to the difficulties involved in testing for hepatitis A virus in imported foodstuffs.[52,53] A universal infant hepatitis A immunisation program in Australia could help mitigate the impact of foodborne outbreaks: however, this would involve substantial cost and take decades to have its full effect.

2.10 Conclusions

In summary, the national hepatitis A immunisation program in Australia has had a significant impact in the targeted population, with evidence suggesting a broader herd protection effect. Ongoing surveillance is required to be sure that the current targeted immunisation strategy is maintaining satisfactory disease control.

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2.12 Appendix 2.1 - PowerPoint presentation

Conference: PHAA 15th National Immunisation Conference

Title: Impact of the national targeted hepatitis A immunisation program in Australia: 2000-2014

Type: Oral Presentation

Theme: Vaccine Preventable Diseases

Session: 3B Vaccine Preventable Diseases Jun 8, 2016

Time: 10:30 AM - 12:00 PM

Acknowledgement

- Frank Beard (NCIRS)
- Aditi Dey (NCIRS)
- Emily Fearnley (ANU)
- Helen Quinn (NCIRS)
- Kerri Viney (ANU)

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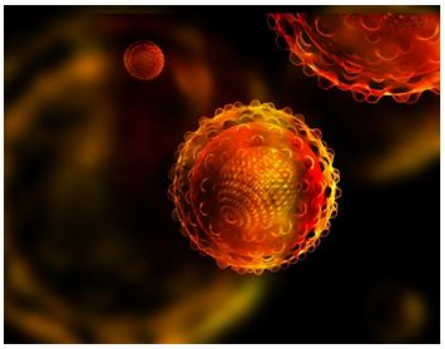
Introduction - hepatitis A



- Significant morbidity globally
- Predominantly transmitted faecal-orally
- Reduced incidence of disease usually associated with improving sanitation and living conditions
- Young children pay a key role in the transmission of hepatitis A
- 50% to 90% of infected children less than 5 years of age are asymptomatic

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Hepatitis A immunisation

- 1994: Vaccine first registered for use in Australia
- 1999: Targeted hepatitis A immunisation program commenced for all Indigenous children in north Queensland
  - Two doses scheduled at 18 and 24 months of age, and catch-up vaccination for children less than six years of age

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Hepatitis A immunisation

- November 2005: Vaccine funded under the National Immunisation Program (NIP), for Indigenous children aged 12 to 24 months old
  - Two doses scheduled before 24 months of age

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Aims

- To review hepatitis A epidemiology in Australia from 2000 to 2014
  - Focus on the impact of the national hepatitis A immunisation program:
    - on the targeted population
    - broader herd protection effect

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Data source

- National Notifiable Diseases Surveillance System (NNDSS)
  - notifications
  - 2000 – 2014
- National Hospital Morbidity Database (NHMD)
  - hospitalisations
  - 2000 – 2013
- Australian Bureau of Statistics (ABS)
  - population estimates
  - 2000 – 2014

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Data analysis

- Descriptive epidemiological study
- Comparison of national notification and hospitalisation rates
  - pre-vaccine: 2000-2005
  - post-vaccine: 2006-2014
- Targeted jurisdictions: Qld, SA, WA and NT
- Non-targeted jurisdictions: NSW, Vic, Tas and ACT
- Poisson Analysis: age-specific incidence rate ratios (IRR) and 95% confidence intervals (95% CI) calculated for different Indigenous and non-Indigenous populations

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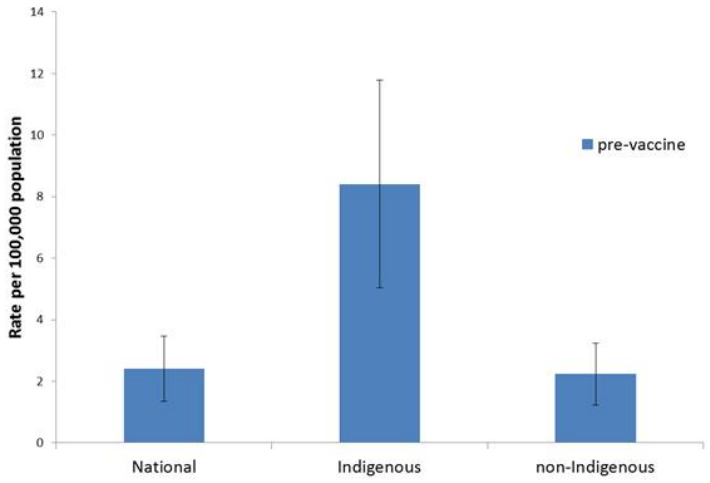
Results - national

Hepatitis A notification rates of Australia; notifications pre-vaccine 2000 to 2005 by year of diagnosis



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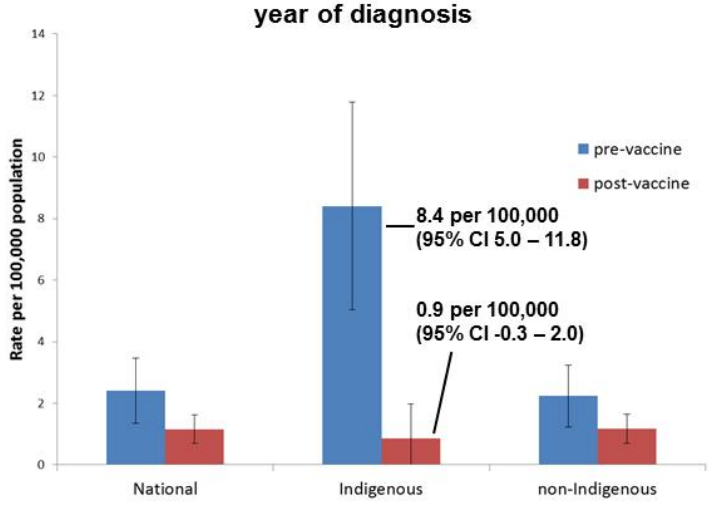
Results - national

Hepatitis A notification rates of Australia; notifications pre-vaccine 2000 to 2005, post-vaccine 2006 to 2014 by year of diagnosis



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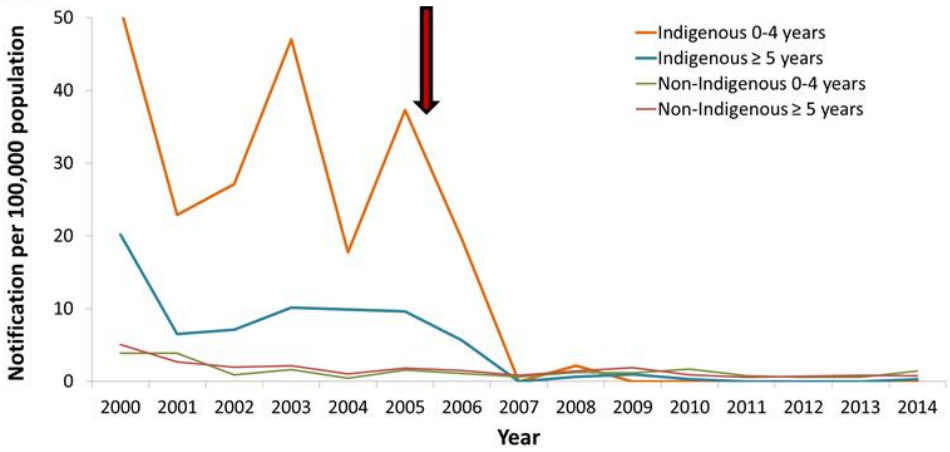
Results: targeted jurisdictions (Qld, NT, SA and WA)

Hepatitis A notification rates among Indigenous and non-Indigenous aged <5 and ≥ 5 years in funded states of Australia; notifications 2000 to 2014 by year of diagnosis



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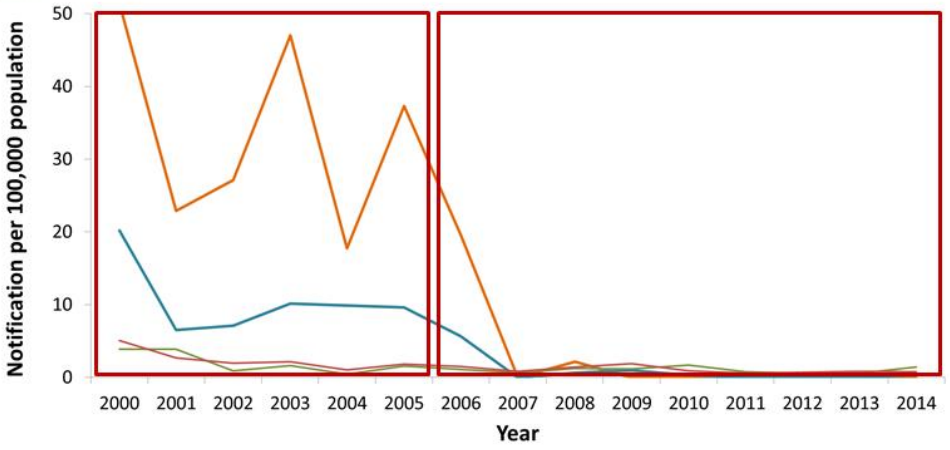
Results: targeted jurisdictions (Qld, NT, SA and WA)

Hepatitis A notification rates among Indigenous and non-Indigenous aged <5 and ≥ 5 years in funded states of Australia; notifications 2000 to 2014 by year of diagnosis



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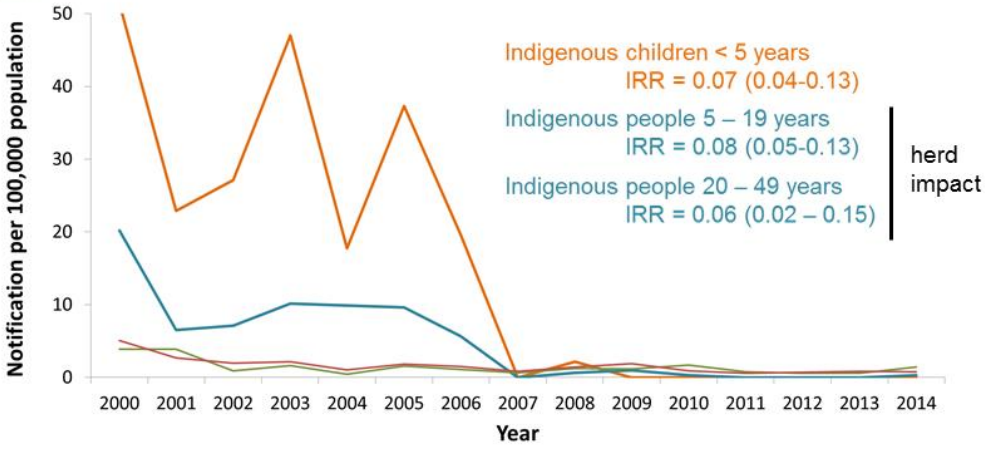
Results: targeted jurisdictions (Qld, NT, SA and WA)

Hepatitis A notification rates among Indigenous and non-Indigenous aged <5 and ≥ 5 years in funded states of Australia; notifications 2000 to 2014 by year of diagnosis



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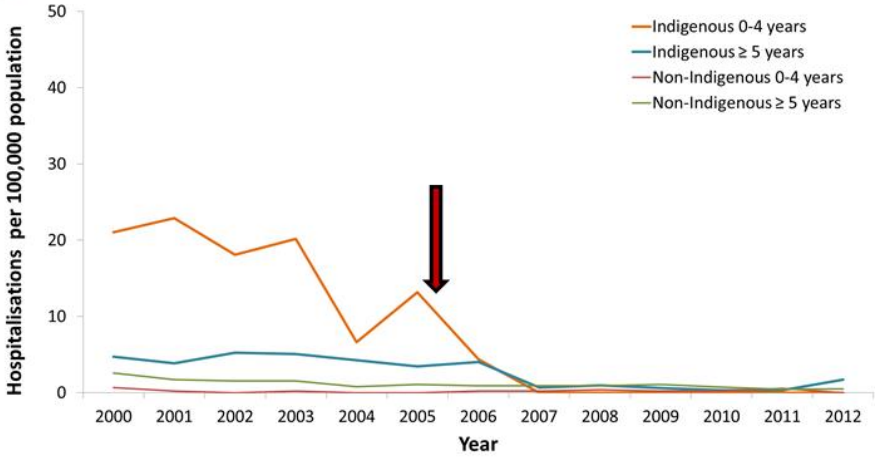
Results: targeted jurisdictions (Qld, NT, SA and WA)

Hepatitis A hospitalisation rates among Indigenous and non-Indigenous aged <5 and ≥ 5 years in funded states of Australia; hospitalisations 2000 to 2013 by year of admission



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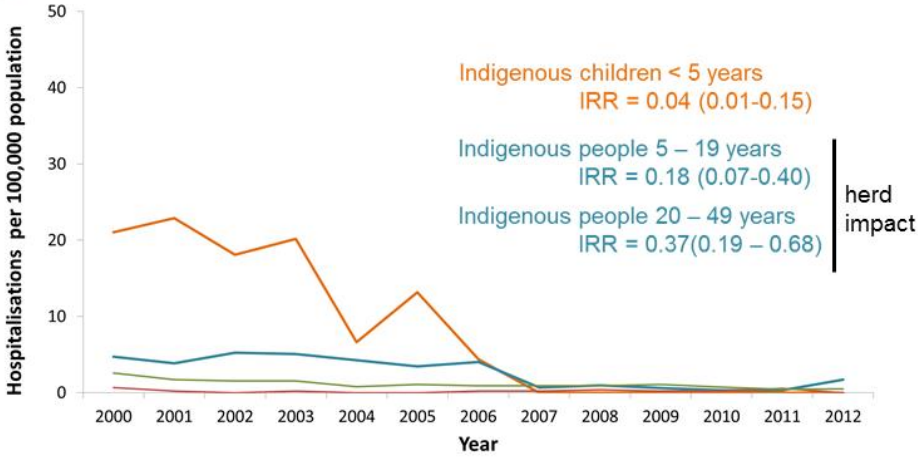
Results: targeted jurisdictions (Qld, NT, SA and WA)

Hepatitis A hospitalisation rates among Indigenous and non-Indigenous aged <5 and ≥ 5 years in funded states of Australia; hospitalisations 2000 to 2013 by year of admission



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Results: comparison between targeted and non-targeted jurisdictions

Indigenous people

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Results: comparison between targeted and non-targeted jurisdictions

- In non-targeted jurisdiction (NSW, ACT, Vic and Tas)
  - Total number of notifications: pre-vaccine 17 & post-vaccine 14
    Total number of hospitalisations: pre-vaccine 23 & post-vaccine 20
  - Zero notifications for Indigenous children < 5 years between 2000-14
  - Very low numbers for other age groups
  - Wide confidence intervals
- Targeted jurisdictions not able to be compared to non-targeted

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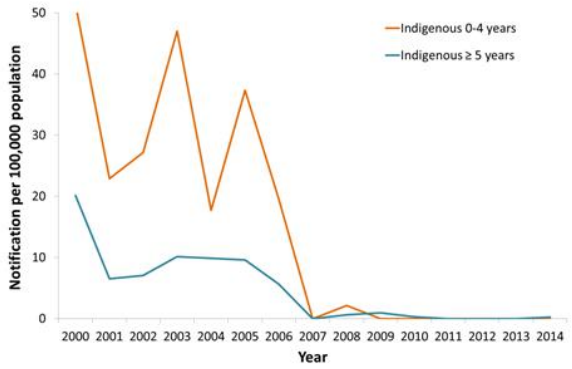
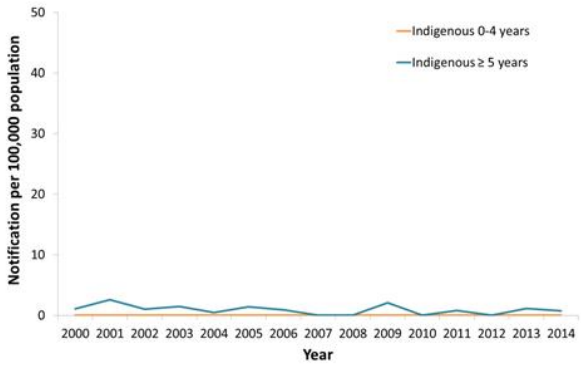
Results: comparison between targeted and non-targeted jurisdictions

Targeted jurisdictions



Non-targeted jurisdictions



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Results: comparison between targeted and non-targeted jurisdictions

Non-indigenous people

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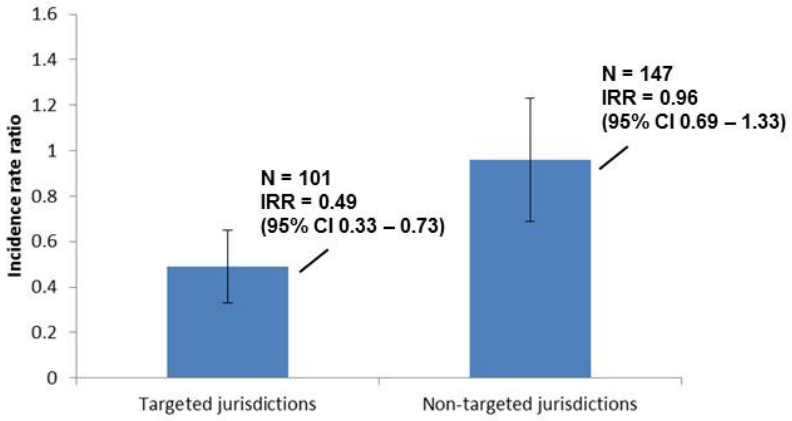
Results: comparison between targeted and non-targeted jurisdictions

Hepatitis A incidence rate ratios for non-Indigenous children (<5 years), Australia; notifications 2000 to 2014 by year of diagnosis



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Limitations

- Descriptive study - difficult to quantify the exact contribution of the vaccination program
- Funding of a hepatitis A immunisation program in north QLD from 1999
  - two-dose coverage - 77% in the Indigenous birth cohort of 2000
  - underestimate the true impact of the national targeted program
- The targeted immunisation of high-risk groups, as recommended in the Australian Immunisation Handbook, may have contributed to the declines Australia-wide
- More general limitations - hepatitis A notifications may underestimate true incidence, particularly in young children

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Conclusions

- Good news story – overall downward trend of hepatitis A notifications and hospitalisations in Australia since 2000
- Notification and hospitalisation rates in Indigenous children aged < 5 years from targeted jurisdictions have declined dramatically
  93% and 96% reduction respectively
- Decreases have occurred in the context of relatively modest hepatitis A vaccination coverage in Indigenous children before 36 months of age -

  2-dose coverage increasing from 31% in 2007 to 60% in 2013
  and 1-dose coverage at 71% during 2013[1, 2]

1. Hull et al., 2009
2. Hull et al., 2013

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Conclusions

- Similar hepatitis A notification rates to USA - 0.4 vs. 0.6 per 100,000[1]
  -national universal program vs targeted program
- Significant herd protection to the Indigenous community aged 5-49 years within targeted jurisdictions
- Broader herd protection effect to the non-Indigenous community residing within targeted jurisdictions

1. Murphy et al., 2016

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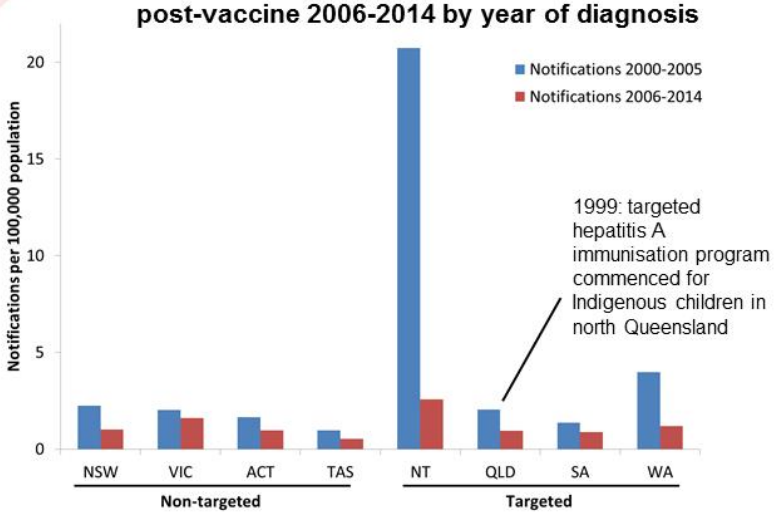
Consideration of results

Hepatitis A notification rate for all Australians, by state and territory and pre- and post- vaccine period; notifications pre-vaccine 2000 to 2005 and post-vaccine 2006-2014 by year of diagnosis



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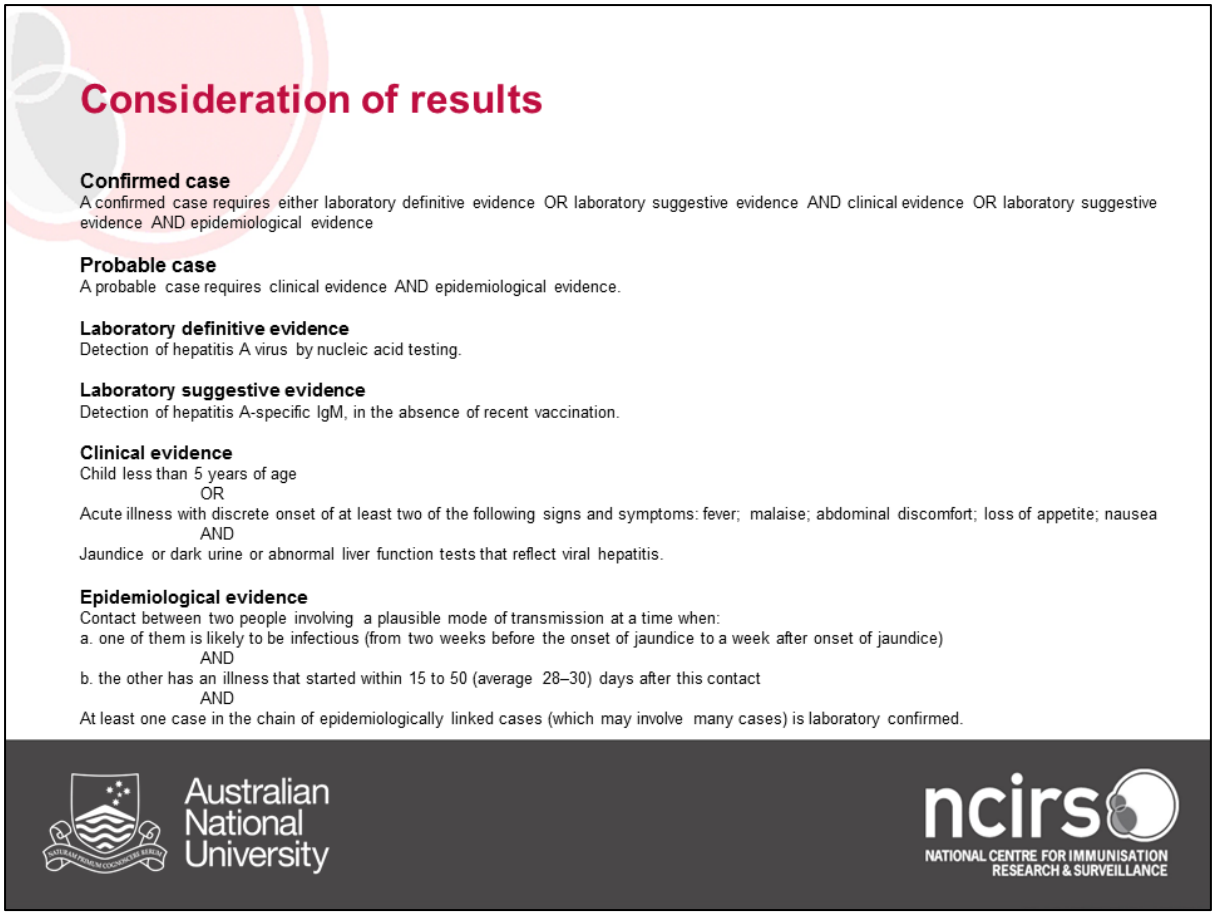
Consideration of results
Confirmed case
A confirmed case requires either laboratory definitive evidence OR laboratory suggestive evidence AND clinical evidence OR laboratory suggestive evidence AND epidemiological evidence
Probable case
A probable case requires clinical evidence AND epidemiological evidence.
Laboratory definitive evidence
Detection of hepatitis A virus by nucleic acid testing.
Laboratory suggestive evidence
Detection of hepatitis A-specific IgM, in the absence of recent vaccination.
Clinical evidence
Child less than 5 years of age
OR
Acute illness with discrete onset of at least two of the following signs and symptoms: fever; malaise; abdominal discomfort; loss of appetite; nausea
AND
Jaundice or dark urine or abnormal liver function tests that reflect viral hepatitis.
Epidemiological evidence
Contact between two people involving a plausible mode of transmission at a time when:
a. one of them is likely to be infectious (from two weeks before the onset of jaundice to a week after onset of jaundice)
AND
b. the other has an illness that started within 15 to 50 (average 28–30) days after this contact
AND
At least one case in the chain of epidemiologically linked cases (which may involve many cases) is laboratory confirmed.
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Chapter 3

Epidemiology and whole genome sequencing of an ongoing point-source *Salmonella* Agona outbreak associated with sushi consumption in western Sydney, Australia 2015

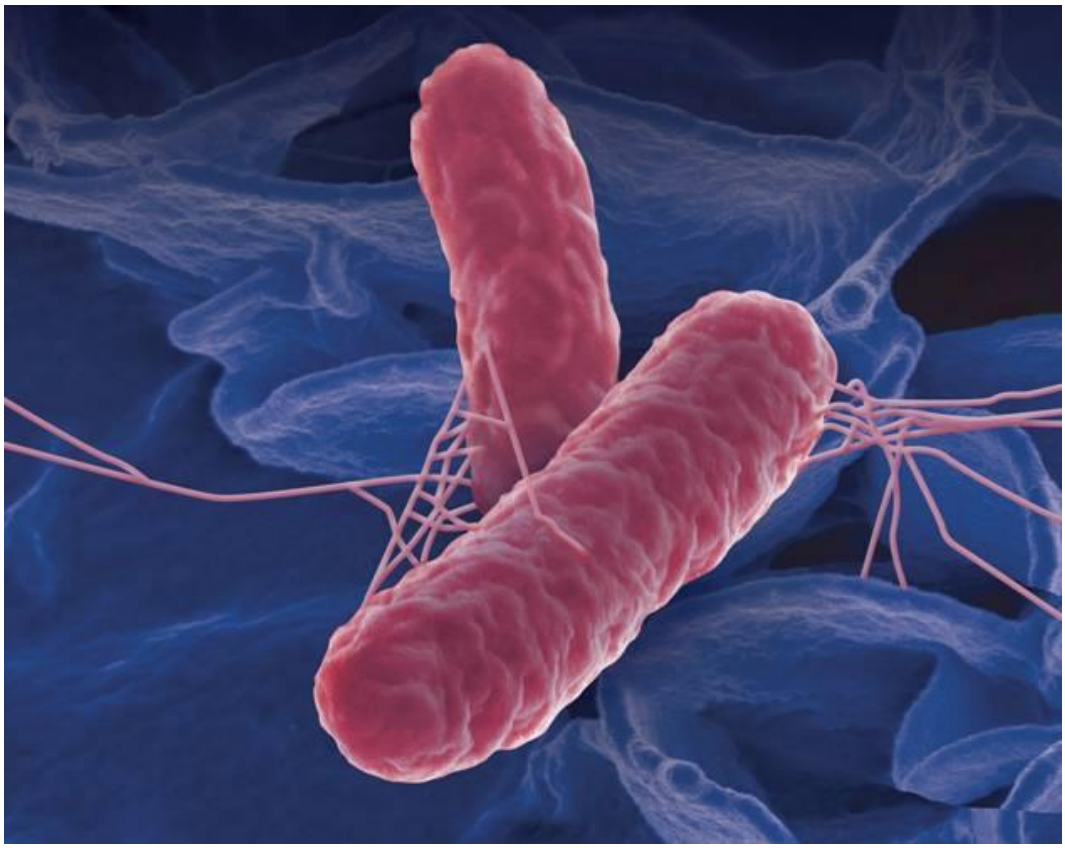

Image from '*Food Poison Journal*'
(Accessed 25 October 2016)
http://www.foodpoisonjournal.com/food-poisoning-information/what-to-know-during-a-salmonella-outbreak/#.WA75_l3ou70

Chapter 3 Contents

3.1 List of Tables

3.2 List of Figures

3.3 Prologue

3.3.1 Background

This chapter represents the second core component of the Master of Philosophy in Applied Epidemiology (MAE) field program, in which I conducted a descriptive case-series epidemiological investigation and assisted with the interpretation and presentation of results. I was initially contacted by the Western Sydney Public Health Unit (WSPHU) at 12:35pm on 4 June 2015 and informed about the *Salmonella* cluster in western Sydney. Three hours later, I was sitting in Dr Shopna Bag's office being briefed of the situation. I went home that evening, with questionnaire in hand, going over and over the delivery of questions for the interviews. I conducted the first three interviews the following day (5 June 2015) and completed the final interview on the 17 June 2015.

3.3.2 My role

I took a lead role in the descriptive case-series epidemiological investigation, interviewing as many cases as I could, scheduling meetings, and attending all meetings that took place with the epidemiological team, the food authority and the laboratory. Meetings, which included both teleconferences and face-to-face, were held regularly between 10 June and 17 September.

Importantly, I was the person that first made the connection between *Salmonella* Agona cases and exposure to sushi in western Sydney. Following the first three interviews on 5 June no common exposures were identified between these cases. After the fourth interview (9 June 2015), Dr. Bag and I suggested that petting animals could be a possible source, with exposure to animals at the Royal Easter Show (17 to 30 March 2016) and the Hawkesbury Show (24 to 26 April 2015). This hypothesis was followed up and the investigatory team had decided to discuss this further during a teleconference scheduled for the following day (10 June 2015). Just prior to this teleconference, I managed to contact the fifth case and conduct an interview. During this interview, a common theme of sushi consumption from a particular shopping complex in western Sydney and illness became plausible. I finished this interview just as the teleconference was starting.

The feedback regarding the petting animals was not encouraging, with different animals used at the two shows. Following this negative result, I suggested to the team that the source could be sushi. Based on this suggestion, the New South Wales (NSW) Department of Primary Industries (DPI) inspected two sushi outlets soon after the teleconference; the results of this first inspection are discussed further in this chapter.

In the time since the outbreak investigation, I have continued to synthesise and analyse results, write and format a manuscript, communicate with co-authors and submit a manuscript to "*Epidemiology and Infection*." I am the lead author on this potential publication and I am currently awaiting feedback from the peer-reviewers.

3.3.3 Lessons learned

I truly learned a lot from this outbreak investigation. I learned how to be part of a multidisciplinary public health team, organise meetings, provide epidemiological information during meetings, interview cases, discuss and support different hypothesis, analyse, interpret and present results, write a manuscript, and communicate effectively and efficiently within a large team. On a number of occasions I communicated directly with the WSPHU, Communicable Diseases Branch (CDB) NSW Health, NSW DPI and NSW Enteric Reference Laboratory to gain a better understanding of their procedures, processes and results.

Another key learning from this outbreak was my growing understanding of whole genome sequencing and its increasing role during outbreak investigations. It appears likely that this modern methodology will become routine during outbreak investigations, and I feel very privileged to have been part of its early evaluation and application with outbreaks in Australia. I was also very fortunate to attend the OzFoodNet workshop in Melbourne during 2016 to learn more about this technology and its application.

I acknowledge that this outbreak included only a small number of cases and did not require the recruitment of controls for a case-control investigation. However, I feel that I have developed a lot of other relevant skills pertaining to how to

conduct an outbreak investigation that will be highly applicable during my next outbreak. I feel very privileged to have been part of this outbreak team.

3.3.4 Public Health impact

This multidisciplinary outbreak investigation was responsible for correcting various hygiene and food safety control defects identified at a sushi outlet. This outlet was responsible for a point-source foodborne outbreak of *S*. Agona in western Sydney, Australia between April and June 2015. *Salmonella* was isolated from food samples collected from the implicated premise and a prohibition order issued. No further cases were identified following this action. This investigation demonstrated a multidisciplinary approach to public health action. In addition to the manuscript currently under review at '*Epidemiology and Infection*,' results of this investigation have already been presented in the '*OzFoodNet—Enhancing Foodborne Disease Surveillance Across Australia*' report (2nd Quarter Summary, 2015 NSW) (Appendix 3.2) and '*The Broad Street Pump'* (June 2016, Issue 43) (Appendix 3.3).

3.3.5 Acknowledgements

Emily Fearnley and Helen Quinn took the lead supervisory roles during this project. I would like to acknowledge the following people for their time and assistance with this outbreak investigation: Shopna Bag (WSPHU); Kirsty Hope and Neil Franklin (CDB, NSW Health); Craig Shadbolt and Alan Edwards (NSW DPI); and Vitali Sintchenko, Qinning Wang and Peter Howard (NSW Enteric Reference Laboratory). I am very grateful to Katrina Roper for her technical guidance, thoughtful review and feedback during the development of this chapter.

3.4 Abstract

During May 2015, an increase in *Salmonella* Agona cases was reported from western Sydney, Australia. We examine the public health actions used to investigate and control this increase. A descriptive case-series investigation was conducted. Six outbreak cases were identified; all had consumed cooked tuna sushi rolls purchased within a western Sydney shopping complex. Onset of illness for outbreak cases occurred between 7 April and 24 May 2015. *Salmonella* was isolated from food samples collected from the implicated premise and a prohibition order issued. No further cases were identified following this action. Whole genome sequence (WGS) analysis was performed on isolates recovered during this investigation, with additional *S.* Agona isolates from sporadic-clinical cases (with unknown epidemiological status) and routine food sampling in New South Wales, January to July 2015. Clinical isolates of outbreak cases were indistinguishable from food isolates collected from the implicated sushi outlet. Five additional clinical isolates not originally considered to be linked to the outbreak were genomically similar to outbreaks isolates, indicating the point-source contamination may have started before routine surveillance identified an increase. This investigation demonstrated the value of genomics-guided public health action, where near real-time WGS enhanced the resolution of the epidemiological investigation.

3.5 Acronyms

BP	Base-Pairs
CDB	Communicable Disease Branch
CI	Confidence Intervals
DNA	Deoxyribonucleic Acid
DPI	Department of Primary Industries
MAE	Master of Philosophy in Applied Epidemiology
NCIMS	Notifiable Conditions Information Management System
NSW	New South Wales
SNP	Single Nucleotide Polymorphisms
UPGMA	Unweighted Pair Group Method with Arithmetic mean
WGS	Whole Genome Sequence
WSPHU	Western Sydney Public Health Unit

3.6 Introduction

Salmonellosis is a zoonotic disease which remains the second most commonly notified gastrointestinal disease in Australia, following campylobacteriosis.[1] Transmission to humans occurs via the consumption of raw or inadequately cooked foods of animal origin, or by food items and untreated water contaminated with infected faeces from a reservoir host.[1-3] The incubation period of salmonellosis is typically 12-36 hours (range 6-72 hours), with symptoms including diarrhoea (sometimes bloody), fever, vomiting, abdominal pain and nausea.[3] The severity of disease is often related to different factors, including the serotype of *Salmonella*, the dose ingested, and the immunocompetency of the patient; death from salmonellosis is a rare event.[3]

Salmonella enterica subsp*. enterica* serovar Agona (*Salmonella* Agona) was originally isolated from cattle in Ghana in 1952, and became an emerging public health problem in the United States of America, the United Kingdom, the Netherlands and Israel following the importation of contaminated Peruvian fish meal during the 1970s.[4-6] Presently, *S*. Agona is recognised as a common global cause of salmonellosis in both animal and humans,[7] and is a contaminant of farmed livestock and vegetables,[8-10] and factory prepared foods.[11-14] *Salmonella* Agona has been ranked among the top 15 most frequent *Salmonella* serotypes in North America, seventh in Europe, and 15th in Australia during 2006.[7,15] Outbreaks of *S.* Agona have occurred in Ireland,[11] United Kingdom,[16,17] United States of America,[17-20] Israel,[21] Finland,[5] France,[13] Germany[22] and Australia[23] with some sources of *S.* Agona identified as chickens,[24,25] cattle,[26] Peruvian fishmeal,[27] dry unsweetened cereals,[19] and powered infant formula.[13]

Whole genome sequencing (WGS) of foodborne bacteria of public health importance provides the ability to distinguish between isolates of interest within an individual outbreak.[28,29] Enhanced management of outbreaks using WGS helps to confirm the contamination source, characterise transmission events using near real-time methodology and increased quality control of data.[28,29] Along with the comprehensive genetic information provided by WGS, comes additional information regarding antibiotic resistance, virulence determinants and genome evolution.[30] As technology becomes less cost-prohibitive and turnaround times

are reduced, WGS is expected to benefit communicable disease surveillance and outbreak investigations of foodborne disease.[28,31,32] It is essential, as the application of WGS advances quickly, that the public health community understands the benefits of the analytical methods used to explore their data.[33]

Salmonellosis is notifiable within New South Wales (NSW),[34,35] with records aggregated within the Notifiable Conditions Information Management System (NCIMS). *Salmonella* isolates from public and private pathology providers, and the NSW Department of Primary Industries (DPI) are routinely referred to the NSW Enteric Reference Laboratory, Centre for Infectious Diseases and Microbiology Laboratory Services for serotyping using the White-Kauffmann-Le Minor scheme (9th Ed 2007).[29] During routine surveillance, the NSW Communicable Disease Branch identified nine cases of *S.* Agona in May 2015, all clustered geographically in western Sydney. This report examines the epidemiological and molecular investigation of an increase in *S.* Agona cases in NSW between January and July, 2015.

3.7 Methods

3.7.1 Epidemiological investigation of the outbreak

A retrospective review of notifications in NCIMS was conducted, with de-identified data extracted for laboratory-confirmed *S*. Agona cases diagnosed within NSW between 1 January 2011 and 31 December 2014. Extracted variables included notification date, onset date and jurisdiction of residence. Average number of cases per year and 95% confidence intervals (95% CI) were calculated (assuming a Poisson distribution of count data) for the entire NSW population, with NSW population estimated obtained from NSW Health.

A descriptive case-series investigation was conducted on all notified cases of *S*. Agona, residing in the western Sydney area, and with a notification date of salmonellosis between March and June 2015. Telephone interviews of cases or surrogates (either a parent or guardian when the case was a child aged less than 16 years) were conducted using a standardised *Salmonella* questionnaire. Questions covered case demographics and illness, food consumption history, travel and environmental exposures seven days prior to the onset of disease.

At the time of the epidemiological investigation it was discussed how we would conducted a case-control analysis if further cases were notified (Appendix 3.1). This methodology was not required during this particular investigation.

3.7.2 Food and environmental investigation of the outbreak

Based on the responses of interviewed cases, the NSW DPI conducted investigations at two separate sushi premises (Sushi-A and Sushi-B), both operating within one large shopping complex in western Sydney. The NSW DPI inspected both Sushi-A and Sushi-B on 17 June 2015, with follow-up inspections conducted at Sushi-B. Food and environmental samples were collected during each inspection and sent to the NSW Enteric Reference Laboratory for *Salmonella* identification and further molecular typing of isolates. Management and staff members at both premises were questioned by the NSW DPI during

these inspections, regarding food preparation techniques, cleaning processes and staff illnesses.

3.7.3 Retrospective whole genome sequence analysis

A retrospective WGS analysis was performed on clinical and food isolates recovered during this descriptive cases-series investigation, along with additional *S*. Agona isolates from sporadic-clinical cases and routine food samples (collected by the NSW DPI) in NSW, during the period January to July 2015. The genomic deoxyribonucleic acid (DNA) was prepared using an automated workstation Chemagic Prepito-D (PerkinElmer). The DNA sequencing libraries were prepared using the Nextera XT DNA preparation kit (Illumina) and the sequencing was performed on the NextSeq 500 (Illumina) with 2 x 150 base-pairs (bp) paired-end chemistry. Sequencing data quality was checked by FastQC v1.0.0 (BaseSpace Labs, Illumina). Single nucleotide polymorphisms (SNP) were identified using CLC Genomics Workbench v8.0 (Qiagen) by mapping reads to the reference genome *S*. Agona 460004 2-1 (GenBank: NZ_CP011259). The significant thresholds for SNP calling were set for a minimum coverage at 20 and a minimum variant frequency at 80%.

The generated SNP list from each of the isolates were exported as Excel files and a binary type SNP matrix representing presence and absence of SNP in each isolates was generated. The clustering analysis was performed using a categorical coefficient with an unweighted pair group method with arithmetic mean (UPGMA) in BioNumerics (Applied Maths). To validate the clustering analysis, *de novo* assembly was performed in the CLC Genomics Workbench with a minimum contig-size set at 200 bp. The assembly was then mapped against the reference genome for SNP calling and phylogeny inferred using a web-based server (https://cge.cbs.dtu.dk/services/CSIPhylogeny/). Maximum likelihood trees at 100 bootstraps were generated from SNP fasta file using MEGA-6.[36]

3.8 Results

3.8.1 Outbreak

Historically, an annual average of 28.3 cases of *S.* Agona (N= 113; 95% CI 17.2 – 39.3) were notified in NSW between 1 January 2011 and 31 December 2014. Within the epidemiological investigation period (March to June 2015), 19 cases residing in the greater western Sydney area were notified, and were included in the descriptive case-series investigation. Sixteen of these 19 clinical cases (84%) were contactable for an interview, of which, six had consumed sushi that had been purchased from an outlet within a large shopping complex in western Sydney. Onset of illness for these six outbreak cases occurred between 7 April and 24 May 2015. These six outbreak cases had a median age of 8 years (age range 3 – 45 years), with five reporting symptoms of diarrhoea (median duration of 5.5 days: range 2 - 8 days), and four with bloody stools. Two cases, both aged less than 14 years, presented to the emergency department with one case hospitalised for three days due to the severity of symptoms.

Of the remaining ten clinical cases of the descriptive case-series investigation, no common exposures were identified during interviews. Salmonellosis experienced by a mother and her new-born baby were possibly hospital related; two cases unrelated to each other had recently returned home from international travel (Vanuatu and Thailand); two regularly attended child-care; and one was a resident of an aged care facility. No high-risk exposures were identified for three cases. Repeated attempts to contact the remaining three cases for an interview were unsuccessful.

On 17 June 2015, food and environmental samples were collected from two different sushi venues (Sushi-A and Sushi-B) operating within a large shopping complex in western Sydney. All food and environmental samples collected from Sushi-A were negative for the isolation of *Salmonella*. Cooked tuna sushi rolls from Sushi-B (Figure 3.1) were found positive for *S.* Agona culture, while the individual ingredients of the sushi rolls and environmental samples were each negative (Table 3.1). *Salmonella* Kiambu was isolated from raw chicken pieces collected from Sushi-B. Due to specific food hygiene and food safety defects identified, Sushi-B was issued with a notice requiring corrective action. Cooked

tuna sushi rolls and the cooked tuna mix (cooked tuna, mayonnaise and sugar) collected on 26 June 2015 from Sushi-B were positive for *S.* Agona (Table 3.1). This subsequent health breach was indicative of inadequate hygiene and food safety controls at Sushi-B that posed a risk to consumers.

On 6 July 2015, immediately following the availability of laboratory results, a Prohibition Order was issued to Sushi-B prohibiting the handling or production of cooked tuna sushi rolls intended for sale on the premises. At the time of issuing the Prohibition Order, a third batch of food and environmental samples were collected. Cooked tuna sushi rolls were positive for *S.* Agona for a third time, as again was the cooked tuna mix (Table 3.1). Further samples were collected on 16 July 2015 from Sushi-B, including a 'test batch' of cooked tuna sushi rolls, all of which were negative for the isolation of *Salmonella* (Table 3.1). On 22 July 2015, the Prohibition Order was lifted from Sushi-B. In total, 35 days had elapsed between initial inspection by the NSW DPI and final lifting of the Prohibition Order (Figure 3.2).

It was revealed that a staff-member at Sushi-B had been ill during early May 2015, with symptoms including vomiting and diarrhoea whilst at home on a rostered day-off; no stool sample was collected for testing. This staff member, when questioned by the NSW DPI, confirmed that they had consumed sushi rolls while at work between 28 and 30 April 2015, as staff members at Sushi-B are entitled to one sushi roll per shift. This staff member could not recall which varieties of sushi were eaten on those days but indicated that it could have been cooked tuna, salmon or chicken. Daily work duties for this staff member included preparing sushi rolls at the designated preparation bench and serving customers.

Figure 3.1: Sushi-B operating within a large shopping complex in western Sydney, New South Wales

Table 3.1: Food and environmental samples collected by the NSW Department of Primary Industries (DPI) from Sushi-B between 17 June and 16 July 2015

Date	Samples collected	Sample type *(Env = Environmental)*	Test Result *(S=Satisfactory U=Unsatisfactory)*
17.06.15	Raw chicken pieces	Food	U (*S.* Kiambu detected)
	Raw sliced beef	Food	S
	Sliced cucumber	Food	S
	Sliced avocado	Food	S
	Composite red cabbage and red pepper	Food	S
	Cooked chicken strips	Food	S
	Chicken and avocado sushi roll	Food	S
	Cooked acidified white rice	Food	S
	Cooked acidified brown rice	Food	S
	Raw whole shell eggs	Food	S
	Chicken avocado and cucumber sushi rolls	Food	S
	2 x Beef and cucumber sushi rolls	Food	S
	2 x Avocado and vegetable sushi rolls	Food	S
	2 x Cooked tuna sushi rolls (cucumber + avocado)	Food	U (*S.* Agona detected)
	Total of 15 environmental samples	Env	S
26.06.15	Unsanitised unwashed lettuce	Food	S
	Cooked acidified white rice	Food	S
	Cooked beef	Food	S
	Composite vegetables	Food	S
	Sliced avocado for sushi rolls	Food	S
	Cooked chicken	Food	S
	Cooked tuna mix (tuna + mayonnaise + sugar)	Food	U (*S.* Agona detected)
	Garnish carrots and cabbage shredded	Food	S
	Cooked tuna and avocado sushi roll	Food	U (*S.* Agona detected)
	Cooked tuna and cucumber sushi roll	Food	U (*S.* Agona detected)
	Avocado and vegetable sushi roll	Food	S
	Chicken teriyaki sushi roll	Food	S
	Beef teriyaki sushi roll	Food	S
	Salmon and avocado sushi roll	Food	S
	Total of 16 environmental samples	Env	S
06.07.15	Cucumber (whole before washing)	Food	S
	Avocado whole	Food	S
	Sliced avocado	Food	S
	Sliced cucumber	Food	S
	Cooked tuna mix (tuna + mayonnaise + sugar)- large container	Food	U (*S.* Agona detected)
	Cooked tuna mix (tuna + mayonnaise + sugar)- small container	Food	U (*S.* Agona detected)
	Cooked acidified white rice	Food	S
	Cooked tuna and avocado sushi roll	Food	U (*S.* Agona detected)
	Cooked tuna and cucumber sushi roll	Food	S
	Nori sheets	Food	S
	Mayonnaise (opened)	Food	S
	Mayonnaise (sealed)	Food	S
	Sugar	Food	S
	Total of 5 environmental samples	Env	S
16.07.15	Total of 22 foods- including all ingredients for new trial batch of cooked tuna sushi rolls and additional foods not previously sampled (white and black sesame seeds, panko breadcrumbs, teriyaki sauce, hot pepper sauce, canned tuna (both sealed and after removing from the can), beef teriyaki sushi rolls and chicken teriyaki sushi rolls)	Food	S
	Sushi preparation bench	Env	S

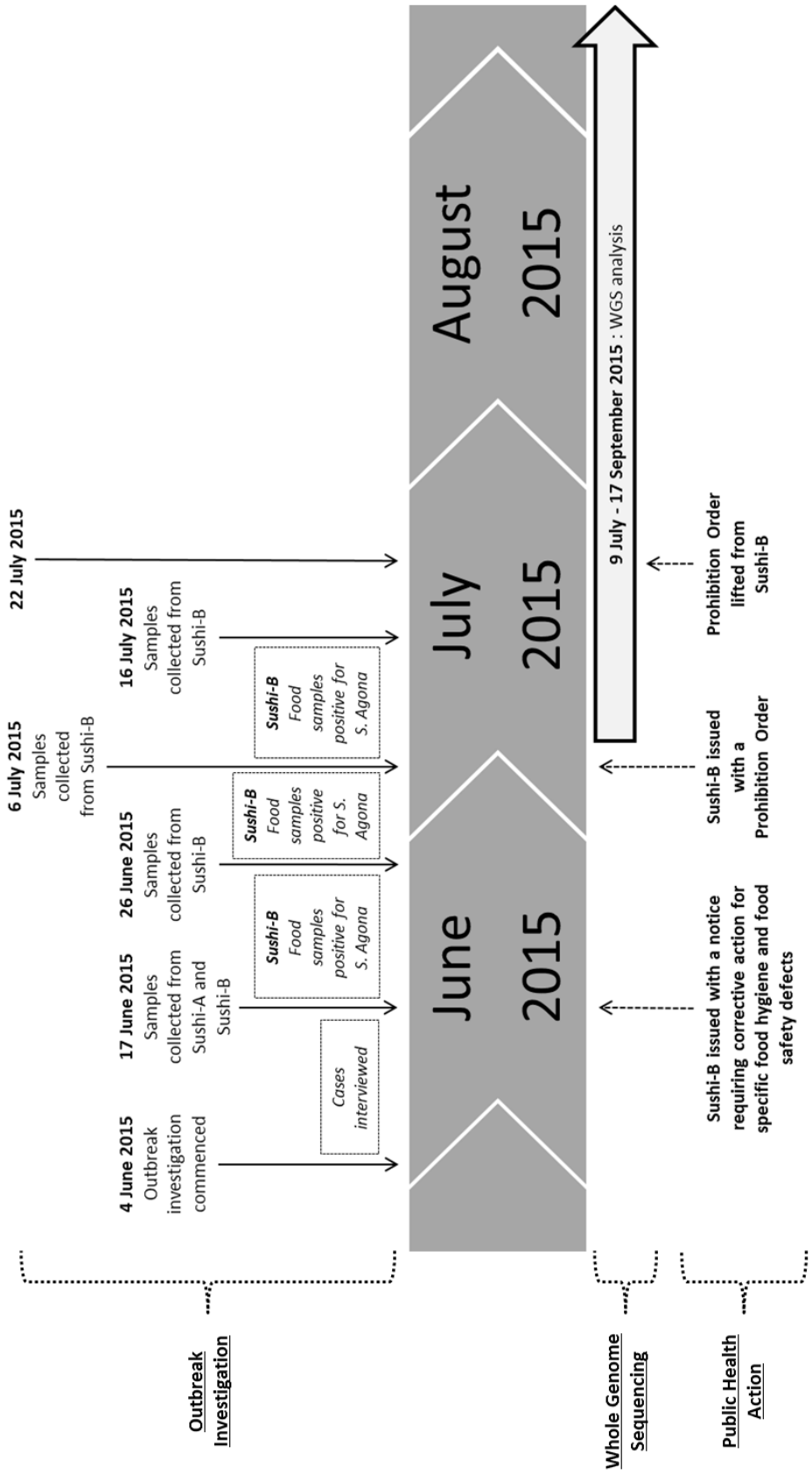

Figure 3.2: Time line of the outbreak investigation, retrospective whole genome sequencing analysis and public health action

3.8.2 Whole genome sequencing

Forty-eight isolates serotyped as *S*. Agona and referred to the NSW Enteric Reference Laboratory between January and July 2015 were subjected to whole genome sequencing. These included 38 clinical isolates (from 35 notified cases) and ten food isolates. The 38 clinical isolates encompassed 21 clinical isolates collected during the descriptive case-series investigation (from the 19 *S.* Agona notifications of residents in the western Sydney area, March to June 2015, and included two repeat samples) and 17 sporadic-clinical isolates (from *S*. Agona notifications in the wider region of NSW, January to July 2015, and included one repeat sample). Based on the epidemiological results of this investigation, six of the 21 clinical isolates collected during the descriptive case-series investigation were classified as outbreak isolates (recovered from people who had consumed sushi purchased from within a large shopping complex in western Sydney). Of the ten food isolates, six were recovered from samples collected from Sushi-B, March to July 2015, and four were collected as part of routine survey work by the NSW DPI, January to March 2015 (Figure 3.3).

The maximum likelihood phylogenetic tree of *S.* Agona, based on the SNP analysis of these 48 isolates, grouped 17 isolates together with a 0 - 1 SNP variation across clustered genomes (Figure 3.3). These included the six outbreak isolates, and six food isolates collected from Sushi-B during the outbreak (Cluster-A, Figure 3.3). Also within Cluster-A were four sporadic-clinical isolates (with unknown epidemiological status) collected in NSW between January and March 2015, and a single clinical isolate recovered from a non-contactable individual who was originally included in the descriptive case-series investigation. All clinical isolates within Cluster-A had similar genetic relatedness to food isolates recovered from Sushi-B during this outbreak (Figure 3.3).

Two isolates of *S*. Agona obtained from raw retail chicken samples (collected between February and March 2015) and re-sampled isolates collected from an elderly individual at an aged care home (Cluster-B, Figure 3.3) had similar genomic content to the outbreak isolates (Cluster-A, Figure 3.3). The SNP variation between isolates of Cluster-A and Cluster-B did not exceed 4 - 8 bp across the entire genome. A mother and her new-born, who had onset dates

within three days of each other and were not related to the outbreak, had indistinguishable *S*. Agona genomes by SNP analysis (Cluster-C, Figure 3.3). *Salmonella* Agona recovered from cases with overseas travel histories were genetically unrelated to the outbreak isolates of Cluster-A (Figure 3.3).

In total, 11 clinical isolates were grouped within Cluster-A by genetic analysis. This included (a) six outbreak isolates; (b) a single clinical isolate recovered from a non-contactable individual who was part of the descriptive case-series investigation; and (c) four sporadic-clinical isolates (with unknown epidemiological status) from cases that were notified outside the epidemiological investigation period and/or area. Common exposure to contaminated foods was confirmed between 7 April and 24 May 2015 during the epidemiological investigation of the outbreak. However, as indicated by the grouping of sporadic-clinical isolates (with unknown epidemiological status) with similar genetic patterns to the cases of the outbreak (Cluster-A), the duration of this point-source contamination issue at Sushi-B cannot be confirmed without supporting epidemiological information (Figure 3.4).

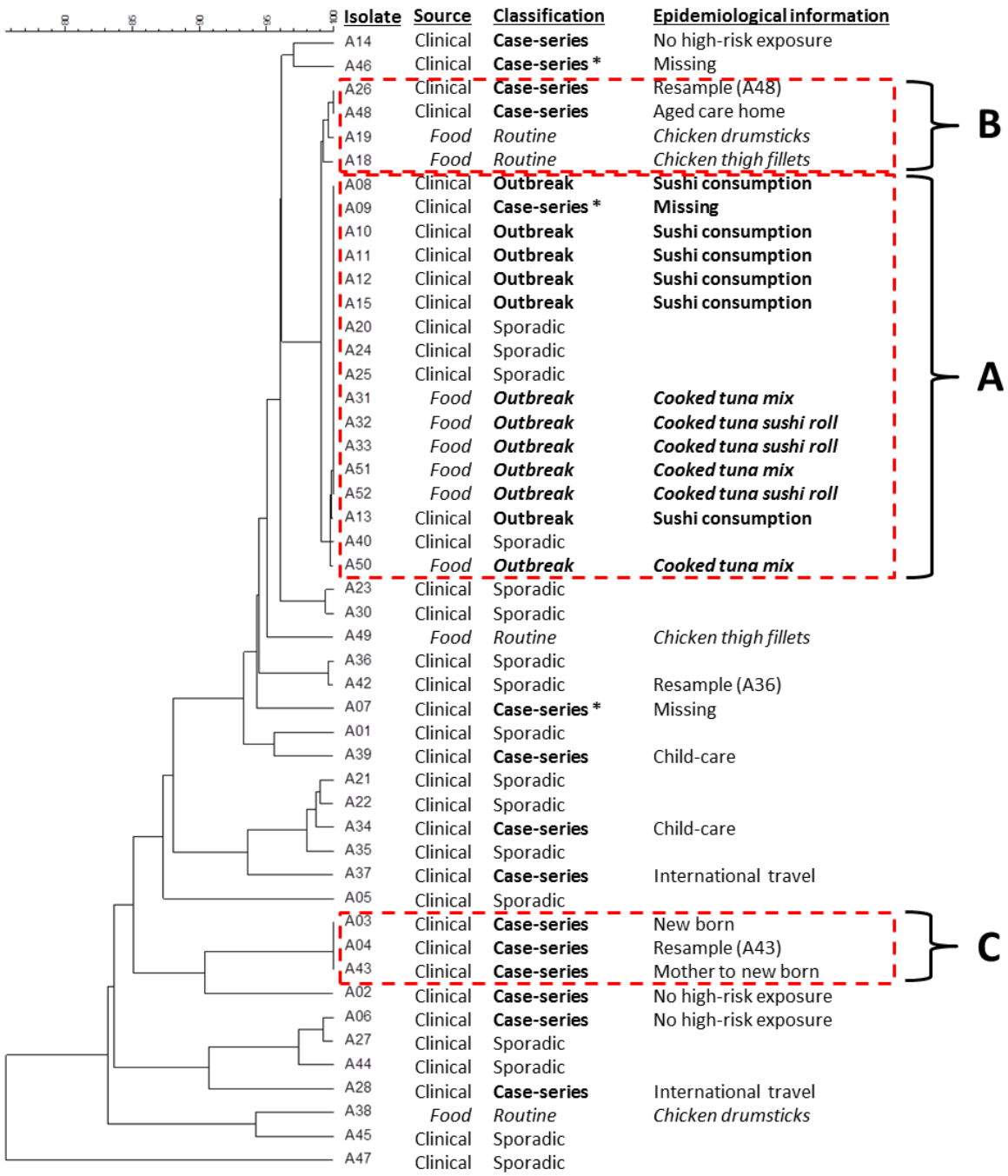

Figure 3.3: Maximum likelihood tree of *Salmonella* Agona isolates based on single nucleotide polymorphism.

** representing clinical cases who were originally included in the descriptive case-series investigation and non-contactable for an interview during this investigation*

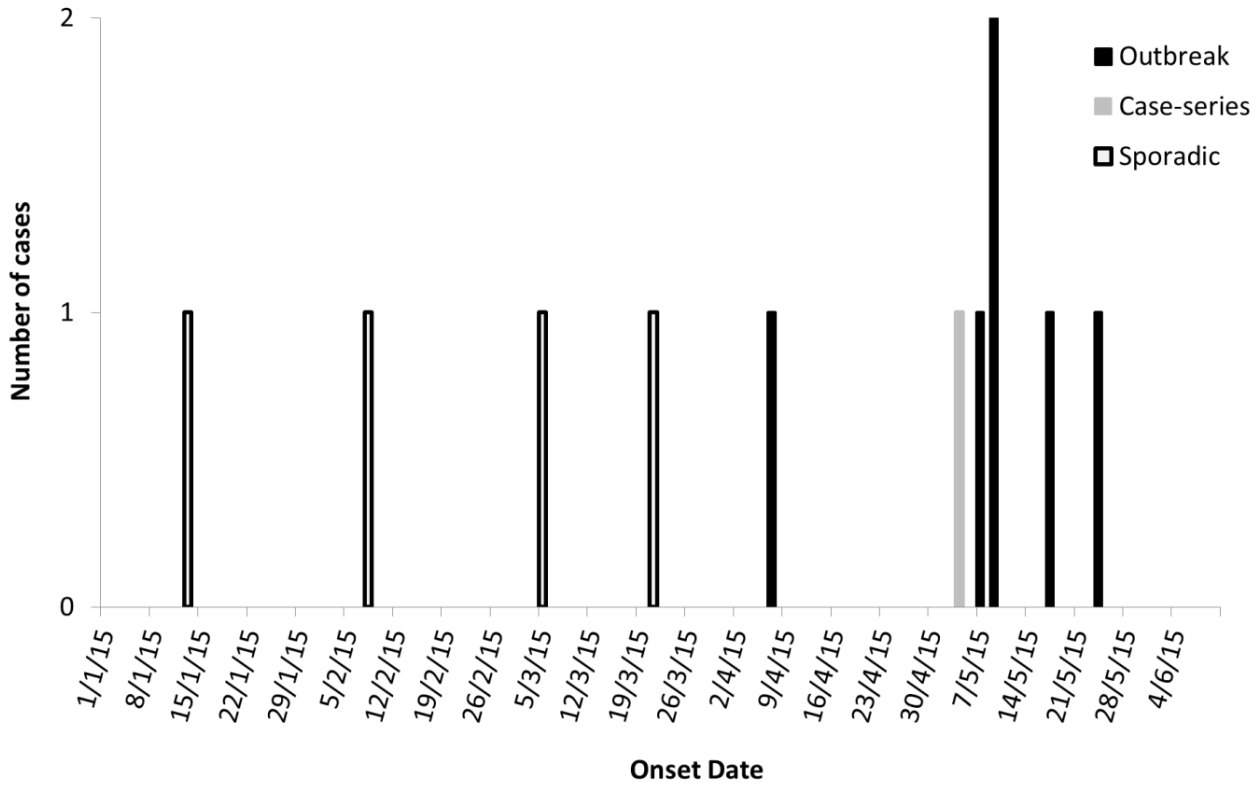

Figure 3.4: Epidemiological curve of *Salmonella* Agona cases (Cluster-A) identified from New South Wales, Australia with an onset date between January and June 2015.

3.9 Discussion

Rapid epidemiological investigation identified contaminated cooked tuna sushi rolls consumed from an individual sushi outlet in western Sydney as the likely vehicle for this outbreak. Once the food outlet had been identified, our multidisciplinary team promptly detected the contamination issue and instigated action to eliminate the ongoing risk to the community. We highlight the public health importance of WGS, as well as the additional value that this modern technology provides. The WGS analysis identified five additional clinical isolates that may have been linked to the outbreak (one clinical isolate recovered from an individual who was originally included in the descriptive case-series investigation and was not contactable for an interview; and four sporadic-clinical isolates [with unknown epidemiological status]). It was speculated that the original contamination-source for this outbreak could have been raw retail chicken meat, based on the limited SNP variation between the isolates of the outbreak (Cluster-A) and the routinely collected chicken meat samples in Cluster-B (Figure 3.3).

The WGS offers increased discriminative power and enhances traditional descriptive epidemiology with detailed phylogenetic relationships between isolates.[37] During this particular outbreak investigation, the SNP analysis, which included clinical isolates that were not originally considered to be part of the outbreak, may have increased the total outbreak size by five cases. However, it is worth noting that the 'threshold' for the maximum SNP differences of *Salmonella* isolates related to an outbreak cluster remains not well defined.[29] Previous WGS reports of *Salmonella* outbreaks have had SNP difference of up to 12 to 30-bp to help define a cluster.[29,31,37] Using a similar threshold, our outbreak would have included an elderly individual from the aged care home (Cluster-B, Figure 3.3), who lacked supporting epidemiological information to link them to this outbreak at Sushi-B. WGS data should not be used in isolation to define an outbreak, and should be used to compliment traditional epidemiological data.[31]

The SNP variation of *S.* Agona isolates obtained from raw retail chicken meat routinely sampled by the NSW DPI during 2015 (Cluster-B, Figure 3.3) and our outbreak (Cluster-A, Figure 3.3) was between 4 and 8-bp over an entire genome of over four million bp.[20] The low number of SNP variation between our outbreak

isolates and strains recovered from the raw chicken meat suggests that these different isolates may share a common source of origin, such as a single producer or processor of chicken meat. In light of the specific food hygiene and food safety defects identified at Sushi-B by the NSW DPI, we hypothesise that there could have been a breakdown of proper hygiene protocol at the implicated sushi outlet while processing contaminated raw chicken meat. This breakdown of proper hygiene resulted in the cross-contamination of the cooked tuna mix and/or containers used exclusively for storage of this product. *Salmonella* Agona is commonly associated with poultry and poultry products,[8] and has a considerable ability to form biofilms on plastic materials.[14] The resistant and persistent nature of *Salmonella* within biofilms[38] may provide some insight for the extended duration of this localised contamination issue at the sushi outlet. Another possible source for cross-contamination could have been an ill staff-member at Sushi-B. However, when considering the WGS results and the possible extended period of this outbreak, it appears unlikely that this staff member was the only source of contamination. An additional undiagnosed human case (i.e. a food handler) linked to this outbreak was also a possibility.

Based on epidemiological results, the duration of this point-source contamination event at Sushi-B was reported to be between 7 April and 24 May 2015. However, as indicated by the clustering of sporadic-clinical isolates (with unknown epidemiological status) within Cluster-A (Figure 3.3), this point-source contamination issue may have started earlier than first suspected (Figure 3.4). This hypothesis was unable to be investigated further during the investigation, as these additional cases linked to the outbreak by WGS were notified with *S*. Agona between six to eight months prior to the WGS-based analysis. Any epidemiological information obtained from these additional cases at the time of this outbreak investigation would have been unreliable due to poor recall of food consumption more than half a year ago. If these additional cases had been interviewed at the time of their illness (as notified cases of *Salmonella* are not routinely interviewed by NSW Health), it may have been possible to link them to the outbreak at Sushi-B, or obtain additional information to help identify the original source that led to the cross-contamination event at Sushi-B.

The probability of a *Salmonella* infection to the consumer from contaminated foods is related to the infectious dose ingested by the person. It is estimated that a person is required to ingest 100 to 1000 bacteria to initiate an infection, with a 10-20% chance of infection related to 100 organisms (model based prediction) and a 60-80% chance related to 10,000 fold increase of organisms;[3] furthermore, Proton Pump Inhibitors (PPIs) appearing to increase the susceptibility of an individual to *Salmonella*.[39] During this outbreak, the low number of cases identified may have been a result of a highly variable organism counts within the contaminated cooked tuna mix. It is possible that following the original cross-contamination event, the infrequent number of notified cases could have been related to mixing and/or diluting of cooked tuna mix between batches; from inadequate cleaning and sanitising of storage containers used exclusively for the cooked tuna mix; or from mild illness where the patient did not seek medical attention.

WGS can assist routine epidemiological investigations, particularly with regards to the prevention of further cases through earlier identification of the outbreak source and important insights into the contamination timeline. This will fundamentally change the epidemiological understanding of transmission dynamics, and open up new, more targeted, strategies for disease control and prevention.[28] Even for this investigation where the final results for the WGS analytical component were not available until eight weeks following the lifting of the prohibition order at Sushi-B (Figure 3.2), the information has been valuable in better understanding the epidemiology of the outbreak. Use of this technology will become more applicable to real-time investigations in the future as speed of sequencing of bacterial genomes improves from weeks and days to perhaps hours.[31,40]

Costs are also an issue when considering the inclusion of WGS as part of outbreak investigations (especially when WGS costs are additional to the costs of conventional laboratory methods), and are not necessarily affordable for routine use. In time, WGS has the potential to allow epidemiological hypotheses to be tested in near real-time, supporting enhanced management and control of communicable diseases and effective public health action.[28] With declining costs, improved speed of WGS and minimising the number of laboratory tests

conducted, this modern technology will have a more permanent role within routine surveillance of notifiable diseases, with high-quality data influencing decision-making and action during an outbreak investigation.

Limitations of this outbreak investigation should be noted. They included poor recall of some cases and surrogates during interviews, a low sample size for the epidemiological investigation, and the descriptive nature of the epidemiological study. This descriptive study measured the occurrences of outcomes rather than incorporating an analytical design that could investigate associations between exposures and outcomes. WGS analysis was completed after the outbreak was concluded, and it was not ideal to follow-up the additional cases within Cluster-A due to the time that had lapsed. Also, due to the passive nature of the notification surveillance system in NSW, this investigation was biased towards people with more severe illness, who were more likely to be tested and had a positive culture. In spite of these limitations, our findings present strong evidence of a traditional epidemiological investigation supported by high-throughput sequencing technology, which implicated a single sushi outlet as the source of this outbreak, and assisted with the hypothesis that this outbreak was caused by cross contamination from raw chicken.

3.10 Conclusion

This multidisciplinary outbreak investigation was responsible for correcting various hygiene and food safety control defects identified at a sushi outlet. This outlet was responsible for a point-source foodborne outbreak of *S*. Agona in western Sydney, Australia between April and June 2015. The high-throughput genome sequencing was also utilised retrospectively and identified additional cases that may have been linked to the outbreak, extending the timeframe of the outbreak and providing additional insight as to the possible source for the outbreak. The genomics-enhanced public health action added value to the descriptive epidemiological investigation and will most certainly play an increasing role in public health surveillance of foodborne diseases, especially as costs of this technology becomes more acceptable and turn-around times of testing are reduced.

3.11 References

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3.12 Appendix 3.1

Case-control study design-1

In addition to interviewing laboratory confirmed cases of *S*. Agona, non-serotyped laboratory positive cases of *Salmonella* sp. were going to be sourced from the NCIMS database and recruited as controls. Two controls would have been matched to every case; chosen from the western Sydney area, of similar age (if feasible) and with notification date similar to that of the case. These controls would have been interviewed in a timely manner using exactly the same questionnaire as cases.

Case-control study design-2

In addition to interviewing laboratory confirmed cases of *S*. Agona, two matched-controls were going to be recruited for each case. Matched-controls would be recruited for the same consulting GP practice of the cases. Controls would have been matched by age and sex, and would have a consultation date similar to the case. Controls would have been interviewed in timely manner using exactly the same questionnaire as cases.

3.13 Appendix 3.2

Source: *OzFoodNet—Enhancing Foodborne Disease Surveillance Across Australia (2nd Quarter Summary, 2015 NSW)*

Notable Foodborne Outbreaks

Salmonella Agona

An increase in *Salmonella* Agona (9 cases) in Western Sydney in May and June 2015 was identified through routine surveillance. A total of 37 cases were notified in NSW between Jan and June 2015, with 13 notified in May and June 2015. The previous five year average in NSW was 28 cases for the entire year.

Sixteen of the more recent NSW cases were interviewed including all 9 located in Western Sydney. Six had consumed sushi from one of two sushi outlets in the same shopping centre, no links were found between the other 10 cases.

For the cases related to the shopping centre, consumption dates ranged from 7 April 2015 to 23 June 2015, 4 from sushi outlet A and 2 from sushi outlet B. Both venues were inspected by the NSWFA and were reported to have potential for cross contamination of ready to eat foods. It was reported no ingredients or staff were shared between the shops but records were not available to confirm this.

Samples were taken from both venues, with sushi outlet A returning positive *Salmonella* Agona results from sushi rolls. Sushi outlet A was inspected another two times during the following 19 days. On all occasions the tuna mix for tuna sushi rolls was positive for *Salmonella* Agona, even though the individual ingredients for this mix and the tools used to make this mix were all negative. The venue was prohibited from selling the tuna product until it showed evidence of *Salmonella* clearance.

Whole genome sequencing was performed on all *Salmonella* Agona isolates for this time period as well as 10 food source isolates obtained during the outbreak and from retail samples of chicken meat earlier in the year. The sequencing showed all six people who reported eating at the two sushi outlets had identical sequencing as did five others who did not report the sushi restaurant or were not interviewed. Three of these were from the first quarter of the year. All of the *S.* Agona isolates from sushi outlet A were also identical to these cases. These were also very similar to two of the raw retail chicken isolates. This analysis suggests the source of the *S.* Agona in this cluster may have been chicken meat, with a common source of chicken for the two sushi venues likely at the time of the outbreak and environmental contamination from raw chicken the source of the *Salmonella* in the businesses.

Campylobacter jejuni outbreak

A foodborne complaint was received by the NSWFA about illness in two people who had consumed food together on 29 April 2015. Symptoms were fever, nausea, vomiting, diarrhoea and abdominal cramps. One person was hospitalised and symptoms lasted for 6 days. Samples were taken for both and were positive for *Campylobacter jejuni*. Foods consumed at the reported dinner were hot noodle dishes.

The investigation by the PHU revealed the pair had eaten together at another restaurant on 28 April 2015, with four other people. At this dinner it was reported the pair shared chicken liver pate. This earlier dinner and dish was deemed the most likely source of the *Campylobacter* illness and the NSWFA inspected the restaurant. They found that as a digital thermometer was not in use to confirm that livers reached the correct safe temperature it is possible that contaminated livers could have resulted in a batch that caused infection in this case. The restaurant was advised of the safe way to prepare the pate, however they voluntarily removed it from the menu.

Salmonella Typhimurium MLVA 3-12-12-9-523

Three NSW residents with *Salmonella* Typhimurium MLVA 3-12-12-9-523 were identified in April through routine surveillance. An investigation was initiated by the PHU and Health Protection NSW. Interviews identified a common exposure of a restaurant at a NSW resort. Additional case finding revealed four different groups with exposures to the restaurant from 16 to 19 April 2015. At least 11 people were reported as ill. The majority of cases reported consuming a dessert containing raw eggs, one case that did not consume this dessert had soft poached eggs for breakfast from the same restaurant.

The local council inspected the restaurant and learned that the restaurant had already

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3.14 Appendix 3.3

Source: *The Broad Street Pump* (June 2016, Issue 43)

The epidemiology of antibiotic resistance: an *Escherichia coli* perspective *(continued from page 6)*

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The added value of genome sequencing in the investigation of *Salmonella* Agona outbreak in Sydney

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Salmonellosis is the second most commonly notified bacterial gastrointestinal disease in Australia. There are currently around 2,500 Salmonella serotypes (serovars) defined according to the Kauffmann-White scheme on the basis of the serologic identification of somatic and flagellar antigens [1]. *Salmonella* Typhimurium is the predominant serotype identified in NSW, accounting for more than half of all *Salmonella* serotypes, followed by the other serotypes such as *S.* Enteritidis and *S.* Virchow. *S.* Agona is ranked among the top 11 most common *Salmonella* serotypes in NSW. This serotype had been recognised as a public health challenge in a few developed countries due to importation of contaminated Peruvian seafood in 1970's [2-3]. Since then *S.* Agona has emerged as a common global cause of salmonellosis in both animal and humans, which is often found in farmed livestock, vegetables and factory-prepared foods [4-7].

The unexpected increase in of *S.* Agona notifications was identified in Western Sydney in May-June 2015 through routine public health laboratory surveillance. A total of 38 cases were notified in NSW during the first half year in 2015, compared to an average of 28 cases per year for the previous five years (Figure 1). The public health officers from NSW Department of Health interviewed recent cases and identified two food outlets in one large metropolitan shopping centre as the common sources for some cases. Food and environmental samples were then collected from the both venues by the NSW Food Authority and positive *S.* Agona cultures were subsequently obtained from the food related sources.

To further investigate the link between clinical cases and food sources, whole genome sequencing (WGS) was performed on the isolates obtained between Jan–Jul 2015 in NSW. A total of 48 *S.* Agona isolates were investigated, including six human isolates from Food Outlets 1 and 2; six food and environment isolates recovered during the outbreak from the Food Outlet 1 and four from other retail outlets during 2015; one from a case with an exposure to the implicated food; and 31 other sporadic clinical isolates of *S.* Agona.

The added value of genome sequencing in the investigation of *Salmonella* Agona outbreak in Sydney (continued from page 7)

The genomic DNA was prepared using an automated workstation Chemagic Prepito-D (PerkinElmer). The DNA sequencing libraries were prepared using the Nextera XT DNA preparation kit (Illumina) and the sequencing was performed on the NextSeq 500 (Illumina) with 2x150 bp paired-end chemistry. Single nucleotide polymorphisms (SNPs) in individual genomes were identified by mapping reads to the reference genome S. Agona 460004 2-1 (NCBI GenBank: NZ_CP011259). The significant thresholds for SNP calling were set for a minimum coverage at 20 and a minimum variant frequency at 80%. The generated SNP list from each of the isolates were exported as excel files and a binary type SNP matrices representing present and absent of SNP in each isolates was generated and imported into Bionumerics (Applied Maths). The clustering analysis was performed using a categorical coefficient with UPGMA as dendrogram in BioNumerics (Applied Maths). To validate the clustering analysis, *de novo* assembly was performed with a minimum contig size set at 200bp. The assembly was then mapped against the reference genome for SNP calling and phylogeny inferred using a web-based server (https://cge.cbs.dtu.dk/services/CSIPhylogeny/). Maximum likelihood phylogenetic trees at 100 bootstraps were generated in MEGA6 [8] to estimate resulting genomic distances between sequenced genomes.

SNP analysis grouped the six clinical isolates collected from the cases involved in two food outlets in the same cluster (A, Figure 2), together with one isolate from a single non-contactable case with exposure. Another four isolates collected from the clinical cases notified early between January and March 2015 were also clustered in the same group. The SNP difference within these isolates were between 0 and 1. The six food and environmental isolates obtained from the Food Outlet 1 had no SNP difference to the clinical cases. Two raw retail chicken isolates collected as part of routine screening (unrelated to this outbreak) were closely related to the epidemiologically linked cases and food isolates collected from the food outlet 1 (4-8 SNPs) (B, Figure 2). Another two cases involving a mother and her new-born had the same SNP profile for the isolates collected (C, Figure 2). Some overseas travellers and sporadic cases had demonstrated very different SNP profiles compared to the outbreak cases (Figure 2). Other genomic results were also inferred from the sequencing data. All isolates were ST13 by MLST, a typical ST type for *S.* Agona. The outbreak isolates harboured a salmonella plasmid pVCM01 which was absent in 48% of non-outbreak isolates. Antibiotic resistance genes were not identified in all outbreak related isolates and some sporadic isolates, while three isolates from patients with overseas travel histories and one sporadic harboured resistance genes to aminoglycoside (*str*A/B), beta-lactam (*bla*TEM-1B), fluoroquinolone (*qnr*S1), sulphonamide(*sul*3) and tetracycline (*tet*A, *dfr*A14).

In conclusion, whole genome sequencing of pathogens of public health importance provides a new capacity to examine relationships between antigenically closely related *Salmonella* isolates potentially associated with community outbreaks. Our sequencing results, combined with epidemiological evidence, strongly suggested that the consumption of the food at Food Outlets 1 and 2caused the outbreak and the chicken meat was most likely the source of contamination. Furthermore, WGS findings indicated that the outbreak started much earlier than was previously estimated. This experience further demonstrated the added value of high resolution and high-throughput capacity of WGS in the investigation of *Salmonella* community outbreaks. As the cost of this technology becomes more acceptable and turnaround times are reduced, WGS is expected to be of utmost benefit to communicable disease surveillance and outbreak investigations. This technology will to play an increasingly important role in public health laboratory surveillance and diagnostic microbiology.

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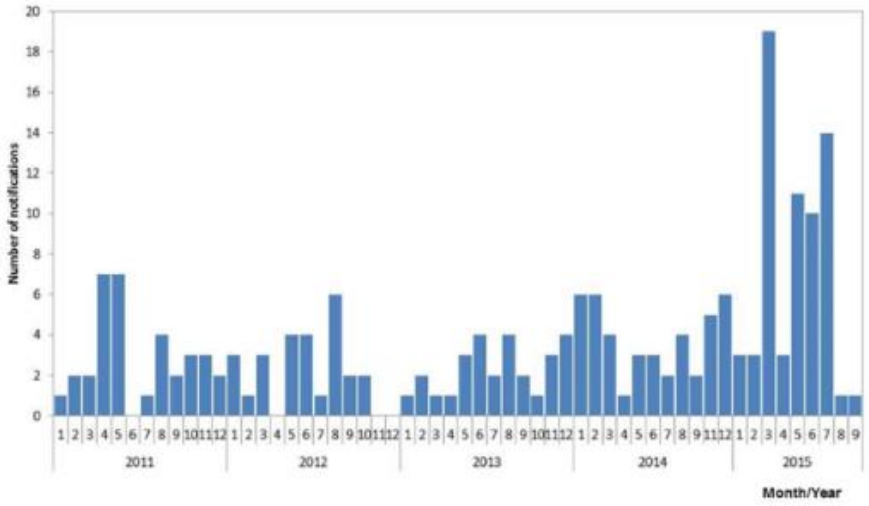


Figure 1. *Salmonella* Agona cases notified between January 2011 and September 2015 in NSW (NSW Department of Health).

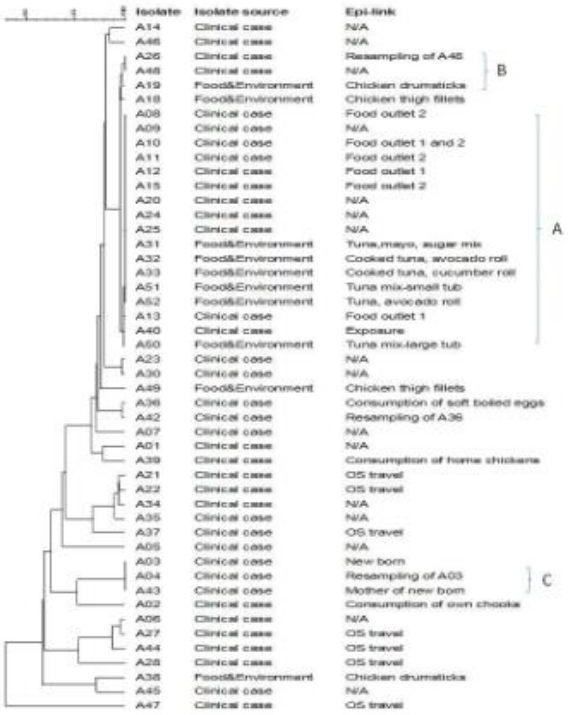
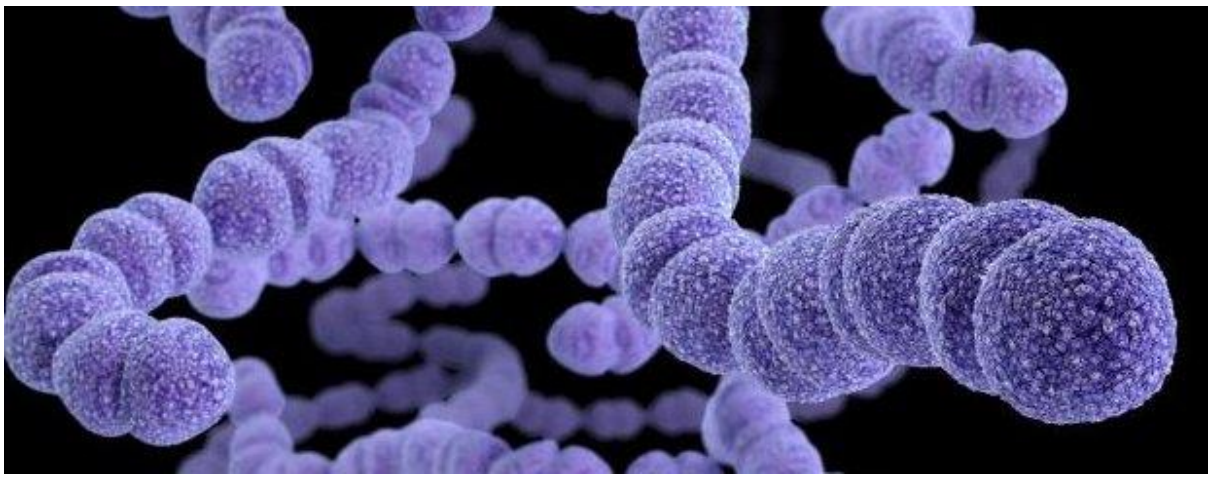


Figure 2. Single nucleoid polymorphism clustering tree of *S.* Agona isolates collected in NSW between January and July 2015 with sample sources and epidemiological links.

Chapter 4

Pneumococcal disease in older people of New South Wales: an investigation of invasive and non-invasive disease using linked datasets within the NSW Public Health Registry



Source : www.pneumogen.net

(*Accessed 18 November 2016*)

Chapter 4 Contents

4.1 List of Tables

4.2 List of Figures

4.3 Prologue

4.3.1 Background

This chapter is set out slightly different to the previous two research chapters. Part I is a systematic literature review and Part II is a data linkage project that I conducted. Together, Part I and II provide valuable information regarding pneumococcal disease in people aged 50 years or older.

Furthermore, when I agreed to undertake this project I really had no idea of what I had got myself into. Pneumococcal disease and data-linkage together in one project – Wow!

4.3.2 My role

I was the principal investigator and analyst for this chapter. I was responsible for developing the main research questions of this project with Peter McIntyre, Sanjay Jayasinghe, Helen Quinn, Frank Beard and Aditi Dey at the National Centre for Immunisation Research and Surveillance (NCIRS), and with Paula Spokes, Robin Gilmour and Nick Rose at the Communicable Disease Branch (CDB), NSW Health. I was also responsible for liaising with Nick Rose and Paula Spokes at the CDB, NSW Health to obtain access to the datasets at North Sydney. I gained ethics approval from ANU for approval to publish results that were generated from this investigation. I cleaned the data from five different datasets (over 24 million records), merged data and verified the merged data with SAS Enterprise Guide while at CDB, NSW Health. I then conducted all of the analyses using Stata while at NCIRS. I conducted the systematic literature review for this chapter and generated all tables and figures.

I have presented the methodology that I used for this analysis at the inaugural NCIRS i-BESIG (immunisation Epidemiology and Biostatistics Special Interest Group) meeting during August 2016. I also prepared and presented my results to the CDB team at NSW Health during a weekly surveillance meeting in November 2016. I am currently liaising with co-authors during preparation of two different manuscripts for publication in peer-review journals, and have also been asked to

present my findings at one of the upcoming Enhanced Invasive Pneumococcal Disease Surveillance Working Group (EIPDSWG) meetings.

4.3.3 Lessons learned

This project represents my first attempt of a data-linkage investigation. I was very fortunate that NCIRS recognised this and enrolled me into a four day course 'Managing Big Data in Health Research' at the University of NSW. In addition, this project also represents my first attempt at using SAS Enterprise Guide for data analysis. To obtain these essential skills for this project, I enrolled in a one day course ('Introduction to SAS') at the University of NSW and a one day course ('Introduction to SAS Enterprise Guide') at NSW Health, North Sydney.

Together these three independent courses allowed me to understand key concepts essential for this analysis, including SAS syntax, the concepts of managing large datasets and data-linkage (Appendix 4.1 – example screen shot from SAS Enterprise Guide). Without this prior education, the complex methodology as detailed in Part II would not have been possible.

In addition to this work presented in Chapter 4, I also assisted with the preparation of pneumococcal slides for the ATAGI meeting in late 2015 by analysing Invasive Pneumococcal Disease (IPD) data from the NNDSS enhanced IPD surveillance dataset. This process allowed me to gain a better appreciation for the complexity of IPD data. I analysed risk factor data for IPD notification for non-Indigenous people ≥65 years of age, and Indigenous people ≥50 years of age.

4.3.4 Public Health impact

This is the first study to estimates of the burden of pneumococcal pneumonia using linked data from the NSW Public Health Registry (PHR) for people aged 50 years or older in NSW. In this investigation, I have demonstrated the validity and usefulness of a complex data-linkage analysis to help investigate important issues that cannot be answered from a single database alone. I verified 'proof of

concept' when using linked data within the NSW PRH to further investigate notifiable diseases in NSW. This verification is an important step when considering the usefulness and future potential of the NSW PHR, as the methodology used here is transferable to other notifiable diseases, since the registry contains information on most notifiable conditions in NSW, not just IPD.

While pneumococcal conjugate and polysaccharide vaccines are well documented to have reduced the incidence of IPD in children and older people, there is growing evidence that documents the reductions in all-cause pneumonia hospitalisation in adults following the introduction of 7vPCV in the United States of America and Australia. Furthermore, post-implementation studies that evaluate the trends in hospitalisation coding of non-invasive pneumococcal community acquired pneumonia (CAP) following the funding of pneumococcal conjugate and polysaccharide vaccines are sparse, especially in adults. Post-implementation studies are necessary to help inform national policy making regarding funding changes of pneumococcal vaccines, and provide additional information that supports evidence-based guidelines.

The timing of this data-linkage investigation that I presented here is highly relevant in light of the recent findings of the Community Acquired Pneumonia in Adults (CAPiTA) Trial in the Netherlands and the Pharmaceutical Benefits Advisory Committee (PBAC) approval for the use of 13vPCV in the adult population of Australia for the prevention of pneumococcal pneumonia and IPD. It was noted in the positive recommendation by the PBAC that the effectiveness of 13vPCV against CAP is likely to be superior to that of 23vPPV, which may have a significant impact upon vaccination funding for the older population of Australia.

4.3.5 Acknowledgements

Kerri Viney, Katrina Roper, Helen Quinn, Frank Beard and Aditi Dey took the lead supervisory roles during this project. I am very grateful to Sanjay Jayasinghe and Peter McIntyre at NCIRS for all of their technical help with the topic of pneumococcal and data-linkage. Also to Paula Spokes, Robin Gilmour and Nick Rose at the Communicable Disease Branch (CDB), NSW Health for their technical guidance with the different datasets. I will also be very grateful to the

thoughtful review and feedback of co-authors during the development of this chapter into two different manuscripts.

4.3.6 Data-source acknowledgement

The Cause of Death Unit Record File (COD URF) is provided by the Australian Coordinating Registry for COD URF on behalf of Australian Registries of Births, Deaths and Marriages, Australian Coroners and the National Coronial Information System. COD URF is held by the NSW Ministry of Health Secure Analytics for Population Health Research and Intelligence.

4.4 Acronyms:

7vPCV	7-valent pneumococcal conjugate vaccine
13vPCV	13-valent pneumococcal conjugate vaccine
23vPPV	23-valent pneumococcal polysaccharide vaccine
ABS	Australian Bureau of Statistics
ACRD	Australian Co-ordinated Registry of Death
ANU	Australian National University
APDC	Admitted Patient Data Collection
CAP	Community Acquired Pneumonia
CDB	Communicable Disease Branch
CDNA	Communicable Diseases Network Australia
CI	Confidence Intervals
COD URF	Cause of Death Unit Record File
CSF	Cerebrospinal fluid
EDDC	Emergency Department Data Collection
EIPDSWG	Enhanced Invasive Pneumococcal Disease Surveillance Working Group
ICD-9-CM	Ninth Revision of the International Classification of Disease coding system
ICD-10-AM	Tenth Revision of the International Classification of Disease coding system - Australian modified
IPD	Invasive Pneumococcal Disease
IRR	Incidence Rate Ratio
NCIMS	Notifiable Conditions Information Management System
NCIRS	National Centre for Immunisation Research and Surveillance

NIP	National Immunisation Program
NNDSS	National Notifiable Diseases Surveillance System
NSW	New South Wales
PBAC	Pharmaceutical Benefits Advisory Committee
PHR	Public Health Registry
PPN	Project-specific Person Number
QLD	Queensland
RBDM	Registry of Birth, Deaths and Marriages
SA	South Australia
VE	Vaccine Effectiveness
VHPSS	Victorian Hospital Pathogens Surveillance Scheme
WA	Western Australia
WHO	The World Health Organization

Part I

Systematic Literature Review

4.5 Prologue to Part I

Part I of this chapter is a systematic literature review of invasive pneumococcal disease (IPD) in older people of Australia. I focused on vaccine coverage and the burden of disease following changes to the funding of different pneumococcal vaccines under the National Immunisation Program (NIP).

4.6 Introduction

Globally, diseases caused by *Streptococcus pneumoniae* (or pneumococcus) are a major public health problem. During 2005, it was estimated by the World Health Organization (WHO) that among all age groups, pneumococcal disease was responsible for approximately 1.6 million deaths.[1] The highest global incidence of pneumococcal disease occurs in young children and the elderly, with approximately 14·5 million episodes of serious pneumococcal disease occurring in children aged less than five years of age during 2000.[2,3]

Streptococcus pneumoniae is a Gram-positive coccus, which colonises the nasopharynx of the host, and is transmitted from person-to-person via respiratory droplets.[4,5] There are over 90 serotypes of pneumococci recognised, which cause conditions such as meningitis, septicaemia, pneumonia, otitis media and sinusitis.[2,4] Invasive pneumococcal disease (IPD) refers specifically to those conditions in which the *S. pneumoniae* infection penetrates a sterile site of the body (including the blood, cerebrospinal fluid [CSF], peritoneal, pleural and joint fluid) and causes symptomatic conditions such as meningitis, bacteraemic pneumonia, and bacteraemia without focus.[2,6] Only a limited number of pneumococcus serotypes are responsible for the majority of IPD cases.[2] IPD has been nationally notifiable in Australia since 2001, with enhanced data being collected by all jurisdictions since 2002.[4]

4.7 Pneumococcal vaccine schedule

Pneumococcal vaccines available in Australia come in two forms: conjugate and polysaccharide vaccines. The recommendations and funding of these vaccines under the National Immunisation Program (NIP) have changed over time and within each state and territory of Australia (Table 4.1).

Table 4.1: Pneumococcal vaccine availability and funding in Australia, 1986-2011

Date	Changes made to pneumococcal vaccine availability and funding
1986	23-valent pneumococcal polysaccharide vaccine (23vPPV) became available in Australia[2,5]
1998	23vPPV was locally funded within the jurisdiction of Victoria, for both non-Indigenous individuals aged 65 years or older, and Indigenous individuals aged 50 years or older[7]
March 2000	23vPPV was nationally funded for all Indigenous people aged 50 years or older
December 2000	7-valent pneumococcal conjugate vaccine (7vPCV) was first registered in Australia[2]
June 2001	7vPCV funded for children at highest risk (including all Indigenous infants, all children with specified underlying medical conditions that predispose them to IPD, and non-Indigenous children residing in Central Australia)[2]
January 2005	7vPCV became nationally funded under the NIP in for all Australian infants, with a three dose schedule at two, four and six months of age (3+0 schedule)[2] 23vPPV was nationally funded for all non-Indigenous individuals aged 65 years or older[2]
July 2011	13-valent pneumococcal conjugate vaccine (13vPCV) replaces the 7vPCV for use in infants[2]

4.8 Methods

A systematic literature review was conducted to identify in the published literature what influence pneumococcal vaccines have had upon the IPD-associated morbidity and mortality in older people of Australia. The following focused research question was chosen for this literature review:

What impact has funded pneumococcal vaccines had upon vaccine coverage and the incidence of invasive pneumococcal disease of older and elderly people in Australia?

Elderly people of Australia (with reference to the NIP pneumococcal funding) are defined as:

- those who are aged 65 years or older

The focused literature search was conducted using the '*Scopus*' database. Table 4.2 defines the search terms used and resulting number of articles sourced at each step of the search procedure.

Table 4.2: Focused literature review search terms and resulting number of articles

History	Search fields	Search terms	Date restrictions	Article Results
#1	TITLE-ABS-KEY	Pneumococcal AND (disease OR vaccin*)	PUBYEAR > 2004	11,379
#2	TITLE-ABS-KEY	elderly	Nil	349,858
#3	TITLE-ABS-KEY	adult	Nil	6,495,465
#4	TITLE-ABS-KEY	Australia	Nil	310,509
#5	ALL	coverage	Nil	444,189
#6	ALL	schedule	Nil	466,753
#7	TITLE-ABS-KEY	invasive	Nil	366,979
#8		#1 AND (#2 OR #3) AND #4 AND (#5 OR #6) AND #7	Nil	27
#9	TITLE-ABS-KEY	review*	Nil	4,052,352
#10		#8 AND NOT #9	Nil	19

Therefore, a total of 19 articles met the inclusion criteria for this literature review; these were written in English and published between 2004 and 2015.

Exclusion criteria for these 19 articles included studies that focused on:

- countries other than Australia (**x1**)
- only people less than 50 years of age (**x5**)
- outbreaks of pneumococcal (**x1**)
- Community Acquired Pneumonia (CAP) and not IPD (**x1**), and
- only the incidence of disease prior to funding of pneumococcal vaccine for elderly people (**x1**)

These nine articles were excluded from the literature review.

4.9 Results and discussion

4.9.1 Data quality

A total of ten articles met the search inclusion criteria for this focused literature review (Table 4.3).

Vaccine coverage was reported by nine of the ten studies.[4-12] Five articles reported vaccine coverage of elderly people,[5,7,10-12] and five reported vaccine coverage of children.[4,6,8-10]

Two articles were national studies[4,5] and used data from the National Notifiable Disease Surveillance System (NNDSS). The NNDSS is managed by the Australian Government Department of Health, with IPD data quality monitored by the Enhanced Invasive Pneumococcal Disease Surveillance Working Group (EIPDSWG) (a sub-group of the Communicable Diseases Network Australia [CDNA]).[4]

Four articles included an analysis of state-wide IPD notification data.[6,7,9,10] Two of these four studies used data collected by the state's enhanced IPD surveillance system, with 2001 data excluded from the analyses (due to poor quality).[9,10] The other two studies included data collected before IPD became nationally notifiable in 2001.[6,7] Data analysed in these two studies was collected locally by either: (a) the Victorian Hospital Pathogens Surveillance Scheme (VHPSS),[7] or (b) the IPD Laboratory Surveillance Network in NSW.[6]

Two of the ten articles used data collected from northern Queensland (QLD), where IPD became locally notifiable in 1996, and IPD data was collected by local public health units.[8,13]

The remaining two articles did not use IPD surveillance data; they used locally collected data to evaluate vaccine coverage within a defined setting.[11,12] These two articles made no attempts to investigate the incidence of IPD within their jurisdiction.

Of the eight articles that reported IPD incidences, population estimates were obtained from either the Australian Bureau of Statistics (ABS)[4-7,9,10] or from the Queensland Treasury's Office of Economic and Statistical Research.[8,13] For

these eight articles, an IPD case was defined by the isolation, or nucleic acid detection of *S. pneumoniae* from a normally sterile site, including blood, CSF, peritoneal, pleural and joint fluid.[4,6,9] An IPD case definition was defined in seven of these eight articles,[4-6,8-10,13] with the eighth article reporting that IPD cases were laboratory confirmed.[7]

Table 4.3: Synthesis of data from of ten articles that met the search inclusion criteria

Author Year [Ref #]	Setting / Study type	Data source / Population estimates	Monitoring periods (pre and post funding)	Vaccine Coverage	Incidence: Pre-funding rate Post-funding rate Incidence Rate Ratio (IRR ($CI_{95\%}$))	Outcomes / Results	Comments
Lowbridge 2015 [6]	**Setting:** Greater Sydney-area (Sydney, Hunter, Illawarra Statically divisions) **Study type:** Ecological analysis of trends of IPD over time	**IPD data source:** IPD Surveillance Network (state-wide) **Population est:** Australian Bureau of Statistics (ABS) population estimates for Greater Sydney - ~ 4.9 to 5.6 million people	**Pre-National Funding** 1998-2004 **Post-National Funding** 2008-2010 *(In 2005 7vPCV nationally available to all children, and 23vPPV nationally available all non-indigenous people ≥ 65 years)*	2005 7vPCV Children **Coverage:** 89%	**≥65 years only- all people** All IPD serotypes: Pre: 35.61 / 100,000 Post: 21.52 / 100,000 IRR 0.60 (0.55-0.67) 7vPCV serotypes only Pre: 24.68 / 100,000 Post: 3.64 / 100,000 IRR 0.15 (0.12-0.19) 13v-non-7v serotypes Pre: 4.83 / 100,000 Post: 4.01 / 100,000 IRR 0.83 (0.65-1.06) 23vPPV-non-13vPCV: Pre: 4.00 / 100,000 Post: 3.69 / 100,000 IRR 0.92 (0.71-1.20) Non vaccine serotype Pre: 2.09 / 100,000 Post: 2.58 / 100,000 IRR 1.23 (0.89-1.72)	Between 1998-2010: 7213 cases of IPD in the greater Sydney area 35% of cases (n= 2525 cases) in people ages ≥ 65 years	7vPCV focused article. However, 23vPPC data in article Direct and indirect impact of pneumococcal vaccines upon the elderly
Menzies 2014 [5]	**Setting:** National analysis **Study type:** Ecological analysis of trends of IPD over time	**IPD data source:** National Notifiable Disease Surveillance System (NNDSS) Inclusion: Non-indigenous Australians ages ≥65 years Exclusion: Victoria (Vic) jurisdiction removed, Indigenous people removed (due to different funding programs) **Population est:** ABS population estimates (2006 census)	**Pre-National Funding** 2002-2004 **Post-National Funding** 2010-2011 *(In 2005 7vPCV nationally available to all children, and 23vPPV nationally available all non-indigenous people ≥ 65 years)*	23vPPV ≥65 years non-Indigenous **2004 Coverage:** 41% to 53% **2006 Coverage:** 51% to 64% **2009 Coverage:** 48% to 56% range per individual jurisdiction (excluding Vic)	**≥65 years only – non-Indigenous** All IPD serotypes: Pre: 25.21 / 100,000 Post: 16.41 / 100,000 IRR 0.65 (0.59-0.71) 7vPCV serotypes only Pre: 17.00 / 100,000 Post: 1.84 / 100,000 IRR 0.11 (0.09-0.14) 23vPPV-non-7vPCV: Pre: 5.65 / 100,000 Post: 9.27 / 100,000 IRR 1.64 (1.14-1.91) Non vaccine serotype Pre: 2.56 / 100,000 Post: 5.30 / 100,000 IRR 2.07 (1.67-2.57)	Between 2002-2011: 3978 cases of IPD notifications for ≥65 years (excluding Vic and indigenous population). No clear impact directly from 23vPPV in elderly people A greater reduction of IPD in ≥65 years could be expected from the indirect effect of 7vPCV vaccination of children. Also increased vaccine coverage of 23vPPV in elderly people would be beneficial.	23vPPV specific for ≥65 years. Mentioned concurrent 7vPCV program for children launched at same time as 23vPPV of elderly people. Vaccine Effectiveness of 23vPPC 61.1% ($CI_{95\%}$:55.1%-66.9%). Quality assurance exercise pertaining to the NIP.

Author Year [Ref #]	Setting / Study type	Data source / Population estimates	Monitoring periods (pre and post funding)	Vaccine Coverage	Incidence: Pre-funding rate Post-funding rate Incidence Rate Ratio (IRR (CI 95%))	Outcomes / Results	Comments
Barry 2012 [4]	**Setting:** National analysis **Study type:** Ecological analysis of trends of IPD over time Point in time analysis	**IPD data source:** IPD Notifications- from the Enhanced Pneumococcal Dataset, NNDSS **Population est:** ABS Australian population estimates	**Pre-National Funding** 2002 **Post-National Funding** 2008 *(In 2005 7vPCV nationally available to all children, and 23vPPV nationally available all non-indigenous people ≥ 65 years)*	2007 7vPCV children (< 1 year & 3 doses) **Indigenous Coverage:** 85% **Non-Indigenous Coverage:** 91% 2008 7vPCV children (< 1 year & 3 doses) **Indigenous Coverage:** 85% **Non-Indigenous Coverage:** 92%	**≥65 years - non-Indigenous only** All IPD serotypes: 2006 – 18.4 / 100,000 2007 – 17.2 / 100,000 2008 – 19.0 / 100,000 7vPCV serotypes only Pre: 14.2 / 100,000 Post: 3.7 / 100,000 IRR 0.26 23v serotypes only Pre: 16.7 / 100,000 Post: 11.9 / 100,000 IRR 0.72 Non vaccine serotype Pre: 1.8 / 100,000 Post: 4.5 / 100,000 IRR 2.5 **≥50 years - Indigenous only** 23v serotypes only 2002: 20.5 / 100,000 2008: 39.5 / 100,000 IRR 1.93 Non vaccine serotype 2002: 4.1 / 100,000 2008: 10.6 / 100,000 IRR 2.59	2007: 476 IPD cases in all people ≥ 65 years of age (92% in non-indigenous people) 2008: 537 IPD cases in all people ≥ 65 years of age (93% in non-indigenous people) Substantial increase of 19A serotype Relatively large vaccine failure due to serotype 19F Herd Immunity impact of 7vPCV	Enhanced Invasive Pneumococcal Disease Surveillance Working Group (EIPDSWG) responsible for finalising IPD data reporting to NNDSS IPD Enhanced Data reporting commenced in 2001, with complete enhanced data collected from all states/territories from 2002
Johnson 2012 [9]	**Setting:** South Australia (SA) **Study type:** Ecological analysis of trends of IPD over time	**IPD data source:** Routine Enhanced Surveillance Data collected by SA Department of Health Exclusion: Indigenous data excluded from the analysis **Population est:** ABS population estimates (2001 and 2006 census data) ~1.57 million people	**Pre-National NIP Funding** 2002-2004 **Post-National NIP Funding** 2007-2009 *(In 2005 7vPCV nationally available to all children, and 23vPPV nationally available all non-indigenous people ≥ 65 years)*	2005 7vPCV children (< 1 year & 3 doses) **SA only Coverage:** 91%	**≥65 years – non-Indigenous only** All IPD serotypes: Pre: 68.4 / 100,000 Post: 50.0 / 100,000 IRR 0.73 (0.58-0.93) 7vPCV serotypes only Pre: 42.4 / 100,000 Post: 11.0 / 100,000 IRR 0.26 (0.17-0.40) 13vPCV-non-7vPCV Pre: 11.0 / 100,000 Post: 17.1 / 100,000 IRR 1.55 (0.94-2.54) 23vPPV-non-13vPCV Pre: 5.7 / 100,000 Post: 11.0 / 100,000 IRR 1.91 (0.99-3.71) Non vaccine serotype Pre: 1.7 / 100,000 Post: 9.3 / 100,000 IRR 5.3 (1.83-15.34)	Large benefit of 7vPCV, with a direct and sustained benefit to children Good evidence that childhood program has provided indirect benefit to adults aged ≥65 Reduced incidence of IPD in adults- a result of childhood vaccination rather than direct benefit from increased uptake of 23vPPV Serotype replacement has reduced initial benefit of program	Decrease of 7vPCV serotypes Increased incidence of 13vPCV and 23vPPV serotypes Ecological study- no cause / effect relation able to be established Benefits of vaccine program at population level Direct and indirect benefits to elderly people aged ≥ 65 years from the two programs

Author Year [Ref #]	Setting / Study type	Data source / Population estimates	Monitoring periods (pre and post funding)	Vaccine Coverage	Incidence: Pre-funding rate Post-funding rate Incidence Rate Ratio (IRR (CI 95%))	Outcomes / Results	Comments
Wallace 2008 [12]	**Setting:** North Coast Area Health Service (NCAHS), NSW **Study type:** Intervention (TV commercial) study	**Data source:** Vaccine ordering pattern of NCAHS population used as a proxy of vaccine coverage in the state CSL Cognos Vaccine Distribution Reporting System Database	**Post-National NIP Funding** 2005/2006 Intervention between June- Sept 2006	2004 23vPPV Adults ≥65 years **NCAHS Coverage:** 41.8% **NSW Coverage:** 47.2% 2007 23vPPV Adults ≥65 years **NCAHS Coverage:** 59.8% **NSW Coverage:** 59.1%	Nil	7 week TV advertisement to raise community awareness of 23vPPV funding changes. Significant increase in vaccine coverage TV campaign was an effective strategy to increase coverage and promote vaccine uptake	Research was conducted to improve vaccine coverage with a 7 week TV campaign Intervention study Used vaccine ordering pattern as a proxy for coverage. No estimates of vaccine leakage or wastage
Andrews 2004 [7]	**Setting:** Victoria **Study type:** Ecological analysis of trends of IPD over time	**IPD data source:** Victorian Hospital Pathology Surveillance Scheme (VHPSS) & Department of Human Services (DHS) **Population est:** ABS population estimates (2001 census data)	**Pre-Victorian Funding** July 1995 to June 1998 **Post- Victorian Funding** July 2001 to June 2002 *(1998- 23vPPV funding specific to Victorians ≥65 years of age)*	1997 23vPPV Elderly **Coverage:** 7% 2000 23vPPV Elderly **Coverage:** 51%	**≥65 years - all people** IRR = 0.64	36% reduction in rate of IPD following the funding changes amongst people ages ≥ 65 years. 115 cases of IPD amongst Victorians aged ≥65 years between July 2001 and June 2002 Publically funded 23vPPV program resulted in the reduction of IPD in elderly Victorians	Ecological assessment of the impact of Australian's first publically funded 23vPPV program against IPD targeting elderly people (≥ 65 years). May 2001- mandatory reporting of IPD required in Victoria
Ridda 2007 [11]	**Setting:** Westmead Hospital, NSW **Study type:** Observational survey within a specific cohort	**Data source:** Hospital patients from Westmead ~ 1997 people admitted within study period – 833 people approached	In response to the 2005 National Pneumococcal Vaccine Funding changes Information collected between 16 May 2005 and 20 February 2006	Before 2005 23vPPV Elderly ≥65 years **Coverage:** 39% After 2005 23vPPV Elderly ≥65 years **Coverage:** 73%	Nil	Due to age of the cohort, self-reporting of ≥65 not reliable Sensitivity: 0.53 Specificity: 0.55 Positive predictive value: 0.90 Negative predictive value: 0.52 Vaccine validation of records required	Vaccine status validated against GP records Funding of 23vPPV, immediate and rapid impact on vaccine uptake of ≥ 65 years

Author Year [Ref #]	**Setting / Study type**	**Data source / Population estimates**	**Monitoring periods (pre and post funding)**	**Vaccine Coverage**	**Incidence: Pre-funding rate Post-funding rate Incidence Rate Ratio (IRR (CI 95%))**	**Outcomes / Results**	**Comments**
Hanna 2010 [8]	**Setting:** Northern Queensland (QLD) **Study type:** Ecological analysis of trends of IPD over time	**IPD data source:** NNDSS QLD, with diagnostic lab information provided to local Public Health Units **Population est:** QLD Treasury's Office of Economic and Statistical Research Non-indigenous ≥65 years ~581,850 in 2006	**Pre-National Funding** 2001-2004 **Post-National Funding** 2006-2009 *(In 2005 7vPCV nationally available to all children, and 23vPPV nationally available all non-indigenous people ≥ 65 years)*	2007 7vPCV Children (< 1 years & 3 doses) **QLD Coverage**: 91%	**≥65 years - non-Indigenous only** All IPD serotypes: Pre: 23.0 / 100,000 Post: 14.1 / 100,000 IRR 0.61 7vPCV serotypes only Pre: 12.5 / 100,000 Post: 2.8 / 100,000 IRR 0.23 23vPPV-non-7vPCV: Pre: 6.9/ 100,000 Post: 6.0 / 100,000 IRR 0.88 23v serotypes only Pre 19.4 / 100,000 Post 8.9/ 100,000 IRR 0.46	Overall, a 77% decline in 7vPCV serotypes in elderly people ≥65 years 7vPCV powerful indirect effect of IPD prevention in elderly people Uncertain if 23vPPV had a direct effect upon elderly ages ≥65 years	Combination of direct and indirect benefits of the vaccines, new vaccines (13vPCV) could prevent more IPD of other serotypes than could be prevented with 7vPCV and 23vPPV Potential for 'replacement' serotypes that are not covered by the two vaccines
Hanna 2006 [13]	**Setting:** Northern Queensland (QLD) **Study type:** Ecological analysis of trends of IPD over time	**IPD data source:** NNDSS QLD, with diagnostic lab information provided to local Public Health Units **Population est:** QLD Treasury's Office of Economic and Statistical Research Indigenous population est: ~ 5650 aged ≥50 years	**Pre-Nth QLD Funding** 1999-2001 **Post-Nth QLD Funding** 2002-2004 *(7vPCV available to children mid 2001 in Nth QLD)*	Nil	**≥50 years - Indigenous only** All IPD serotypes: Pre: 71.0 / 100,000 Post: 41.0 / 100,000 IRR 0.58 7vPCV serotypes only Pre: 19.0 / 100,000 Post: 15.0 / 100,000 IRR 0.63 23v serotypes only Pre: 49.0 / 100,000 Post: 31.0 / 100,000 IRR 0.79	Herd immunity effect Continued decline of IPD in Indigenous people since 1996 (when 23vPPV available in QLD) 19 cases of IPD of Indigenous people ≥ 50 years between 1999 and 2004: 63% (n=12) between 1999-01 86% declined of IPD in Indigenous people aged ≥ 50 years since 23vPPV funding in 1996	Encouraging High vaccine coverage Good vaccine effective in population
Lehamnn 2010 [10]	**Setting:** Western Australia (WA) **Study type:** Ecological analysis of trends of IPD over time	**IPD data source:** Enhanced IPD Surveillance Vaccine Impact Surveillance Network – NNDSS and Hospitalisation datasets **Population est:** ABS population estimates (2006 census data) ~ 2.2 million people in WA, and about 3.5% of these people are Indigenous	**Pre-National Funding** 2002-2004 **Post-National Funding** 2005-2007 *(In 2005 7vPCV nationally available to all children, and 23vPPV nationally available all non-indigenous people ≥ 65 years)*	2005 7vPCV Children (<1 year & 3 doses) **Indigenous Coverage: 75%** **Non Indigenous Coverage**: 88% 2005 23vPPV Indigenous Adults (50-64 years) **Coverage:** ~ 31%	**≥65 years - non-Indigenous only** All IPD serotype: Pre: 19.2 / 100,000 Post: 13.0 / 100,000 IRR 0.68 (0.5-0.9) 7vPCV serotypes only Pre: 12.7 / 100,000 Post: 6.5 / 100,000 IRR 0.51 (0.4-0.7) Non 7vPCV serotypes Pre: 5.6 / 100,000 Post: 5.8 / 100,000 IRR 1.04 (0.7-1.7) 23vPPV non 7vPCV Pre: 3.3 / 100,000 Post: 4.6 / 100,000 IRR 1.39 **50 - 64 years - Indigenous only** All IPD serotype: Pre: 76.1 / 100,000 Post: 86.3 / 100,000 IRR 1.13 (0.5-2.6) 7vPCV serotypes only Pre: 12.7 / 100,000 Post: 10.8 / 100,000 IRR 0.85 (0.1-11.7) Non 7vPCV serotypes Pre: 57.1 / 100,000 Post: 75.5 / 100,000 IRR 1.32 (0.5-3.5)	IPD incidence rate decreased remarkably in children and non-indigenous adults IPD due to 7vPCV schedule Non – 7vPCV serotypes have increased An immunisation register covering all age groups should be established	Herd effect of 7vPCV Insufficient time frame to get true effect of the vaccine program 2005 to 2007

4.9.2 Coverage of the 23vPPV

Before the jurisdictional funding of 23vPPV in Victoria during 1998, very low coverage (7%) was reported among elderly people in 1997.[7] However, after implementation of the jurisdicational funding, coverage of this group rapidly increased to 51% in 2000.[7] A rapid increase of 23vPPV coverage was not evident in Western Australia (WA) following the NIP funding of the polysaccharide vaccine for elderly Indigenous people in 2000; in 2005, it was estimated that about 31% of the WA Indigenous population aged 50-64 years were vaccinated with 23vPPV.[10]

Prior to the 2005 NIP funding of 23vPPV for elderly non-Indigenous people, national vaccine coverage of non-Indigenous people aged 65 years or older was between 41% and 53% in 2004.[5] Following funding, coverage for this cohort increased slightly to between 51% and 64% in 2006, and 48% and 56% in 2009.[5] In NSW, coverage for all people aged 65 years or older was between 39% and 47% before 2005, and between 59% and 73% after 2005.[11,12]

4.9.3 Coverage of the 7vPCV

At the time of NIP funding of the 7vPCV in 2005, high vaccine coverage of children aged less than 12 months and who had received three doses was reported throughout Australia. In 2005, 7vPCV coverage was 89% for all children in NSW[6]; 91% for all children in South Australia (SA)[9]; and in WA 88% for non-Indigenous children and 75% for Indigenous children[10]. In the following years, national coverage reached 92% for non-Indigenous children, and 85% for Indigenous children between 2007 and 2008[4], and 91% for all children in Queensland (QLD) in 2007.[8]

Overall, funding of the polysaccharide vaccine resulted in some increased vaccine coverage among targeted age groups, while higher coverage of conjugate vaccines has been achieved in younger children.

4.9.4 Incidence of IPD in non-Indigenous people aged 65 years or older

All IPD serotypes:

The concurrent funding of pneumococcal conjugate and polysaccharide vaccines in Australia has been responsible for an overall decrease of IPD cases among elderly non-Indigenous people. Funded pneumococcal vaccines have been responsible for a 35% decrease in the national incidence of elderly non-Indigenous IPD cases (Incidence Rate Ratio [IRR] = 0.65)[5], and a jurisdictional decrease of 27% in SA (IRR = 0.73)[9], and 40% in NSW (IRR = 0.60).[6]

Overall, the national incidence rate of elderly IPD cases for non-Indigenous people has dropped from 25 cases per 100,000 population before 2005, to about 16.5 cases per 100,000 population after 2005.[5]

Serotypes of the 23vPPV:

Polysaccharide vaccines appear to have reduced the incidence of IPD cases caused by the serotypes specific to the 23vPPV. The incidence of IPD cases caused by the 23 serotypes of the polysaccharide vaccine has decreased nationally since 2005 (IRR = 0.72),[4] and within the jurisdiction of northern QLD (IRR = 0.46).[8] At the same time, the incidence of non-vaccine types (serotypes not included in the 23vPPV) have increased nationally (IRR = 2.1 - 2.5),[4,5] and within the jurisdictions of NSW and SA (IRR = 1.23 and 5.3 respectively).[6,9] It would appear, from these results alone, that the 23vPPV has had a significant impact upon reducing the incidence of IPD cases in the elderly non-Indigenous population.

However, it is important to note that an evaluation of the incidence of IPD among elderly people should not only consider the direct impact of the 23vPPV, but also be evaluated in the context of the concurrently funded childhood conjugate vaccines. The overall effectiveness of the pneumococcal polysaccharide vaccine program for elderly individuals is complicated, especially when considering the moderate coverage of 23vPPV in each jurisdiction, and the relatively low effectiveness of the 23vPPV vaccine (vaccine effectiveness (VE) of approximately 61%),[5] alongside the high coverage and effectiveness of the

funded conjugate vaccines. The 7vPCV is not only highly effective at reducing the burden of IPD, it also reduces the nasopharynx bacterial carriage of 7vPCV serotypes within an immunised person, which reduces person-to-person transmission of 7vPCV specific serotypes, and induces a substantial indirect impact upon non-immunised people (via herd immunity).[5]

Serotypes of the 7vPCV:

Since funding of pneumococcal conjugate vaccines, the incidence of IPD cases caused by the 7vPCV specific serotypes has decreased considerably within the elderly non-Indigenous population of Australia. Nationally, the incidence of IPD cases caused by the 7vPCV specific serotypes within this cohort has decreased by 74% - 89% (IRR = 0.11 - 0.26)[4,5] and by 49% in WA (IRR = 0.51)[10] and 85% in NSW (IRR = 0.15).[6] While 7vPCV is not administered to elderly people, the reduced nasopharynx carriage of 7vPCV serotypes within children has indirectly reduced the number of IPD cases caused by these serotypes among elderly people by reducing the transmission of respiratory droplets from person-to-person.

Serotypes specific only to the 23vPPV (23vPPV-non-7vPCV and 23vPPV-non-13vPCV):

When considering the serotypes specific only to the 23vPPV (i.e. 23vPPV-non-7vPCV and 23vPPV-non-13vPCV), the impact of the 23vPPV program targeting elderly non-Indigenous people becomes questionable. The incidence of IPD cases caused by 23vPPV-non-7vPCV serotypes has increased nationally by 64% since 2005 (IRR = 1.64)[5] and within WA by 39% (IRR = 1.39),[10] while decreasing by 12% in northern QLD (IRR = 0.88)[8]. Similar jurisdictional variation regarding the incidence of IPD cases caused by 23vPPV-non-13vPCV are also evident in NSW (IRR = 0.92)[6] and SA (IRR = 1.91).[9]

4.9.5 Incidence of IPD in Indigenous people aged 50 years or older

While the impact of the 23vPPV funding program upon the elderly non-Indigenous population was able to be interpreted from the results presented in the reviewed articles, the same cannot be said for the older Indigenous community. Incidence rate ratios for older Indigenous people were presented nationally (2002-2011),[5] and for the jurisdiction of northern QLD (2001-2009)[8] and WA (2002-2007).[10] However, these ratios measure the relative difference of the funding changes to the NIP during 2005, rather than the targeted 23vPPV funding changes for older Indigenous people in 2000.

Nationally, the incidence of IPD cases caused by 23vPPV specific serotypes among older non-Indigenous people (aged ≥50 years) increased by 93% after 2005 (IRR = 1.93), as did the non-vaccine serotypes (serotypes not covered by the 23vPPV) (IRR = 2.59).[4] The national burden of IPD in older Indigenous people also increased over time, from 20.5 cases/100,000 people in 2002, to 39.5 cases/100,000 people in 2008.[4]

By jurisdiction, the incidence of IPD cases caused by all IPD serotypes among older Indigenous people has decreased by 42% in northern QLD (IRR = 0.58),[13] while increasing by 13% in WA (IRR = 1.13).[10] The higher incidence of IPD within WA was largely caused by the serotypes not included in the 7vPCV (IRR for 23vPPV-non-7vPCV = 1.32), rather than by the serotypes of the 7vPCV (IRR = 0.85).[10] The reduced incidence of IPD in northern QLD could have been a result of the reduced incidence of IPD caused by the serotypes of the 7vPCV (IRR = 0.63), as well as the serotypes included in the 23vPPV (IRR = 0.79).[13]

4.10 Summary

From the analysis of ten selected publications meeting the inclusion criteria for the literature review, there is suggestive evidence that the 23vPPV program had had an impact on the incidence of IPD in older people of Australia. However, this impact was weakened when considering the potential herd immunity impact of the concurrent childhood pneumococcal conjugate vaccine program. Conflicting evidence was reported regarding the 23vPCV-non-7vPCV serotypes and 23vPPV-non-13vPCV serotypes among elderly non-Indigenous people in different jurisdictions. The heterogeneity of these results are possibly due to different contributing factors, such as the highly variable 23vPPV vaccine coverage within each jurisdiction; the different NIP recommendations that target different at-risk people and groups; and the community knowledge and awareness regarding the NIP funding changes.[2,11,12] The need to improve the vaccine coverage of 23vPPV among the elderly Australian population was also identified.

There appears to be stronger supporting evidence that the childhood pneumococcal conjugate vaccine program has had a significant indirect impact (via herd immunity) on the incidence of IPD in older Australians than the targeted pneumococcal polysaccharide vaccine program. The pneumococcal conjugate vaccines appear very effective at reducing the nasopharyngeal carriage of *S. pneumoniae* and person-to-person transmission of vaccine serotypes to susceptible older people.[5] As a consequence of the effective herd immunity provided by the conjugate vaccines, there is also jurisdictional evidence to suggest that different replacement serotypes (non-vaccine serotypes) are infecting more vaccinated and unvaccinated people, which appear to be eroding the overall benefits of the pneumococcal vaccine programs.[4-6,8,9]

Vaccines and vaccine schedules need to be constantly monitored to ensure that they are cost effective and protect as many people as possible. Robust surveillance systems (with serotyping data) are essential for controlling IPD in Australia, so that public health epidemiologists can monitor the changing epidemiology of the disease over time, investigate the changing incidence of IPD within each jurisdiction, evaluate the impact of different vaccines, and monitor the

increasing impact of non-vaccine/replacement serotypes. However, it is worthwhile noting that such ecological studies (as reviewed here) have limitations, and caution is required when interpreting results. Biases are introduced to an ecological study over time, including changes and improvements made to diagnostic, surveillance and laboratory techniques, which are constantly incorporated to improve the overall collection of enhanced IPD data.[6]

Despite these limitations, this review generally confirms that funded pneumococcal vaccines in Australia have had a positive impact upon reducing the incidence of IPD within the older population. It also highlights the importance of continued and regular monitoring of IPD surveillance data. It is anticipated that further analysis of the linked datasets within the NSW Public Health Registry (which includes IPD notification, hospitalisation, emergency and deaths) will allow for this continues monitoring of IPD cases in the older NSW population, along with further investigation of the morbidity and mortality associated with pneumococcal disease, in particular pneumococcal pneumonia.

Part II

NSW Public Health Registry: created using linked data

4.11 Prologue to Part II

This second part of the investigation was a large data linkage project to better identify the impact that funding of different pneumococcal vaccine (under the NIP) has had on the burden of disease in the older population in NSW. Data on invasive and non-invasive pneumonia (ICD-10-AM codes J13 and J18.1) was examined using hospitalisation, notification, emergency and death datasets from NSW. This work was conducted at the Communicable Disease Branch, NSW Health. This study would be the first to accurately quantify hospital coding of pneumococcal pneumonia that is attributable to laboratory confirmed IPD in NSW.

4.12 Introduction

4.12.1 Background

Post-implementation studies that evaluate the trends in hospitalisation coding of community acquired pneumonia (CAP) following the funding of pneumococcal conjugate and polysaccharide vaccines are sparse, especially in adults.[14] While pneumococcal vaccines are well documented to have reduced the incidence of IPD in children and elderly (as documented in Part I), there are also some documented reductions in all-cause pneumonia hospitalisation in adults following the introduction of 7vPCV in the United States of America[15,16] and Australia,[17] and in children from Canada.[18] *Streptococcus pneumoniae* is the most commonly identified pathogen in hospitalised adults with CAP.[17,19,20] Post-implementation studies are necessary to help inform national policy making regarding funding changes of pneumococcal vaccines, and provide additional information that supports evidence-based guidelines. The timing of this investigation is highly relevant in light of the recent Pharmaceutical Benefits Advisory Committee (PBAC) approval for the use of 13vPCV in the adult population of Australia for the prevention of pneumococcal pneumonia and IPD.[21] The PBAC acknowledged that the effectiveness of 13vPCV against CAP not associated with IPD is superior to that of 23vPPV,[21] and that CAP is a much bigger contributor to total disease burden than is IPD.

4.12.2 New South Wales Public Health Registry

Notification, hospitalisation, emergency and death data are useful for assessing the burden of diseases, but limitations of these data sources in isolation impact on their usefulness. Invasive pneumococcal disease (IPD) notifications in NSW are based on agreed national surveillance case definitions, with inclusion criteria based on rigorous laboratory evidence. However, enhanced data about morbidity (emergency department presentation and hospitalisation) and mortality in IPD notification datasets is often incomplete. Linking hospitalisation, emergency department and death datasets to IPD notification data allows more complete capture of morbidity and mortality due to invasive pneumococcal disease.

Using the NSW Public Health Registry (PHR) (an established linked dataset including IPD and emergency department and hospital data) allows first, assessment of data completeness amongst IPD notifications and second, estimation of the proportion of hospitalisations coded as pneumococcal pneumonia which are associated with IPD, facilitating more accurate estimation of the burden of pneumococcal disease in people aged 50 years and over in NSW.

4.12.3 Aims of project

The aims of this project were to determine the morbidity and mortality associated with pneumococcal disease (invasive and non-invasive) using linked IPD notifications, pneumococcal disease related hospitalisations and emergency records and registration of death data in the older population of NSW. A further aim was to investigate the impact that the pneumococcal vaccination program has had upon the burden of disease within this cohort.

4.12.4 Research questions

For older people (aged 50 years or older) of NSW:

a) What proportion of hospital admissions coded for pneumococcal pneumonia (ICD-10-AM codes J13 and J18.1) were associated with an IPD notification between 2002 and 2012?

b) What proportion of cases captured by each of the datasets of the NSW PHR for IPD episodes with a linked hospital admission coded as pneumococcal pneumonia (ICD-10-AM codes J13 and J18.1) died between 2002 and 2012?

c) Where did people reside in NSW who were notified with IPD **and** were without an associated hospital or emergency record in the NSW PHR datasets between the years 2002 and 2012?

4.13 Methods

4.13.1 Datasets

Data for this analysis were obtained from the NSW PHR. The PHR contains aggregated data from five abridged NSW public health surveillance systems (Table 4.4) and contains linked health records, with a unique Project-specific Person Number (PPN) assigned to each record. The creation of the PHR is covered by the NSW Public Health Act 2010 (Section 97), and the following analysis was covered by ethics approval from the Australian National University ethics committee (ANU/2016/197). Data-linkage was conducted using SAS Enterprise Guide (2013; Version 6.1-M1; SAS Institute Inc., Cary NC, USA).

Table 4.4: Administrative datasets which comprise the New South Wales Public Health Registry

Type of records	NSW administrative datasets	Acronym of surveillance system	Complete date range available	Number of records available
Hospitalisation	Admitted Patient Data Collection	APDC	01/07/2001 – 31/03/2015	13,537,957
Emergency Department	Emergency Department Data Collection	EDDC	01/07/2005 – 31/03/2015	9,528,460
Notifications	Notifiable Conditions Information Management System	NCIMS	01/01/1993 – 31/12/2013	695,335
Death Records	Registry of Birth, Deaths and Marriages	RBDM	01/01/1985 – 31/03/2015	245,324
	Australian Co-ordinated Registry of Death	ACRD	01/01/1994 – 31/12/2012	183,369

4.13.2 Ascertainment of hospital cases

APDC database:

The Admitted Patient Data Collection (APDC) database contains records for all admitted patient services provided by NSW Public Hospitals, Public Psychiatric Hospitals, Public Multi-Purpose Services (an integrated health and aged care services, which provides a flexible and sustainable service options for rural and remote communities), Private Hospitals, and Private Day Procedures Centres. Each record represents an individual hospital admission event of a patient, and the period of care, not the completed disease episode. The APDC database contains 51 diagnostic fields, including the primary diagnosis (i.e. the condition that was associated with the highest use of resources) and up to 50 additional diagnoses, completed by certified medical archivists after hospital discharge, following review of medical notes.[17,22] The diagnoses of the patient were coded using the tenth revision of the International Classification of Disease coding system-Australian modified (ICD-10-AM).

Hospital admissions:

The hospitalisation database was restricted to include only hospital admissions with an ICD-10-AM code within any of the 51 diagnostic fields that indicated pneumococcal disease and unspecified pneumonia (Table 4.5). This heterogeneous group of hospital codes were chosen as they should capture all cases of pneumococcal disease, allowing for incorrect hospital coding. Dates of admission were restricted to between 01/01/2002 and 31/12/2012. Age at admission was restricted to 49 years and older, so as to account for anyone who had been hospitalised prior to their IPD notification event on or just after their 50th birthday.

Hospital-episodes:

To account for inter- and intra-hospital transfers, and follow-up and rehabilitative care associated with pneumococcal disease, hospital admissions were

aggregated into hospital-episodes (*where a hospital-episode of an individual was defined as the grouping of consecutive hospital admissions that were coded for pneumococcal disease or unspecified pneumonia and occurred within 30 days of one another*). Start-date, start-age, end-date and end-age of each hospital-episode were maintained, as were the number of hospital admissions that had been combined and the cumulative time spent in hospital. In addition, pneumococcal 'flags' were created for each hospital-episode. The first two flags were 'pneumococcal meningitis' and 'pneumococcal septicaemia', and were defined as all cases where *S. pneumoniae* was coded as the causative pathogen (ICD-10-AM code: G00.1 and A40.3 respectively). The third flag included presumptive 'pneumococcal pneumonia', and was defined as all cases where *S. pneumoniae* was coded as the causative pathogen (ICD-10-AM code: J13) or were coded as lobar pneumonia (ICD-10-AM code: J18.1). The final group was 'unspecified pneumonia', and included all hospitalisations coded as pneumonia and without a causative organism identified (Table 4.5).

Single hospital record:

Following the creation of hospital-episodes, hospital records were flattened to a single line per PPN. Each PPN including start-date, start-age, end-date and end-age for each hospital-episode, cumulative time spent in hospital, elapsed time between each episodes and cumulative counts of each pneumococcal flags at a hospital-episode level. Finally, each PPN was assigned an overall pneumococcal condition flag, based on a defined pneumococcal disease hierarchy (Table 4.6).

Table 4.5: Diagnostic codes and classification of pneumococcal disease and pneumonia using hospitalisation coding (source of information: Jardine et al. 2010[17])

ICD-10-AM / ICD-10 coding	ICD-9-CM coding	Wording of condition	Pneumococcal flag
G00.1	320.1	Pneumococcal meningitis	Pneumococcal meningitis
A40.3	038.2	Pneumococcal septicaemia	Pneumococcal septicaemia
J13	481	Pneumococcal pneumonia	Pneumococcal pneumonia
J18.1	481	Lobar pneumonia, unspecified	
J15.9	482.9	Bacterial pneumonia, unspecified	Unspecified pneumonia
J18.0	485	Bronchopneumonia, unspecified	
J18.2	514	Hypostatic pneumonia, unspecified	
J18.8	486	Other pneumonia, organism unspecified	
J18.9	486	Pneumonia, organism unspecified	

Table 4.6: Pneumococcal hierarchy groups used at an individual level

Pneumococcal hierarchy group	Definition, using hospital coding
(i) Pneumococcal meningitis	A patient coded with pneumococcal meningitis anytime during their hospital stay
(ii) Pneumococcal septicaemia	A patient coded with pneumococcal septicaemia anytime during their hospital stay, and without pneumococcal meningitis coding
(iii) Pneumococcal pneumonia	A patient coded with pneumococcal pneumonia anytime during their hospital stay, and without pneumococcal meningitis or pneumococcal septicaemia coding
(iv) Unspecified pneumonia	A patient coded with unspecified pneumonia anytime during their hospital history, and without pneumococcal meningitis or pneumococcal septicaemia or pneumococcal pneumonia coding

4.13.3 Ascertainment of emergency cases

The Emergency Department Data Collection (EDDC) database contains information about patient presentations to the emergency department of public hospitals in NSW. This dataset included a single diagnostic field per emergency event, and was coded using either the ninth revision of the International Classification of Disease coding system (ICD-9-CM) or ICD-10-AM.

Emergency events, emergency-episodes and single emergency records per PPN were created in the same manner as described above for hospital records, with the following exceptions. Pneumococcal disease and unspecified pneumonia emergencies (using both ICD_10_AM and IDC-9-CM codes: Table 4.5) were filtered using the single primary diagnosis field only. Also, dates of emergency presentation were restricted between 1/07/2005 and 31/12/2012.

4.13.4 Ascertainment of notified cases

The Notifiable Conditions Information Management System (NCIMS) contains confirmed cases of IPD notified to the NSW Department of Health by laboratories, hospitals and medical practitioners. A confirmed case of IPD is defined by laboratory definitive evidence of *S. pneumoniae* in a normally sterile site of the body, and includes isolation of *S. pneumoniae* by culture or detection by nucleic acid test. The abbreviated NCIMS dataset of the PHR included a single diagnostic field for each case, while lacking enhanced data fields such as focus of infection, serotype of infective agent and vaccination status of the case.

Notifications were filtered to include confirmed cases of IPD who were 50 years of age or older, and with notification dates between 1/01/2002 to 31/12/2012. Duplicate records were removed from the dataset when two IPD notifications were recorded for the same individual within 30 days of one another.

4.13.5 Ascertainment of deceased cases

The Registry of Births, Deaths and Marriages (RBDM) and the Australian Co-ordinating Registry of Death (ACRD) contains mortality information for deaths

occurring in NSW; RBDM recording fact-of-death (all records of death; no coding of the cause of death) and ACRD recording cause-of-death (coded using ICD-10 classification of disease).

Records of the RBDM were filtered for date of death between 1/01/2002 to 1/03/2013 (to account for death occurring after final hospital-episode), and duplicates (using PPN) were removed. The RBDM dataset does not record age at death, so no further filtering was conducted.

Records of the ACRD were filtered for date of death between 1/01/2002 to 1/03/2013 (to account for death occurring after final hospital-episode), age at death of 50 years or older, and cause of death coded due to pneumococcal disease and unspecified pneumonia (Table 4.5). Duplicates (using PPN) were removed from the dataset.

4.13.6 Merging of records

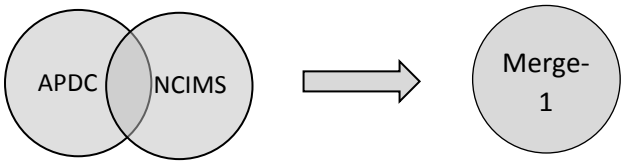
For each of the following merge procedures, the ‘PPN’ variable was used as the single linking variable.

With regards to the accompanying figures below:

- a Merge circle is a temporary dataset;
- a Cohort circle is an endpoint dataset;
- a grey circle represents when the complete dataset was maintained during the merge procedure; and
- a white circle represents when non-linked data was dropped from the merge.

Creation of Cohort 1 and 2

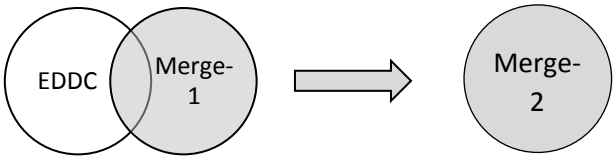
a) The flattened APDC records and filtered NCIMS datasets were merged to create Merge-1



All records were maintained during this merging process (*grey circles*)

Merged records were validated for each PPN and flagged (IPD_episode_flag) when the notification date occurred within 30 days of an individual hospitalisation-episode. For individuals with an IPD_episode_flag, the hospitalisation-episode number was recorded, as were the tally of pneumococcal disease/unspecified pneumonia hospitalisation-episodes that followed this IPD notification.

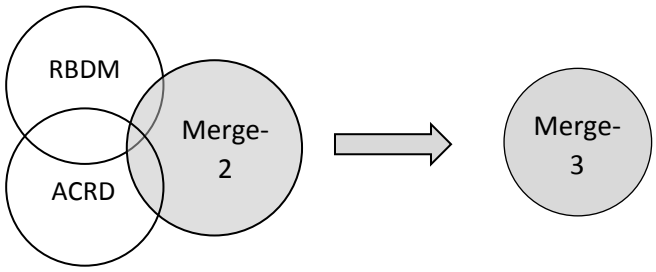
b) The flattened EDDC records and Merge-1 datasets were merged to create Merge-2



Unlinked EDDC records (*white circle*) were dropped from Merge-2

This merging procedure was used exclusively to account for notification records without a linked hospitalisation-episode from Merge-1. Merged records were validated for each PPN and flagged (IPD_episode_flag) when the notification date occurred within 30 days of an emergency-episode and in the absence of a hospitalisation-episode.

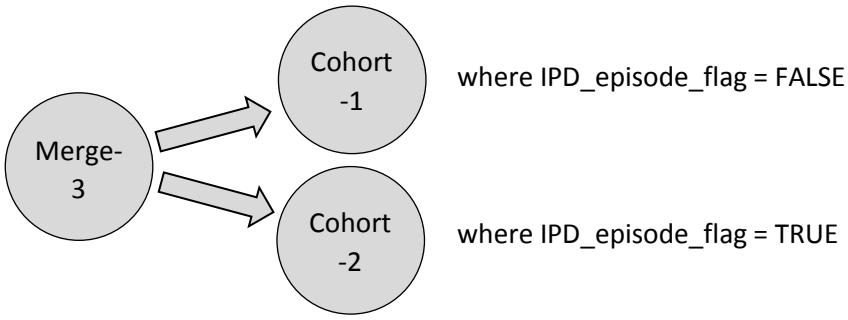
c) Filtered RBDM, ACRD and Merge-2 datasets were merged to create Merge-3



Unlinked RBDM and ACRD records were dropped from Merge-3

Merged records were validated for each PPN and flagged (death_flag) when death occurred within 14 days of the (i) notification date, (ii) separation date of the final hospital-episode or (iii) departure date of the final emergency-episode recorded of an individual.

d) Creation of Cohort-1 and Cohort-2 from Merge-3



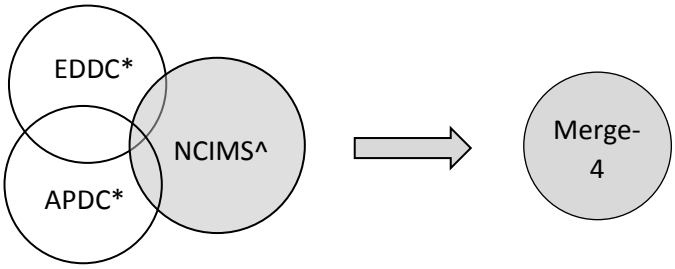
Merge-3 was separated into two separate cohorts based on the IPD_episode_flag

- Cohort-1 contained filtered hospitalisation records coded for pneumococcal disease or unspecified pneumonia and **without** a linked IPD notification record. Records filtered for 50 years of age or older.
- Cohort-2 contained IPD notification records **with** either a linked hospitalisation or emergency record coded for pneumococcal disease or unspecified pneumonia.

Creation of Cohort 3 and 4

Notifications of IPD without an associated hospitalisation-episode or emergency-episode coded for pneumococcal disease or unspecified pneumonia (i.e. IPD notifications that were not part of Cohort-1 or Cohort-2) were re-merged with the original hospitalisation and emergency datasets of the NSW PHR (i.e. the non-filtered APDC and EDDC datasets).

e) Non-filtered APDC and EDDC datasets and the unlinked NCIMS dataset were merged to create Merge-4



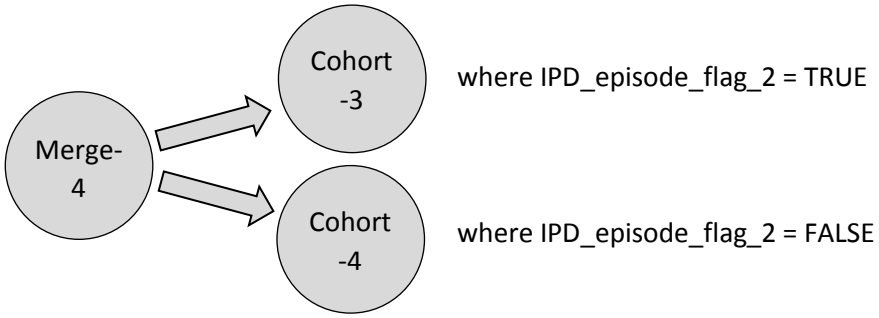
APDC and EDDC records that did not merge with NCIMS records were dropped

* original datasets of the NSW PHR with all hospitalisations and emergencies codes

^ IPD notifications without a linked hospitalisation-episode or emergency-episode

This merging procedure resulted in a single notified record merging with multiple hospitalisation and emergency records. Merged records were validated for each PPN and flagged (IPD_episode_flag_2) when the notification date occurred within 30 days of the hospitalisation admission or emergency arrival dates. Flagged records were sorted by length of elapse-time between notification date and hospitalisation admission or emergency arrival date in ascending order. The first records (including the shortest elapse-time and all unlinked IPD notifications) were retained for each PPN.

f) Creation of Cohort-3 and Cohort-4 from Merge-4



Merge-4 was separated into two cohorts based on the IPD_episode_flag_2

- Cohort-3 contained IPD notification records **with** either a linked hospitalisation or emergency record coded for other diagnoses (i.e. not pneumococcal disease).
- Cohort-4 contained IPD notification records **without** a linked hospitalisation or emergency record identified within the NSW PHR.

4.13.7 Population estimates

Age-specific and Indigenous-specific mid-year estimates of resident population size for the NSW population were obtained from NSW Health.

4.13.8 Data analysis

Overall

A descriptive statistical analysis was conducted for the overall data, where numbers and proportions of pneumococcal and unspecified pneumonia cases were calculated.

Pneumococcal pneumonia from Cohort-1 and Cohort2 only

A second descriptive statistics analysis was conducted on filtered data from Cohort-1 and 2. Records were filtered for hospital code specifically for presumptive pneumococcal pneumonia (ICD-10-AM codes J13 and J18.1).

For the following analysis:

- '*invasive pneumococcal pneumonia*' was defined as an IPD notification with a linked hospital-episode coded for pneumococcal pneumonia, and
- '*presumptive non-invasive pneumococcal pneumonia'* was defined as hospital-episode coded for pneumococcal pneumonia and without a linked IPD notification.

Numbers, frequencies and proportions of pneumococcal pneumonia cases were calculated. Rates were calculated using NSW Health population estimates as the denominator and are presented for the cumulative NSW population, or as age-specific and Indigenous-specific subpopulation rates per 100,000 population. Age groups were assigned as follows: 50-64, 65-69, 70-74 and 75 years and over. Rates were also calculated to compare two time periods, i.e. before the introduction of the concurrent immunisation program of 7vPCV for children and 23vPPV for older people (pre-vaccine 2002-2004) and after (post-vaccine 2005-2012). Other descriptive statistics include median number of bed days in hospital (and range) and number of hospital-episodes following the linked IPD episode.

Period-specific incidence rate ratios (IRRs), 95% confidence intervals (95% CI), and p-values were calculated using a negative binomial regression analysis, due to over dispersion of count data (as indicated by a significant p-value for the likelihood-ratio test of alpha=0, indicating that the negative regression model is more appropriate than the Poisson model). The time-series analyses of monthly rates were expressed as ratios between time-periods that followed the reference month (January, 2002). IRRs were considered as significant at the 5% level ($p<0.05$). Data analyses were conducted using STATA software (version 13.1; StataCorp, College Station, Texas, United States of America).

IPD records without a linked hospitalisation or emergency record (Cohort-4)

Geo-mapping of unlinked IPD notifications between 2002 and 2012 was created using ArcGIS Online (2016; http://www.arcgis.com/home/index.html; Esri, Redlands California, United States of America). Unlinked notifications were plotted using the postcode variable; data points were enlarged to help reduced re-identification of plotted cases.

4.14 Results

4.14.1 Hospital case ascertainment

From the 13,537,957 available records of the APDC dataset, 285,422 hospital admissions satisfied the filtering criteria for inclusion within this analysis. This in turn represented 238,531 hospitalisation-episodes of pneumococcal disease and unspecified pneumonia of 191,461 unique individuals aged 50 years and over in NSW (Figure 4.1).

4.14.2 Emergency case ascertainment

From the 9,528,460 available records of the EDDC dataset, 41,127 emergency presentations satisfied the filtering criteria for inclusion within this analysis. This in turn represented 39,918 emergency-episodes of pneumococcal disease and unspecified pneumonia of 35,815 unique individuals aged 50 years and over in NSW (Figure 4.2).

4.14.3 Notification case ascertainment

From the 695,335 available records of the NCIMS dataset, 3,605 notifications satisfied the filtering criteria for inclusion within this analysis. Two records occurred within 14 days of one another for an individual and a duplicate was randomly dropped. These 3,604 records represented 3,551 unique individuals aged 50 years and over in NSW, with 42 individuals having two separate IPD episodes and five individuals with three IPD episodes (Figure 4.3).

4.14.4 Deceased case ascertainment

From the 245,324 available records of the RBDM dataset, 175,406 deaths satisfied the filtering criteria for inclusion within this analysis (Figure 4.4). From the 183,369 available records of the ACRD dataset, 8,783 deaths satisfied the filtering criteria for inclusion within this analysis (Figure 4.5).

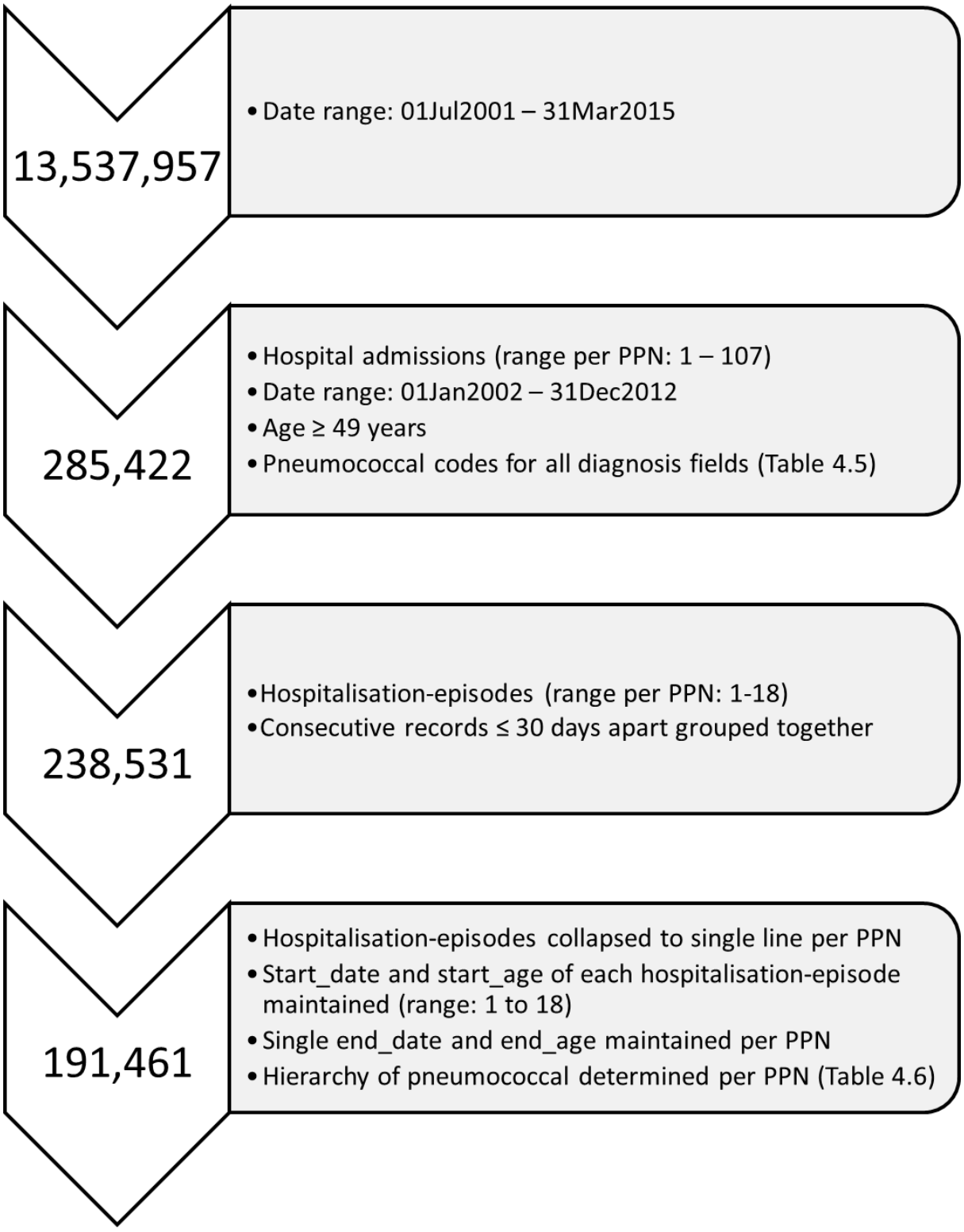


Figure 4.1: Step-wise filtering results of the Admitted Patient Data Collection (APDC) dataset for data-linkage inclusion

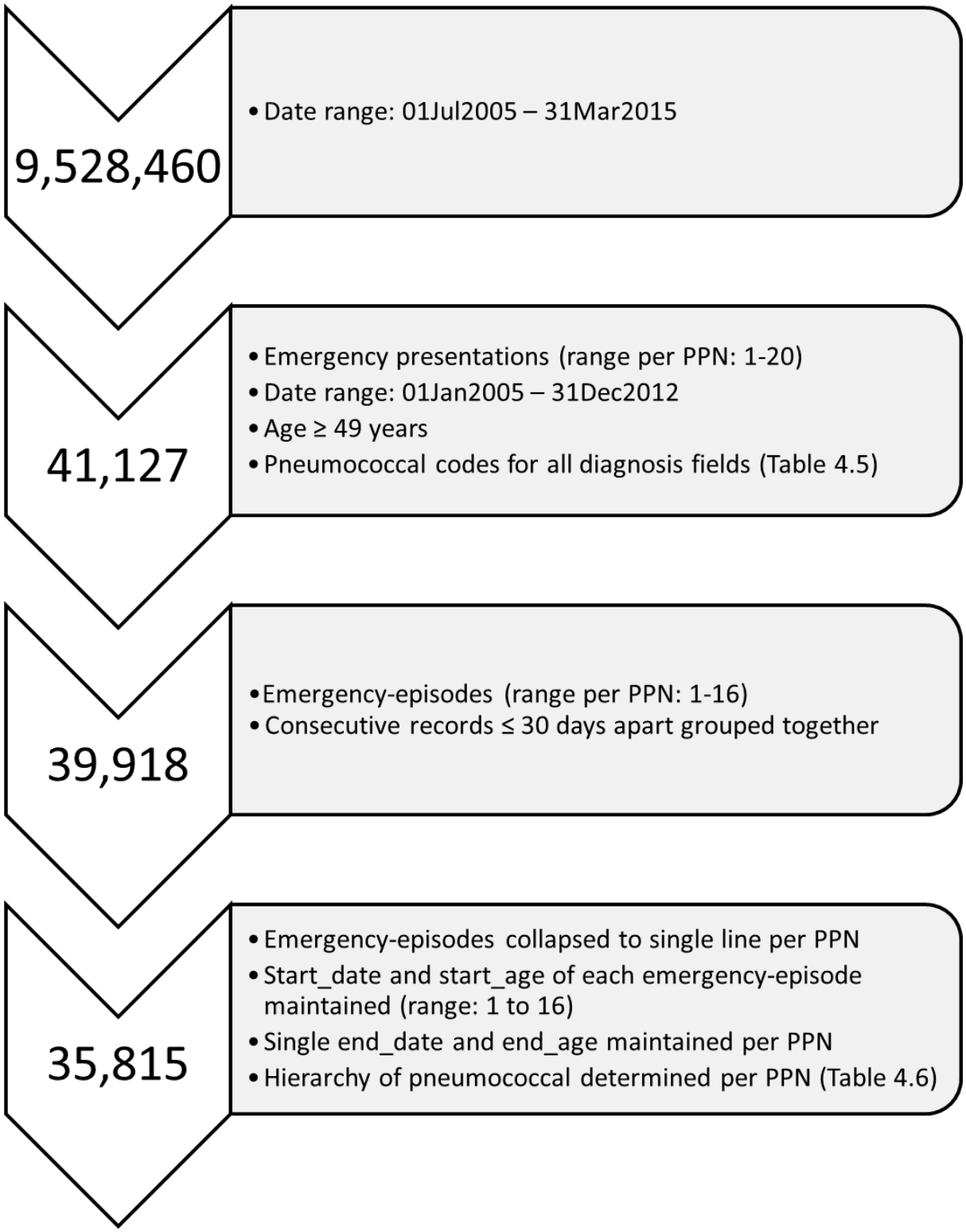


Figure 4.2: Step-wise filtering results of the Emergency Department Data Collection (EDDC) dataset for data-linkage inclusion

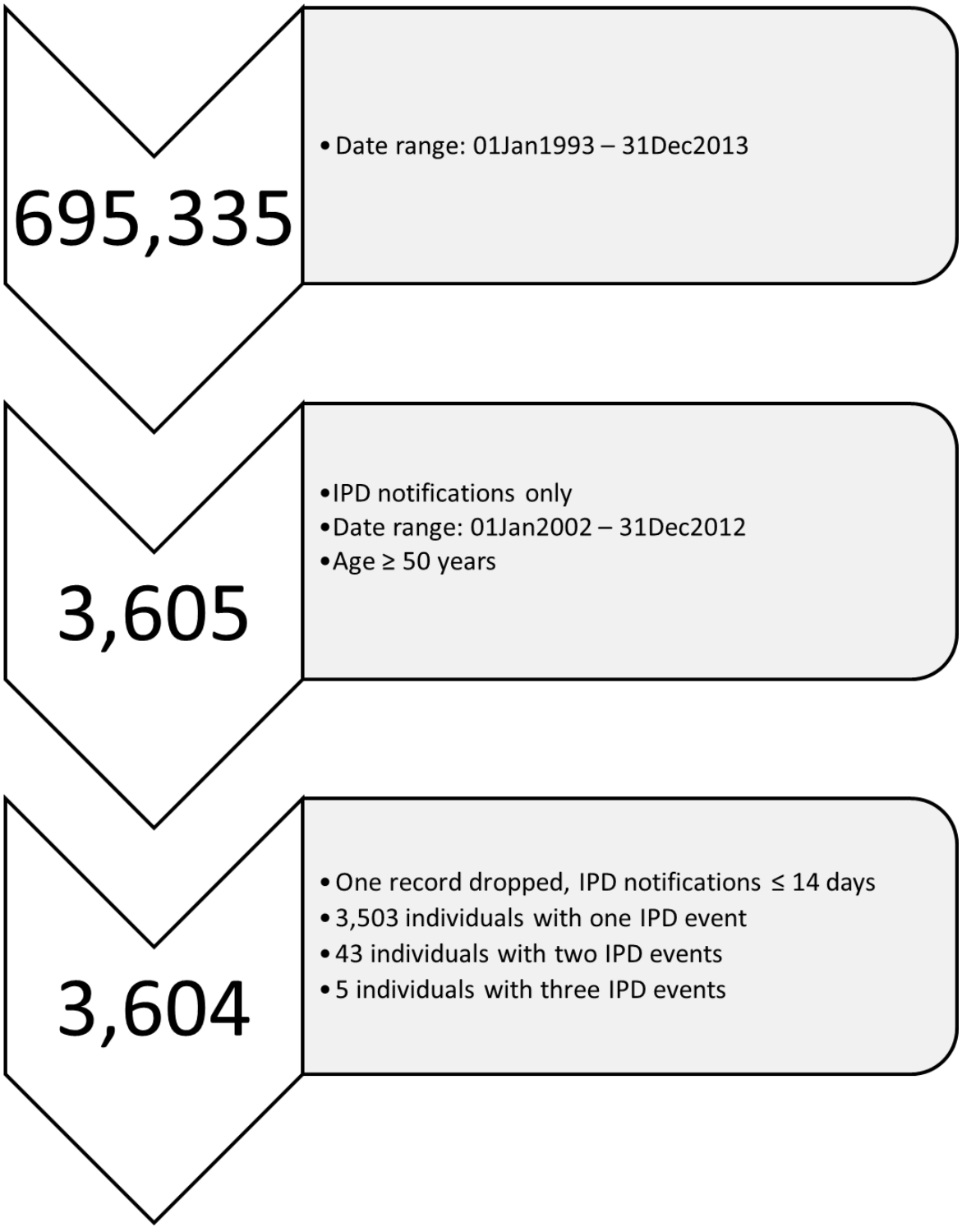


Figure 4.3: Step-wise filtering results of the Notifiable conditions Information Management System (NCIMS) dataset for data-linkage inclusion

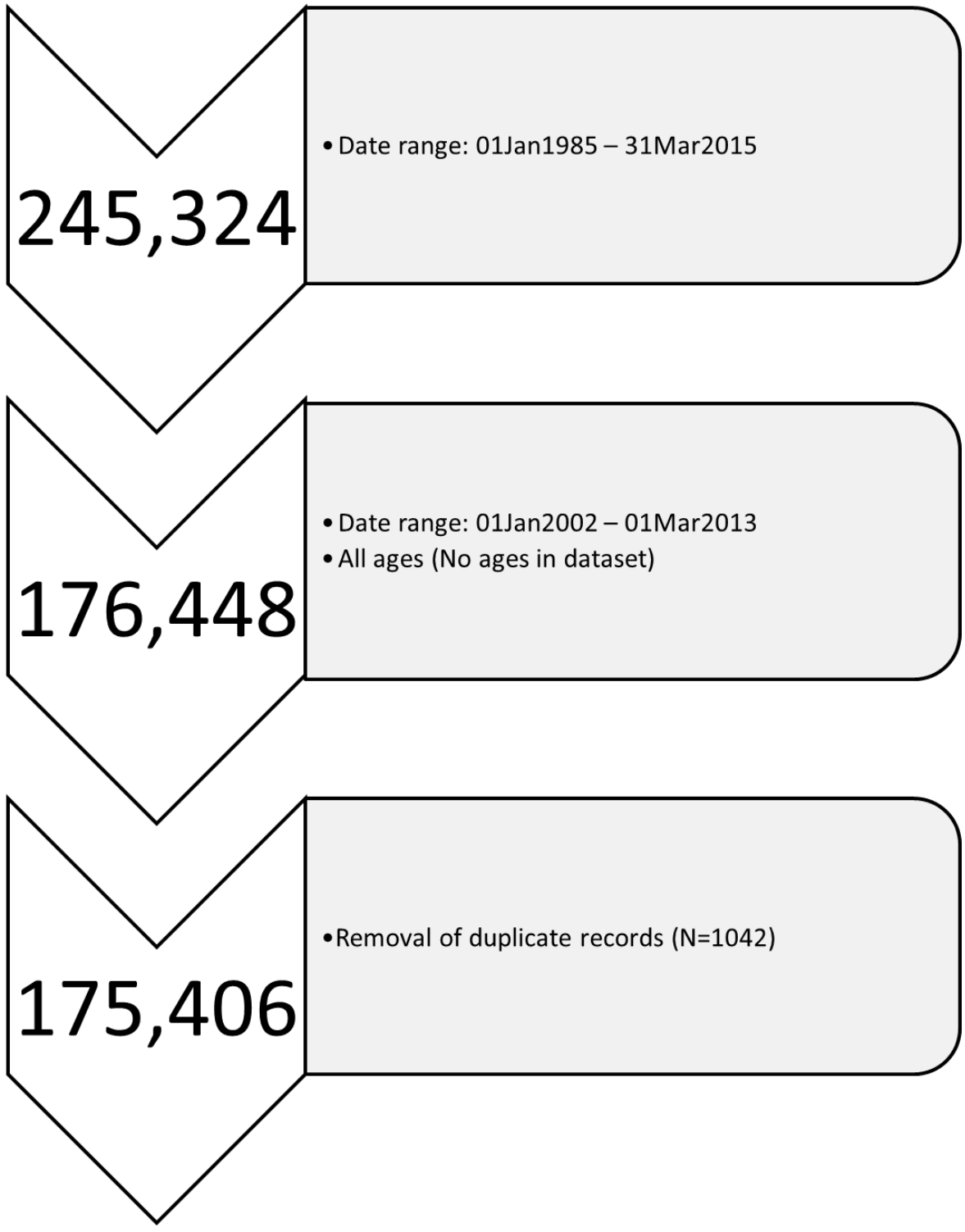


Figure 4.4: Step-wise filtering results of the Registry of Birth, Deaths and Marriages (RBDM) dataset for data-linkage inclusion

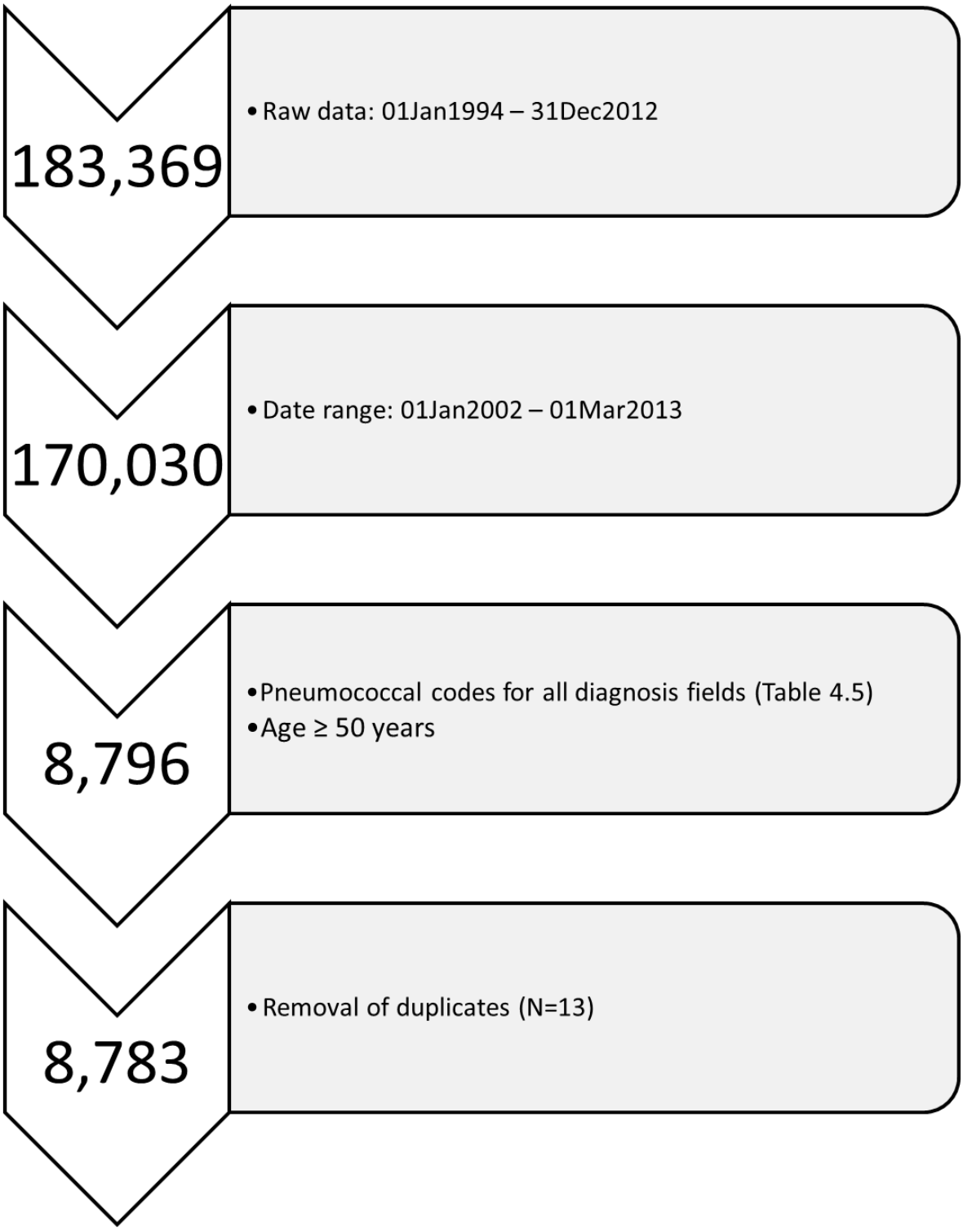


Figure 4.5: Step-wise filtering results of the Australian Co-ordinated Registry of Death (ACRD) dataset for data-linkage inclusion

4.14.5 Overall linkage success

Of the 3,604 notifications within Merge-3, 82.8% (N= 2,983) linked to a hospitalisation-episode or emergency-episode coded for pneumococcal disease or unspecified pneumonia within the PHR; emergency-episodes only accounting for 0.7% of these linked records (21 of 2,983).

Of the remaining 621 notifications within Merge-4, 76.8% (N=477) linked to a hospitalisation or emergency record (i.e. not coded for pneumococcal disease) within the PHR; emergency-episodes only accounted for 0.8% of these records (4 of 477).

Within Cohort-4, 43.0% (62 of 144) of unlinked IPD notifications also had a hospitalisation date recorded within the NCIMS dataset. This indicates that 2.3% (82 of 3,604) of IPD notifications in NSW for people aged 50 years and over did not have either a linked hospital administration, an emergency presentation, or a hospitalisation date recoded in NCIMS between 2002 and 2012.

At the end of the merging procedure, samples sizes for the four different cohorts were as follows:

Cohort-1 N = 191,988 (summary statistics presented in Table 4.7)

*(filtered hospitalisation records coded for pneumococcal disease or unspecified pneumonia and **without** a linked IPD notification record)*

Cohort-2 N = 2,983 (summary statistics presented in Table 4.7)

*(IPD notification records **with** either a linked hospitalisation or emergency record coded for pneumococcal disease or unspecified pneumonia)*

Cohort-3 N = 477

*(IPD notification records **with** either a linked hospitalisation or emergency record coded for all other diagnoses [i.e. not pneumococcal disease])*

Cohort-4 N = 144

*(IPD notification records **without** a linked hospitalisation or emergency record identified within the NSW PHR)*

Table 4.7: Pneumococcal disease and unspecified pneumonia of individuals 50 years or older as coded from hospital discharge records in NSW, 2002-2012
(^ rates per 100,000 population; * Individuals are not exclusive to a sub-group; # age at first hospital admission)

			Total (number)	Deaths (number)	% Total by All-Cause	% Deaths by All-Cause	Total Rates ^	Mortality Rates ^
Cohort 1 & 2		All-cause hospitalisation	189613	---	100.00	---	799.19	---
	Sub-groups of pneumococcal disease *	Meningitis	120	25	0.06	0.01	0.51	0.105
		Septicaemia	1437	446	0.76	0.24	6.06	1.88
		Pneumonia	**8914**	**1516**	**4.70**	**0.80**	**37.57**	**6.39**
		Unspecified pneumonia	183628	42385	96.84	22.35	773.96	178.65
	Age groups # (*222 missing*)	50-64 yrs	37571	4186	19.81	2.21	283.38	31.57
		65-69 yrs	18489	2923	9.75	1.54	608.34	96.17
		70-74 yrs	23061	4538	12.16	2.39	925.30	182.08
		≥ 75 yrs	110270	31366	58.16	16.54	2233.90	635.43
	Gender (*3 missing*)	Male	99411	---	52.43	---	877.56	---
		Female	90199	---	47.57	---	727.55	---
	Indigenous status	Non-Indigenous	186373	42858	98.29	22.60	13.49	1.83
		Indigenous	3165	430	1.67	0.23	27.71	2.22
		Not specified	75	6	0.04	0.003	---	---
Cohort-1 only		All-cause hospitalisation	186668	---	100.00	---	786.78	---
	Sub-groups of pneumococcal disease *	Meningitis	17	1	0.01	0.001	0.07	0.004
		Septicaemia	290	84	0.16	0.04	1.22	0.35
		Pneumonia	**7526**	**1223**	**4.03**	**0.66**	**31.72**	**5.15**
		Unspecified pneumonia	182296	41992	97.66	22.50	768.35	176.99
	Age groups # (*221 missing*)	50-64 yrs	36573	4033	19.59	2.16	275.86	30.42
		65-69 yrs	18166	2853	9.73	1.53	597.71	93.87
		70-74 yrs	22721	4455	12.17	2.39	911.66	178.75
		≥ 75 yrs	108987	30911	58.39	16.56	2207.91	626.21
	Gender (*3 missing*)	Male	97878	---	52.43	---	864.03	---
		Female	88787	---	47.56	---	716.16	---
	Indigenous status	Non-Indigenous	183460	42104	98.28	22.56	782.18	179.51
		Indigenous	3134	423	1.68	0.23	1157.94	156.29
		Not specified	74	6	0.04	0.003	---	---
Cohort-2 only		All-cause hospitalisation	2945	---	100.00	---	12.41	---
	Sub-groups of Pneumococcal *	Meningitis	103	24	3.50	0.81	0.43	0.10
		Septicaemia	1147	362	38.95	12.29	4.83	1.53
		Pneumonia	**1388**	**293**	**47.13**	**9.95**	**5.85**	**1.23**
		Unspecified pneumonia	1332	393	45.23	13.34	5.61	1.66
	Age groups # (*1 missing*)	50-64 yrs	998	153	33.89	5.20	7.53	1.15
		65-69 yrs	323	70	10.97	2.38	10.63	2.30
		70-74 yrs	340	83	11.54	2.82	13.64	3.33
		≥ 75 yrs	1283	455	43.57	15.45	25.99	9.22
	Gender	Male	1533	---	52.05	---	13.53	---
		Female	1412	---	47.95	---	11.39	---
	Indigenous status	Non-Indigenous	2913	754	98.91	25.60	12.42	3.21
		Indigenous	31	7	1.05	0.24	11.45	2.59
		Not specified	1	0	0.03	0	---	---

4.14.6 Cohort-1 & Cohort-2: Invasive and non-invasive pneumococcal pneumonia (ICD-10-AM codes J13 and J18.1) only

This section focuses on those individuals with a hospital code specifically for presumptive pneumococcal pneumonia (ICD-10-AM codes J13 and J18.1) within cohorts 1 and 2 only.

Descriptive:

Of the 189,613 individuals identified with a hospital admission coded with presumptive pneumococcal codes or unspecified pneumonia, 8,914 (4.7%) were coded as pneumococcal (ICD-10-AM codes J13 and J18.1). Of these 8,914 individuals, 15.6% (N= 1,388) had a linked notification record in NCIMS (invasive pneumococcal pneumonia), and a collective total of 1,410 laboratory confirmed IPD notifications (Table 4.7); with 20 individuals having two or three IPD episodes. The remaining 7,526 (84.4%) individuals had a collective total of 8,550 hospital admissions coded as presumptive pneumococcal pneumonia in the absence of a sterile site isolate (Table 4.7).

For the 1,388 individuals with invasive pneumococcal pneumonia, 11.9% (N= 165) had a hospital admission coded as pneumococcal disease occurring before their IPD notification, and after their 50th birthday. The median number of bed days for the hospital-episode directly linked to the IPD notification was 12 days (N= 1,404; range 1 – 309 days). The number of bed days increased from 10 days (N= 489; range 1 – 309 days) for those aged 50 – 64 years, to 14 days (N= 603; range 1 – 179 days) for those aged 75 years or older. Of individuals with a notification date between 2002 and 2011, 21.2% (272/1,282) had a hospital-episode coded as pneumococcal or unspecified pneumonia (any hospital code from Table 4.5) following their IPD episode; 14.7% (N= 189) having a single hospital-episode, 4.4% (N= 56) having two, and 2.1% (N= 27) having three or more hospital-episodes.

Indigenous status within the NSW PHR was 100% complete for notifications of invasive pneumococcal pneumonia, with 2.2% (30 of 1,388 individuals) being in people who identified as Indigenous. The rate of invasive pneumococcal

pneumonia was highest in Indigenous people aged 65-69 years (13.0 cases per 100,000 population), followed by 50 – 64 (11.6 cases per 100,000 population), and 70 – 74 (10.0 cases per 100,000 population); no cases were recorded in Indigenous people aged 75 years and older between 2002 and 2012. A median of three cases (range 0 – 5 cases) were notified per year in people who identified as Indigenous.

Time series:

The monthly rate of hospital admissions coded for presumptive non-invasive pneumococcal pneumonia declined significantly over time (N= 8,550; IRR = 0.993; 95% CI 0.991 – 0.994; P < 0.001), as did the monthly rate of hospital admissions for unique individuals (N= 7,526; IRR = 0.992; 95% CI 0.991 – 0.994; P < 0.001) (Figure 4.6). The monthly rate of invasive pneumococcal pneumonia also declined significantly (N= 1,410; IRR = 0.996; 95% CI 0.993 – 0.999; P < 0.001), however not to the same magnitude as presumptive non-invasive pneumococcal pneumonia (Figure 4.6).

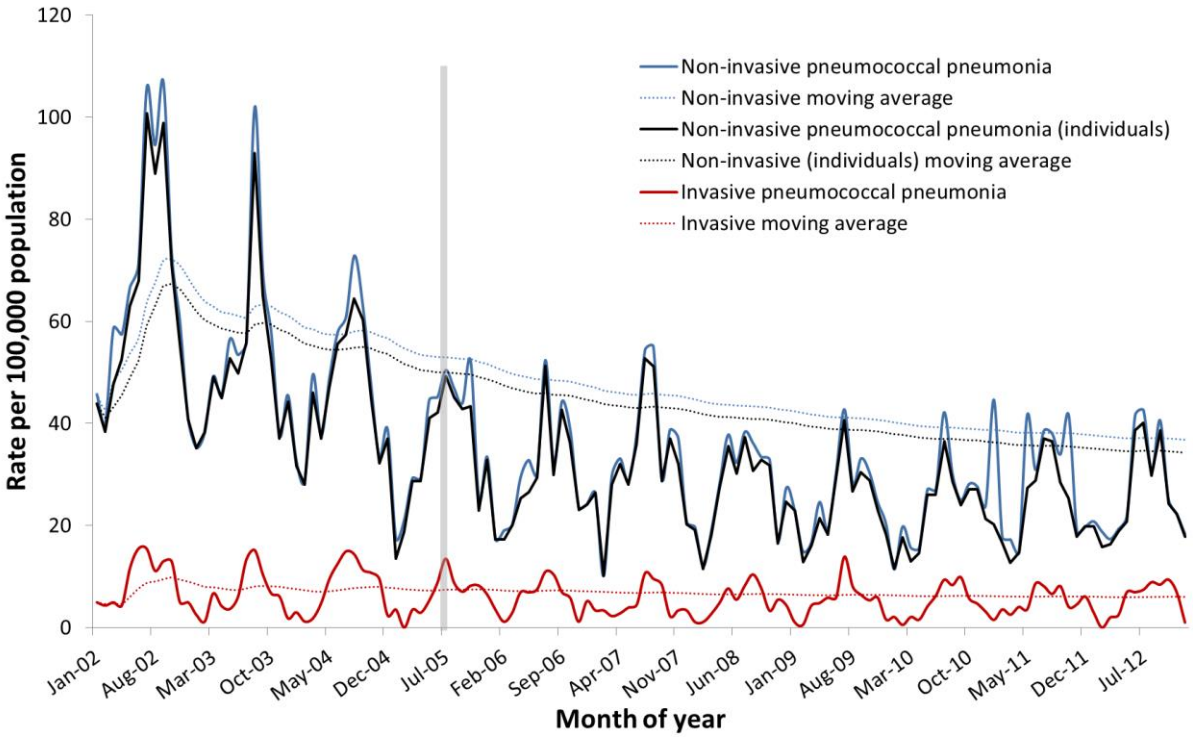


Figure 4.6: Monthly rates of pneumococcal pneumonia (J13 & J18.1) per 100,000 population of NSW people aged 50 years or older 2002 - 2012.

Vertical grey box represents the concurrent changes to the NIP for 7vPCV and 23vPPV

Age groups:

The rate of hospital admissions coded for presumptive non-invasive pneumococcal pneumonia between 2002 and 2012 increased significantly with age, from 14.94 cases per 100,000 population for 50 to 64 years, to 73.07 cases per 100,000 population for 75 years and older (IRR = 5.146; 95% CI 4.555 – 5.814; P< 0.001) (Figure 4.7). A similar trend was observed for invasive pneumococcal pneumonia, with rates increasing from 3.70 cases per 100,000 population for 50 to 64 years, to 12.30 cases per 100,000 population for 75 years or older (Figure 4.7).

Vaccination periods:

The rate of hospital admissions coded as presumptive non-invasive pneumococcal pneumonia declined by 48.2% (IRR = 0.518; 95% CI 0.453 – 0.592; P< 0.001) in the post-vaccine period (2005-2012) when compared to the pre-vaccine period (2002-2004), with the rate dropping from 56.56 cases per 100,000 population (2002-2004) to 29.20 cases per 100,000 population (2005-2012). Mortality rates for presumptive non-invasive pneumococcal pneumonia (within 14 days) declined by 65.1% (IRR = 0.341; 95% CI 0.288 – 0.424; P< 0.001) in the post vaccine period, decreasing from 11.47 cases per 100,000 population between 2002 and 2004, to 3.97 cases per 100,000 population between 2005 and 2012.

The rate of invasive pneumococcal pneumonia declined by 32.0% (IRR = 0.680; 95% CI 0.537 – 0.861; P= 0.001) in the post vaccine period, decreasing from 7.83 cases per 100,000 population between 2002 and 2004, to 5.31 cases per 100,000 population between 2005 and 2012. When death was associated with invasive pneumococcal pneumonia (death occurring within 14 days of diagnosis), the rate of IPD notifications with a linked hospital-episode coding as pneumococcal pneumonia declined by 53.1% (IRR = 0.469; 95% CI 0.335 – 0.657; P< 0.001) in the post vaccine period, decreasing from 2.06 cases per 100,000 population between 2002 and 2004, to 0.96 cases per 100,000 population between 2005 and 2012.

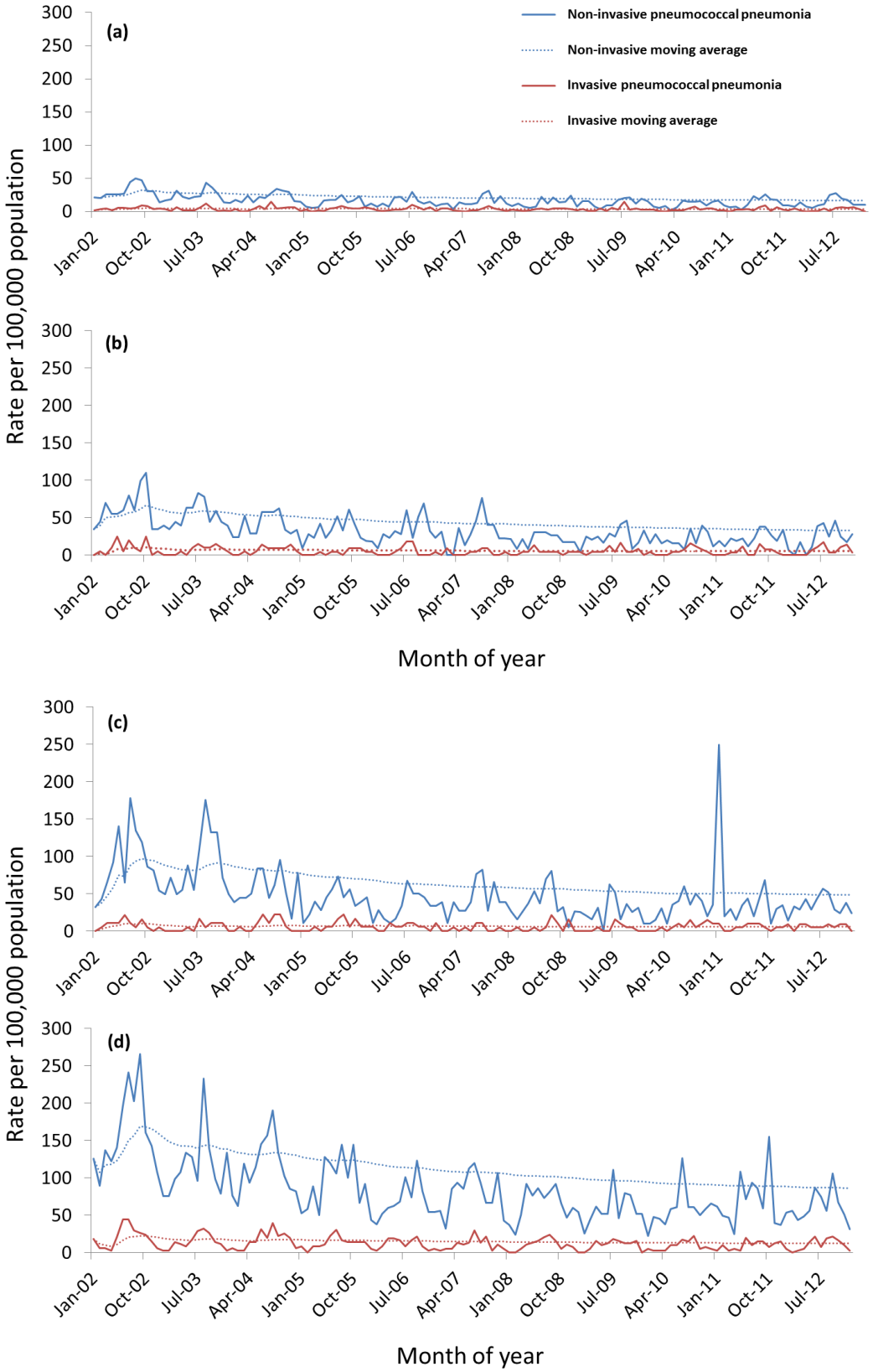


Figure 4.7: Monthly rates of pneumococcal pneumonia (J13 & J18.1) per 100,000 population of NSW people 2002 – 2012: (a) 50-64 years of age, (b) 65-69 years of age, (c) 70-74 years of age, and (d) 75 years and older

Completeness of mortality from invasive pneumococcal pneumonia (Cohort-2 only)

For the 1,388 individuals with laboratory confirmed invasive pneumococcal pneumonia, 293 (21.1%) deaths occurred within 14 days of this event (Figure 4.8). The NCIMS dataset captured 57.7% (N= 169) of these deaths, ranging between 38.2% in 2005 and 76.0% in 2002, with a mortality rate of 0.71 cases per 100,000 population between 2002 and 2012. The APDC dataset captured 87.0% (N= 255), ranging between 78.1% in 2003 and 95.0% in 2004. The RBDM dataset captured 98.3% (N= 288), while ACRD captured 22.9% (N= 67) (Figure 4.8). Of the deaths captured by ACRD, 50.7% (N= 34) were coded as pneumococcal pneumonia (J13), 3.0% (N= 2) as lobar pneumonia, 4.5% (N= 3) as pneumococcal septicaemia, and 41.8% (N= 28) as unspecified pneumonia.

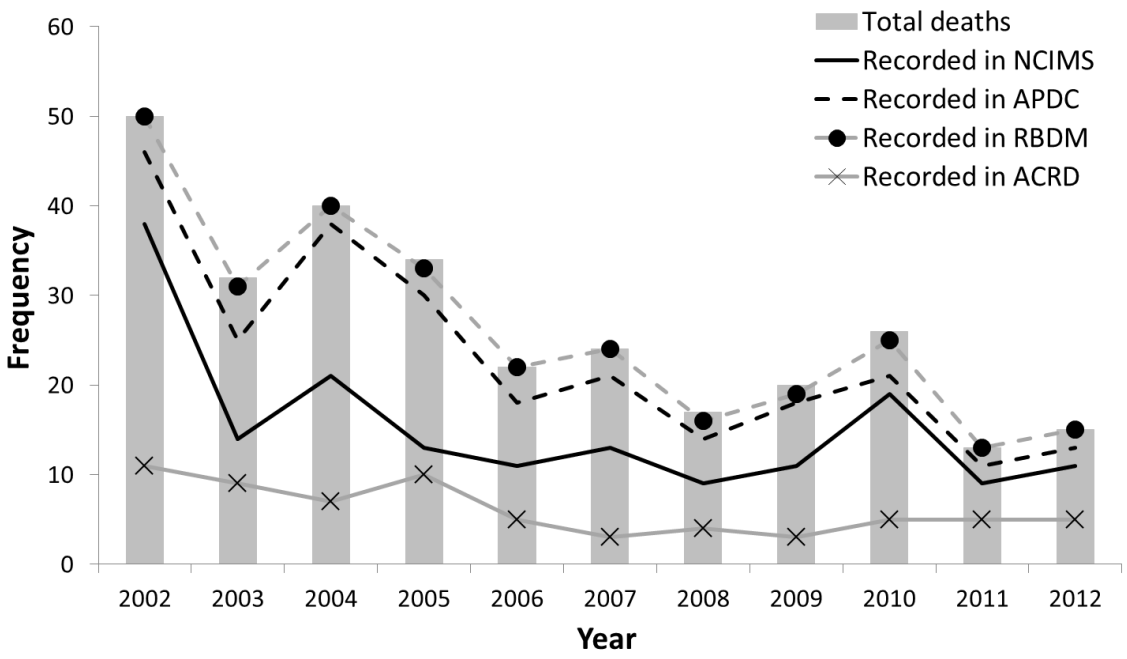


Figure 4.8: Record of mortality occurring within 14 days of laboratory confirmed invasive pneumococcal pneumonia, and different datasets of the NSW PHR capturing this information

4.14.7 Geo-mapping of unlinked IPD notifications in NSW (Cohort-4 only)

Cases of IPD that were without a linked hospital or emergency record in NSW were largely concentrated on the eastern coast of NSW and towards the state and territory borders (Figure 4.9a). A similar spatial distribution was also evident for IPD cases without a linked hospital or emergency record in NSW and without a hospitalisation date recoded in NCIMS (Figure 4.9b). In particular, Sydney was a hotspot for unlinked IPD notifications between 2002 and 2012 (Figure 4.10).

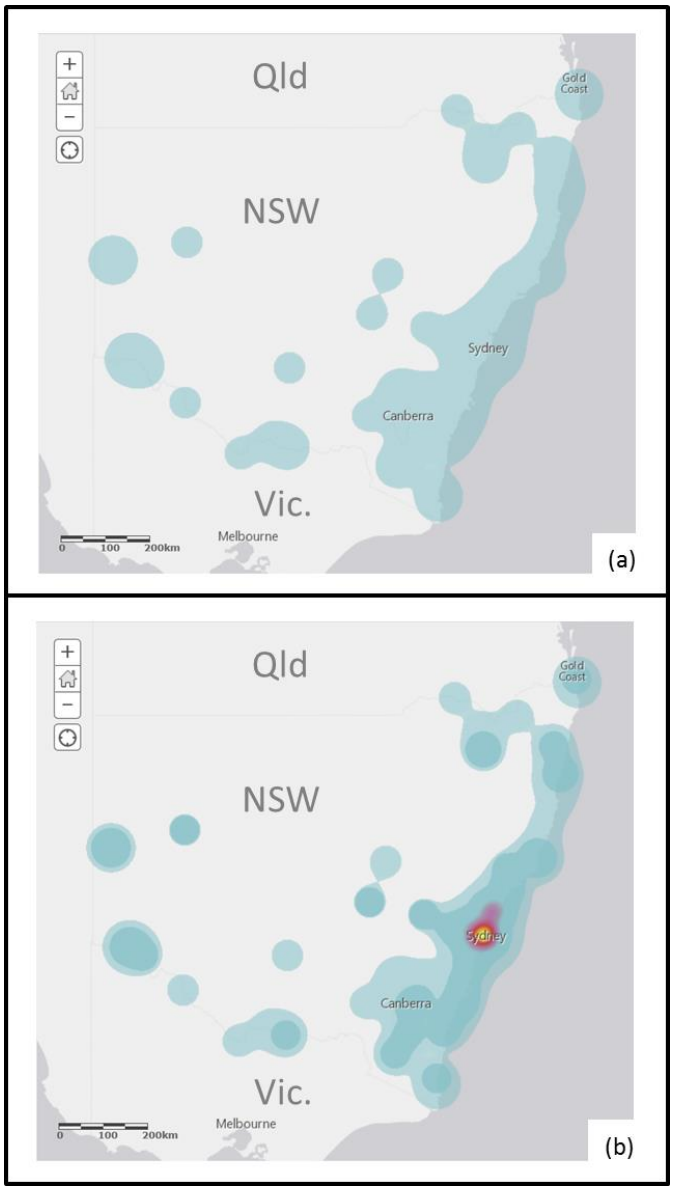


Figure 4.9: Geo-mapping of unlinked IPD notifications in NSW between 2002 and 2012: (a) IPD cases without a linked hospital or emergency record in NSW (N=144), (b) IPD cases without a linked hospital or emergency record in NSW and without a hospitalisation date recoded in NCIMS (N=82).

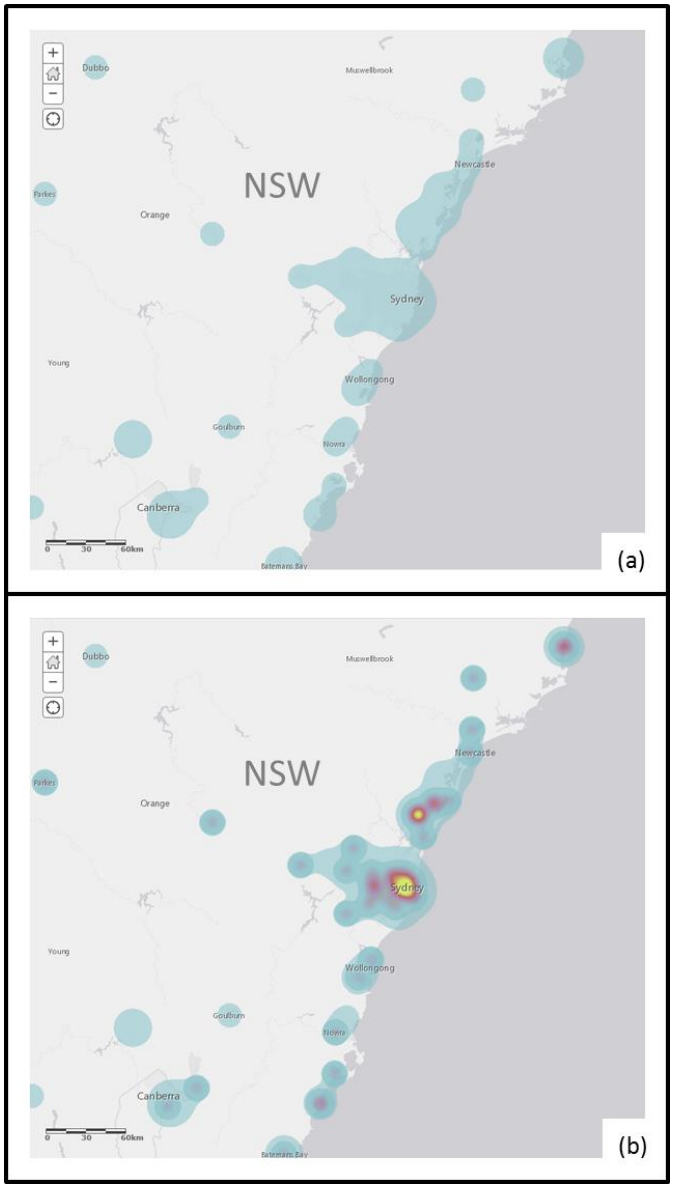


Figure 4.10: Geo-mapping of unlinked IPD notifications around Sydney between 2002 and 2012: (a) IPD cases without a linked hospital or emergency record in NSW, (b) IPD cases without a linked hospital or emergency record in NSW and without a hospitalisation date recoded in NCIMS.

4.15 Discussion

This is the first study in Australia to estimate in detail the burden of pneumococcal pneumonia using the linkage of surveillance and hospitalisation data. In this investigation, I was able to demonstrate that approximately one in seven hospital admissions that are assigned ICD-10-AM codes for pneumococcal pneumonia (J13 and J18.1) in adults aged 50 years or older also had a notification as IPD in the laboratory based surveillance system. This would mean that the remaining six hospital admissions could be classified as presumptive non-invasive pneumococcal pneumonia. The incidence rate of this presumptive non-invasive pneumococcal pneumonia was significantly less (by 48.2%) in the period post-2005 when universal child and adult pneumococcal vaccination programs were introduced compared to the pre-2005 years. The decline was greater (by 65.1%) when limited to those presumptive non-invasive pneumococcal pneumonia hospitalisations that were associated with death, suggesting a possible greater impact from the vaccination programs on more severe disease. Overall, the rate of presumptive non-invasive pneumococcal pneumonia hospitalisation increased with age, from 14.94 cases per 100,000 population for 50 to 64 years, to 73.07 cases per 100,000 population for 75 years and older. The 23vPPV that was used for adults has not been consistently shown to be effective against non-invasive pneumococcal pneumonia hospitalisations.[21] Therefore, it is not entirely clear the reasons attributable for this reduction in presumptive non-invasive pneumonia hospitalisations in older people of NSW.

Invasive and non-invasive pneumococcal pneumonia

It has been demonstrated in Australia that *S. pneumoniae* is the most commonly identified pathogen (between 14% and 42%) in hospitalised adults with CAP.[17,19,20] The 7vPCV used in the children program has provided substantial indirect protection against IPD to adults.[23,24] Furthermore, a post-implementation analysis of national data presented strong evidence to suggest the 7vPCV nationally funded program was also responsible for an overall reduction of all-cause pneumonia hospitalisations in Australia.[17] Consistent patterns of change across all age groups were identified,[17] with the observed trends in younger

people comparable to those documented in North America, where a 4 dose schedule, including a booster dose (3+1 schedule) is offered.[25-27] The non-invasive pneumococcal pneumonia trends observed in older people could be related to a herd impact of the pneumococcal conjugate vaccination program; rather than from the polysaccharide pneumococcal vaccine or non-specific confounding effects, including changes in diagnostic coding or clinical practices in NSW hospitals. However, further investigation would be required to confirm this.

In addition to the reduced rate and severity of non-invasive pneumococcal pneumonia hospitalisations in elderly people over this period, there has also been a reduction in the length of stay in hospitalisations due to pneumococcal pneumonia. Community acquired pneumonia constitutes the large majority of pneumococcal disease in adults. Therefore the burden of pneumococcal pneumonia both invasive and non-invasive is a key parameter in the cost effectiveness assessments that inform publicly funding vaccination programs in Australia. Australia is unique among high-income countries in that it funds three primary doses of pneumococcal conjugate vaccine for children with no booster dose (3+0 schedule), with studies such as this being important to ascertain the indirect impact of this 3+0 schedule.[28] To date, Australian studies have demonstrated reductions in the incidence of IPD following the funding of the 7vPCV which were comparable to those in the United Kingdom (UK) and the USA where a booster dose is offered in the second year of life using a 2+1 and 3+1 schedules respectively.[6,29,30]

The descriptive nature of this data-linkage study makes it difficult to quantify the exact contribution that the pneumococcal conjugate vaccination program has had upon hospitalisations. The use of ICD-10-AM hospital codes has been demonstrated to have good sensitivity (98%) and specificity (97%) in medical record notation of all-cause pneumonia in the hospitalisation of older people in Australia.[17,31] A ratio of 6:1 for non-invasive to invasive pneumococcal pneumonia was identified in this investigation, which differs to estimates from a systematic review of diagnostic techniques for pneumococcal pneumonia (ratio 3:1).[32] The estimate presented here could represent the lower limit of the true ratio, as admissions have been reported by hospital coding only and lacks further validity through diagnostic testing of the causative agent of disease.[32]

Another possibility for the decline of presumptive non-invasive pneumococcal pneumonia hospitalisations as reported here, could be due to the recommendations made during clinical audits to improve the concordance of CAP management through promotion of the Pneumococcal Severity Index.[33] The Pneumococcal Severity Index, which became a recommended guideline in Australia during 2003,[17] is a tool to help regulate those cases of CAP that could be treated as outpatients and those that should be admitted to hospital.[34] Following reports that documented low compliance with the Pneumococcal Severity Index,[35,36] it is possible that increased awareness (by a multi-faceted education intervention[33]) and a systematic shift to improve management of pneumococcal pneumonia cases as outpatients has coincided with the 2005 funding changes to the pneumococcal conjugate vaccines under the NIP. Further work is required to confirm this as discharge diagnosis of pneumonia hospitalisations are usually based on clinical and radiologic findings and are without necessarily microbiological confirmation. It is possible that a proportion of pneumococcal pneumonia does not get identified as such and therefore escapes capture by relevant hospital discharge diagnosis codes.[32]

Significant declines in the rate of invasive pneumococcal pneumonia between the pre- and post-vaccine periods were also documented during this investigation. Notification rates declined in the post-vaccine period by 32.0% overall, and by 53.1% when death was associated with invasive pneumococcal pneumonia (within 14 days). Therefore, it is reasonable to assume that the pneumococcal vaccinations have had a significant impact on the incidence of invasive pneumococcal pneumonia in adults in Australia; as well as causing a reduction in the severity of disease and mortality associated with invasive pneumococcal pneumonia. However, following the findings of the Community Acquired Pneumonia in Adults (CAPiTA) Trial in the Netherlands,[37] the results presented here would be particularly important if funding of the 13vPCV were to be considered for older adults in Australia.

Australia has continued the 3+0 schedule when 13vPCV replaced 7vPCV in mid-2011.[28] Somewhat unlike with 7vPCV, the indirect impact against pneumococcal disease from 13vPCV appears to be less with a 3+0 schedule, than schedules with a second year booster.[28] Therefore, it is possible that a direct 13vPCV adult

program may have greater benefit in our setting, where we offer a 3+0 children schedule, compared to those settings that have children schedules that contain a booster dose. However, there is currently lack of data to estimate accurately the potential benefit of a direct 13vPCV program on non-invasive pneumococcal pneumonia in adults. In the CAPiTA study, 13vPCV had 45% efficacy against non-invasive pneumococcal pneumonia caused by vaccine serotypes in adults aged 65 years and over,[37] with the cost-effectiveness of such programmatic change in Australia remaining questionalble.[28] If a direct 13vPCV adult program were to be considered in Australia, then results from this data-linkage investigation would be an important addition to the cost-effectiveness evaluation.

The decrease of IPD notifications with a linked hospital-episode coded for pneumococcal pneumonia have occurred in the context of relatively modest 23vPPV coverage, with coverage for all people aged 65 years or older in NSW being between 59% and 73% after 2005.[11,12] As outlined in Part I of this chapter, these decreases may have also been influenced by the potential herd immunity impact of the concurrent childhood pneumococcal conjugate vaccine program that commenced in 2005. Unfortunately, it was not possible to further investigate the proportion of infection due to 23vPPV, 23vPPV-non-7vPCV serotypes, 23vPPV-non-13vPCV serotypes and non-vaccine serotypes among older people of Chohort-1 and 2. One limitation of the datasets within the NSW PHR was the absence of serotype information within abridged NCIMS dataset. In NSW, enhanced IPD data has been collected since 2002,[4] and include addition information such as IPD serotype, focus of infection, and vaccination status of the individual. However, these variables were not available for this analysis.

Mortality from invasive pneumococcal pneumonia

In this investigation, I also demonstrated that the completeness of mortality data for invasive pneumococcal pneumonia within the notification dataset was only 58% complete, ranging between 38% and 76% per year. For older people of NSW with invasive pneumococcal pneumonia, the rate of mortality reported by NCIMS (0.71 cases per 100,000 population between 2002 and 2012) appears to be an underestimate of the total rate of mortality from the linked dataset (1.23

cases per 100,000 population between 2002 and 2012). This could potentially have a big impact upon our understanding of the mortality associated with pneumococcal pneumonia, and any economic evaluation of the pneumococcal vaccination programs in Australia.[30] Both hospitalisation and RBDM data capture a higher proportion of deaths associated with invasive pneumococcal pneumonia (87% and 98% respectively). However, as standalone datasets, neither dataset can identify invasive pneumococcal pneumonia cases with ICD-10-AM coding; ICD-10-AM coding alone cannot distinguish between invasive and non-invasive cases.

Geo-mapping of unlinked IPD notification in NSW

Finally, the geo-mapping of IPD cases that were without a linked hospital or emergency record in NSW was also demonstrated in this investigation. The notification database (NICMS) in NSW uses the residential postcode of each case as the place of the IPD notification, while APDC and EDDC record the location of the hospital or emergency department where the individual attended. Therefore, a person who is a resident of NSW would be notified within NCIMS and could have attended a hospital or emergency department outside of NSW. This would help to explain the number of IPD notifications near the Australian Capital Territory and along the borders with SA and Victoria. The concentration of IPD notifications in Sydney and other major towns along the eastern coast of NSW might be further explained by the domestic or international travel of people, where the case, again, has attended a hospital outside NSW.

Validity of methodology and limitations

The methodology and ICD-10-AM codes used in this analysis appear to be validated, with 82.8% (2983 of 3604) of IPD notifications successfully linked to hospital admissions and emergency presentations coded for pneumococcal disease or unspecified pneumonia (as listed in Table 4.5). Also the proportion of IPD notifications without a linked hospital or emergency record is within the false positive rate of probabilistic linkage. The false positive rate of probabilistic linkage

for the NSW PHR is around 5/1,000.[38] Therefore, it would be expected that within a dataset of 190,000 individuals there would be approximately 950 incorrect linkages. The number of IPD cases without a linked hospital or emergency record (N=114; Cohort-4) identified in this investigation is within the expected range.

There were certain limitations of this investigation. This is a descriptive investigation; therefore, inferences of any causal links between changes in incidences of pneumococcal pneumonia disease in adults and vaccination are only speculative. Possible alternate explanations are changes to admission procedure, coding practices, treatment guidelines and improved methods of diagnostic testing; all of which could have influenced the declining monthly patterns that was identified during the post-vaccination period. Other influences to the post-vaccine decline of non-invasive pneumococcal pneumonia include the prevalence of smoking, which increases the likelihood of pneumococcal pneumonia, and coverage of influenza vaccination, which decreases the likelihood of pneumococcal pneumonia. In Australian adults aged 18 years of older, smoking rates have declined from 22% in 2001 to 16% in 2011-12,[39] while influenza vaccination coverage for people aged 65 years or older in NSW was stable during this investigation period, at 78.9% in 2004 and 72.7% in 2009.[40,41] In addition, this investigation was limited by the lack of serotype information from both the notification dataset. It was not possible to comment on the propensity for certain serotypes to cause invasive disease and those opportunistic serotypes less likely to become invasive within an individual. Also, it was not possible to investigate the risk associated with having co-morbidities,[23] which would be elevated among the older population of NSW.

4.16 Conclusion

Among adults, pneumococcal pneumonia causes significant mortality and morbidity.[32] While the 23vPPV funded program under the NIP has been shown to reduce the incidence of IPD in elderly people, uncertainty remains regarding their effectiveness against reducing the hospitalisation rate due to CAP. The effectiveness of conjugate vaccines against CAP is likely to be superior to that of polysaccharide vaccines,[21] as conjugate vaccines are more immunogenic than polysaccharide vaccines.[23,24] In this study I documented that approximately one in seven hospital admissions coded for pneumococcal pneumonia in adults aged 50 years or older in NSW was due to invasive pneumococcal disease. The remaining six hospital admissions were due to presumptive non-invasive pneumococcal pneumonia. I also documented significant declines in the rate and severity of hospitalisations due to presumptive non-invasive pneumococcal pneumonia in elderly people of NSW from 2002 to 2012. For older people of NSW, mortality associated with invasive pneumococcal pneumonia may be misrepresented within the notification dataset, with the true rate being approximately twice as high. The misrepresentation of mortality due to invasive pneumococcal pneumonia and significant declines in presumptive non-invasive pneumococcal pneumonia in older people of NSW could have a major impact on cost-effectiveness of pneumococcal vaccine program in Australia.[14] The conjugate vaccine may be preventing a significant number of non-invasive pneumococcal pneumonia hospitalisations in older people over time and having a positive impact on the health of older people. Continued monitoring of pneumococcal pneumonia and vaccine impact is required in Australia to maximise the effectiveness of the different pneumococcal vaccination schedules in Australia.

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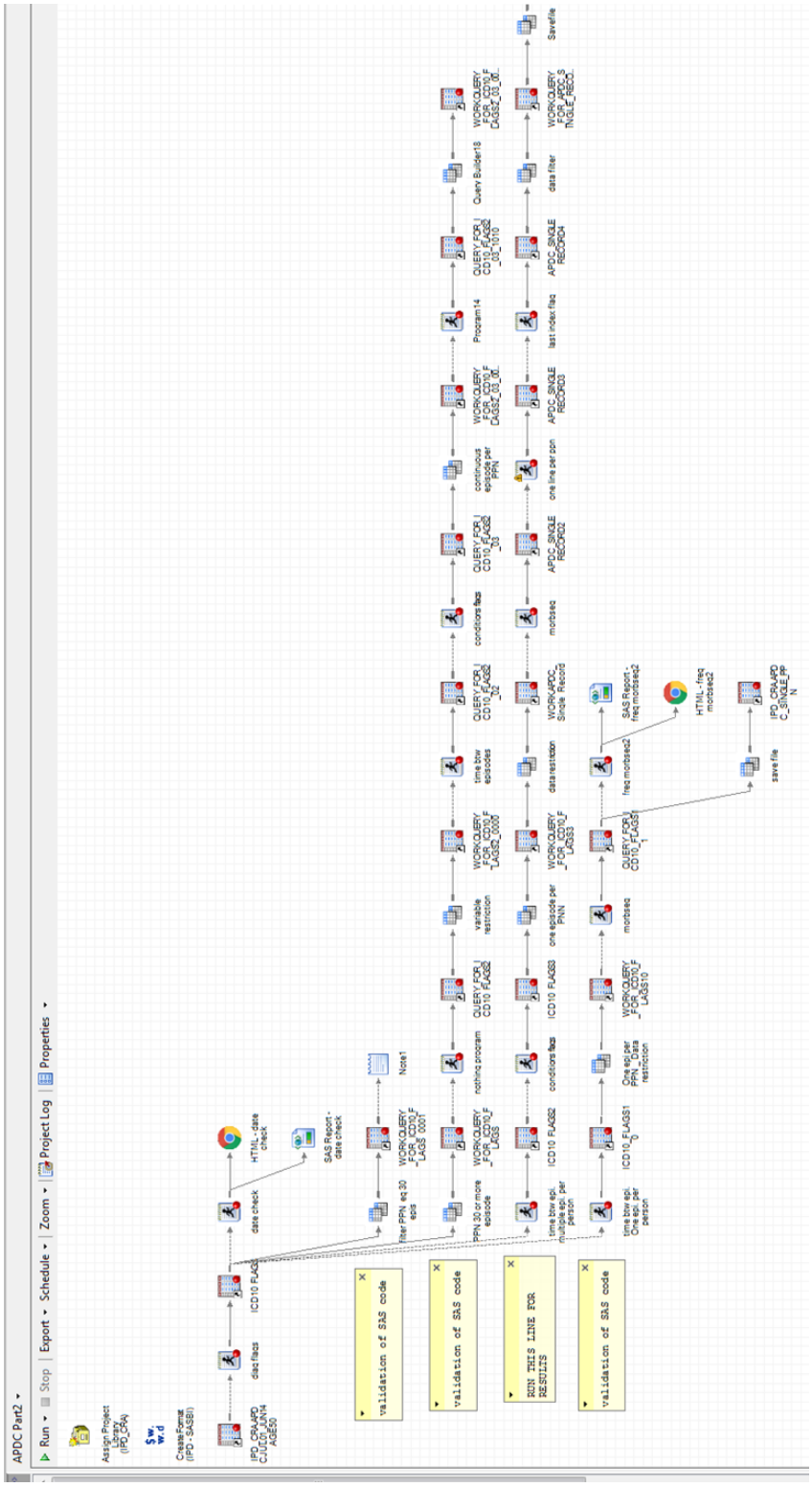
4.18 Appendix 4.1

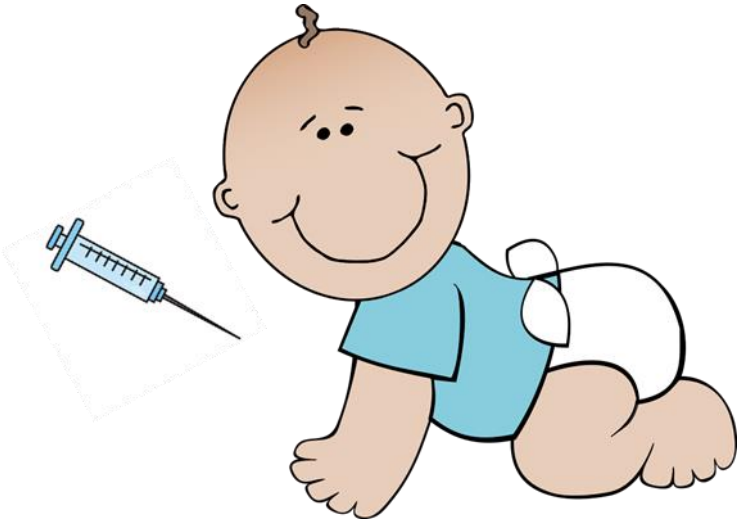
Example screen shot from SAS Enterprise Guide



Chapter 5

AusVaxSafety sentinel active SMS-based surveillance system

"a surveillance system for adverse events following influenza vaccination administered to children aged between six months and five years"



Chapter 5 Contents

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5.3 Prologue

5.3.1 Background

This chapter represents the final core component of the MAE field program in which I conducted an evaluation of AusVaxSafety sentinel active SMS-based surveillance system. I was very fortunate to be in a position to evaluate this system during its second year of operation. For this chapter, I follow the structural framework as outlined by the US Centres for Disease Control and Prevention (CDC) - Updated guidelines for evaluating public health surveillance systems.[1] For ease of reading I have combined the result and discussion sections. The timeliness of this evaluation was of particular importance and highly relevant; this evaluation was required to ensure that this relatively new system was working well, achieving its aims, and helping to restore and maintain parental and public confidence in seasonal influenza vaccines for children.

5.3.2 My role

As principal investigator, I designed and validated three different questionnaires for the purpose of conducting interviews of the AusVaxSafety stakeholders. These included an online questionnaire hosted on Survey Monkey for steering committee members and two separate telephone-administered questionnaires, the first for the AusVaxSafety administration staff member and a second for the Vaxtracker and SmartVax administration staff members. I entered data from these questionnaires into a dataset that I constructed and evaluated the responses of the stakeholders to gain a better understanding of how AusVaxSafety was performing during the 2015 influenza season. I assessed the operation of the system as it relates to the seven different surveillance system attributes. I have presented the results of this assessment together with recommendations to assist with the ongoing function of this active surveillance system.

I also attended regular teleconferences hosted and chaired by the National Centre for Immunisation Research and Surveillance (NCIRS), which included steering committee members and jurisdictional co-ordinators. I have presented

interim results from this evaluation at the NCIRS Academic meeting in October 2016. Also, results and recommendations from this evaluation were included in the final report presented to the Australian Government Department of Health (HEALTH) as part of the 2016 reporting commitments of AusVaxSafety; as well as made available (in its entirety) to steering committee members of AusVaxSafety.

I was also responsible for producing a Vaccine Safety Surveillance information sheet targeting a lay audience for an ethics application at NCIRS. The information sheet targeted parents and cares of children who were between the ages of six months and five years and had been administered seasonal influenza vaccine at The Sydney Children's Hospitals Network (Appendix 5.1).

5.3.3 Lessons learned

I have learned a lot from this opportunity of evaluating an active and relatively new surveillance system, including a better understanding of system attributes, how to conduct an interview and increase participation of stakeholders, and how to analyse qualitative data. It was a complex process evaluating AusVaxSafety. I was required to understand the system, figure out the important attributes to evaluate and synthesise both qualitative and quantitative information into this final report. Also, after re-listening to the recordings that I conducted with administration staff, I now have a better appreciation of the time required to draw themes from recorded interviews. I have also learned a great deal about the influenza vaccination recommendation in Australia, vaccine safety, how best to monitor adverse events, and the negative impact that a well-publicised adverse event can have to vaccine uptake in a defined cohort.

5.3.4 Public Health impact

Following the federal government's decision in 2010 to suspend the national use of all seasonal trivalent influenza vaccines for children, Australia has been trying to make changes to its adverse events surveillance systems to align with

recommendations of the Horvath Review.[2] AusVaxSafety was quickly established to occupy this important niche.

AusVaxSafety is essential to monitor for potential adverse events following immunisation to help increase public confidence in influenza vaccines administered to children. Since 2010, an increasing number of parents have become more concerned about the side effects and safety issues of the influenza vaccine, and less concerned about the severity of influenza illness. The negative press associated with the 2010 Fluvax® vaccine remains prominent in 2015. AusVaxSafety has an important role to play in restoring the confidence of parents and vaccine providers regarding childhood influenza vaccination. Among the other roles of AusVaxSafety, this sentinel active surveillance system is in place to help increase coverage of the seasonal influenza vaccine and to be seen as being proactive when it comes to vaccine safety.

When considering public health impact, the timing of this evaluation is highly significant. AusVaxSafety is a national system with the potential to expand and reform adverse event surveillance in Australia. The real-time nature of the AusVaxSafety system means that data are collected, aggregated, cleaned and analysed quickly, with results disseminated to the local and national community in near real-time during active surveillance. It is important, at this early stage, to take a step back and gain a better understanding of the data that are being collected and analysed. A systematic evaluation of AusVaxSafety was conducted to ensure that the results and recommendations of AusVaxSafety are based on data that are (a) of the highest quality; (b) complete and valid; (c) representative of the cohort; and (d) useful to parents and the public health community. It is also essential that the system is simple, flexible and stable, and that data flow is efficient, seamless and timely. Finally, it is important that problems of the system are identified and rectified quickly.

On a personal note, as a parent it is reassuring to know that AusVaxSafety is doing what it is doing and, based on the results of this evaluation, is doing it very well. My son (age three and a half years) has been a recruit of the AusVaxSafety during 2015 and 2016. It is encouraging to know, beforehand, that the vaccines being administered to him have a good safety profile, and that the reported

adverse events experienced after vaccination are within acceptable limits. I have provided information to this system; I have witnessed the importance of this active surveillance system first-hand; and I am happy that these valuable results are being generated in real-time and with minimal extra work to the public health community.

When it comes to vaccine safety, AusVaxSafety simply makes sense.

5.3.5 Acknowledgements

Helen Quinn and Kerri Viney took the lead supervisory roles during this project. I am very grateful to Alexis Pillsbury and Kristine Macartney at NCIRS and Katrina Roper at ANU for their technical guidance, thoughtful review and feedback during the development of this chapter. Also thank you to the stakeholders that completed the questionnaire, enabling me to complete this evaluation. Thank you ☺

5.4 Abstract

AusVaxSafety sentinel active SMS-based surveillance system was established following the Australian federal government temporary suspension of the national use of all 2010 seasonal trivalent influenza vaccines for children aged between six months and five years. It was developed to actively monitor, detect and report adverse events following immunisation (AEFIs) with influenza vaccine from children aged between six months and five years in as near to real-time as possible. AusVaxSafety is a clinical resource, designed to enable transparency and improve public trust when it comes to vaccine safety.

Following the 2015 influenza season, AusVaxSafety was evaluated to assess the usefulness of the information collected; determine the performance, efficiency and effectiveness of the system; identify strengths and limitations of the surveillance system; and provide feedback to stakeholders regarding recommendations to the system. A short online questionnaire was developed for the steering committee members of AusVaxSafety and a longer telephone administered questionnaire was developed for the key administration staff of the system. Qualitative responses from all stakeholders were categorised into common themes. AusVaxSafety data collected during the 2015 influenza season were also explored.

During the 2015 influenza season the AusVaxSafety system demonstrated, in real-time, that influenza vaccines registered for used in children aged six months to five years were safe, well tolerated, and that the rates of AEFIs experienced were within expected ranges. The AusVaxSafety system was well accepted by participants, with 99% of parents/carers agreeing to participate and 76% (N= 3,340) returning a completed survey. No safety signals were identified during the 2015 influenza season.

AusVaxSafety demonstrated that it was a very useful system, providing very timely feedback to enable trust and transparency regarding vaccine safety. During the first two years of operation, AusVaxSafety can already be seen as being proactive when it comes to vaccine safety and working to restore professional and public confidence regarding the recommendations of the NIP. It is anticipated that AusVaxSafety will continue to expand, not only throughout

Australia, but also with the number of vaccines that it monitors. AusVaxSafety has enormous potential, not only to provide real-time information on the childhood influenza vaccine safety, but can also serve to reinforce consumer confidence in vaccines for all ages, in these times where there are pockets of low immunisation in Australia.

5.5 Acronyms

ACT	Australian Capital Territory
AEFI	Adverse Event Following Immunisation
CDC	US Centres for Disease Control and Prevention
FAST	Follow up and Active Surveillance of Trivalent influenza vaccine
FIR CUSUM	Fast Initial Response Cumulative Summation
GP	General Practice
HEALTH	Australian Government Department of Health
ICD-10	Tenth revision of the International Classification of Disease coding system
MAE	Master of Philosophy in Applied Epidemiology
NCIMS	Notifiable Conditions Information Management System
NFA	No Further Action taken
NIP	National Immunisation Program
NSW	New South Wales
NT	Northern Territory
PAEDS	Paediatric Active Enhanced Disease Surveillance
QLD	Queensland
RNA	Ribonucleic acid
SA	South Australia
SAE	Serious Adverse Event
SMS	Short Message Service
TGA	Therapeutic Goods Administration
TIV	Trivalent Influenza Vaccine
QIV	Quadrivalent Influenza Vaccine
VIC	Victoria
WA	Western Australia
WHO	World Health Organization

5.6 Introduction

5.6.1 Influenza Disease

Influenza is an infectious single-stranded ribonucleic acid (RNA) virus, which represents a pathogenic viral group sub-divided into two antigenic types that cause epidemic disease in humans (influenza virus type A and B).[3] Symptoms are generally acute and include an abrupt onset of fever, cough and sneezes, accompanied by malaise, myalgia, sore throat and headaches.[3-5] Usually, these symptoms are resolved in 5-7 days, with the cough persisting for an additional week or more.[4] Complications associated with influenza disease include pneumonia, croup, acute bronchitis, otitis media and an exacerbation of chronic medical conditions, with children particularly suffering from high temperatures that can induce febrile seizures.[3,5] Influenza can also cause severe respiratory-illness with multisystem complications that can result in death.[3]

Influenza virus is spread from person to person by direct contact facilitated by contaminated respiratory secretion or contaminated droplet transmission through the act of sneezing and coughing.[5] The incubation period of influenza disease is 1-3 days.[3] In adults, the peak communicability of influenza virus is during the first three to five days after the onset of symptoms, while in children communicability can last up to ten days.[4] Seasonal influenza epidemics can be explosive, and are facilitated by a high proportion of asymptomatic and mild cases, along with efficient transmission dynamics during optimal condition. At a community level, the annual attack rate of influenza is generally 5-10%, while in 'closed' populations including households and institutions such as childcare, schools and aged-care facilities, attack rates can be two to three times higher.[3,4] Epidemics usually occur during the winter months in temperate environments, and during somewhat predictable times of the year in tropical and sub-tropical zones (such as during rainy seasons).[4]

5.6.2 Influenza Vaccines

Vaccination remains the most effective measure to prevent infection and to avoid the complications associated with influenza illness.[6] The seasonal quadrivalent

influenza vaccine (QIV) is recommended for all adults and children over the age of six months who are concerned with reducing their likelihood of becoming ill with influenza.[7] Certain high-risk groups are funded under the National Immunisation Program (NIP), and include pregnant women; people aged 65 years or older; people who identify as Aboriginal and/or Torres Strait Islander and are aged between 6 months and five years or 15 years and older; and all persons aged six months or older with specific medical condition that put them at high risk of influenza related complications.[6] In addition to these NIP recommendations, seasonal influenza vaccines have been funded by the Western Australian Department of Health since 2008 for children between the age of six months and four years.[8-10] The funding of these vaccines in Western Australia (WA) was in response to the influenza-related deaths of three preschool aged children during 2007.[9]

Due to the highly variable nature of the influenza virus and constantly changing geographic distributions of pathogenic serotypes an annual review of the influenza vaccine is necessary. Prior to 2016, trivalent influenza vaccines (TIV) were funded in Australia, with these vaccines including components of influenza type A(H1N1), A(H3N2), and influenza type B (with the newly funded QIV contains a second influenza type B strain). The exact formulation of these vaccines change in response to seasonal strain variation, with changes recommended by the World Health Organization (WHO) in response to best available global serosurveillance data,[11] and are approved locally by the Australian Influenza Vaccine Committee.[3] Since becoming widely available in Australia in 1999,[3] there have been six reformulations to the influenza A(H1N1) serotype, 11 reformulations to the influenza A(H3N2) serotype and 11 reformulations to influenza type B in the TIVs.[12-27] Seasonal influenza vaccines are particularly challenging to the registration and distribution process given the short time between influenza seasons and lengthy manufacture process.[2] This was quite apparent during 2015 with lengthy manufacturing delays experienced due to the double-serotype change of the seasonal TIV.[28]

5.6.3 2010 Influenza Season

In 2010, soon after the distribution of the seasonal TIV to vaccine providers (8 March 2010) and public launch of the childhood influenza vaccination program in WA (19 March, 2010), emergency department clinicians noticed an apparent increase of children (<5 years of age) presenting to a specialist paediatric referral hospital following vaccination with TIV.[8,9] Symptoms included fever, vomiting, and febrile seizures.[8,9] This signal was identified in WA due to the high uptake of funded vaccines provided by the local Department of Health.[29,30] This issue required urgent attention to ascertain whether the signal represented a true increase of adverse event following immunisation (AEFI) and, if so, whether the AEFIs were related to all 2010 seasonal TIVs; to a single manufacturer; or a single batch.[9] The WA influenza immunisation program was temporarily suspended on the 22 April, 2010.[2,9] The following day the Australian federal government suspended the national use of all 2010 seasonal TIVs for children aged between six months and five years.[2,9] This was the first time in Australian history that an immunisation program had been suspended due to AEFI.[9]

During the 46 days of the 2010 childhood influenza vaccination program in WA, a total of 63 children (between the ages of six months and five years) presented to emergency departments with febrile seizures occurring within 72 hours after vaccination (Figure 5.1).[9] This rate of febrile seizures (4.4 per 1000 doses) was more than 200 times higher than other population-based estimates.[9] The highly elevated odds of febrile seizures was clearly associated with receipt of Fluvax® and Fluvax Junior® (CSL Biotherapies) 2010 seasonal influenza vaccine formulation.[9] Similar issues with this vaccine brand were also identified in other jurisdictions of Australia.[31,32] The national influenza vaccine program for children was re-established three months later on 30 July, 2010.[2,30]

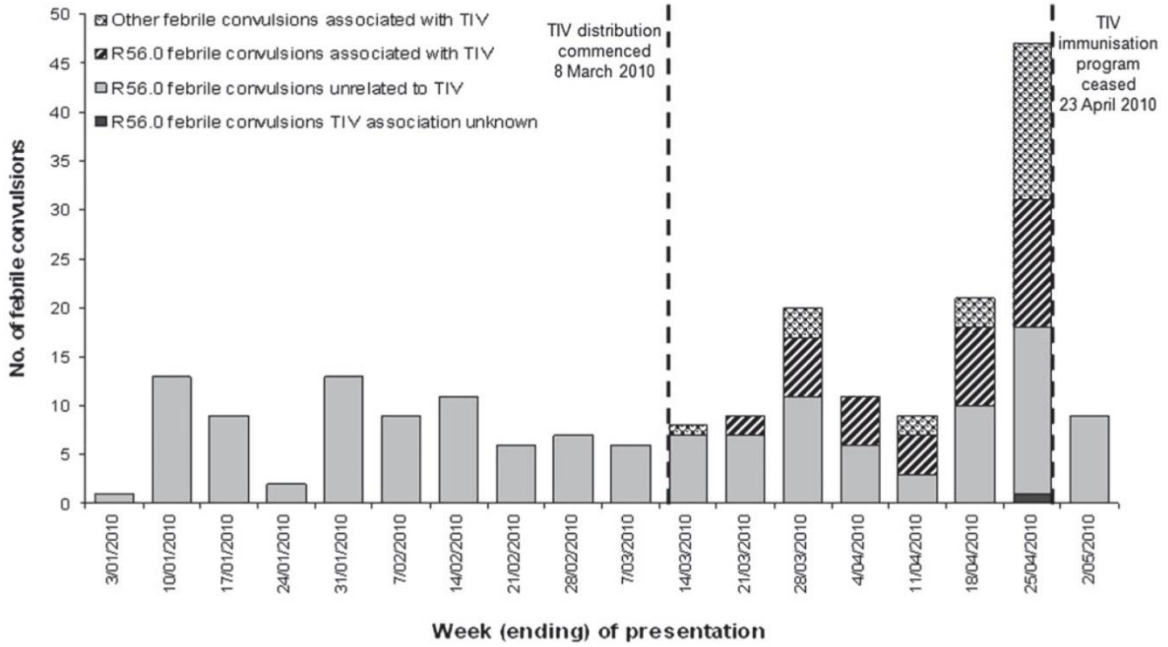

Figure 5.1: Children aged between six months and five years of age presenting with febrile seizures (febrile convulsions: ICD-10 code R56.0) to nine different Perth hospital emergency departments between 01 January and 02 May, 2010. (TIV = trivalent influenza vaccine).[9]

Fluvax® and Fluvax Junior® (CSL Biotherapies) have since been deregistered for children between six months and five years of age and are no longer recommended for children under the age of ten years.[3] Of greater concern has been the negative and ongoing effect that these unprecedented AEFI have had on parental attitudes and behaviours regarding childhood vaccinations. Since 2010, parents have become more concerned about the side effects and safety issues of the influenza vaccine and less concerned about the severity of influenza illness.[10] The uptake of government funded TIV has decreased significantly in WA since 2010 (Figure 5.2).[10]

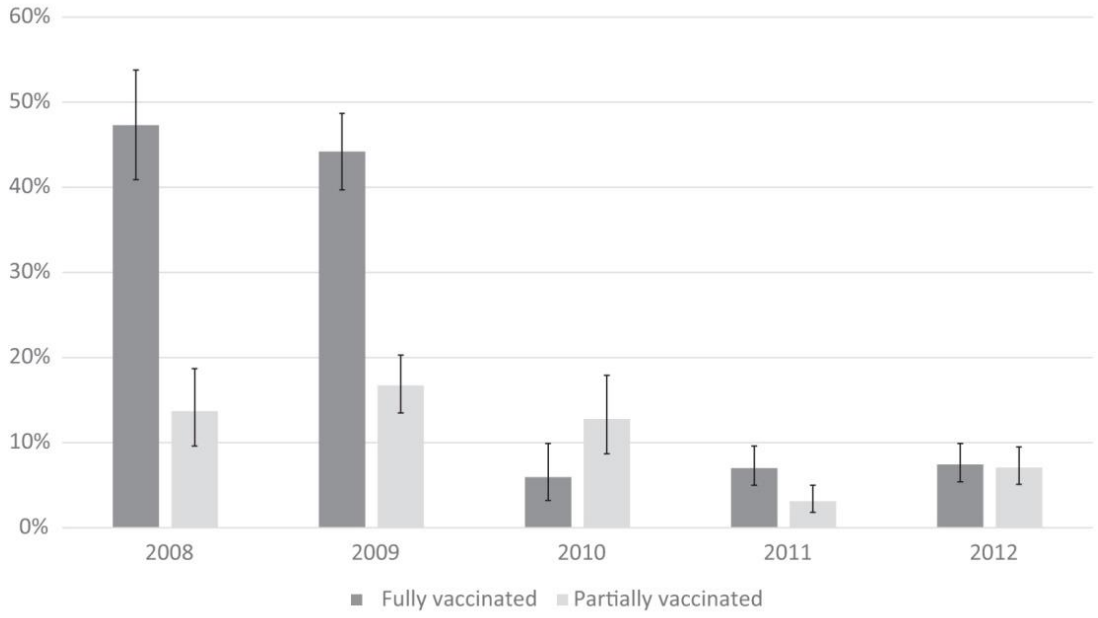

Figure 5.2: Vaccine uptake in children presenting with influenza-like-illness over time in Western Australia.[10]

5.6.4 Surveillance of AEFI in Australia

In Australia, the routine surveillance of AEFI is undertaken by the Therapeutic Goods Administration (TGA).[33] The passive surveillance system of TGA ensures that vaccines and medicines maintain an acceptable safety profile following registration by collecting voluntary information reported by health professionals and members of the public.[33] Inadequacies in this passive surveillance of vaccine safety were identified and recommendation made in March 2011.[2] In response to these recommendations,[2] AusVaxSafety was established in 2014 to actively monitor, detect and report AEFIs from an individual cohort (children aged between six months and five years) and following a particular vaccination (seasonal influenza) in as near to real-time as possible.[34] Results are disseminated in near real-time to stakeholders and the public to help restore professional and public confidence regarding the recommendations of the NIP.

5.6.5 Purpose of evaluation

Following the 2015 influenza season, AusVaxSafety was evaluated to:

- assess the usefulness (*defined as the ability to contribution to the monitoring, detection and provision of real-time feedback on potential safety signals*) of the information collected;
- determine the performance *(defined as the function, operation and utility of AusVaxSafety during active surveillance*), efficiency and effectiveness of the system;
- identify strengths and limitations of the surveillance system; and
- provide feedback to stakeholders regarding recommendations to the system.

5.7 Methods

This chapter follows the structure of the framework as outlined by the US Centres for Disease Control and Prevention (CDC) - Updated guidelines for evaluating a public health surveillance systems.[1] The AusVaxSafety system used aggregate data collected by two different supporting tools: Vaxtracker and SmartVax. The functionality of Vaxtracker and SmartVax are described in more detail in the Results section.

5.7.1 Stakeholder engagement and consultation

Interviews were conducted to determine the level of engagement stakeholders had with the system; to seek their opinions about the system attributes; and understand the strengths and weaknesses of the system. The steering committee members of AusVaxSafety were administered a short online questionnaire that included a series of closed and short-open ended questions. A longer face-to-face/telephone administered questionnaire was developed for the key administration staff of AusVaxSafety, Vaxtracker and SmartVax; these questionnaires had a greater emphasis placed on open ended questions. Qualitative responses from all stakeholders were categorised into common themes.

5.7.2 Data exploration

AusVaxSafety data collected during the 2015 influenza season were explored. This dataset was an aggregation of data collected by the supporting tools of Vaxtracker and SmartVax. Summary statistics (counts and proportions) were used to describe the reporting of AEFI in children aged between 6 months and five years. Details of these summary statistics are described below for each of the relevant system attributes.

5.7.3 System attributes

Seven key system attributes were assessed from the AusVaxSafety system during its second year of operation. These included:

1. Simplicity
2. Flexibility
3. Data quality
4. Acceptability
5. Representativeness
6. Timeliness, and
7. Stability.

The surveillance attributes of sensitivity and predictive value positive were not evaluated here as they were not considered to be applicable to the AusVaxSafety system. AusVaxSafety is a sentinel active surveillance system designed to collect information on AEFIs experienced by the participating children. It is concerned with the identification of all AEFIs, and not the proportion of AEFIs detected by the system, or the proportion of reported AEFIs that are true AEFIs. It is the responsibility of the AusVaxSafety steering committee to interpret these signals and act upon them immediately, as required. Also, the active surveillance of AusVaxSafety is unique and as yet there is no 'gold standard' to compare the results generated by this system to the 'true condition' in the population under surveillance. In order to measure the sensitivity of AusVaxSafety, we would require access to data collected external to the system that has previously determined the true frequency of AEFIs with influenza vaccines for children aged between six months and five years.[1] At the time of finalising this chapter this information was not yet readily available. Therefore, this attribute was not further evaluated here in this chapter.

Simplicity

This attribute was evaluated with reference to the overall structure and ease of operation of the AusVaxSafety system. The seamless movement of information was evaluated, with particular attention given to the consistent, timely and regular multi-level flow from Vaxtracker and SmartVax into AusVaxSafety.

Flexibility

An understanding of this attribute was obtained throughout the 2015 influenza season by attending monthly AusVaxSafety meeting, as these meetings were an important platform for the exchange of information, ideas and problems experienced by different jurisdictions. This attribute was evaluated with qualitative information gathered from stakeholder interviews.

Data quality

Data quality was evaluated by completeness and validity of data collected, as well as protocols and procedures in place to monitor error within the generated datasets. This attribute was reliant on many different factors, which have been outlined by the 'Nationally Agreed Protocols for Program Action and Communication.'[2] These include an agreed national minimum dataset for AusVaxSafety; a nationally consistent AEFI reporting form and framework for supporting tools of AusVaxSafety; development of an agreed case definition for SAE; and agreed triggers that initiate further investigation. Data quality was evaluated on how these factors were met during 2015 and the proportion of 'unknown' or 'blank' fields reported by respondents.

Acceptability

Interaction between participants and AusVaxSafety was assessed by an analysis of the number of participants enrolled in the system at the time of child vaccination (participant rate), the number of completed surveys (completion rate), the completeness of each survey-field (question completion rate), and the timeframe to complete the survey (average time for survey completion). A retrospective analysis of the two supporting tools (Vaxtracker and SmartVax) was also conducted to investigate the acceptability of each tool.

Representativeness

This attribute was evaluated with regards to the ability of AusVaxSafety to accurately and consistently describe the AEFI rates, as well as the distribution patterns of these AEFI rates within the study cohort. This was evaluated by

comparing supporting tools, individual jurisdictions, the public health setting from which data were collected, vaccine brands and symptoms experienced by the child.

Timeliness

Qualitative and quantitative data was collected from operational staff of Vaxtracker, SmartVax and AusVaxSafety as to the speed of data flow from supporting tools into AusVaxSafety. AusVaxSafety steering committee members were interviewed as to their opinions regarding the regularity of reports generated by AusVaxSafety (including weekly reports, final report, and data available on the NCIRS website) and how quickly the AusVaxSafety system identified, interpreted and dealt with a SAE signal.

Stability

Qualitative and quantitative data were collected from key administration staff at the end of the 2015 influenza season. Questions relating to reliability and continuous operation were asked, along with specific questions regarding unscheduled outages, down time, and identification of issues associated with getting the supporting tool back online. Similar questions were also asked of AusVaxSafety operational staff.

5.7.4 Usefulness

After each of the system attributes were independently assessed, the level of usefulness of AusVaxSafety was addressed. Usefulness was assessed with regards to the performance of AusVaxSafety during the 2015 influenza season, and the ability of the AusVaxSafety to:

- monitor adverse events experienced by children aged six months to five years following influenza immunisation;
- value-add to our understanding of AEFI experienced by children in this cohort, with near real-time data allowing rapid signal detection; and
- detect changing trends.

5.8 Results and discussion

5.8.1 Operation of AusVaxSafety

The initiative of AusVaxSafety is led by NCIRS, and funded by the Australian Government Department of Health.[35] The purpose and objectives of this surveillance system have been identified and outlined by NCIRS.[34] AusVaxSafety is to facilitate the prompt identification of any adverse event (signal) of seasonal influenza vaccine administered to children under the age of five and to instigate appropriate implementations for public health action to eliminate the risk (if and when a signal is identified).

Recruitment / Case definition: Eligibility for participation includes a child administered seasonal influenza vaccine in an appropriate setting (general practice [GP], hospital, public clinic); who is aged between six months and five years (i.e. maximum age of four years and 364 days); whose parents/carer agrees to participate; and whose parent/carer understands English, has a mobile phone and access to the internet.

Serious Adverse Event: A serious adverse event (SAE) was categorised according to the criteria of any untoward medial event that resulted in death, was life threatening, or required hospitalisation.[36,37] Under Australian legislation, all SAEs identified by AusVaxSafety were reported to the corresponding state or territory Health Department and to the TGA.[37]

Source of information: The AusVaxSafety surveillance system captures data from two individual supporting tools:

- Vaxtracker – operating in New South Wales (NSW), Victoria (VIC), and South Australia (SA); and
- SmartVax* – operating in WA and VIC.

* during 2015, SmartVax also includes a functional component called ‘Follow up and Active Surveillance of Trivalent influenza vaccine’, or FAST. For the rest of the evaluation, unless stated otherwise, SmartVax will be evaluated in its entirety.

Both tools use modern technology that is accessible by most people. This technology includes mobile phones (for Short Message Service [SMS] and computer assisted telephone interviews) and computers (for emails and online surveys). These supporting tools of AusVaxSafety actively follow-up parents/carers of children recently vaccinated against influenza and collect information regarding any AEFIs experienced by that child. AusVaxSafety utilises this aggregated information; the flow of information is illustrated in Figure 5.3.

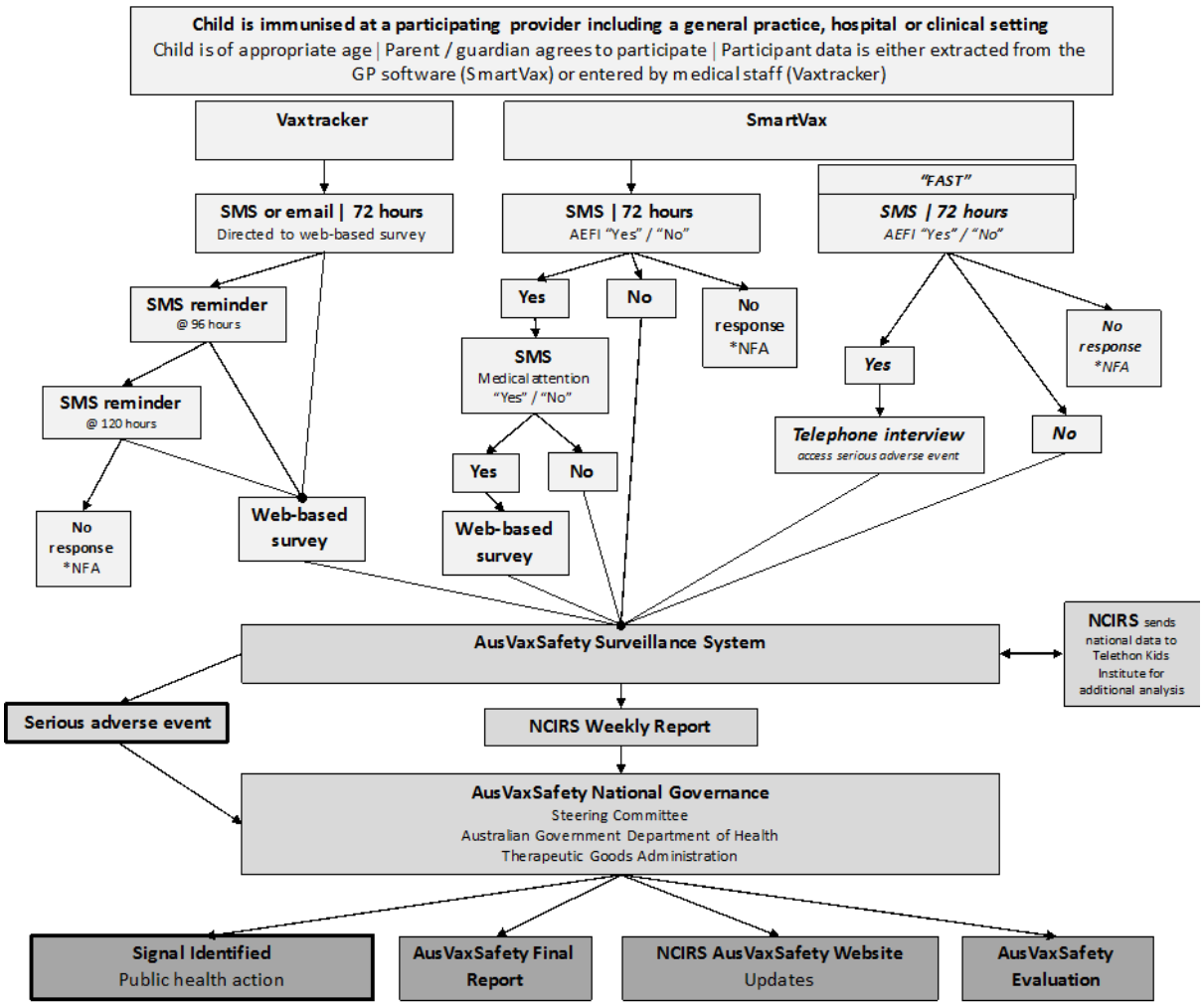

Figure 5.3: Data flow of the AusVaxSafety surveillance system, from data collection to final dissemination of results

(NFA = No Further Action taken if there is no response from the parent or carer)

5.8.2 Overview of the SmartVax and Vaxtracker tools

During the 2015 influenza season, SmartVax and Vaxtracker collected demographic details of participants, vaccine brand, underlying medical conditions, concomitant vaccines, reactions and their symptoms, and whether further healthcare was consulted following influenza vaccines. Similarities and differences of the two supporting tools are detailed in Table 5.1.

5.8.3 Stakeholder engagement

Key administration staff of Vaxtracker, SmartVax and AusVaxSafety were each available for interview, while only a modest number of steering committee members responded to the online questionnaire (38.1%; 8 of 21 surveys completed). Overall, stakeholders were engaged from different Health Departments and Research Institutes within NSW, the Australian Capital Territory (ACT), VIC, Queensland (QLD) and WA.

Table 5.1: Key differences between SmartVax and Vaxtracker informing the AusVaxSafety system evaluation

	Tool attribute	SmartVax	Vaxtracker	Comments for AusVaxSafety
At the time of immunisation	**Primary setting of system**	Mainly general practices -also set up in hospitals and clinical settings (including community clinics)	Hospitals and clinical settings (including Aboriginal Medical Services and community clinics) -also set up in general practices	*Together*, both systems cover all immunisation settings. *Individually*, some differential targeting possible (children of different health status prior to immunisation)
	Participant enrolment	Automatic (with an 'opt out' option)	Consent forms (requires participant's signature for enrolment)	SmartVax- participants may be unaware of their role in AusVaxSafety Vaxtracker- participants are aware of their role in AusVaxSafety
	Data entry of participant's details	Automatic extraction - built to compliment general practice software, however manual entry is possible	Manual entry only	Could influence attributes of AusVaxSafety, such as acceptability and flexibility

72 hours following immunisation	**Primary automated contact**	SMS - 72 hours after immunisation	SMS - 72 hours after immunisation and email	Similar for both systems
	Follow up action required by the participant	SMS reply – Yes / No	Directed to web survey via hyperlink	Simple for participants, with more information collected by Vaxtracker on initial contact
	Primary automated follow up question	Q: Thanks for caring to immunise [name]. We want to know if there were any reactions to the vax. Kindly reply YES or NO	Q: In the three days following the vaccination, did [name] experience any illness or symptoms?	Different questions -a consideration for the analysis of aggregated data in AusVaxSafety - possible biases associated with wording of the question
	Other questions asked during primary contact	Nil (no details about underlying conditions extract/asked of participants)	Asks about concomitant vaccines, underlying conditions, allows participants to make free text comments, and collects details regarding the nature of an adverse event	A lot of detail to provide at initial contact for Vaxtracker participants
	Secondary automated follow up question	Q: As a result of the vaccination reaction, did you visit a doctor, medical centre, after hours service, or hospital emergency dept? Please answer YES or NO	Not required for this tool	Numerous texts required by SmartVax to collect data
	Tertiary automated follow up question	[Medical Centre name]. Thanks for responding. Could you please complete a 2 minute survey by following: http//www……	Not required for this tool	Numerous texts required by SmartVax to collect data
Adverse event reported	**Assessment of adverse event**	Medically attended reactions are flagged to the general practice's software inbox and in some states to the local health authority. Can also be seen by SmartVax staff (not identifying details) to monitor level of adverse events	Manually monitored by registered nurse or doctor. Responses from participants require regular monitoring though high level public health staff are alerted via email to possible serious symptoms reported	An important attribute for the success of AusVaxSafety

Non-responders	**Participants who don't respond to the primary automated contact**	No additional SMS sent as follow up	2nd SMS sent at 96 hours following immunisation 3rd SMS sent at 120 hours following immunisation	Helps to improve the overall participation rate of AusVaxSafety
Data flow	**Data extraction requirements during active surveillance of AusVaxSafety**	Weekly	Weekly	Timelines of data flow is important for AusVaxSafety reporting commitments

5.8.4 System attributes

Results from stakeholder interviews and interrogation or exploration of the data were incorporated within each of the evaluated system attributes.

Simplicity

Generally, stakeholders were satisfied with the simplicity of the AusVaxSafety system.

The use of two different data collection tools for a single system inherently means it is less simple than some other surveillance systems. During stakeholder consultation, concerns were raised regarding the "*cohesion of multiple databases*" utilised by the AusVaxSafety system. In particular, issues related to the data generated by different supporting tools, with different primary roles. Vaxtracker functionality was "*purpose-built*" for AusVaxSafety operations and required data entry via an easy-to-use web-platform. While SmartVax (which includes the FAST component) was built to identify safety signals associated with vaccination as its primary role, using data extracted automatically from general practice software; research and analysis, as employed by the AusVaxSafety system, are secondary roles.

Purpose-built flat-files containing data are available from the Vaxtracker tool, and can be accessed by AusVaxSafety administration staff at any time with a "*click of*

a button." Whereas, SmartVax data was generated in a different format during 2015 and therefore required cleaning and reformatting before being manually sent to AusVaxSafety administration staff. SmartVax data preparation, for AusVaxSafety purposes was, at times, "*problematic*" during 2015. It was suggested during stakeholder consultation, that this attribute could be improved by removing the need for data manipulation, by adding further functionality to the SmartVax tool, adjusting the output data generated by SmartVax, and establishing a direct link between SmartVax and AusVaxSafety.

Once SmartVax and Vaxtracker data had been received by the AusVaxSafety system, further data cleaning, alignment and merging was required before analysis. It was apparent from this evaluation that data movement within the AusVaxSafety system is not entirely seamless. However, it was noted that the synergistic relationship of Vaxtracker, SmartVax and AusVaxSafety is still in its early stage of configuration. There are a lot of changes still to be made as this organic relationship evolves rapidly overtime.

> *"This is what real-time data looks like, it's messy and things happen…let's fix it and move on"*
>
> *"It doesn't stop, and everyone is ok with that it is a little bit messy, that is the nature of what we are doing. It's not going to be perfect and clean and without problems"*
>
> *"Inherent biases of the two different* [tools]" i.e. SmartVax and Vaxtracker

Flexibility

Overall, 71.4% (5/7) of the steering committee members who took part in this evaluation were satisfied with the flexibility of AusVaxSafety, with 42.9% (3/7) being very satisfied. Administration staff of SmartVax, Vaxtracker and AusVaxSafety were each satisfied with the flexibility of their respective tool/system. It was noted by stakeholders that these tools/systems were flexible with "*certain restraints*", and that changes to the functionality would be dependent on the complexity of the modification requested.

AusVaxSafety appears to be a flexibility system, with protocols and dedicated personnel in place to address minor issues quickly and cost effectively. Flexibility of the AusVaxSafety system would be a "*case by case issue,*" with minor changes theoretically addressed at any time during its operation, while more complex issues may need to be addressed at the completion of the active surveillance time period. AusVaxSafety demonstrated good flexibility halfway thought the 2015 influenza season, with the incorporation of serious neurological events (SNE) into active surveillance using the Paediatric Active Enhanced Disease Surveillance (PAEDS) network.

Some stakeholders commented that they don't believe that the flexibility of AusVaxSafety was "*tested*" formally during the 2015 influenza season. However, the flexibility attribute of AusVaxSafety would be tested in its entirety if this system were to be promoted for the active safety surveillance of another scheduled vaccine under the NIP.

Data quality

Aggregated AusVaxSafety data for the 2015 influenza season, for the most part, was complete and valid. 'Age of Participants,' 'Vaccine Brand' and 'Vaccination Date' were each 100% complete; 'Sex' was 94.2% complete (99.0% and 80.6% complete for SmartVax and Vaxtracker, respectively); and 'Concomitant Vaccines' was 94.1% complete (100% and 77.3% complete for SmartVax and Vaxtracker, respectively). One variable with poor data completeness was 'Aboriginal and Torres Strait Islander Status', with a 73.7% completion rate (64.4% and 94.2% completed for SmartVax and Vaxtracker, respectively). 'Underlying Medical Condition' was reported by Vaxtracker and the FAST component of the SmartVax tool only; 97.1% complete for Vaxtracker (with 33 missing records from a single GP) and 100% complete for FAST. 'Underlying Medical Condition' data was not reported by the remaining component of the SmartVax tool during 2015.

> *"Good data quality, extra info (underlying condition)* [from Vaxtracker]*"*

Acceptability

The AusVaxSafety system was well accepted by participants during the active surveillance period of 2015. Of the 4,441 children vaccinated for influenza at participating health settings during 2015, 99.0% of their parents/carers agreed to participate. Of the 4,396 surveys that were sent out by SMS or email, 76.0% were completed, resulting in the collection of 3,340 post-vaccination reports. The median response time of the 3,340 surveys was 4.7 days (range: three – 48 days) after vaccination (noting that surveys were sent out three days after vaccination).

Overall, Vaxtracker had a higher acceptance rate for completed surveys than SmartVax (79.7% and 74.8% respectively); however, SmartVax collected more than twice as many completed surveys than Vaxtracker (N= 2,424 and N=915, respectively). When considering the FAST component of the SmartVax tool, it had an acceptance rate of 85.9% for completed surveys; however, FAST only represented 6.9% (N=231) of all completed surveys during 2015.

The response rate to whether the participant had experienced an 'AEFI with Influenza Vaccine' was 99.5% complete (range: 99.3% to 100% for SmartVax and Vaxtracker, respectively). Of the 385 surveys reporting that their child had experienced an 'AEFI with Influenza Vaccine', 26.5% (N=102) had incomplete symptom variables for the AEFI. Three surveys contributed by Vaxtracker were partially complete, with either two or four symptoms missing per AEFI. The remaining 99 surveys were contributed by SmartVax, all of which had no symptoms recorded for these AEFIs. This non-reporting of symptoms within SmartVax was a result of the three step data collection method used (i.e. primary, secondary and tertiary automated follow up question, as detailed in Table 5.1). Participants were able to provide answers to the first two text messages without completing the web-link survey (detailing the symptoms of the AEFI) in the third message. This system omission represents a missed opportunity to collect valuable information about the types and severity of the AEFI.

"It's exciting! Problems resolved quickly and efficiently"

Representativeness

The SmartVax tool contributed 72.6% (8/11) of completed surveys during 2015, while Vaxtracker contributed 27.4% (3/11).

- SmartVax largely collected data from WA, as well as from a single GP in VIC. Overall, 57.4% (1863/3248) of SmartVax data were collected from a community clinic, 34.4% (1116/3248) from GPs and 8.3% (269/3248) from hospitals.
- Vaxtracker collected data from participants in NSW, SA and VIC. Overall, 48.9% (561/1148) of Vaxtracker data were collected from hospitals, 47.1% (541/1148) from GPs and 4.0% (46/1148) from Aboriginal medical services.

Stakeholders identified that "*there remains some issues with governance of the data,*" at the jurisdictional level within the AusVaxSafety model. This issue will need to be address in the future.

> *"Victoria had some sites directly reporting to SAEFVIC via Vaxtracker and others via WA Health (Smartvax)"*

Another issue was that AusVaxSafety data for 2015 was not nationally representative, with data absent from the Northern Territory, ACT, QLD and Tasmania. Ongoing jurisdictional ethical issues were the reason for the absence of data from some of these states and territories, despite concerted efforts by local public health staff.

Of the vaccine brands available to children aged between six months and five years, Vaxigrip represented 96.2% (N=3125) and 80.1% (N=920) of data contributed by SmartVax and Vaxtracker, respectively (Table 5.2). Unfortunately, it was not possible to determine whether this was representative of the general population, with sales of different vaccine brands not freely-available to the public.

> *"mainly only one brand of vaccine studied"*

Table 5.2: Vaccine brand representativeness, including total number of vaccination administered and number of AFFI with influenza vaccine reported by the supporting tools of AusVaxSafety during the 2015 influenza season

	SmartVax		Vaxtracker	
Vaccine brand	**Total # of vaccinations (# AEFI reported)**	**% of AEFI reported**	**Total # of vaccinations (# AEFI reported)**	**% of AEFI reported**
Agrippal	0 (0)	0.0%	16 (1)	6.3%
Fluarix	114 (6)	5.3%	133 (10)	7.5%
Fluquadri	3 (0)	0.0%	11 (2)	18.2%
Influvac	1 (0)	0.0%	68 (11)	16.2%
Vaxigrip	3125 (226)	7.2%	920 (129)	14.0%

In general, a higher proportion of AEFIs were reported by Vaxtracker participants than by SmartVax (13.3% and 7.2% respectively) (Table 5.2). This discrepancy of AEFI reporting between the two tools could be an artefact relating to the method of recruiting participants. SmartVax is used routinely for all vaccination (not just influenza vaccines administered to children aged six months to five years) as part of the health provider's duty of care. Vaxtracker participants were actively recruited and required written consent before participating. During recruitment, Vaxtracker participants were informed of why they were being recruited and how their data were being used. This may have led Vaxtracker participants being more likely to report all minor reactions experienced following vaccination. This discrepancy of AEFI reporting between the two supporting tools of AusVaxSafety requires close monitoring during future active surveillance.

Higher rates of fevers (7.2% [N=66] and 3.4% [N=82]), local reactions (4.0% [N=37] and 1.2% [N=30]) and seizures (0.3% [N=3] and 0.1% [N=2]) were reported by Vaxtracker participants than SmartVax participants. These higher rates by Vaxtracker participants could be a result of this tool largely collected

data from hospital clinics. During 2015, 48.9% of Vaxtracker data was collected from hospital clinics, as opposed to 8.3% for SmartVax. Again, this discrepancy of reporting between the two supporting tools of AusVaxSafety requires close monitoring during future active surveillance.

Timeliness

All stakeholders were satisfied with the timeliness of AusVaxSafety reporting of AEFI experienced by children aged six months to five years, with 50.0% (5/10) of the steering committee who replied being very satisfied. There were no issues identified regarding the timely flow of data from supporting tool to AusVaxSafety during 2015. SmartVax data was presented to AusVaxSafety at a regular time each week, while Vaxtracker data was readily available to AusVaxSafety administration staff when required.

AusVaxSafety successfully fulfilled all of its reporting requirements in 2015 in a very timely manner. Ten 'weekly' reports were generated between 01 April and 05 July, 2015, with reports initially available weekly for eight consecutive weeks, and then fortnightly (once negotiated with HEALTH) over a four week period. No safety signals were identified during the 2015 influenza season, and the AusVaxSafety system demonstrated, in real-time, that AEFI with influenza vaccines were within anticipated ranges for young children aged six months to five years of age.

The final report, which covered surveillance data collected between 01 April and 31 August, 2015 was made available to HEALTH for comments in November 2015, and was accepted by HEALTH a month later. There was also a "*rapid turnaround"* of results generated during 2015 with a "*publication in Eurosurveillance prior to the northern hemisphere season*" of influenza.

In addition to these reports, AusVaxSafety also disseminated results quickly by periodically updating its webpage (http://ncirs.edu.au/surveillance/ausvaxsafety/), distributing press releases through GP networks, publishing articles and delivering presentations at conferences both in Australia and abroad (2015 New

Zealand Immunisation Conference, Hamilton; Influenza Symposium, Melbourne).[38]

AusVaxSafety successfully provided "*very timely feedback on safety of the vaccines*" while also providing "*reassurance*" to parents and vaccine providers. However, it was suggested by stakeholders that there was still room to "*improve the timeliness*" of reporting when going forward with the AusVaxSafety system, with "*further active dissemination*" of good news required.

Stability

The steering committee was generally satisfied with the stability of AusVaxSafety, with 50.0% of those who replied being very satisfied. Administration staff of SmartVax, Vaxtracker and AusVaxSafety were each satisfied with the stability of their respective tool/system. Vaxtracker had a minor issue of non-access for about two hours following an important update. This non-access issue was due to an operator error, where the Vaxtracker tool was not properly restarted following the update. A single participant was inconvenienced by this disruption. It was noted that, if Vaxtracker were to fail completely, there are contingency plans in place, whereby data can be accessed by administrators from the back-end of the platform, packaged up and manually sent to the AusVaxSafety system in a timely manner.

SmartVax had no outages during 2015. However, an important issue was raised during this evaluation regarding the overall stability of the SmartVax tool. SmartVax is installed locally within each public health setting and can be viewed as a data extraction tool. Essentially, the tool relies upon the functionality and stability of the platform from which it extracts data. Therefore, if SmartVax is disabled locally, or the local platform fails, then real-time data from that practice will not be available for the weekly analysis. However, this should not be a major issue, as data is not lost or destroyed; its extraction is simply delayed. Also noteworthy, AusVaxSafety is concerned with detecting a cumulative signal during the influenza season, not signal detection from data of an isolated week.

5.8.5 Usefulness

All stakeholders were satisfied with the usefulness of AusVaxSafety to monitor adverse events experienced by children; 85.7% of those who responded were very satisfied. Likewise, stakeholders were satisfied with the performance of AusVaxSafety; with 71.4% being very satisfied. AusVaxSafety "*did what it was supposed to do*" during the 2015 influenza season, supporting health care workers and patients with real-time safety information for seasonal influenza vaccines, and aiding the duty-of-care responsibilities following vaccination.

Soon after commencing active surveillance, AusVaxSafety quickly assembled a relatively large sample size, and was able to provide a reliable safety profile for the 2015 seasonal influenza vaccines. This rapid data collection was aided by an increasing number of sentinel sites enrolled in AusVaxSafety in 2015, compared to the previous year. Early safety reports were disseminated to the public and relevant stakeholders in a very timely manner. Another success of the AusVaxSafety system was the quick identification of SAEs, which allowed the steering committee to manage these cases in near real-time. The AusVaxSafety system demonstrated great potential and can been seen to be "*giving back to the public health community.*"

> *"*[AusVaxSafety] *is huge."*
>
> *"*[AusVaxSafety] *adds to public trust, and public trust is a huge issue with vaccinations"*
>
> *"Very timely feedback on safety of the vaccines"*
>
> *"Confirmed no* [safety] *signal"*

Another success of the AusVaxSafety model was the addressing of problems in real time, with procedures and protocols in place to resolve issues quickly and efficiently. The "*flu season is short and sharp*" so it is essential that all procedures and protocols are in place for when they are required. There "*were teething problems*" during the 2015 operation of the AusVaxSafety system, but "*no major issues.*" The ability for AusVaxSafety to value-add to our understanding of AEFI experienced by children in this cohort and detect changing trends looks promising at this early stage of active surveillance, especially with the ongoing collection

and more efficient analysis of underlying medical conditions collected by the supporting tools.

5.9 Going forward

Stakeholders, when asked, were in support of promoting the AusVaxSafety active surveillance system for other vaccines funded under the NIP. They believed that the 'usefulness' of the AusVaxSafety model was the greatest attribute to promote, followed by 'timeliness,' 'data quality,' 'simplicity,' and 'acceptability.' It was also noted that the promotion of AusVaxSafety should be recommended *"when it makes sense to do so."*

Recommended vaccines suitable for AusVaxSafety included:

> *"Pertussis containing vaccines"* including *"pregnancy pertussis vaccine"* and *"18 month booster pertussis vaccine"*
>
> All *"pregnancy vaccines"*
>
> *"Zoster vaccine"*
>
> *"Live attenuated influenza vaccines"*

5.10 Summary

Among all stakeholders interviewed during this evaluation:

a) 100% (N=11) believed AusVaxSafety was effective with the real-time identification of an adverse event experienced by a child aged six months to five years, with 45.5% (N=5) rating it very effective.

b) 81.8% (N=9) believed AusVaxSafety was effective with initiating an appropriate review of an identified adverse event experienced by a child aged six months to five years, with 27.3% (N=3) rating it very effective. One stakeholder believed AusVaxSafety was neither effective nor ineffective and another chose not to comment.

c) 90.9% (N= 10) believed AusVaxSafety was effective with adding to current knowledge regarding the safe use of influenza vaccine administered to children aged six months to five years, with 45.5% (N=5) rating it very effective. One stakeholder believed AusVaxSafety was neither effective nor ineffective.

d) 72.7% (N=8) believed AusVaxSafety was effective with restoring professional and public confidence regarding the safe use of influenza vaccine administered to children aged six months to five years. No stakeholders rated AusVaxSafety being very effective at this, and 27.3% (N=3) of stakeholders chose not to comment.

During the 2015 influenza season, the AusVaxSafety system demonstrated, in real time, that influenza vaccines registered for use in children aged six months to five years were safe, well tolerated, and that the AEFIs experienced were within expected ranges. The AusVaxSafety system was well accepted by participants during active surveillance, with 99.0% of parents/carers agreeing to participate and 76.0% returning a completed survey. AusVaxSafety also demonstrated that it was a very useful system, designed for the public, to enable trust and transparency regarding vaccine safety. AusVaxSafety has enormous potential when it comes to vaccine safety.

5.11 Recommendations

To improve the usefulness of the AusVaxSafety system, the following actions are recommended:

High priority

1. Increase the dissemination of results to the public, primarily targeting web-based information, GP newsletters and articles that target parents

   "Greater community and health provider engagement through communication strategies"

2. The promotion of AusVaxSafety as "*part of post-marketing surveillance*" of vaccines, which "*becomes just part of the vaccination program rather than a boutique program run on the side*"
3. Standardising the questions asked by the different tools, so that AusVaxSafety is not comparing whether a child has experienced 'reactions' (SmartVax) with whether a child has experienced any 'illness or symptoms' (Vaxtracker)
4. Improve the geographic representativeness of AusVaxSafety, with data collected nationally
5. Continue to improve the "*cohesion of multiple databases*" utilised by the AusVaxSafety system. Standardise the data variables collected, the naming of variables, and coding of data to establish consistencies between the two supporting tools

Medium priority

6. Improve the data completeness for underlying conditions within the AusVaxSafety system
7. Improve data completeness for response to the symptoms experienced by a child who experiences an AEFI with influenza vaccine
8. Include *"a brief explanatory note on interpreting the Bayesian analysis charts* [in the weekly reports] *could be helpful for a broader audience"* (referring to the Fast Initial Response Cumulative Summation [FIR CUSUM] methodology used for the real-time detection of a 'safety signal,' and monitoring of an excess in adverse events.[38] This Bayesian analysis was used to determine the likelihood that any detected signal was real versus a chance event)

Low priority

9. Promotion of AusVaxSafety internationally e.g. New Zealand

5.12 Conclusions

Following the Australian federal government suspension of the national use of all 2010 seasonal TIVs for children aged between six months and five years, AusVaxSafety was established to occupy an important niche to help repair the damage caused by this suspension. AusVaxSafety is a clinical resource that fulfils two recommendations made by an independent review[2] to improve vaccine safety surveillance in Australia. AusVaxSafety is designed to detect vaccine safety signals first and foremost, while also enabling trust and transparency for parents and vaccine providers regarding vaccine safety. During the 2015 influenza season, AusVaxSafety was well accepted by participants, with three of every four parents/carers who agreed to participate returning a completed survey. No safety signals were identified and AusVaxSafety demonstrated, in real-time, that AEFI with influenza vaccines were within anticipated ranges for young children aged six months to five years.

AusVaxSafety successfully provided very timely feedback regarding the safety of vaccines, while also providing reassurance to parents and vaccine providers. During the first two years of operation, AusVaxSafety can already be seen as being proactive when it comes to vaccine safety and working to restore professional and public confidence regarding the recommendations of the NIP. AusVaxSafety has already provided one of the fastest turnaround times for the dissemination of real-time data regarding influenza vaccine administered to children, with rapid publication of results locally and internationally. It is anticipated, as AusVaxSafety enters its third year of active surveillance, it will continue to be trustworthy and transparent system, while providing real-time vaccine safety data to the public health community. It is also anticipated that AusVaxSafety will continue to expand, throughout the jurisdictions of Australia, and with the number of vaccines that it reports on.

When it comes to vaccine safety, AusVaxSafety simply makes sense.

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5.14 Appendix 5.1

Vaccine safety surveillance information sheet for AusVaxSafety targeting a lay audience at The Sydney Children's Hospitals Network

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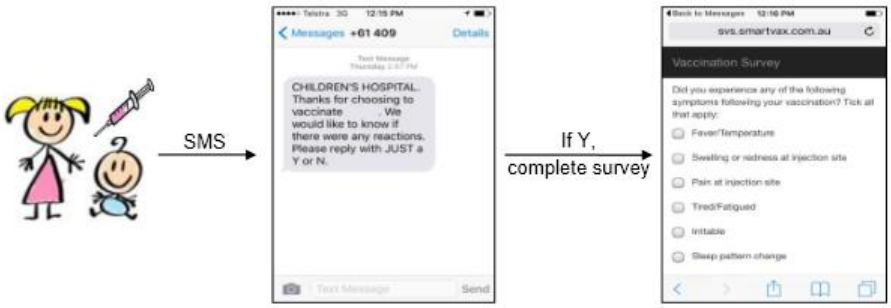
Parent/Guardian Information Sheet

Vaccine Safety Surveillance

Investigators: "*to be added for each local site Governance approval*"
(Site: "*to be added for each local site Governance approval*")

Thank you for vaccinating your child today and for considering participation in the Vaccine Safety Surveillance being conducted by the National Centre for Immunisation Research and Surveillance through The Sydney Children's Hospitals Network. As your immunisation provider we are committed to your child's health and the active monitoring of vaccine safety.

How does SmartVax work?
Our clinic participates in a routine program for monitoring vaccine safety, called SmartVax. SmartVax is an electronic tool designed to collect follow-up information from parents about how their children respond to vaccines. SmartVax works by sending an SMS to your mobile device, 3 days after your child's vaccination. The SMS asks if your child has experienced any reactions following their vaccine. If you reply yes, you will be directed to an online survey asking you to report in more detail on your child's health following vaccination. Our clinic will be notified of any reactions that you report and will follow these up so that we can continue the care of your child. Any suspected reactions will be notified to the state public health authority as required under legislation. In addition to this, SmartVax data from our clinic is sent to a centralised secure database, together with data from other clinics around Australia.



We see the follow-up of patients following a vaccination as an important part of our duty of care at our clinic, and the combining together of national data on vaccine safety is a valuable mechanism for monitoring trends and changes in reactions following vaccination.

Your participation in this Vaccine Safety Surveillance will allow you to play a role in the ongoing monitoring of vaccine safety in Australia.

What information is collected?
Name (stored at local clinic only), age, sex, Aboriginal and/or Torres Strait Islander status, type of vaccine received, date of vaccine, brand of vaccine, any reaction to the vaccine (fever, rash, pain/redness/or swelling at the injection site, vomiting, seizures, fatigue, or other symptoms within three days of their vaccination), if medically attendance was required following a reaction.

Privacy and Confidentiality
Any information collected as part of this active surveillance will remain confidential and be stored in a safe and secure location. Only staff within this clinic will have access to identifiable information. Only de-identified information will be combined with that of other clinics in the SmartVax database. De-identified data analysed by the National Centre for Immunisation Research and Surveillance for the purpose of monitoring vaccine safety may be presented in reports, journal publications and presented at conferences; however your child's name will not be published. Data will be destroyed five years after completion of the project in line with the National Health and Medical Research Centre guidelines on research practice.

Opting-out of this active surveillance
Participation in this project is completely **voluntary** and if you decide **not** to take part or decide to withdraw at any time, this will not otherwise affect your child's care at the hospital. If you elect to withdraw prior to publication, any information collected about your child will be destroyed.

Please feel free to discuss your options with your immunisation provider.

If you have any questions about this study, please do not hesitate to contact "*add local contact/nurse / position / contact phone number*".

This active surveillance has been approved by the Sydney Children's Hospitals Network Human Research Ethics Committee (HREC). If you have any concerns about the conduct of this study, please do not hesitate to contact the Executive Officer of the HREC on (02) 9845 3066, and quote approval number XXXXXXX.

Thank you for vaccinating your child today, you may keep this information sheet for future reference.

Chapter 6

Teaching - Lesson from the Field and structured teaching session for the 2016 MAE cohort

Chapter 6 Contents

6.1 List of Tables

6.2 Prologue

This final chapter of my bound volume fulfils a core component of the MAE program, in which I prepared and administered (a) a 'Lesson from the Field' (LFF) to my peers of the MAE15 cohort, and (b) two structured teaching sessions to the new MAE16 cohort during their first semester at the Australian National University.

Lesson from the filed

My LFF was a data analysis project, which focused on using postcodes to assign place of residence within Australia, as well as creating new variables based on historical targeted funding of the hepatitis A vaccine under the National Immunisation Program in Australia. I chose this topic for my LFF as I found myself exploring the hepatitis A data in Chapter 2 in different ways to those that we had been taught during course block. For Chapter 2, I was required to explore new syntax and commands in Stata and thought that these were of relevance to the other members of MAE15 cohort. I presented this LFF during March 2016.

Structured teaching session

The first part of my structured teaching session included teaching during the Outbreak Investigation course block for the MAE15 cohort. My role was to assist with the final session that detailed how to conduct an outbreak investigation.

The second part included a larger session conducted solely by MAE15 cohort. Our teaching session included three different topics, which focused on different themes and epidemiological processes tailored for the MAE16 cohort. I was part of the group that focused on administering questionnaires when conducting an outbreak investigation.

Before completing these teaching components of the MAE, I didn't realise how much planning, research and consultation was required for a self-directed learning exercise (LFF) and a one-hour teaching session. I was very lucky to have good support from Emily, Helen and Kerri during the construction of my

LFF. The structured teaching session conducted by the MAE15 cohort was a collective effort of all members, with everyone playing their part in very different ways. Overall, this was a fun and rewarding exercise, from which I learned a lot and hope that I was able to pass on some knowledge and enthusiasm to both the cohort members of MAE15 and MAE16.

Acknowledgements

Emily Fearnley, Helen Quinn and Kerri Viney took lead supervisory roles during the preparation of the LFF. I would also like to acknowledge the MAE15 cohort members that were involved with our teaching exercise: Alicia Arnott, Anthony Draper, Tanyth de Gooyer, Tambri Housen and Jana Lai.

6.3 Lesson from the Field

Title: ***Data Analysis - Using postcodes to assign place of residence within Australia, and create new variables based on historical targeted funding of the hepatitis A vaccine under the National Immunisation Program***

6.3.1 Learning objectives

By the end of this LFF you should be able to:

- inspect a dataset and remove duplicates;
- create simple Stata syntax using the "inrange" command to assign state of residence when only postcodes are known;
- create new variables based on the historical changes made under the NIP;
- generate age-specific tables, and;
- use the immediate stata incidence-rate ratio command (iri), and interpret results

6.3.2 Introduction to the LFF exercise

Postcodes

Australian postcodes are used to sort and send mail to the correct people and addresses. All postcodes in Australia have four digits and are placed at the end of the address. The allocation of postal addresses to state and territories such as Northern Territory, Tasmania, Western Australia and South Australia are uniform; each having a consecutive 1000 digit block for the jurisdictions. However, the same cannot be said for New South Wales and Australian Capital Territory, with small blocks of postal codes being assigned alternatively to each jurisdiction. Table 1 highlights this issue for New South Wales and Australian Capital Territory.

Table 6.1: Postal ranges for each state and territory of Australia

State/Territory	Postcode range*
New South Wales (NSW)	**1000—2599** **2619—2899** **2921—2999**
Australian Capital Territory (ACT)	**0200—0299** **2600—2618** **2900—2920**
Victoria (Vic)	**3000—3999** **8000—8999**
Queensland (Qld)	**4000—4999** **9000—9999**
South Australia (SA)	**5000—5999**
Western Australia (WA)	**6000—6999**
Tasmania (Tas)	**7000—7999**
Northern Territory (NT)	**0800—0999**

**including large volume receivers and Post Office boxes*

Therefore, specialised syntax is required to assign a state or territory to each postcode of residence when this information has not been supplied in your dataset.

Please note that postcode assignment within Australia is not this simple and there are many exceptions to the rules of Table 1.

For example: *0872 crosses NT/SA/WA*
2618 crosses NSW/ACT
2620 crosses NSW/ACT
3585 crosses Vic/NSW
3644 crosses Vic/NSW
4383 crosses Qld/NSW
4825 crosses Qld/NT

Hepatitis A vaccine in Australia

Hepatitis A vaccine was first registered in Australia in 1994 and is recommended for at-risk groups including travellers, people with an increased risk of exposure to hepatitis A virus (based on their occupation and life-style), and those who are at increased risk of severe disease. In February 1999, as a response to an increasing number of cases in north Queensland, regional Queensland funding of hepatitis A vaccine was provided for all Aboriginal and Torres Strait Islander (henceforth referred to as Indigenous) children, with two doses at 18 and 24 months of age. In November 2005, targeted funding of hepatitis A vaccine was made available under the NIP for all Indigenous children aged 12 to 24 months old residing in Queensland, the Northern Territory, South Australia and Western Australia. Two doses were originally funded at 12 months and 18 months of age for Indigenous children in NT and WA, and at 18 and 24 months of age for Indigenous children in Qld and SA, changing to 12 and 18 months for Indigenous children residing in all four jurisdictions in July 2013.

6.3.3 Background

You have been asked to analyse the National Notifiable Diseases Surveillance System (NNDSS) database for hepatitis A reported in Indigenous people of Australia for 2007, and provide an incidence rate ratio (IRR) (95% confidence intervals) using the following formula:

$$\frac{\text{Incidence of hepatitis A in children aged < 5 years of age from vaccine targeted jurisdictions*}}{\text{Incidence of hepatitis A in children aged < 5 years of age from vaccine non-targeted jurisdictions^}}$$

** where vaccine targeted jurisdictions are QLD, NT, SA and WA*
^ where vaccine non-targeted jurisdictions are NSW, ACT, VIC and TAS

This IRR will help you interpret whether the targeted hepatitis A vaccine program has been successful. Your boss informs you that the estimated population size for children aged < 5 years are **46,290** in the targeted jurisdictions and **34,224** in the non-targeted jurisdictions.

Nice you think. This should be easy done and should not take too long.

However, after looking at the dataset (attached excel file 'Hep_A_mock_dataset'), you realise there is no data field for state_code ☹

What do you do?

6.3.4 Instructions

Getting started

1. After opening up Stata, import the provided spread sheet called 'Hep_A_mock_dataset' (making sure to tick the box for 'import first row as variable names')
2. Open up a new 'do file' and name it appropriately
   (for example: your name, date, and Hep A Notification_postcodes to state_code)
3. set more off

Inspect your dataset

4. codebook
5. tabulate postcode
6. check for duplicates, and remove any that you find

QUESTION 1

Using 'duplicates report' 'duplicates list' and 'duplicates drop' how many duplicates did you remove from the dataset?

ANSWER: 3

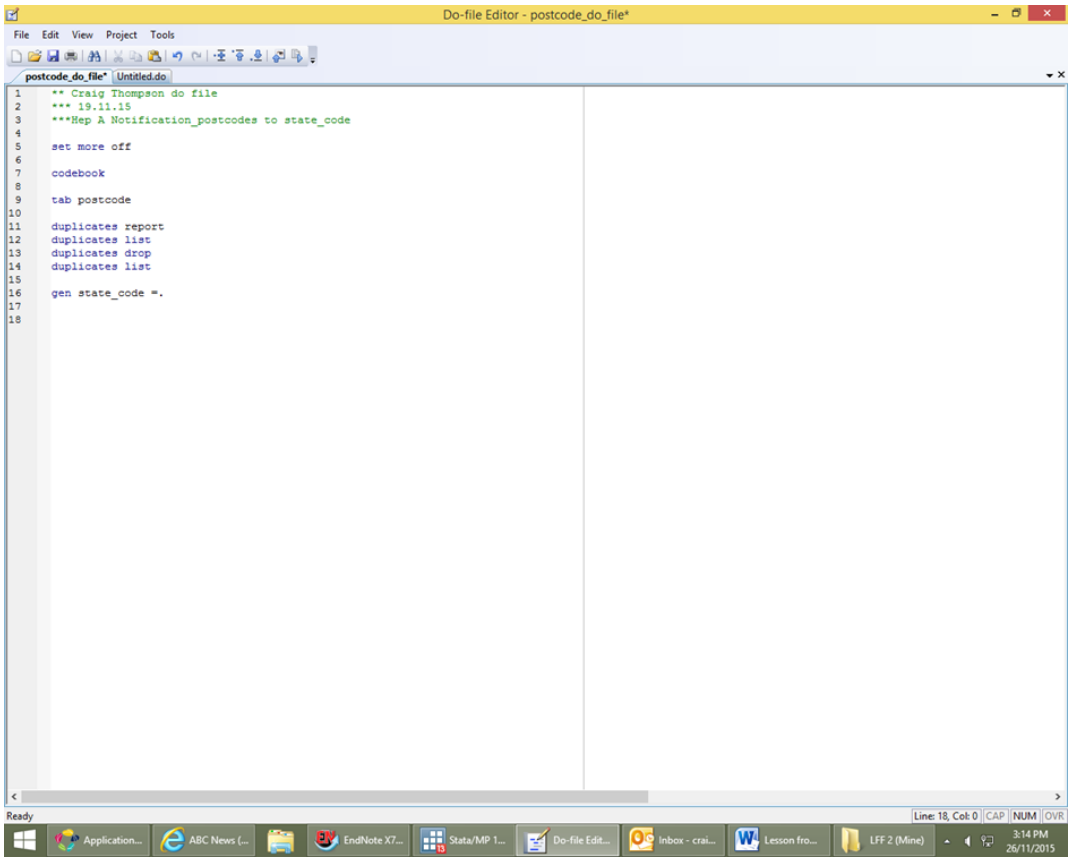
Generate new variable

7. generate a new variable, call it ‘state_code’, and assign a missing value to each of the new cells

QUESTION 2

What syntax do you write for Instruction 7?

ANSWER: gen state_code =.



Before going any further, you decide to use the following rule for recoding the new variable-state_code:

1 = ACT
2 = NSW
3 = TAS
4 = VIC

Non-targeted jurisdictions

5 = SA
6 = NT
7 = QLD
8 = WA

Targeted jurisdictions

Now, you stop to think of an easy way to code the postcodes of 1000 to 2599 to represent the state of New South Wales, and remember a great command to help out……

It's called **inrange**

Recoding postcodes to state codes

8. For the first line of syntax you write:

replace state_code = 2 if inrange(postcode,1000,2599)

(where you are telling Stata to replace the newly created variable 'state_code' with the number 2 (which will be relabelled "NSW" later) if the corresponding postcode is within the range of 1000 to 2599 (inclusive))

9. You check if this syntax has worked, and decide to tabulate state_code

QUESTION 3

How many postcodes were inrange of 1000-2599 in your dataset?

ANSWER: 65

10. Confident your syntax is correct, you decide to complete the remaining syntax for NSW.

QUESTION 4

What syntax do you write for postcode ranges 2619-2899 and 2921-2999?

ANSWER: replace state_code = 2 if inrange(postcode,2619,2899)

replace state_code = 2 if inrange(postcode,2921,2999)

11. And do so again for ACT and the other states and territories

QUESTION 5

(a) What syntax do you write for the ACT postcodes?

ANSWER: ***replace state_code = 1 if inrange(postcode,200,299)***

replace state_code = 1 if inrange(postcode,2600,2618)

replace state_code = 1 if inrange(postcode,2900,2920)

(b) What syntax do you write for the VIC postcodes?

ANSWER: ***replace state_code = 4 if inrange(postcode,3000,3999)***

replace state_code = 4 if inrange(postcode,8000,8999)

(c) What syntax do you write for the QLD postcodes?

ANSWER: ***replace state_code = 7 if inrange(postcode,4000,4999)***

replace state_code = 7 if inrange(postcode,9000,9999)

(d) What syntax do you write for the SA postcodes?

ANSWER: ***replace state_code = 5 if inrange(postcode,5000,5999)***

(e) What syntax do you write for the WA postcodes?

ANSWER: ***replace state_code = 8 if inrange(postcode,6000,6999)***

(f) What syntax do you write for the TAS postcodes?

ANSWER: ***replace state_code = 3 if inrange(postcode,7000,7999)***

(g) What syntax do you write for the NT postcodes?

ANSWER: ***replace state_code = 6 if inrange(postcode,800,999)***

Assigning state codes to targeted and non-targeted jurisdictions

12. The targeted jurisdictions (SA, NT, QLD and WA) have been coded above as values>4. You want to create a new variable called targeted_state_code, assigning a value of 1 within this new variable only if the corresponding values in the state_code variable are greater than 4.

QUESTION 6

What syntax do you write to create this new variable and assign a value = 1 if the state_code variable is >4?

ANSWER: gen targeted_state_code = 1 if state_code >4

13. Now the non-targeted jurisdictions (ACT, NSW, TAS and VIC), these have been coded with values < 5. Again, you want to create a new variable called non_targeted_state_code, assigning a value of 1 within this new variable only if the corresponding values in the state code variable are less than 5.

QUESTION 7

What syntax do you write to create this new variable and assign a value = 1 if the state_code variable is <5?

ANSWER: gen non_targeted_state_code = 1 if state_code <5

14. Almost there. According to our boss' instructions, we want to tabulate the number of Indigenous children from the targeted jurisdictions (targeted_state_code) only if their age is less than 5 years.

QUESTION 8

In a single line, what syntax do you write to tabulate those individuals only who are in the targeted_state_code if their onset age was <5?

ANSWER: tab targeted_state_code if onset_age <5

15. You do the same from the non_targeted jurisdictions, again for Indigenous children who were less than 5 years of age only.

ANSWER: tab non_targeted_state_code if onset_age <5

16. At long last, the final step. Calculating the IRR and CI's….yippppeeeee

Using the immediate stata incidence-rate ratio command (iri), you want to use your r esults from the tables you constructed for Instruction 14 and 15.

Using the following syntax

IRI X Y X1 Y2

where

X is the total incidence of hepatitis A within the targeted jurisdiction of Indigenous children under the age of 5 years (Instruction 14)

Y is the total incidence of hepatitis A within the non-targeted jurisdiction of Indigenous children under the age of 5 years (Instruction 15)

X1 is the estimated population size for Indigenous children aged < 5 years in the targeted jurisdictions (originally given to you by your boss 46,290)

Y1 is the estimated population size for Indigenous children aged < 5 years in the non-targeted jurisdictions (originally given to you by your boss 34,224)

QUESTION 9

(a) What is the IRR and confidence intervals of hepatitis A disease among Indigenous children aged <5 years when you compare the targeted jurisdictions to that of the non-targeted jurisdiction?

ANSWER: iri 11 27 46290 34224

IRR= 0.30 (CI95 0.13 – 0.63)

(b) Why do we use an incidence rate ratio calculation?

ANSWERS FROM THE GROUP:

- ***We use an IRR calculation because it allows us to measure whether there is a statistically significant difference between 2 rates. It gives us a confidence interval and a p-value to accept or reject the null hypothesis that there is no difference.***
- ***IRR tells us how many times higher the rate of hepatitis is in the targeted states than the non-targeted states. It gives an indication of the strength of association between incidence and the vaccination program.***
- ***Comparing rates of notifications of hepatitis A between targeted and non-targeted jurisdictions***
- ***So we can compare the incidence between vaccine provided jurisdictions to non-provided jurisdictions to see if the hep A vaccine is effective among indigenous children aged<5. If IRR is <1, it has a prevention fraction in the exposed population.***
- ***It compares the relationship between the number of notifications in the targeted jurisdictions and the non-targeted jurisdictions to give a measure of how many times greater one rate is compared to the other.***
- ***To compare the incidence of the targeted population against the non-targeted population***

Congratulations. You have the result you need.

But what does this mean??

You will need to interpret this result for your boss on Tuesday. You decide to provide answers for the following questions in the context of the targeted funding of the hepatitis A vaccine.

During the teleconference meeting

QUESTION 10

(a) Are there few cases of hepatitis A notified from targeted jurisdictions compared to non-targeted jurisdictions?

ANSWERS FROM THE GROUP:

- ***Yes there are fewer cases of hepatitis A in targeted jurisdictions***
- ***11 versus 27 (ie less than half the number of cases). The rate, though, is 0.00024 vs 0.00079, so the ratio is around a third of the cases in non-targeted jurisdictions***
- ***Yes, 11 cases of hepatitis A were notified from targeted jurisdictions compared to 27 notifications from non-targeted jurisdictions***

(b) Are the numbers of cases significantly different between the two jurisdictions?

ANSWERS FROM THE GROUP:

- ***Yes the rate is significantly different between targeted and non-targeted jurisdictions***
- ***Yes (p=0.0004)***
- ***Yes, the confidence interval of the incidence rate ratio does not cross one and the p-value for the one-tailed test is < 0.05***

(c) What is the difference between the two different p-values that you have been provided with by Stata?

ANSWERS FROM THE GROUP:

- ***0.0002 (0.0004 vs 0.0002) - 1 p value tests for statistical significance in one direction while the second p-value tests for statistical significance in both directions only one direction. The 2nd p value is to determine whether there is a relationship in any direction. ie. Is the null hypothesis rejected either because it is smaller or larger not just one.***
- ***The first is the result of a one-sided significance test, the second from a two-sided test.***
- ***p-values for one- and two-tailed tests***
- ***The bottom one is 2 x the one above; 0.0002x2=0.0004, One and two-sided exact significant tests?***
- ***The "midp" ones? …0.0002. or conceptually? I think conceptually, the "2*PR" one is two-tailed, so gives the probability of the difference between the targeted and non-targeted jurisdictions in two directions, so the difference being either lower or higher… but the "Pr" one is one-tailed so is the probability of the difference either being higher or lower… does that make sense?!***
- ***1st is the 1 tailed fisher exact p value and the 2nd is the 2 tailed fisher exact p value.***

(d) What are the main limitations of the results you have generated?

ANSWERS FROM THE GROUP:

- ***There are only small numbers, how many are of unknown Indigenous status?***
- ***did the targeted vaccination of Indigenous kids also have an effect on non-Indigenous kids - we didn't measure that***

- *There are postcodes that cross jurisdictions so people could have been incorrectly classified into different states.*
- *Don't know how IRs changed over time – the rate ratio may not have changed since previous years*
- *IRR is measure of association only, not causation*
- *don't know what other factors may have led to lower incidence in targeted states (real or artefact)*
- *Only notified cases are included (those children sought health care and tested)*
- *Don't know vaccination history of cases*
- *Postcode – place of diagnosis may not be place of residence (Indigenous population may be highly mobile)*
- *Are the population data provided for Indigenous children specifically or for all children?*
- *The incidence is a crude rate, with no person-time at risk.*
- *Not sure if the cases are vaccinated (fully or partially) or not?*
- *Don't know about other confounding factors, such as vaccination coverage in those states*
- *You are only able to compare targeted against untargeted*
- *You have not compared individual targeted states*
- *You are using estimates of your target population and non-targeted populations*

(e) What additional information would you like to be provided with for further analysis of hepatitis A in Australia?

ANSWERS FROM THE GROUP:

- ***I would like to know the numbers of people with unknown Indigenous status notified with Hep A. I'd like to know a cost analysis of the program***
- ***I'd like to know, seeing as though this has been successful, if it can be applied to other populations in Australia that are over notified (to provide further herd vaccination)***
- ***I suppose in terms of general Hep A analysis I'd like to know the age and sex and ethnographic breakdown as time continues so we can target different populations in the future***
- ***I might also like to know more about risk factors and how this has changed since the vaccination program.***
- ***incidence over previous years***
- ***Vaccination coverage in targeted jurisdictions***
- ***Vaccination history of cases and 'controls' – look at protective effect of vaccine (case control study)***
- ***Secondary benefits of vaccinating children – e.g. less hepatitis A in adults due to vaccination in children***
- ***What is the sero prevalence of hep A immunity among indigenous children aged <5 to estimate population at risk.***
- ***Is there any difference of the vaccine effectiveness in different age groups?***
- ***What makes at risk groups at risk? - barriers and facilitators to vaccination***
- ***Actual number of people under 5 vaccinated for hepatitis A in each state***
- ***Actual target population numbers of age under 5***

END OF EXERCISE

6.4 MAE Teaching Exercise for Cohort MAE 16

Administering questionnaires when conducting an outbreak investigation

6.4.2 Overall purpose of session:

1. To introduce some of the considerations (and challenges) associated with conducting interviews as part of outbreak investigations
2. To provide a practical exercise to give an experience of interviewing (especially for those who are more green among the group) and to illustrate strategies to overcome challenges we have identified.

6.4.3 Objectives:

By the end of this session, MAE2016 will students will have the skills and knowledge regarding:

a) How to deal with interviewees who are concerned about the privacy of their information collected as part of the interview process

b) Some techniques you can use to maximise interviewee recall of information

c) How keep an interview on track while also managing additional information about the investigation which interviewees may disclose as part of an open ended question

6.4.4 Introductions of MAE2015 presenting session

Australian National University

Objectives of the Session

By the end of this session you will be able to;

- Understand and apply some key principles to enhance interviews as part of an outbreak investigation
- Create strategies to overcome three common challenges faced when interviewing cases

3

Australian National University

Key Learning

You will be provided the opportunity to gain practical experience to identify strategies for:

- maximising interviewee recall
- keeping interviewees on topic
- handling interviewees privacy concerns raised during outbreak interviews

https://www.youtube.com/watch?v=O6gKLQpEkfY

4

Australian National University

10 key principles

- Practice
- Find a quiet space
- Be non-judgmental
- Avoid leading the interviewee
- Accurately record responses
- Ensure confidentiality
- Gently re-direct
- Probe
- Use interpreters if required
- Thank the interviewee and explain how the information will be used

5

Australian National University

The Scenario

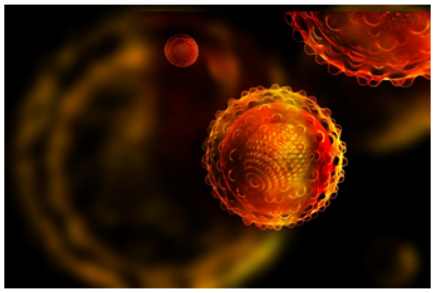
- You are an epidemiologist placed in the Victorian Department of Health.
- There have been a number of hepatitis A cases notified over the past few months.
- You have been asked to undertake a hypothesis generating questionnaire to determine possible exposure sources

6

Australian National University

You check Heymanns

- Hepatitis A – long incubation period with an average of 28-30 days (range 14-50 days)
- Faecal / oral transmission
- Signs and symptoms
  - Diarrhea
  - Abdominal discomfort
  - **Jaundice**
  - Fever
  - Nausea / loss of appetite



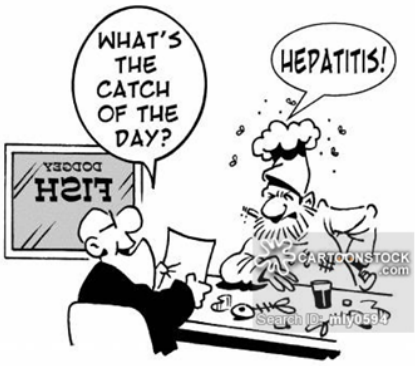
Heymann, D. 2015. Control of Communicable Disease Manual. American Public Health Association Press, eISBN: 978-0-87553-274-5

7

Australian National University

We will give you….

- Outbreak brief
- Pathology result
- Calendar
- Screenshot from OzFoodNet
- Interview questionnaire
  - Symptoms
  - Exposure information



8

Australian National University

Discussion Questions

- What were the features of the person that you interviewed?
- How did they behave?
- How did you respond?
- What you would do differently if you encountered this person again?

9

Australian National University

Objectives of the Session

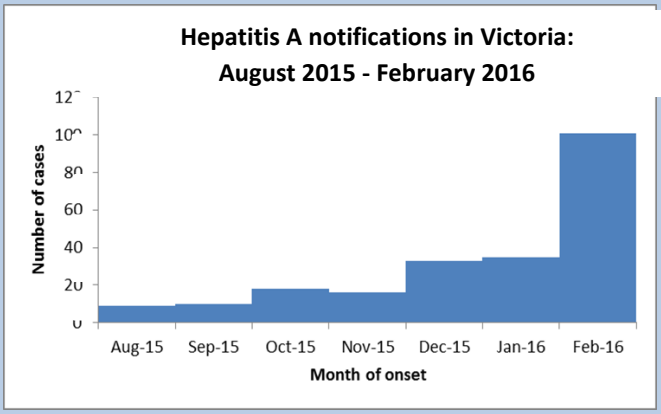
Recap

- Understand and apply some key principles to enhance interviews as part of an outbreak investigation
- Create strategies to overcome three common challenges faced when interviewing cases

10

6.4.5 Scenario

You have just arrived at the Victorian Department of Health to take up a post as an epidemiologist. Your new manager - Dr Bilirubin – asks you to investigate a possible outbreak of Hepatitis A amongst the local population.



Dr Bilirubin provides you with the names, contact telephone numbers and laboratory results that have just arrived for three individuals with laboratory confirmed Hepatitis A, as well as a questionnaire used by the public health unit to investigate outbreaks. Your task is to contact one of these cases and using the information provided to you, conduct an interview in an attempt to try and identify the potential source of infection. Dr Bilirubin also suggests you have a calendar handy when you call and mentions as she walks away: “interviews are like a box of chocolates – you never know what you’re gonna get”.

6.4.6 Important information about Hepatitis A - Occurrence and transmission

The Hepatitis A virus replicates in the liver, is excreted in bile and shed in the stool. As such, transmission occurs predominantly via the faecal-oral route and the incidence of disease is higher in countries where hygiene and environmental sanitation are poor. Worldwide, most infection results from exposure to contaminated food or water.

In industrialised countries such as Australia, infection with Hepatitis A is more likely to occur:

- amongst household and sexual contacts of an acute case
- in childcare centres with children in nappies
- following overseas travel to countries with endemic Hepatitis A (Asia, Africa, South-Pacific, Central and South America)
- amongst injecting drug users
- from outbreaks

Although infrequent, foodborne outbreaks of Hepatitis A have occurred in Australia, including large outbreaks associated with consumption of contaminated raw oysters (1997) and semidried tomatoes (2009), and more recently, associated with frozen berries (2015).

Incubation period and clinical illness

The average incubation period is 28-30 days (range 14-50 days, or approx 2-7 weeks). The disease can vary from an asymptomatic illness lasting 1 – 2 weeks to a severely disabling disease that can persist for several months. Approximately 10% - 50% of infected infants and children (< five years of age), and 70% - 95% of infected adults have recognisable clinical symptoms that initially include: fever, malaise, anorexia, nausea and abdominal pain, followed by jaundice, dark urine and pale-coloured stools.

Testing of serum samples can provide serological evidence of recent Hepatitis A infection.

During case follow up, the date of onset of jaundice is often used to determine the incubation (and exposure) period.

6.4.7 Practical exercise

During a 15 minute break out exercise, each person in the MAE16 each had the opportunity to conduct a 1:1 interview one of these "types" of cases. Cases (interviewees) were the cohort member of MAE15, and each were assigned one of the three following scenarios to follow during the interview.

Each person in the MAE16 were given a mock hepatitis A questionnaire, a mock calendar (as an aide for the interview) and the Pathology results for their interviewee. All of the resources used during the teaching session are as follows.

Scenario A – prompting memory recall

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You are the interviewee, Indra Pina, aged 32 (DOB: 25 June 1983), resident of Melbourne. You were born in Australia but are of Indian heritage (your parents are Indian).

You are very busy and have a poor memory. Your first response to every question is that "I Really can't remember", and emphasize that "it was a long time ago".

Mainly use the 'history of illness' and 'details' columns to guide your responses.

Hopefully the interviewer will use a calendar, to remind you of weekend activities, public holidays or major events and prompt your recall.

It is important that you disclose/confirm that you got jaundice on 14 February 2016. You may need to assist the MAE in determining the acquisition period (14-50 days prior to jaundice onset: 29 Dec 15 to 1 Feb 16)

If the MAE says any 'unusual' terms (jaundice, acquisition period) ask for clarification. Please make sure that you allow the MAE16 to complete the interview in the allocated time.

Symptoms		**Onset Date of Symptom**	**History of illness**
Diarrhoea	Yes	10/2/2016 (continued for 3 days)	Diarrhoea on the day <u>after</u> Indian Independence Day lunch (January 26) but you put that down to spicy Indian food you ate at the lunch You remember feeling sick (nausea, headache) at work one day a week or so after that initial episode and vomited. Then the diarrhoea started after lunch. (When prompted.... It was awkward as you had a team meeting that day the director of your company attended....team meetings are usually on Wednesdays,....you had cake at the meeting for your Manager's 10 year anniversary....your manager said "10 on the 10th"...yeah it must have been Weds 10 Feb) Diarrhoea wouldn't stop for 3 days (you were supposed to go out on Friday night (12 Feb) for a friend's birthday. You stayed away from work for two days and had a temperature on Thurs. You woke up one Sunday remember that your mum said you had yellow eyes. (When prompted....you cancelled your Valentine's day dinner that night and cried for 3 days. Confirm that it was 14 Feb if asked by interviewer). Your eyes were still yellow the next day when someone at work commented. That afternoon you went to the Dr and that's when you got tested (had a blood sample taken).
Nausea	Yes	10/2/2016	
Vomiting	Yes	10/2/2016	
Abdominal pain	Yes	10/2/2016	
Jaundice	Yes	14/2/2016	
Headache	Yes	10/2/2016	
Fever	Yes	11/2/2016	
Other	Nil		

Exposures		
Exposure	**Details**	**Date(s)**
Did you travel overseas during your acquisition period? No	Last time you were overseas was in January 2008 to Mumbai.	2008
Did you attend any restaurants during your acquisition period? Yes	There was an Indian Independence Day luncheon at a restaurant you went to (on Tuesday 26 January). You think the restaurant was called Bombay by Night. (*Only disclose the following if the interviewer prompts your recall....* You went to breakfast with friends at the Top Paddock Café in Richmond and you had hot cakes with friends that had berries and fresh cream. You remember this because it because it tasted so good, especially as you tasted some of your friend's Eggs Benedict and the sauce on the top tasted a bit strange...it was on the weekend before the Independence Day lunch because your friends were visiting all week from interstate).	26/1/2016 (23/1/2016)
Did you attend any major sporting events during your incubation period where you ate take-away food? Yes	You went to the 1 day cricket one weekend in January at the MCG with your dad and watched the cricket which was Australia and India. (*When prompted*: Sunday January 17, and ate chips only.) (You also went to the Australian Open on Saturday 30 Jan, but only remember this when asked the question below)	17/1/2016
Did you consume any foods containing frozen berries during your incubation period? Yes	Mention you ate berries and cream "at the tennis". (If the interviewer prompts you, say it was a Saturday and you saw the women's final – a friend had a spare ticket..confirm it was 30 Jan if asked)	30/1/2016
Did you consume any raw seafood/shellfish during your incubation period? No	Vegetarian	

Scenario B – Concerns about privacy

You are the interviewee, Tony Fratelli, aged 54 (DOB: 28/9/61), resident of Melbourne. You are a businessman who lives in Melbourne CBD.

You are VERY concerned about why you are being contacted: how did you get my details? I thought this was between me and my doctor? What is this information going to be used for?

You even ask for the name of the interviewer and their position and phone number. You are reluctant at each question and continually seek assurance re: privacy and confidentiality.

Mainly use the 'history of illness' and 'details' columns to guide your responses.

Hopefully the interviewer will use a calendar, to remind you of weekend activities, public holidays or major events and prompt your recall.

It is important that you disclose/confirm that you got jaundice on 14 February 2016. You may need to assist the MAE in determining the acquisition period (14-50 days prior to jaundice onset: 29 Dec 15 to 1 Feb 16)

If the MAE says any 'unusual' terms (jaundice, acquisition period) ask for clarification. Please make sure that you allow the MAE16 to complete the interview in the allocated time.

Symptoms		**Onset Date of Symptom**	**History of illness**
Diarrhoea	Yes	10/2/2016 (3 days duration)	*(Express some concern about the personal nature of this information that you are disclosing)* Diarrhoea initially on Wednesday 10th February. Remembers feeling sick at work that day (nausea, headache) which made it hard to concentrate in an important client meeting. Diarrhoea wouldn't stop for 3 days and your stomach was cramping a lot. You felt really hot on Thurs 11, you could have had a fever, but it might have just been a hot day. When you woke up on Sunday 14 Feb, your wife told you that you had yellow eyes. Your eyes were still yellow on the Tuesday of that week (16 Feb) and your wife insisted she take you to the doctor. That afternoon you went to the Dr and that's when you got a blood sample taken.
Nausea	Yes	10/2/2016	
Vomiting	No		
Abdominal pain	Yes	10/2/2016	
Jaundice	Yes	14/2/2016	
Headache	Yes	10/2/2016	
Fever	Yes	11/2/2016	
Other	Nil		

Exposures		
Exposure	**Details**	**Date(s)**
Did you travel overseas during your incubation period? No	*(Ask why this is important and how this relates to having Hep A)* Last time you went overseas was in December 2014 to London.	2014
Did you attend any restaurants during your incubation period? Yes	*(Indicate your concern that you don't want this information to get back to the restaurant, because you frequently have business meetings there)* Went to restaurant at Crown Casino on Fri 23 Jan. Ate steak tartare, there was a raw egg on top.	23/1/2016
Did you attend any major sporting events during your incubation period where you ate take-away food? Yes	Went to the cricket at the MCG on January 17 and which was Australia and India. Was in a corporate box, but only had beer. *(You might be concerned that the Hepatitis might be related to drinking, also ask that they don't mention anything to his wife as he is supposed to be reducing how much he drinks)* Was in a corporate box at the Australian Open tennis on the last Sat for the women's final (30 Jan) and ate loads of canapés and had some red wine. *(Reitterate drinking concern)* Rattle off all the canapés you can think of and at the end also mention they had big sundae glasses full of berries and cream.	Cricket Sun 17 Jan Tennis Sat 30 Jan
Did you consume any foods containing frozen berries during your incubation period? Yes	Berries and cream at the Australian Open.	30/1/2016
Did you consume any raw seafood/shellfish during your incubation period? No	Allergic to shellfish	

Scenario C – Off topic interviewee

You are the interviewee, Wendy de Waffler, aged 25 (DOB 29 Jan 1991), who is a young single mother from Ballarat. You have an opinion on just about everything and are easily side tracked.

You love a chat and will easily stray away from the questions you are asked. You will not initially respond yes or no but will embark on wild and elaborate stories. Waffle on a bit but the responses you need to provide are below.

Mainly use the 'history of illness' and 'details' columns to guide your responses.

Hopefully the interviewer will use a calendar, to remind you of weekend activities, public holidays or major events recall.

It is important that you disclose/confirm that you got jaundice on 14 February 2016. You may need to assist the MAE in determining the acquisition period (14-50 days prior to jaundice onset: 29 Dec 15 to 1 Feb 16)

If the MAE says any 'unusual' terms (jaundice, acquisition period) ask for clarification. Although we encourage you to free style a bit, please make sure that you get the key food items and exposure dates across and allow the MAE16 to complete the interview in the allocated time.

Symptoms		**Onset Date of Symptom**	**History of illness**
Diarrhoea	Yes	10/2/2016 (3 days duration)	Diarrhoea on Wednesday 10th February. Remember watching My Kitchen Rules and having to run to the toilet. Had a headache that day, but didn't think it was unusual – always have a headache (the kids drive you crazy!) Diarrhoea wouldn't stop for 3 days. Woke up on the Sunday morning and you boyfriend told you that you looked yellow. Remember it was Sunday morning of 14/2/2014 because it was Valentines Day. Went to the Dr on the 15/2/2016 and got tested because that was the day that the free bulk billing Dr was open so you waited until then. (You also had a headache on 30 Jan – you'd been out the night before for your birthday).
Nausea	Yes	Always feels nauseous	
Vomiting	No		
Abdominal pain	Yes	10/2/2016	
Jaundice	Yes	14/2/2016	
Headache	Yes	10/2/2016	
Fever	Yes	11/2/2016	
Other	Yes – go nuts and mention whatever you like		

Exposures		
Exposure	**Details**	**Date(s)**
Did you attend travel overseas during your incubation period? No	Never been overseas – feel free to waffle on about how she always wanted to go somewhere but then you had kids.	
Did you attend any restaurants during your incubation period? Yes	Went to Sizzler on Friday January 29th because it was your birthday. Waffle on about what you ate, you ate from the salad bar and had loads of soft serve for dessert. Went to a pub afterwards.	29/1/2016
Did you attend any major sporting events during your incubation period where you ate take-away food? Yes	You took the train to Melbourne and went to the Australian Open for the women's final (the last Saturday in January) and ate about 10 cups of berries and cream. You go every year and get a ground pass and eat the berries and cream, except this year your boyfriend took you as a surprise for your birthday to Rod Laver Arena.	30/1/2016
Did you consume any foods containing frozen berries during your incubation period? Yes	Berries and cream at the Australian Open. Before you went to the tennis your boyfriend made you a smoothie at home on 30 January because you were hungover after your birthday – you are pretty sure the smoothie had frozen berries *(dunno how long they had been in the freezer)*, but he did make you a fried egg *(eggs are dodgy, right?*).	30/1/2016
Did you consume any raw seafood/shellfish during your incubation period? Yes	Went with the whole family to the beach on New Years Eve in Portland Victoria and ate raw oysters. Your brother bought them from Coles in Portland, they could have been a bit off because they tasted a bit slimy.	31/12/2016

Mock hepatitis A questionnaire

Outbreak Questionnaire:

Hepatitis A

Illness Summary

Name:	**DOB:**	**Gender: M F**
Address:	**Suburb:**	**Postcode:**
Phone Number:		

Illness Summary

Onset Date: / / Time of onset …… Date of Specimen collection: / /

Type of specimen: Faeces/ blood/ urine/ other

Symptoms		Onset Date of Symptom	History of illness
Diarrhoea	☐ Yes ☐ No ☐ Unknown Duration(days): ……		
Nausea	☐ Yes ☐ No ☐ Unknown		
Vomiting	☐ Yes ☐ No ☐ Unknown		
Abdominal pain	☐ Yes ☐ No ☐ Unknown		
Jaundice	☐ Yes ☐ No ☐ Unknown		
Headache	☐ Yes ☐ No ☐ Unknown		
Fever	☐ Yes ☐ No ☐ Unknown		
Other	Describe……		

INTERVIEWER USE

Acquisition date:

Jaundice date is regarded as onset date for calculating acquisition/exposure period. Hepatitis A incubation period is 14 – 50 days (approx 2-7 weeks) before the onset of jaundice occurs. Based on the information above the likely period of acquisition is between;

Earliest possible acquisition date: Latest Possible acquisition date:

Privacy statement read? Y / N

Privacy factsheet requested? Y / N

Exposures

During the person's acquisition period [Date 1 (___/___/_____) to Date 2 (___/___/_____)] measure the following outbreak exposures.

Exposure	Details	Date(s)
Did you travel overseas during your acquisition period? ☐ Yes ☐ No ☐ Unknown		
Did you attend any restaurants during your acquisition period? ☐ Yes ☐ No ☐ Unknown		
Did you attend any major sporting events during your acquisition period where you ate take-away food? ☐ Yes ☐ No ☐ Unknown		
Did you consume any foods containing frozen berries during your acquisition period? ☐ Yes ☐ No ☐ Unknown		
Did you consume any raw seafood/shellfish during your acquisition period? ☐Yes ☐No ☐Unknown		

Signature

Name of Interviewer(please print clearly) _____

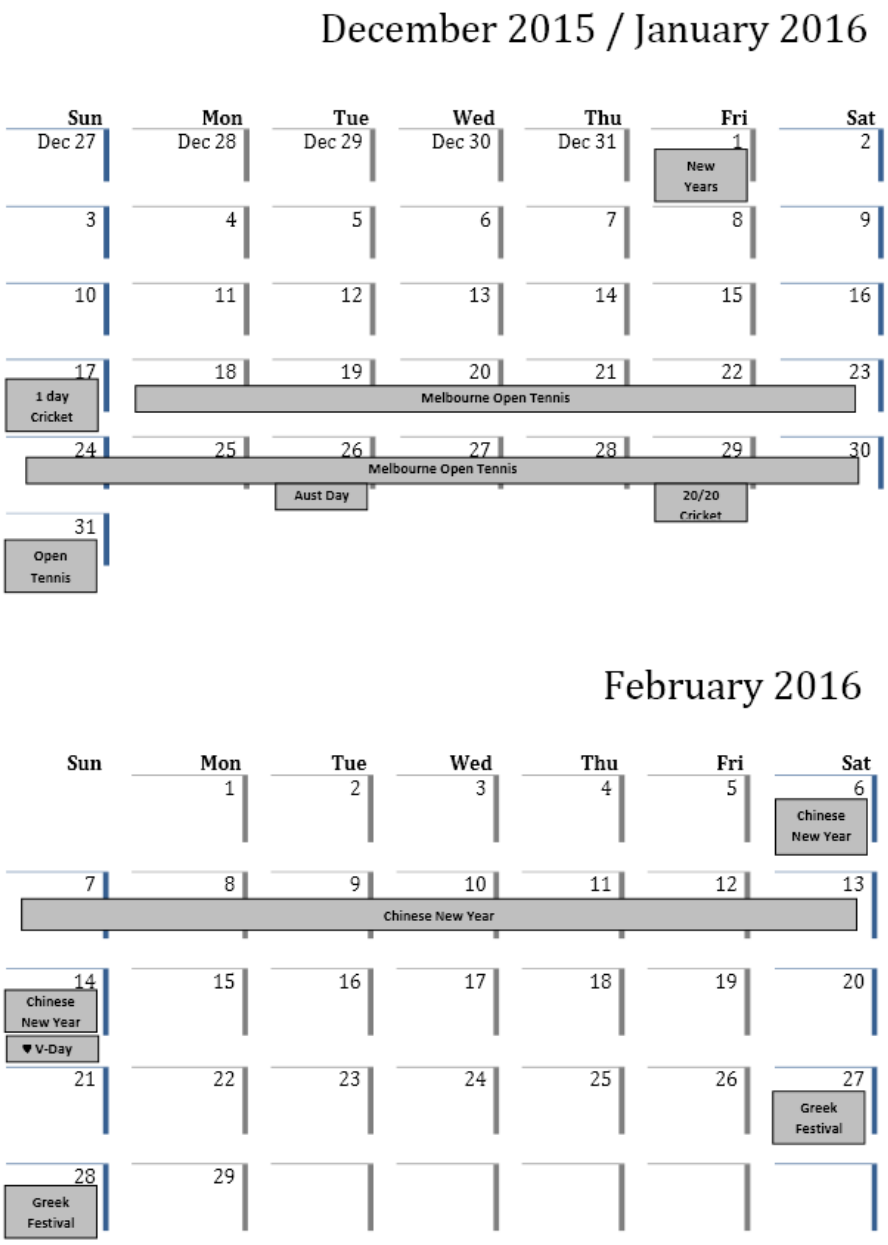
Signature _____

Date / / How long did this questionnaire take to complete? _____

_____

Investigation notes

Mock calendar



Pathology results for Scenario A

MAE Laboratories
PATHOLOGY RESULTS

Patient Details

Name: Indra Pina **DOB:** 25/6/1983 **Gender:** Female

Address: 7 Chifley St **Suburb:** South Yarra
Postcode: 3001

Phone Number: 040000069678

Testing Summary

Request Date: 15/2/2016 Requesting Dr: S. Smith Date of Specimen collection: 15/2/2016

Type of specimen: Serum

Results

Hepatitis A Virus IgG by Chemiluminescent Microparticle Immunoassay (Serum)

HAVAb-IgG (CMIA): Not detected

Hepatitis A Virus IgM by Chemiluminescent Microparticle Immunoassay (Serum)

HAVAb-IgM (CMIA): DETECTED

Serological evidence of recent Hepatitis A infection.

THIS IS A NOTIFIABLE DISEASE

A copy of this report will be forwarded to Victorian Department of Health.

Clinical comments:

Presented with jaundice; onset date 14/02/2016

Authorised by: Dr Doheaps (Pathologist) 16/2/2016

Our ref: MAE15 A

Pathology results for Scenario B

MAE Laboratories
PATHOLOGY RESULTS

Patient Details

Name: Anthony Fratelli **DOB:** 28/9/1961 **Gender:** Male

Address: 33/165 Bourke St **Suburb:** Melbourne
Postcode: 3000

Phone Number: 04000566519681651

Testing Summary

Request Date: 16/2/2016 Requesting Dr: IVA Richards Date of Specimen collection: 16/2/2016

Type of specimen: Serum

Results

Hepatitis A Virus IgG by Chemiluminescent Microparticle Immunoassay (Serum)
HAVAb-IgG (CMIA): Not detected

Hepatitis A Virus IgM by Chemiluminescent Microparticle Immunoassay (Serum)
HAVAb-IgM (CMIA): DETECTED

Serological evidence of recent Hepatitis A infection.

THIS IS A NOTIFIABLE DISEASE
A copy of this report will be forwarded to Victorian Department of Health.

Clinical comments:

Presented with jaundice; onset date 14/02/2016

Authorised by: Dr Doheaps (Pathologist) 18/2/2016

Our ref: MAE15.B

Pathology results for Scenario C

MAE Laboratories
PATHOLOGY RESULTS

Patient Details

Name: Wendy de Waffler **DOB:** 25/8/1991 **Gender:** Female

Address: 7 Main St **Suburb:** Ballarat
Postcode: 3090

Phone Number: 040000069721

Testing Summary

Request Date: 15/2/2016 Requesting Dr: C. Bumpkin Date of Specimen collection: 15/2/2016

Type of specimen: Serum

Results

Hepatitis A Virus IgG by Chemiluminescent Microparticle Immunoassay (Serum)

HAVAb-IgG (CMIA): Not detected

Hepatitis A Virus IgM by Chemiluminescent Microparticle Immunoassay (Serum)

HAVAb-IgM (CMIA): DETECTED

Serological evidence of recent Hepatitis A infection.

THIS IS A NOTIFIABLE DISEASE

A copy of this report will be forwarded to Victorian Department of Health.

Clinical comments:

Presented with jaundice; onset date 14/02/2016

Authorised by: Dr Doheaps (Pathologist) 17/2/2016

Our ref: MAE15 C

6.4.8 Evaluation of the teaching exercise

Once the session had been completed, we asked the MAE16 members for some feedback.

Table 6.2: Average evaluation scores from MAE16 members

(Likert scale: 5 = strongly agree and 1 = strongly disagree)

Score	Average
Content	4.8
Instructor presentation	4.7
Methods	4.8
Learned something new	4.6
Engagement	4.7
Asking questions	4.7

The session was well received, with positive and constructive comments received:

- *A little bit more about the other personality types*
- *This was awesome, a great idea! Maybe more or an opportunity to experience all scenarios?*
- *Good interactive session*
- *Well done MAE 2015*
- *No improvements required*
- *Really helpful; gave some good ideas to help when interviewing*
- *All very interactive sessions; solidified concepts; skills learned in the course block*
- *Good session, good idea to present people with experience(?)*

Chapter 7

Submitted manuscripts

Chapter 7 Contents

7.1 Journal article published at '*Vaccine*'

Vaccine 35 (2017) 170–176

Contents lists available at ScienceDirect

Vaccine

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

Impact of the national targeted Hepatitis A immunisation program in Australia: 2000–2014

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ABSTRACT

In November 2005, hepatitis A vaccine was funded under the Australian National Immunisation Program for Aboriginal and Torres Strait Islander (Indigenous) children aged 12–24 months in the targeted jurisdictions of Queensland, South Australia, Western Australia and the Northern Territory.

We reviewed the epidemiology of hepatitis A from 2000 to 2014 using data from the Australian National Notifiable Diseases Surveillance System, the National Hospital Morbidity Database, and Australian Bureau of Statistics causes-of-death data. The impact of the national hepatitis A immunisation program was assessed by comparison of pre-vaccine (2000–2005) and post-vaccine time periods (2006–2014), by age group, Indigenous status and jurisdiction using incidence rate ratios (IRR) per 100,000 population and 95% confidence intervals (CI).

The national pre-vaccine notification rate in Indigenous people was four times higher than the non-Indigenous rate, and declined from 8.41 per 100,000 (95% CI 5.03–11.79) pre-vaccine to 0.85 per 100,000 (95% CI 0.00–1.99) post-vaccine, becoming similar to the non-Indigenous rate. Notification and hospitalisation rates in Indigenous children aged <5 years from targeted jurisdictions declined in the post-vaccine period when compared to the pre-vaccine period (notifications: IRR = 0.07; 95% CI 0.04–0.13; hospitalisations: IRR = 0.04; 95% CI 0.01–0.16). As did notification rates in Indigenous people aged 5–19 (IRR = 0.08; 95% CI 0.05–0.13) and 20–49 years (IRR = 0.06; 95% CI 0.02–0.15) in targeted jurisdictions. For non-Indigenous people from targeted jurisdictions, notification rates decreased significantly in children aged <5 years (IRR 0.47; 95% CI 0.31–0.71), and significantly more overall (IRR = 0.43; 95% CI 0.39–0.47) compared to non-Indigenous people from non-targeted jurisdictions (IRR = 0.60; 95% CI 0.56–0.64).

The national hepatitis A immunisation program has had a significant impact in the targeted population with relatively modest vaccine coverage, with evidence suggestive of substantial herd protection effects.

1. Introduction

Hepatitis A causes significant morbidity globally (affecting approximately 120 million people annually [1]), with the incidence of disease usually inversely correlated with level of sanitation and access to safe drinking water [2–4]. With improving sanitation and living conditions in Australia, the annual notification rate of hepatitis A has declined from 123 notifications per 100,000 population in 1961 to 1 per 100,000 population in 2014 [5,6]. A number of person-to-person and foodborne outbreaks of hepatitis A have occurred in Australia over the past twenty years, including very large outbreaks associated with raw oysters (1997) and semi-dried tomatoes (2009) [7–15].

Hepatitis A vaccine was first registered for use in Australia in 1994 and has since been recommended for high-risk groups [16]. In response to an increasing number of hepatitis A cases and the death of three Aboriginal and Torres Strait Islander (henceforth referred to as Indigenous) children in north Queensland, a hepatitis A immunisation program commenced in February 1999 for all Indigenous children in this region (north Queensland has a population of approximately 600,000 people, of which 1.2% are Indigenous children aged under 5 years) [17,18]. Two doses of hepatitis A vaccine were scheduled at 18 and 24 months of age,

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0264-410X/

and catch-up vaccination recommended for children <6 years of age [16,17]. Following the north Queensland program, a rapid decline in hepatitis A notifications was reported in the Indigenous and non-Indigenous populations [17].

In November 2005, hepatitis A vaccine was funded under the Australian National Immunisation Program (NIP) for all Indigenous children aged 12–24 months residing in four of the eight states and territories of Australia, namely Queensland, South Australia, Western Australia and the Northern Territory, due to a high risk of acquiring hepatitis A and hospitalisation from it [16]. Two doses were originally scheduled at 12 months and 18 months of age in the Northern Territory and Western Australia, and at 18 and 24 months of age in Queensland and South Australia, changing to 12 and 18 months of age in all four jurisdictions in July 2013 [16,19]. Over the period 2006–2010, decreases in hepatitis A notifications in the Indigenous Australian population was reported [20]. These decreases in targeted jurisdictions occurred in the context of relatively modest hepatitis A vaccination coverage in Indigenous children before 36 months of age, with two-dose coverage increasing from 31% in 2007 to 60% in 2013, and one-dose coverage at 71% during 2013 [19,20].

The aim of our study was to review the epidemiology of hepatitis A in Australia from 2000 to 2014, focusing on the impact of the national hepatitis A immunisation program on both the directly targeted population (Indigenous children in the targeted jurisdictions) and broader herd protection effects Australia-wide.

2. Methods

2.1. Study design and study period

We undertook a descriptive epidemiological study, with comparison of notifications and hospitalisations in the period before (2000–2005) and after (2006–2014) the introduction of the targeted hepatitis A immunisation program in Australia.

2.2. Data sources

2.2.1. Notifications

Confirmed and probable cases of hepatitis A are notifiable to the National Notifiable Diseases Surveillance System (NNDSS) under the public health legislation of each jurisdiction [21]. A confirmed case of hepatitis A requires either laboratory definitive evidence (detection of hepatitis A virus by nucleic acid testing); or laboratory suggestive evidence (detection of hepatitis A-specific immunoglobulin M antibodies in the absence of recent vaccination) plus clinical evidence; or laboratory suggestive evidence plus epidemiological evidence (contact between two people involving a plausible mode of transmission at a time when one of them is likely to be infectious and the other has an illness that started within 15–50 days after this contact and at least one case in the chain of epidemiologically linked cases is laboratory confirmed) [22]. A probable case requires clinical evidence plus epidemiological evidence [22].

For this analysis, notification data included all confirmed and probable cases of hepatitis A from the NNDSS with an onset date between 1 January 2000 and 31 December 2014. For cases with no recorded onset date, we used the earliest recorded date among the fields of date of specimen, date of notification, and date when the notification was received. Variables extracted comprised onset date, age, sex, jurisdiction of residence, Indigenous status, place of acquisition, whether died from disease, and vaccination status. The analysis of the 'place of acquisition' data field was restricted to the years 2010–2014, where data completeness was 80% or greater.

2.2.2. Hospitalisations

The National Hospital Morbidity Database (NHMD) is an administrative database maintained by the Australian Institute of Health and Welfare. Private and public hospital discharge summaries are used to capture data relating to administrative, demographic and clinical information on patients hospitalised in Australia [21]. Using the International Statistical Classification of Disease and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) code B15 (hepatitis A), all eligible hospital admissions coded as hepatitis A (either as the principal or other diagnosis) and with an admission date between 1 January 2000 and 31 December 2013 (latest data available) were included in this analysis.

Variables extracted comprised primary or other diagnosis, date of admission, age, sex, jurisdiction of residence, Indigenous status, length of stay (bed days) and mode of separation from hospital. Jurisdiction of residence and age specific hospitalisation data were only available between 1 January 2000 and 30 June 2012.

2.2.3. Mortality

Mortality data related to hepatitis A were obtained from the NNDSS, NHMD and the Australian Bureau of Statistics (ABS). ABS causes of death data included in this analysis were deaths due to hepatitis A (ICD-10: code B15) as the primary underlying cause, for deaths registered between 2007 and 2011 (latest data available).

2.2.4. Population estimates

National, jurisdictional, age-specific and Indigenous-specific mid-year estimates of resident population sizes were obtained from the ABS [23].

2.3. Data analysis

We compared notification and hospitalisation rates for two time periods, i.e. before the introduction of the hepatitis A targeted immunisation program (pre-vaccine 2000–2005) and after (post-vaccine 2006-latest available data), and for targeted (Queensland, South Australia, Western Australia and the Northern Territory) and non-targeted (New South Wales, Victoria, Tasmania and the Australian Capital Territory) jurisdictions.

Notification and hospitalisation rates were calculated using ABS population estimates as the denominator and are presented as age-specific, jurisdiction-specific, or Indigenous-specific subpopulation rates per 100,000 population. Descriptive statistics included median age (and range) and average length of hospital stay. Place of acquisition for Indigenous and non-Indigenous people was compared and tested for significance using a Fisher's exact test. Age-specific incidence rate ratios (IRR), 95% confidence intervals (95% CI) and p-values were calculated for Indigenous and non-Indigenous populations at the national level, and for targeted and non-targeted jurisdictions, assuming a Poisson distribution. If the 95% CI for any age-specific or total IRR did not overlap with the corresponding comparison group, this was considered evidence of a difference beyond that expected from random variation. Analyses were conducted using STATA software (version 13.1; StataCorp, College Station, Texas USA).

Ethical approval was not required as de-identified aggregated population-based data were used for routine public health surveillance purposes only.

3. Results

3.1. Secular trends

A total of 5096 hepatitis A notifications were recorded in the NNDSS between January 2000 and December 2014, of which

5004 (98%) were confirmed and 92 (2%) were probable cases. The overall national notification rate declined from 4.25 per 100,000 in 2000 to 0.97 per 100,000 in 2014, with a nadir of 0.65 per 100,000 in 2011. The national notification rate in Indigenous people declined from 8.41 per 100,000 (95% CI 5.03–11.79) during the pre-vaccine period to 0.85 per 100,000 (95% CI −0.28 to 1.98) during the post-vaccine period, while the notification rate in non-Indigenous people declined from 2.24 per 100,000 (95% CI 1.22–3.25) pre-vaccine to 1.17 per 100,000 (95% CI 0.71–1.63) post-vaccine.

In the NHMD, 3398 hospitalisations were recorded between January 2000 and December 2013 with a diagnosis that included hepatitis A. The overall national hospitalisation rate declined from 2.31 per 100,000 in 2000 to 0.89 per 100,000 in 2013, with a nadir of 0.53 per 100,000 in 2012. The national hospitalisation rate in Indigenous people declined from 4.23 per 100,000 (95% CI 3.52–4.94) during the pre-vaccine period to 1.09 per 100,000 (95% CI 0.46–1.73) during the post-vaccine period, while the hospitalisation rate in non-Indigenous people declined from 1.45 per 100,000 (95% CI 0.95–1.96) pre-vaccine to 0.87 per 100,000 (95% CI 0.62–1.13) post-vaccine. Of the 3398 hospitalisations, 1781 (52%) had hepatitis A identified as the primary diagnosis, with a median length of stay of 3 days for these 1781 hospitalisations (range: 1–55 days).

Eight deaths (age range 5–≥65 years) were recorded by the ABS between 2007 and 2011 with hepatitis A as the primary underlying cause (data available for post-vaccine period only); six of these deaths were of people aged ≥65 years. Fewer deaths were recorded in the other data sources; NNDSS (2000–2014) and NHMD (2000–2013) captured five deaths each. Matching of deaths between data sources was not possible using the data fields available.

3.2. Age and sex distribution

The median age of notified and hospitalised hepatitis A cases in Australia was similar between the pre-vaccine (notifications: 28 years, range 0–93; hospitalisations: 41 years, range 0–93) and post –vaccine periods (notifications: 27 years, range 0–97; hospitalisations: 41 years, range 0–97). Overall, 6.9% of notified and 2.7% of hospitalised cases were aged <5 years. The average male to female notification ratio was 1.61:1 (range 1.16:1–2.54:1) in the pre-vaccine period, and 1.21:1 (range 0.95:1–1.47:1) in the post-vaccine period.

3.3. Indigenous status

Between 2000 and 2014, 6% (326/5096) of people notified with hepatitis A were recorded as Indigenous, 77% (3895/5096) as non-Indigenous and 17% (875/5096) as unknown or missing Indigenous status. Completeness of this data field was higher for the targeted jurisdictions (87% complete; 1807/2073) than non-targeted jurisdictions (80% complete; 2418/3023). Of people hospitalised with hepatitis A between 2000 and 2013, 6% (196/3398) were recorded as Indigenous, 92% (3137/3398) as non-Indigenous and 2% (65/3398) as unknown or missing Indigenous status. Between January 2000 and June 2012, completeness of this data field was slightly higher for the non-targeted jurisdictions (99% complete; 1877/1899) than targeted jurisdictions (97% complete; 1118/1158).

3.4. Vaccination status

Of all notifications (N = 5096), 13 (0.3%) were reported as fully vaccinated (three during the pre-vaccine period and ten during the post-vaccine period), 36 (0.7%) as partially vaccinated (four during the pre-vaccine period and 32 during the post-vaccine period), and 5047 (99%) were of unknown vaccination status.

3.5. Place of acquisition

Of the 882 notifications with a recorded place of acquisition between 2010 and 2014, 72% (638/882; annual range 56–87%) were acquired overseas. Common places of overseas acquisition included the Oceania region (15.2% [134/882]), southern-east Asia (17.1% [151/882]) and southern-central Asia (21.3% [188/882]). The proportion of hepatitis A notifications acquired overseas was significantly higher in non-Indigenous people (73%; 636/874) than in Indigenous people (25%; 2/8) ($p > 0.05$).

3.6. Jurisdiction

3.6.1. Targeted jurisdictions (Queensland, Northern Territory, South Australia and Western Australia)

In the targeted jurisdictions, notifications dropped from 411 in 2000 (rate 2.2 per 100,000) to 73 in 2014 (0.3 per 100,000), and hospitalisations from 188 in 2000 (1.0 per 100,000) to 24 during the first half of 2012 (0.1 per 100,000) (Fig. 1). Between 2000 and 2005, Indigenous people residing within targeted jurisdictions had an 11.6 times higher notification rate, and a 3.9 times higher hospitalisation rate of hepatitis A than Indigenous people residing within non-targeted jurisdictions (Table 1).

The notification rate in Indigenous people residing within targeted jurisdictions declined by 93% overall (IRR = 0.07; 95% CI 0.05–0.10) in the post-vaccine period. Age-specific declines were also identified (Table 1). The overall notification rate in non-Indigenous people declined by 57% (IRR = 0.43; 95% CI 0.39–0.47) (Table 1). Hospitalisations in Indigenous people declined by 82% overall (IRR = 0.18; 95% CI 0.12–0.27). Age-specific declines were also identified (Table 1). In non-Indigenous people, the overall hospitalisation rate declined by 46% (IRR = 0.54; 95% CI 0.48–0.62) (Table 1).

The largest decreases in notification and hospitalisation rates were in the Northern Territory (88% and 86%, respectively) and Western Australia (70% and 64%, respectively) (Fig. 2).

3.6.2. Non-targeted jurisdictions (New South Wales, Victoria, Tasmania and the Australian Capital Territory)

Notifications in Indigenous people residing in non-targeted jurisdictions declined by 53% (IRR = 0.47; 95% CI 0.23–0.95) in the post-vaccine period. An age-specific decline of 68% was identified for the 5–19 years age group (IRR = 0.32; 95% CI 0.11–0.95), while there were no notifications in children aged <5 years during the entire study period. Notifications in non-Indigenous people declined by 40% (IRR = 0.60; 95% CI 0.56–0.64). No significant reduction was identified in the non-Indigenous <5 years age group (IRR = 0.96; 95% CI 0.69–1.33) (Table 1).

Hospitalisations in Indigenous people declined by 30% however, this was not statistically significant (IRR = 0.70; 95% CI 0.38–1.27), while hospitalisations in non-Indigenous people declined by 33% (IRR = 0.67; 95% CI 0.61–0.73) (Table 1).

4. Discussion

In the population directly targeted by the national hepatitis A immunisation program in Australia (Indigenous children aged <5 years residing in targeted jurisdictions), we documented significant declines in hepatitis A notification and hospitalisation rates (93% and 96%, respectively) between the pre- and post-vaccine periods. The program also appears to have provided substantial herd protection to both the Indigenous and non-Indigenous popu-

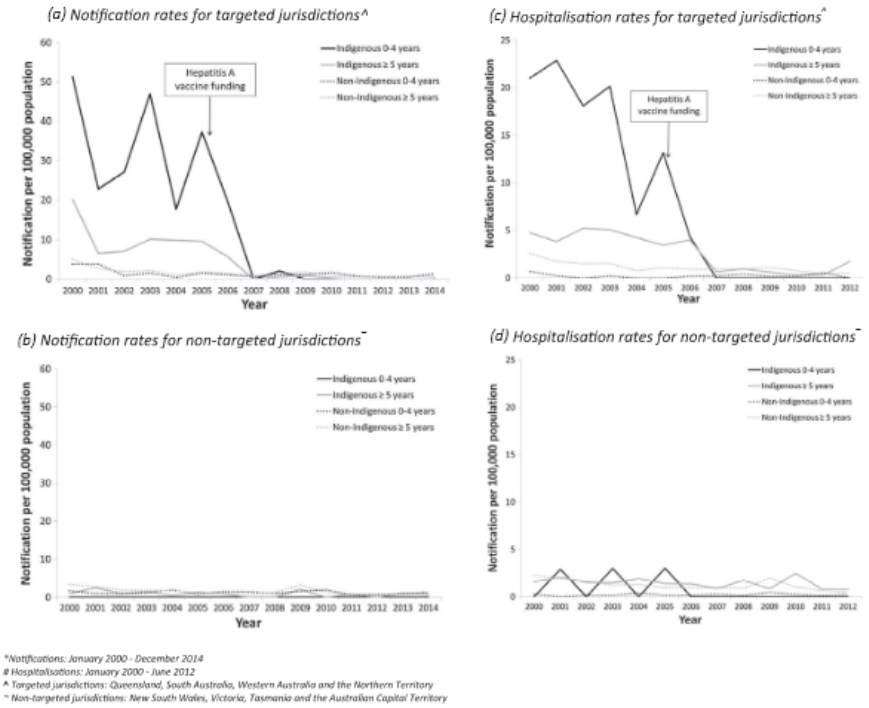

Fig. 1. Targeted and non-targeted hepatitis A notification (*Notifications: January 2000 - December 2014*) and hospitalisation (*Hospitalisations: January 2000 - June 2012*) rates of Australia, by Indigenous status, age group and year. (a) Notification rates for targeted jurisdictions (*Targeted jurisdictions: Queensland, South Australia, Western Australia and the Northern Territory*). (b) Notification rates for non-targeted jurisdictions (*Non-targeted jurisdictions: New South Wales, Victoria, Tasmania and the Australian Capital Territory*). (c) Hospitalisation rates for targeted jurisdictions (*Targeted jurisdictions: Queensland, South Australia, Western Australia and the Northern Territory*). (d) Hospitalisation rates for non-targeted jurisdictions (*Non-targeted jurisdictions: New South Wales, Victoria, Tasmania and the Australian Capital Territory*).

lations aged 5–49 years within targeted jurisdictions. Notification rates declined in the post-vaccine period by 92% for the 5–19 years Indigenous age group, and by 94% for the 20–49 years age group, compared to 68% and 33%, respectively, in non-targeted jurisdictions, with the decrease being significantly different to the non-targeted jurisdictions for the latter age group. In non-Indigenous people, the notification rate in targeted jurisdictions decreased by 51% for children aged <5 years, and by 57% overall, with the overall decrease being significantly different to the overall decrease in non-targeted jurisdictions.

These decreases in targeted jurisdictions occurred in the context of relatively modest hepatitis A vaccination coverage in Indigenous children [24,25]. Young children play a key role in the transmission of hepatitis A to other children and adults, as they are usually asymptomatic (or only mildly symptomatic) and have lower levels of personal hygiene [17,18,26]. We also documented significant, albeit lower, decreases in hepatitis A notifications between the pre- and post-vaccine periods in both Indigenous and non-Indigenous populations in non-targeted jurisdictions (53% and 40%, respectively). These decreases may also be partly attributable to the targeted national immunisation program, given the extensive population movement of Indigenous people between states and territories of Australia [27].

The national targeted hepatitis A immunisation program appears to have been highly effective at reducing the incidence of disease in Australia. However, the descriptive nature of our study makes it difficult to quantify the exact contribution of this program. Of note, the funding of a hepatitis A immunisation program in north Queensland from 1999 (with estimated two-dose coverage of 77% in the Indigenous birth cohort for the year 2000 [17]) may have led us to underestimate the true impact of the national targeted program. Other factors, including the targeted immunisation of high-risk groups (such as travellers to hepatitis A endemic areas, and people with an increased risk of exposure to hepatitis A based on their occupation or lifestyle) as recommended in the Australian Immunisation Handbook [16], may also have contributed to the declines Australia-wide. However, available information indicates that hepatitis A vaccination coverage of adults in high-risk groups such as travellers to hepatitis A endemic areas, although recommended since 1994, is relatively low [28,29]. More general limitations of the data we analysed are that hepatitis A notifications may underestimate true incidence, particularly in young children, and may be influenced by changes in diagnostic and public health follow-up practices over time and across jurisdictions, while hospitalisation data can be influenced by access to hospital care, changes in admission practices, and cod-

Table 1
Hepatitis A notifications and hospitalisations, by age group, Indigenous status and pre-/post-vaccine period, Australia, 2000–2014; rates, counts and incidence rate ratios (95% CI).

	Age group (years)	Pre-vaccine (2000–2005)		Post-vaccine [a]		Incidence rate ratio[b]	
		Non-Indigenous[c] (N)	Indigenous[c] (N)	Non-Indigenous[c] (N)	Indigenous[c] (N)	Non-Indigenous (95% CI)	Indigenous (95% CI)
(a) Targeted jurisdictions: Queensland, South Australia, Western Australia and the Northern Territory							
Notifications	<5	2.09 (55)	33.91 (90)	0.99 (46)	2.41 (10)	**0.49 (0.33–0.73)**	**0.07 (0.04–0.13)**
	5–19	2.24 (194)	18.37 (120)	1.33 (185)	1.46 (16)	**0.59 (0.48–0.73)**	**0.08 (0.05–0.13)**
	20–49	3.30 (604)	6.13 (48)	1.30 (404)	0.38 (5)	**0.39 (0.35–0.45)**	**0.06 (0.02–0.15)**
	50–64	1.63 (116)	2.36 (3)	0.66 (88)	0.81 (2)	**0.41 (0.31–0.54)**	0.29 (0.05–1.73)
	⩾65	1.01 (52)	0.00 (0)	0.35 (33)	0.98 (1)	**0.34 (0.22–0.52)**	–
	Total	2.44 (1021)	13.85 (261)	1.04 (756)	1.08 (34)	**0.43 (0.39–0.47)**	**0.07 (0.05–0.10)**
Hospitalisations	<5	0.19 (5)	16.99 (45)	0.26 (9)	0.62 (2)	1.45 (0.49–4.33)	**0.04 (0.01–0.16)**
	5–19	0.54 (47)	5.26 (35)	0.43 (44)	1.04 (8)	0.82 (0.54–1.23)	**0.18 (0.09–0.40)**
	20–49	1.95 (359)	4.51 (35)	0.89 (200)	1.72 (16)	**0.46 (0.39–0.55)**	**0.37 (0.20–0.66)**
	50–64	1.53 (108)	1.54 (2)	0.88 (87)	0.00 (0)	**0.61 (0.46–0.81)**	–
	⩾65	1.76 (91)	0.00 (0)	0.94 (65)	0.00 (0)	**0.55 (0.40–0.76)**	–
	Total	1.45 (610)	6.20 (117)	0.77 (405)	1.15 (26)	**0.54 (0.48–0.62)**	**0.18 (0.12–0.27)**
	Age group (years)	Pre-vaccination (2000–2005)		Post-vaccination[b]		Incidence rate ratio[b]	
		Non-Indigenous[c] (N)	Indigenous[c] (N)	Non-Indigenous[c] (N)	Indigenous[c] (N)	Non-Indigenous (95% CI)	Indigenous (95% CI)
(b) Non-targeted jurisdictions: New South Wales, Victoria, Tasmania and the Australian Capital Territory							
Notifications	<5	1.21 (55)	0.00 (0)	1.23 (92)	0.00 (0)	0.96 (0.69–1.33)	–
	5–19	2.21 (319)	1.96 (10)	1.79 (393)	0.57 (5)	**0.81 (0.70–0.94)**	**0.32 (0.11–0.95)**
	20–49	2.89 (907)	1.09 (6)	1.43 (720)	0.70 (7)	**0.50 (0.46–0.56)**	0.67 (0.23–1.99)
	50–64	1.12 (133)	0.00 (0)	0.77 (164)	0.86 (2)	**0.69 (0.55–0.87)**	–
	⩾65	1.07 (102)	2.07 (1)	0.64 (107)	0.00 (0)	**0.59 (0.45–0.78)**	–
	Total	2.12 (1516)	1.19 (17)	1.25 (1476)	0.55 (14)	**0.60 (0.56–0.64)**	**0.47 (0.23–0.95)**
Hospitalisations	<5	0.18 (8)	1.48 (3)	0.23 (12)	0.00 (0)	1.28 (0.52–3.14)	–
	5–19	0.53 (77)	0.81 (4)	0.61 (99)	0.28 (1)	1.18 (0.87–1.58)	0.20 (0.02–1.80)
	20–49	1.79 (562)	2.50 (14)	1.01 (383)	2.08 (15)	**0.60 (0.52–0.68)**	0.88 (0.42–1.82)
	50–64	1.56 (185)	0.90 (1)	1.15(177)	1.99 (4)	**0.76 (0.62–0.93)**	2.67 (0.30–23.88)
	⩾65	2.22 (211)	2.34 (1)	1.19 (142)	0.00 (0)	**0.54 (0.44–0.67)**	–
	Total	1.45 (1043)	1.61 (23)	0.94 (813)	1.10 (20)	**0.67 (0.61–0.73)**	0.70 (0.38–1.27)

N = number of cases.
Bold IRR denote significant reductions (p-value < 0.05).
[a] Post-vaccine period-Notifications: January 2006-December 2014; Hospitalisations: January 2006-June 2012.
[b] Comparison of pre- and post-vaccine periods.
[c] Average annual rate per 100,000 total population.

ing error. As recommended by the Australian Institute of Health and Welfare, all hospitalisation data was included for analyses of Indigenous status [30]. However, data relating to Indigenous status from the non-targeted jurisdictions should be interpreted with caution, as weighted completeness for Indigenous identification in public hospitals during 2011–12 was below the level considered acceptable (80%) in Tasmania, the Australian Capital Territory, and Victoria [30].

Declines in hepatitis A in Indigenous populations following targeted childhood immunisation programs have also been reported in the United States of America (USA), although without clear evidence of broader herd protection impacts on the non-Indigenous population [31–34]. However Indigenous Australians make up a greater proportion (2.4%) of the Australian population than Native Americans and Alaskan Natives do in the USA (0.9%) [33,35]. Substantial herd protection effects arising from universal childhood hepatitis A immunisation programs have been documented in Israel, Argentina and the USA, with the USA introducing a national universal program in 2006 following evidence of substantially higher decreases in incidence in states with universal programs already in place [36–40]. However, targeted hepatitis A vaccination programs have generally been estimated to be more cost-effective in lower incidence settings than universal programs [41]. The World Health Organization recommends mass vaccination programs in countries moving from high to intermediate hepatitis A endemicity, but targeted programs in countries with low endemicity [1]. The USA is the only low endemicity country of similarly high income to Australia that has introduced a universal childhood program, as of 2011 the hepatitis A notification rate in the USA was similar to that reported in Australia (0.4 and 0.6 per 100,000, respectively) despite reasonable vaccination coverage in the USA among children aged 19–35 months (78–87% one-dose coverage and 50–57% two dose coverage in 2011) [42]. In most Western European countries hepatitis A incidence has also declined to below 1.0 per 100,000, in the context of immunisation programs targeting only individuals at high risk [43]. Universal routine vaccination of children has been associated with increased age of infection, and hence risk of more severe disease [44,45]. In the context of the targeted Australian immunisation program we found no change in the median age of notified and hospitalised cases between pre- and post-vaccine periods.

The relatively low hepatitis A seroprevalence in the Australian population (approximately 55% in persons aged less than 70 years, from Victoria during 2008 [46]) leaves a large pool of susceptible individuals. Non-immune individuals in Australia, and other developed countries, remain at risk of hepatitis A, particularly when they travel to endemic countries and during foodborne outbreaks linked to the global food economy, such as those which occurred in Australia in 2009, associated with imported semi-dried tomatoes [9], in the USA in 2013, associated with imported pomegranate arils [37,47], and in Europe, Australia and New Zealand, associated with raw and frozen berries [7,48–51]. The majority of hepatitis A cases (ranging from 56% to 87% between 2010 and 2014) in Australia now acquire their infection while travelling to endemic countries. Increasing hepatitis A vaccine coverage among travellers will reduce the risk of importation and subsequent sec-

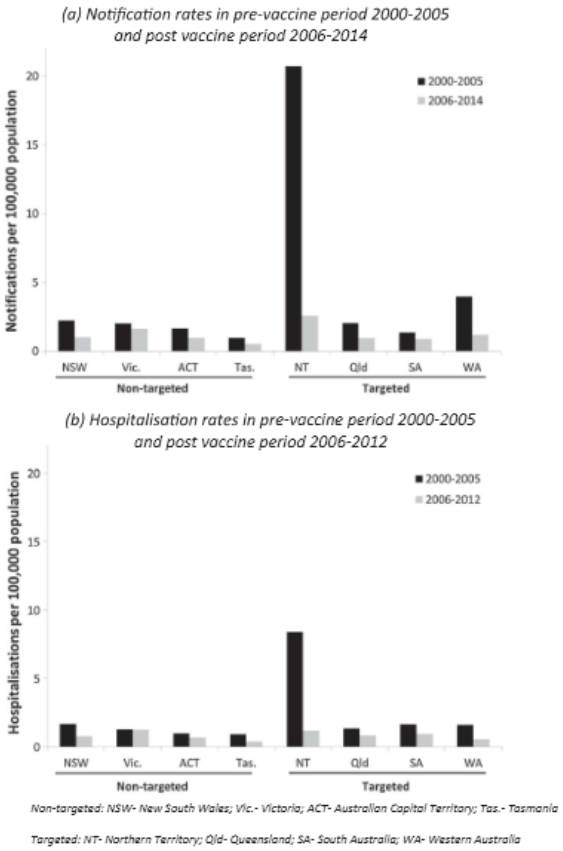

Fig. 2. Hepatitis A notification and hospitalisation rates by jurisdiction, and pre-/post-vaccine period, Australia, 2000–2014. (a) Notification rates in pre-vaccine period 2000–2005 and post vaccine period 2006–2014. (b) Hospitalisation rates in pre-vaccine period 2000–2005 and post vaccine period 2006–2012. Non-targeted: NSW - New South Wales; Vic. - Victoria; ACT - Australian Capital Territory; Tas. - Tasmania. Targeted: NT - Northern Territory; Qld - Queensland; SA - South Australia; WA - Western Australia.

ondary spread. However, this has proven difficult to achieve in Australia and further research is needed to inform effective strategies to increase community awareness of hepatitis A vaccines and access to vaccination services [28,29]. Foodborne outbreaks are also difficult to prevent, even with rigorous food safety standards in place, due to the difficulties involved in testing for hepatitis A virus in imported foodstuffs [52,53]. A universal infant hepatitis A immunisation program in Australia could help mitigate the impact of foodborne outbreaks, however, this would involve substantial cost and take decades to have its full effect.

5. Conclusions

In summary, the national hepatitis A immunisation program in Australia has had a significant impact in the targeted population, with evidence suggesting a broader herd protection effect. Ongoing surveillance is required to be sure that the current targeted immunisation strategy is maintaining satisfactory disease control.

Authors' contributions

CT, AD, EF and FB designed the study. CT reviewed the literature, conducted the statistical analyses, analysed the data and wrote the initial draft of the manuscript. AD, EF, BP and FB supervised the analysis and assisted with writing the manuscript. All authors contributed by making critical revisions to the manuscript and all have approved the final article.

Conflict of interest statement

The authors have no conflicts of interests to declare

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Epidemiology and whole genome sequencing of an ongoing point-source *Salmonella* Agona outbreak associated with sushi consumption in western Sydney, Australia 2015

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SUMMARY

During May 2015, an increase in *Salmonella* Agona cases was reported from western Sydney, Australia. We examine the public health actions used to investigate and control this increase. A descriptive case-series investigation was conducted. Six outbreak cases were identified; all had consumed cooked tuna sushi rolls purchased within a western Sydney shopping complex. Onset of illness for outbreak cases occurred between 7 April and 24 May 2015. *Salmonella* was isolated from food samples collected from the implicated premise and a prohibition order issued. No further cases were identified following this action. Whole genome sequence (WGS) analysis was performed on isolates recovered during this investigation, with additional *S.* Agona isolates from sporadic-clinical cases and routine food sampling in New South Wales, January to July 2015. Clinical isolates of outbreak cases were indistinguishable from food isolates collected from the implicated sushi outlet. Five additional clinical isolates not originally considered to be linked to the outbreak were genomically similar to outbreak isolates, indicating the point-source contamination may have started before routine surveillance identified an increase. This investigation demonstrated the value of genomics-guided public health action, where near real-time WGS enhanced the resolution of the epidemiological investigation.

Key words: Outbreak, public health action, *Salmonella* Agona, sushi, whole genome sequencing.

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INTRODUCTION

Salmonellosis is a zoonotic disease which remains the second most commonly notified gastrointestinal disease in Australia, following campylobacteriosis [1]. Transmission to humans occurs via the consumption of raw or inadequately cooked foods of animal origin, or by food items and untreated water contaminated with infected faeces from a reservoir host [1–3]. *Salmonella enterica* subsp. *enterica* serovar Agona (*Salmonella* Agona) is recognised as a common global cause of salmonellosis in both animals and humans [4], and is a contaminant of farmed livestock and vegetables [5–7], and factory-prepared foods [8–11]. *S.* Agona has been ranked among the top 15 most frequent *Salmonella* serotypes in North America, seventh in Europe, and 15th in Australia during 2006 [4, 12]. Outbreaks of *S.* Agona have occurred in Ireland [8], UK [13, 14], USA [14–17], Israel [18], Finland [19], France [10], Germany [20] and Australia [21], with some sources of *S.* Agona identified as chickens [22, 23], cattle [24], Peruvian fishmeal [25], dry unsweetened cereals [16] and powered infant formula [10].

Whole genome sequencing (WGS) of foodborne bacteria of public health importance provides the ability to distinguish between isolates of interest within an individual outbreak [26, 27]. Enhanced management of outbreaks using WGS helps to confirm the contamination source, characterize transmission events using near real-time methodology and increased quality control of data [26, 27]. Along with the comprehensive genetic information provided by WGS, comes additional information regarding antibiotic resistance, virulence determinants and genome evolution [28]. As technology becomes less cost-prohibitive and turnaround times are reduced, WGS is expected to benefit communicable disease surveillance and outbreak investigations of foodborne disease [26, 29, 30]. It is essential, as the application of WGS advances quickly, that the public health community understands the benefits of the analytical methods used to explore their data [31].

Salmonellosis is notifiable within New South Wales (NSW) [32, 33], with records aggregated within the Notifiable Conditions Information Management System (NCIMS). *Salmonella* isolates from public and private pathology providers, and the NSW Department of Primary Industries (DPI) are routinely referred to the NSW Enteric Reference Laboratory, Centre for Infectious Diseases and Microbiology Laboratory Services for serotyping using the White-Kauffmann-Le Minor scheme (9th Ed 2007) [27]. During routine surveillance, the NSW Communicable Disease Branch identified nine cases of *S.* Agona in May 2015, all clustered geographically in western Sydney. This report examines the epidemiological and molecular investigation of an increase in *S.* Agona cases in NSW between January and July, 2015.

METHODS

Epidemiological investigation of the outbreak

A retrospective review of notifications in NCIMS was conducted, with de-identified data extracted for laboratory-confirmed *S.* Agona cases diagnosed within NSW between 1 January 2011 and 31 December 2014. Extracted variables included notification date, onset date and jurisdiction of residence. Average number of cases per year and 95% confidence intervals (95% CI) were calculated for the entire NSW population, with NSW population estimates obtained from NSW Health.

A descriptive case-series investigation was conducted on all notified cases of *S.* Agona, residing in the western Sydney area, and with a notification date of salmonellosis between March and June 2015. Telephone interviews of cases or surrogates (either a parent or guardian when the case was a child aged <16 years) were conducted using a standardised *Salmonella* questionnaire. Questions covered case demographics and illness, food consumption history, travel and environmental exposures 7 days prior to the onset of disease.

Food and environmental investigation of the outbreak

Based on the responses of interviewed cases, the NSW DPI conducted investigations at two separate sushi premises (Sushi-A and Sushi-B), both operating within one large shopping complex in western Sydney. The NSW DPI inspected both Sushi-A and Sushi-B on 17 June 2015, with follow-up inspections conducted at Sushi-B. Food and environmental samples were collected during each inspection and sent to the NSW Enteric Reference Laboratory for *Salmonella* identification and further molecular typing of isolates. Management and staff members at both premises were questioned by the NSW DPI during these inspections, regarding food preparation techniques, cleaning processes and staff illnesses.

Retrospective WGS analysis

A retrospective WGS analysis was performed on clinical and food isolates recovered during this descriptive cases-series investigation, along with additional *S.* Agona isolates from sporadic-clinical cases and routine food samples (collected by the NSW DPI) in NSW, during the period January to July 2015. The genomic deoxyribonucleic acid (DNA) was prepared using an automated workstation Chemagic Prepito-D (PerkinElmer). The DNA sequencing libraries were prepared using the Nextera XT DNA preparation kit (Illumina) and the sequencing was performed on the NextSeq 500 (Illumina) with 2 × 150 base-pairs (bp) paired-end chemistry. Sequencing data quality was checked by FastQC v1.0.0 (BaseSpace Labs, Illumina). Single nucleotide polymorphisms (SNP) were identified using CLC Genomics Workbench v8·0 (Qiagen) by mapping reads to the reference genome *S.* Agona 460004 2–1 (GenBank: NZ_CP011259). The significant thresholds for SNP calling were set for a minimum coverage at 20 and a minimum variant frequency at 80%.

The generated SNP list from each of the isolates were exported as Excel files and a binary type SNP matrix representing presence and absence of SNP in each isolates was generated. The clustering analysis was performed using a categorical coefficient with a UPGMA (unweighted pair group method with arithmetic mean) in BioNumerics (Applied Maths). To validate the clustering analysis, *de novo* assembly was performed in the CLC Genomics Workbench with a minimum contig-size set at 200 bp. The assembly was then mapped against the reference genome for SNP calling and phylogeny inferred using a web-based server (https://cge.cbs.dtu.dk/services/CSIPhylogeny/). Maximum likelihood trees at 100 bootstraps were generated from SNP fasta file using MEGA-6 [34].

RESULTS

Progression of the outbreak

Historically, an annual average of 28·3 cases of *S.* Agona ($N = 113$; 95% CI 17·2–39·3) were notified in NSW between 1 January 2011 and 31 December 2014. Within the epidemiological investigation period (March–June 2015), 19 cases residing in the greater western Sydney area were notified, and were included in the descriptive case-series investigation. Sixteen of these 19 clinical cases (84%) were contactable for an interview, of which, six had consumed sushi that had been purchased from one of two different outlets within a large shopping complex in western Sydney. Onset of illness of these six outbreak cases occurred between 7 April and 24 May 2015. These six outbreak cases had a median age of 8 years (age range 3–45 years), with five reporting symptoms of diarrhoea (median duration of 5·5 days: range 2–8 days), and four with bloody stools. Two cases, both aged <14 years, presented to the emergency department with one case hospitalised for three days due to the severity of symptoms.

Of the remaining 10 clinical cases of the descriptive case-series investigation, no common exposures were identified during interviews. Salmonellosis experienced by a mother and her new-born baby were possibly hospital related; two unrelated cases had recently returned home from international travel (Vanuatu and Thailand); two regularly attended childcare; and one was a resident of an aged care facility. No high-risk exposures were identified for three cases. Repeated attempts to contact the remaining three cases for an interview were unsuccessful.

On 17 June 2015, food and environmental samples were collected from two different sushi venues (Sushi-A and Sushi-B) operating within a large shopping complex in western Sydney, as both were implicated by the cases. Samples from both Sushi-A and Sushi-B were representative of the complete sushi handling process, including raw ingredients and their storage containers, prepared cooked ingredients and their storage containers, and the final sushi product for consumption. *Salmonella* was not detected from any of the food or environmental samples collected from Sushi A. Cooked tuna sushi rolls from Sushi-B were found positive for *S.* Agona culture, while the individual ingredients of the sushi rolls and environmental samples were each negative (Table 1). Due to specific food hygiene and food safety defects identified, Sushi-B was issued with a notice requiring corrective action. On 6 July 2015, a Prohibition Order was issued (immediately following the availability of laboratory results) to Sushi-B, prohibiting the handling or production of cooked tuna sushi rolls intended for sale on the premises (Fig. 1).

It was revealed that a staff-member at Sushi-B had been ill during early May 2015, with symptoms including vomiting and diarrhoea whilst at home on a rostered day-off; no stool sample was collected for testing. This staff member, when questioned by the NSW DPI, confirmed that they had consumed sushi rolls while at work between 28 and 30 April 2015, as staff members at Sushi-B are entitled to one sushi

Table 1. *Food and environmental samples collected by the NSW Department of Primary Industries (DPI) from Sushi-B between 17 June and 16 July 2015*

Date	Samples collected	Sample type	Test result (*S* = *satisfactory*, *U* = *unsatisfactory*)
17·06·15	Total of 15 environmental samples	Environmental	S
	Total of 12 food samples (including raw whole shell eggs)	Food	S
	2 × cooked tuna sushi rolls (cucumber + avocado)	Food	U (*S. Agona* detected)
	Raw chicken pieces	Food	U (*S. Kiambu* detected)
26·06·15	Total of 16 environmental samples	Environmental	S
	Total of 11 food samples	Food	S
	Cooked tuna and avocado sushi roll	Food	U (*S. Agona* detected)
	Cooked tuna and cucumber sushi roll	Food	U (*S. Agona* detected)
	Cooked tuna mix (tuna + mayonnaise + sugar)	Food	U (*S. Agona* detected)
06·07·15	Total of 5 environmental samples	Environmental	S
	Total of 11 food samples (including opened mayonnaise)	Food	S
	Cooked tuna and avocado sushi roll	Food	U (*S. Agona* detected)
	Cooked tuna mix (tuna + mayonnaise + sugar) – large container	Food	U (*S. Agona* detected)
	Cooked tuna mix (tuna + mayonnaise + sugar) – small container	Food	U (*S. Agona* detected)
16·07·15	Multiple environmental samples	Environmental	S
	Total of 22 food samples (including all ingredients for new trial batch of cooked tuna sushi rolls)	Food	S

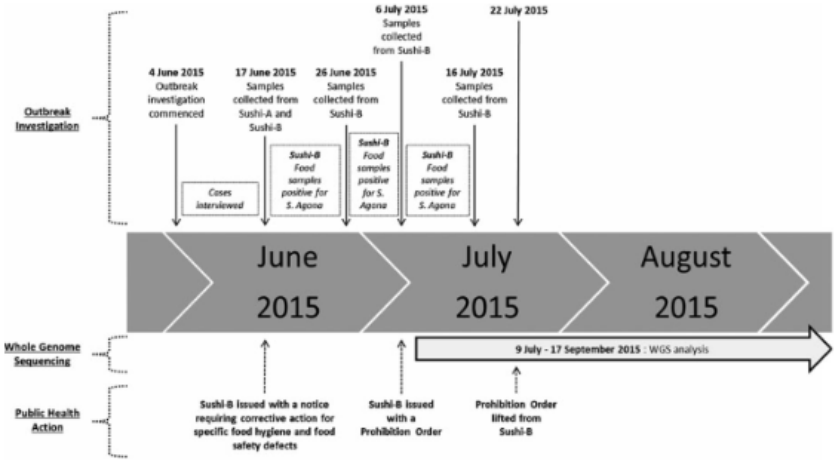

Fig. 1. Time line of the outbreak investigation, retrospective WGS analysis and public health action.

roll per shift. This staff member could not recall which varieties of sushi were eaten on those days but indicated that it could have been cooked tuna, salmon or chicken. Daily work duties for this staff member included preparing sushi rolls at the designated preparation bench and serving customers.

Whole genome sequencing

Forty-eight isolates serotyped as *S.* Agona and referred to the NSW Enteric Reference Laboratory between January and July 2015 were subjected to WGS. These included 38 clinical isolates (from 35

notified cases) and 10 food isolates. The 38 clinical isolates encompassed 21 clinical isolates collected during the descriptive case-series investigation (from the 19 *S.* Agona notifications of residents in the western Sydney area, March–June 2015, and included two repeat samples) and 17 sporadic-clinical isolates (from *S.* Agona notifications in the wider region of NSW, January–July 2015, and included one repeat sample). Based on the epidemiological results of this investigation, six of the 21 clinical isolates collected during the descriptive case-series investigation were classified as outbreak isolates (recovered from people who had consumed sushi purchased from within a large shopping complex in western Sydney). Of the 10 food isolates, six were recovered from samples collected from Sushi-B, March–July 2015, and four were collected as part of routine survey work by the NSW DPI, January–March 2015 (Fig. 2).

The maximum likelihood phylogenetic tree of *S.* Agona, based on the SNP analysis of these 48 isolates, grouped 17 isolates together with a 0–1 SNP variation across clustered genomes (Fig. 2). These included the six outbreak isolates, and six food isolates collected from Sushi-B during the outbreak (Cluster-A, Fig. 2). Also within Cluster-A were four sporadic-clinical isolates collected in NSW between January and March 2015, and a single clinical isolate recovered from a non-contactable individual who was originally included in the descriptive case-series investigation. All clinical isolates within Cluster-A had similar genetic relatedness to food isolates recovered from Sushi-B during this outbreak (Fig. 2).

Two isolates of *S.* Agona obtained from raw retail chicken samples (collected between February and March 2015) and re-sampled isolates collected from an elderly individual at an aged care home (date of onset 3 April 2015) (Cluster-B, Fig. 2) shared similar genomes with the outbreak isolates (Cluster-A, Fig. 2). The SNP variation between isolates of Cluster-A and Cluster-B did not exceed 4–8 bp across the entire genome. A mother (date of onset 25 March 2015) and her new-born (date of onset 22 March 2015), who were not related to the outbreak, had indistinguishable *S.* Agona genomes by SNP analysis (Cluster-C, Fig. 2). *S.* Agona recovered from cases with overseas travel histories were genetically unrelated to the outbreak isolates of Cluster-A (Fig. 2).

In total, 11 clinical isolates were grouped within Cluster-A by genetic analysis. This included (a) six outbreak isolates; (b) a single clinical isolate recovered from a non-contactable individual who was part of the descriptive case-series investigation; and (c) four sporadic-clinical isolates from cases that were notified outside the epidemiological investigation period and/or area. Common exposure to contaminated foods was confirmed between 7 April and 24 May 2015 during the epidemiological investigation of the outbreak. However, as indicated by the grouping of sporadic-clinical isolates with similar genetic patterns to the cases of the outbreak (Cluster-A), the duration of this point-source contamination issue at Sushi-B cannot be confirmed without supporting epidemiological information (Fig. 3).

DISCUSSION

Rapid epidemiological investigation identified contaminated cooked tuna sushi rolls consumed from an individual sushi outlet in western Sydney as the likely vehicle for this outbreak. Once the food outlet had been identified, our multidisciplinary team promptly detected the contamination issue and instigated action to eliminate the ongoing risk to the community. We highlight the public health importance of WGS, as well as the additional value that this modern technology provides. The WGS analysis identified five additional clinical isolates that may have been linked to the outbreak (one clinical isolate recovered from an individual who was originally included in the descriptive case-series investigation and was not contactable for an interview; and four sporadic-clinical isolates). It was speculated that the original contamination-source for this outbreak could have been raw retail chicken meat, based on the limited SNP variation between the isolates of the outbreak (Cluster-A) and the routinely collected chicken meat samples in Cluster-B (Fig. 2), with the timing of this cross-contamination event remaining uncertain.

The WGS offers increased discriminative power and enhances traditional descriptive epidemiology with detailed phylogenetic relationships between isolates [35]. During this particular outbreak investigation, the SNP analysis, which included clinical isolates that were not originally considered to be part of the outbreak, may have increased the total outbreak size by 183%. However, it is worth noting that the 'threshold' for the maximum SNP differences of *Salmonella* isolates related to an outbreak cluster remains not well defined [27]. Previous WGS reports of *Salmonella* outbreaks have had SNP differences of up to 12–30-bp to help define a cluster [27, 29, 35]. Using a similar threshold, our outbreak would

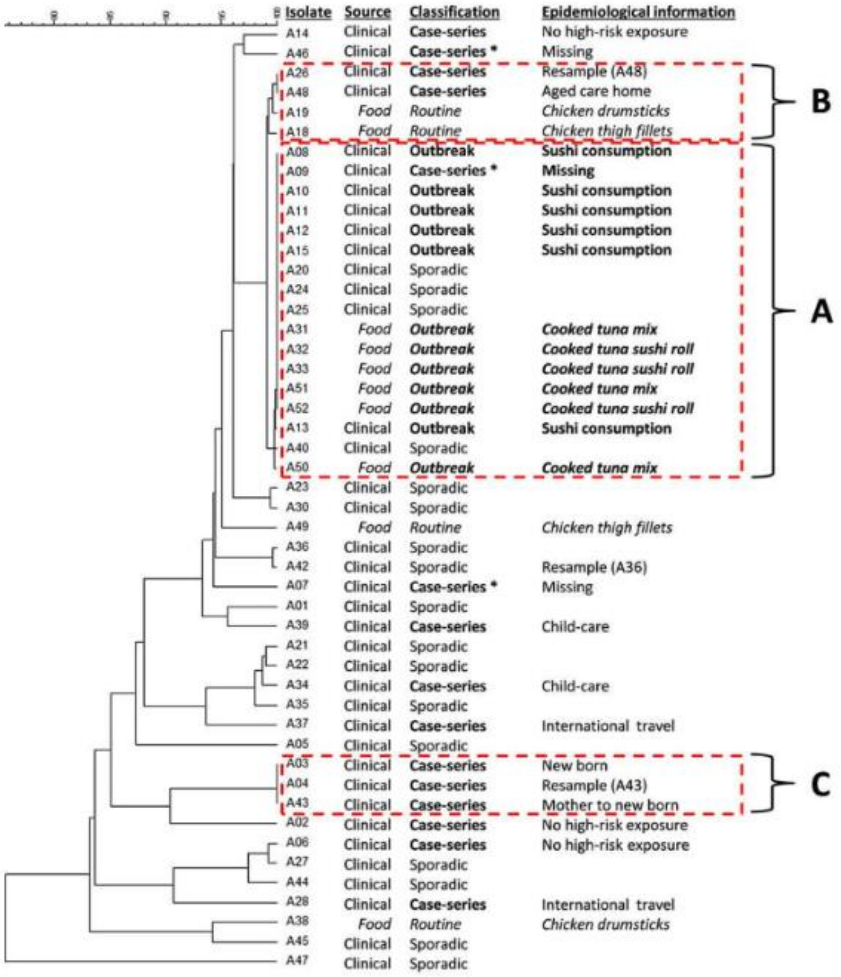

Fig. 2. Maximum likelihood tree of *S.* Agona isolates based on SNP. * *representing clinical cases who were originally included in the descriptive case-series investigation and non-contactable for an interview during this investigation.*

have included an elderly individual from the aged care home (Cluster-B, Fig. 2), who lacked supporting epidemiological information to link them to this outbreak at Sushi-B. WGS data should not be used in isolation to define an outbreak, and should be used to compliment traditional epidemiological data [29].

The SNP variation of *S.* Agona isolates obtained from raw retail chicken meat routinely sampled by the NSW DPI during 2015 (Cluster-B, Fig. 2) and our outbreak (Cluster-A, Fig. 2) was between 4-bp and 8-bp over an entire genome of over 4 million bp [17]. The low number of SNP variation between our

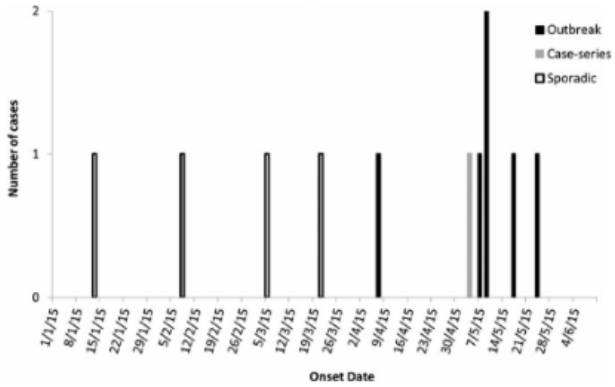

Fig. 3. Epidemiological curve of *S.* Agona cases (Cluster-A) identified from NSW, Australia with an onset date between January and June 2015.

outbreak isolates and strains recovered from the raw chicken meat suggests that these different isolates may share a common source of origin, such as a single producer or processor of chicken meat. In light of the specific food hygiene and food safety defects identified at Sushi-B by the NSW DPI, we hypothesise that there could have been a breakdown of proper hygiene protocol at the implicated sushi outlet while processing contaminated raw chicken meat. This breakdown of proper hygiene resulted in the cross-contamination of the cooked tuna mix and/or containers used exclusively for storage of this product. *S.* Agona is commonly associated with poultry and poultry products [5], and has a considerable ability to form biofilms on plastic materials [11]. The resistant and persistent nature of *Salmonella* within biofilms [36] may provide some insight for the extended duration of this localised contamination issue at the sushi outlet. Another possible source for cross-contamination could have been an ill staff-member at Sushi-B. However, without supporting clinical or microbiological evidence from this ill staff-member, it remains uncertain whether this staff member was the source of contamination at Sushi-B, or an additional undiagnosed case linked to this outbreak.

Based on epidemiological results, the duration of this point-source contamination event at Sushi-B was reported to be between 7 April and 24 May 2015. However, as indicated by the clustering of sporadic-clinical isolates within Cluster-A (Fig. 2), this point-source contamination issue may have started earlier than first suspected (Fig. 3). This hypothesis was unable to be investigated further during the investigation, as these additional cases linked to the outbreak by WGS were notified with *S.* Agona between 6 and 8 months prior to the WGS-based analysis. Any epidemiological information obtained from these additional cases at the time of this outbreak investigation would have been unreliable due to poor recall of food consumption more than half a year ago. If these additional cases had been interviewed at the time of their illness (as all notified cases of *Salmonella* are not routinely interviewed by NSW Health), it may have been possible to link them to the outbreak at Sushi-B, or obtain additional information to help identify the original source that led to the cross-contamination event at Sushi-B.

The probability of a *Salmonella* infection to the consumer from contaminated foods is related to the infectious dose ingested by the person. It is estimated that a person is required to ingest 100–1000 bacteria to initiate an infection, with a 10–20% chance of infection related to 100 organisms (model-based prediction) and a 60–80% chance related to 10 000-fold increase of organisms [3]; furthermore, PPIs (Proton Pump Inhibitors) appear to increase the susceptibility of an individual to *Salmonella* [37]. During this outbreak, the low number of cases identified may have been a result of a highly variable organism counts within the contaminated cooked tuna mix. It is possible that following the original cross-contamination event, the infrequent number

of notified cases could have been related to mixing and/or diluting of cooked tuna mix between batches; from inadequate cleaning and sanitising of storage containers used exclusively for the cooked tuna mix; or from mild illness where the patient did not seek medical attention.

Pulse-field gel electrophoresis (PFGE) and multilocus variable-number tandem-repeat analysis (MLVA) have been commonly used for analysis of *Salmonella* outbreaks [29]. PFGE has been the 'gold standard', with high discriminatory power and established guidelines for interpreting banding patterns; however, remains relatively slow, labour intensive and produces results that are subjective to interpretation [26, 29]. When available for individual serotypes, MLVA is fast, high-throughput, highly discriminatory and provides results that can be harmonised between laboratories [26, 27, 29]. While MLVA has become the standard method for strain typing of *Salmonella* Typhimurium in Australia, there is no established MLVA scheme for less common serovars such as *S.* Agona. In contrast, WGS provides ultimate discriminatory power and an additional ability to infer the timeline of an outbreak, with the potential to replace routine strain typing methods in the future.

During this outbreak investigation, we demonstrated the significant potential for WGS to assist with routine epidemiological investigations, particularly with regards to the prevention of further cases through timely identification of the outbreak source (assuming WGS was routine) and important insights into the contamination timeline. This will fundamentally change the epidemiological understanding of transmission dynamics, and open up new, more targeted strategies for disease control and prevention [26]. Even for this investigation where the final results for the WGS analytical component were not available until 8 weeks following the lifting of the prohibition order at Sushi-B (Fig. 1), the information has been valuable in better understanding the epidemiology of the outbreak. Use of this technology will become more applicable to real-time investigations in the future as speed of sequencing of bacterial genomes improves from weeks and days to perhaps hours [29, 38].

There are significant challenges associated with application of WGS to public health surveillance. Standardisation of testing and reporting, data sharing and governance, and the bioinformatics infrastructure capable of handling large volumes of data are among the most urgent ones [26]. Costs are also an issue when considering the inclusion of WGS as part of outbreak investigations (especially when WGS costs are additional to the costs of conventional laboratory methods), and are not necessarily affordable for routine use. In time, WGS has the potential to allow epidemiological hypotheses to be tested in near real-time, supporting enhanced management and control of communicable diseases and effective public health action [26]. With declining costs, improved speed of WGS and minimising the number of laboratory tests conducted, this modern technology will have a more permanent role within routine surveillance of notifiable diseases, with high-quality data influencing decision-making and action during an outbreak investigation.

Limitations of this outbreak investigation should be noted. They included poor recall of some cases and surrogates during interviews, a low sample size for the epidemiological investigation, and the descriptive nature of the epidemiological study. This descriptive study measured the occurrences of outcomes rather than incorporating an analytical design that could investigate associations between exposures and outcomes. WGS analysis was completed after the outbreak was concluded, and it was not ideal to follow-up the additional cases within Cluster-A due to the time that had lapsed. Also, due to the passive nature of the notification surveillance system in NSW, this investigation was biased towards people with more severe illness, who were more likely to be tested and had a positive culture. In spite of these limitations, our findings present strong evidence of a traditional epidemiological investigation supported by high-throughput sequencing technology, which implicated a single sushi outlet as the source of this outbreak, and assisted with the hypothesis that this outbreak was caused by cross contamination from raw chicken.

CONCLUSION

This multidisciplinary outbreak investigation was responsible for correcting various hygiene and food safety control defects identified at a sushi outlet. This outlet was responsible for a point-source foodborne outbreak of *S.* Agona in western Sydney, Australia between April and June 2015. The high-throughput genome sequencing was also utilised retrospectively and identified additional cases that may have been linked to the outbreak, extending the timeframe of the outbreak and providing additional insight as to the possible source for the outbreak. The genomics-enhanced public health action added value to the descriptive epidemiological investigation

and will most certainly play an increasing role in public health surveillance of foodborne diseases, especially as costs of this technology becomes more acceptable and turn-around times of testing are reduced.

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DECLARATION OF INTEREST

None.

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