Applied epidemiology of communicable and non-communicable diseases, Victoria, 2016–2017

A thesis submitted for the degree of Master of Philosophy (Applied Epidemiology) of The Australian National University

November 2017

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This research is supported by an Australian Government Research Training Program (RTP) Scholarship.

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Originality statement

'I hereby declare that this submission is my own work and that to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at ANU or any other educational institution, except where due acknowledgement is made in the text. Any contribution to the research by others, with whom I have worked at the Murdoch Childrens Research Institute or the Victorian Government Department of Health and Human Services or elsewhere, is explicitly acknowledge 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.'

Rosemary Jean Wright

10 November 2017

For Jean Walmsley, née Lang, my Nanna, and infectious disease nurse at The Prince Henry Hospital of Sydney in the 1930s.

1908 to 1999

Acknowledgements

I would like to thank my field supervisors Lucinda Franklin, Nicola Stephens, Anne-Louise Ponsonby, and my academic supervisor Katrina Roper. Thank you for your guidance, encouragement and support.

I also thank Tanyth de Gooyer, my unofficial supervisor, mentor and friend, for all her assistance during 2017, and my fellow MAE Scholars, especially Siobhan St George, Julie Collins, Katherine Todd for helping me through the tough times and making the MAE such an enjoyable experience.

And last but not least, my family, including my mother Jennifer Wright for hours of proofreading, my father Barry Wright for his belief in me, and most of all my partner Steven Seguna, for disrupting his life to enable me to undertake the MAE, putting up with the late nights and just being there for me.

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Abbreviations

AIR	Australian Immunisation Register
ABS	Australian Bureau of Statistics
ANU	Australian National University
ASPREN	Australian Sentinel Practices Research Network
CDC	Centers for Disease Control and Prevention (USA)
CDES	Communicable Disease Epidemiology and Surveillance Unit
CDNA	Communicable Disease Network Australia
CDPC	Communicable Disease Prevention and Control
CI	Confidence Interval
DEDJTR	Department of Economic Development, Jobs, Transport and Resources
DHHS	Victorian Government Department of Health and Human Services
E. coli	*Escherichia coli*
EHO	Environmental Health Officer
ERP	Estimated resident population
FluCAN	Influenza Complications Alert Network
GP	General practitioner
HREC	Human Research Ethics Committee
HUS	haemolytic uraemic syndrome
ICU	Intensive Care Unit
IgE	immunoglobulin E
IRSD	Index of Relative Socio-Economic Disadvantage for Area
IQR	interquartile range
LFF	Lessons from the field
MAE	Master of Philosophy in Applied Epidemiology

MACS	Melbourne Atopy Cohort Study
MAS	German Multicenter Atopic Study
MDU	Microbiological Diagnostic Unit Public Health Laboratory
MCRI	Murdoch Childrens Research Institute
MLVA	Multiple Locus Variable-number Tandem Repeat Analysis
mg/ml	milligrams per millilitre
NNDSS	National Notifiable Disease Surveillance System
NISC	National Influenza Surveillance Committee
OR	Odds ratio
PAEDS	Paediatric Active Enhanced Disease Surveillance
PARIS	Pollution and Asthma Risk Infant Study
PCR	polymerase chain reaction
PHESS	Public Health Event Surveillance System
PHLN	Public Health Laboratory Network
PHO	Public Health Officer
SEIFA	Socio-Economic Indexes for Areas
SD	standard deviation
STEC	Shiga toxin-producing *Escherichia coli*
STm	*Salmonella* Typhimurium
VAED	Victorian Admitted Episodes Dataset
WHO	World Health Organization
WHO CCRI	World Health Organization Collaborating Centre for Reference and Research on Influenza
VPDC	Victorian Perinatal Data Collection

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Abstract

In this thesis, I present the projects and activities I have undertaken as a Master of Philosophy in Applied Epidemiology (MAE) Scholar in Victoria between February 2016 and November 2017. I was placed with the Environmental and Genetic Epidemiology Research Group at the Murdoch Childrens Research Institute (MCRI), and the Communicable Disease Epidemiology and Surveillance Unit at the Victorian Department of Health and Human Services (DHHS). At MCRI I worked on the Barwon Infant Study, a birth cohort study designed to investigate how early life environment can influence the development of immune disorders and neurodevelopmental outcomes. At DHHS, I had the opportunity to lead an outbreak investigation, undertake an evaluation of a public health surveillance system, and an epidemiological study. Through these placements I experienced the day-to-day activities of a research institute and a state public health unit.

At MCRI I conducted a data analysis on the prevalence of aero-allergen sensitisation in infancy in the Barwon region in Victoria. Sensitisation to aero-allergens in infancy is considered rare and as a result few studies report the prevalence in infants. My data fills this gap in the literature using data from a population-derived cohort study. I reported the findings of this study at the Training Programs in Epidemiology and Public Health Interventions Network Global Scientific Conference, and the Australasian Epidemiological Association Conference in 2017.

My surveillance evaluation involved the first stakeholder consultation of the Influenza Complications Alert Network (FluCAN), which was established in 2009 as part of Australia's response to the A(H1N1/09) pandemic in order to provide sentinel surveillance of influenza requiring hospitalisation. As part of the evaluation I made a number of recommendations to improve the usefulness and operation of the surveillance system many of which have already been implemented. I presented the outcomes of this evaluation to key stakeholders at the annual National Influenza Surveillance Committee in 2017.

I conducted an epidemiological study on Shiga toxin-producing *Escherichia coli* (STEC) using 15 years of Victorian data. The primary aims of this project were to describe the epidemiology of STEC in Victoria and to investigate the length of exclusion of cases in

'high-risk' groups (including food handlers, child and health care workers, and children attending child care) by diagnostic method. The results of this study will inform Victoria's policy regarding the exclusion of cases in these 'high-risk' groups from workplaces and child care.

I also conducted an outbreak investigation, including a case-control study in order to identify the source of an outbreak of *Salmonella* Typhimurium at a Melbourne café. The results of the case-control study indicated that hollandaise sauce was the likely cause of the outbreak and led to public health action. The high proportion of cases hospitalised in this outbreak demonstrates the serious health implications of salmonellosis and the potential consequences of deficient storage and food handling processes for high-risk food products such as hollandaise sauce.

In this thesis, I present my experience of the MAE program, and demonstrate my fulfillment of the requirements of the program and the contribution my work has made to public health in Victoria.

Chapter I:

Summary of field experience

Applied epidemiology of communicable and non-communicable disease, Victoria, 2016–2017

Field placement

My field placement for Master of Philosophy in Applied Epidemiology (MAE) was shared between the Environmental and Genetic Epidemiology Research Group at the Murdoch Childrens Research Institute (MCRI) in my first year, and the Communicable Disease Epidemiology and Surveillance Unit at the Victorian Department of Health and Human Services (DHHS) in my second year. This gave me the opportunity to explore epidemiology of both communicable and non-communicable diseases as part of the MAE.

MCRI

The role of the Environment and Genetic Epidemiology Research Group (the Group) at MCRI is to improve the prevention of non-communicable diseases including immune disorders such as type 1 diabetes and food allergies. The Group aims to better understand the interplay between genetic and environmental factors which may contribute to the increase in prevalence of these conditions. This is being investigated using the Barwon Infant Study (BIS), a major birth cohort study conducted by Barwon Health in collaboration with MCRI and Deakin University. The BIS commenced in June 2010 with the recruitment of pregnant women attending antenatal appointments at the Geelong Hospital and St John of God Hospital where 90% of births in the Barwon region (a geographically defined region in the South West of Victoria) occur. This prospective study includes mothers and their infants and intends to follow infants to school age. The study involves the collection and testing of bio-specimens from mothers and infants, physical reviews of infant health and development, skin-prick-testing for the diagnosis of allergies, and parental questionnaires.

My placement with the Group represents the first MAE placement at MCRI outside of the International Child Health Group. MCRI created this MAE placement with the primary focus to investigate the association between prenatal exposure to plastic product chemicals (i.e. bisphenols which are used in the manufacture of hard, clear plastics and in epoxy resins sometimes used in the lining of metal cans, and phthalates which are used as plasticisers in food packaging and as solvents in cosmetic products such a nail polishes and fragrances) and the development of food allergy in 12-month-old-infants from the BIS cohort. This was to be the basis of both my data analysis and epidemiological study. Unfortunately, the laboratory measurement of bisphenol and

phthalate levels in maternal urine samples was not completed during the term of my placement at MCRI. While I made a substantial contribution to the ground work for this project including a literature review, analysis of preliminary data, and development of datasets, I was not able to complete this project as originally planned.

Seeking to take advantage of access to data from a large cohort study in order to gain epidemiological experience, I instead worked with MCRI colleagues to initiate a project focusing on the prevalence of sensitisation to aero-allergens in 12-month-old infants in the Barwon region, which is presented in Chapter II. This gave me valuable experience in turning raw data into variables for analysis, and developed my understanding of allergies and different statistical approaches to missing data.

The change to the subject and timing of my projects meant my placement at MCRI was sometimes challenging, particularly as the shared nature of my placement meant that I couldn't move onto the next project while waiting for data. I was, however, able to gain insight and have involvement in other activities associated with working at a research institute on a large cohort study.

DHHS

The Communicable Diseases Epidemiology and Surveillance Section (CDES) is part of the Health Protection Branch at DHHS. The purpose of this Branch is to reduce the incidence of preventable disease by protecting the community against hazards resulting from, or associated with, communicable disease, food, water or the environment. CDES is responsible for the daily surveillance of notifications of communicable disease, the monitoring and analysis of notifications over time, the reporting of communicable disease data, and for the management and quality of communicable disease data. Epidemiologists working in the section are required to maintain a detailed understanding of the epidemiology of diseases under surveillance to ensure detection of outbreaks and notifications of importance. CDES also provides epidemiological support to other areas of the Health Protection Branch including the provision of data to inform the development of public health prevention and control programs.

My placement at with CDES gave me hands-on experience of jurisdictional public health activities as well as the opportunity to undertake disease surveillance and cluster and outbreak investigations. I was also able to use connections established by

DHHS with key surveillance partners such as the Commonwealth Department of Health and Prof Allen Cheng, Director of Australia's Influenza Complications Alert Network (FluCAN), to expand my knowledge of surveillance at a national level.

The projects Chapters III, IV and V present the key activities I conducted at DHHS in the second year of my MAE.

Summary of requirements

The field projects that I completed as part of the core requirements of the MAE are summarised in Table 1. Further details are presented in the Abstract of this thesis and in Chapters II–V.

I presented one of my MAE projects (Chapter II) at two conferences in 2017:

- 9th Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET) Global Scientific Conference in Chiang Mai, Thailand.
- Australasian Epidemiological Association (AEA) Annual Scientific Meeting, Sydney, Australia.

A manuscript based on the case-control study of *Salmonella* Typhimurium at a Melbourne café that resulted in the hospitalisation of a high proportion of cases and has been drafted and is ready for submission to the *Communicable Diseases Intelligence* journal. I also developed a communication on improvements to hospital reporting of the timeliness of hepatitis B birth dose for Victorian infants.

I developed a 'lesson from the field' based on my experiences working with longitudinal data at MCRI, and also contributed to teaching of first-year MAE Scholars at their initial course block at the Australian National University.

Table 1: Summary of completion of core MAE requirements

	Data analysis	Evaluation of a surveillance system	Epidemiological study	Outbreak investigation	Conference presentation	Late draft of an article for publication	Communication for a lay audience	Teaching activities
Chapter II: Prevalence of aero-allergen sensitisation in infancy	✓				✓			
Chapter III: Evaluation of Australia's Influenza Complications Network	✓	✓						
Chapter IV: Epidemiology of STEC and exclusion of high-risk cases	✓		✓					
Chapter V: An outbreak of salmonellosis with a high proportion of hospitalised cases	✓			✓		✓		
Appendix A							✓	
Appendix B								✓

Other placement activities

In addition to the projects undertaken to fulfil the core requirements of the MAE, I undertook a number of other activities which contributed to the work of my placements.

At MCRI I completed a literature review to investigate the evidence for an association between prenatal exposure to phthalates and bisphenols and allergic disease. This was intended to inform my own epidemiological study on this topic, however, as previously explained, this was not completed during the term of my placement at MCRI. The literature review is being used by researchers in the Barwon Investigator Group who will undertake the study when the final laboratory data becomes available. I also analysed the preliminary laboratory data to identify factors which affect the level of these chemical in urine samples, such as the time of the day the sample was collected and the type of container samples were stored in (amber glass or polypropylene storage tubes). In addition, I contributed to the development of the BIS reference dataset, a collection of standard covariates for the cohort study, such as parental use of household chemical products and area of residence using the Australian Bureau of Statistics (ABS) Statistical Area Level 1. This involved cleaning data, recoding data to account for changes in the way in which questions were asked over time, and suggesting improvements to the design and wording of questionnaires.

At DHHS I contributed to a number of cluster investigations including a number of *Salmonella* Mississippi cases which were related to interstate and overseas travel, and a larger cluster of *Salmonella* Typhimurium cases with a common Multiple Locus Variable-number Tandem Repeat Analysis (MLVA) profile. I also investigated a suspected norovirus outbreak at a wedding and identified an outbreak of *Salmonella* Typhimurium amongst dinners at a restaurant while undertaking active case ascertainment for another outbreak of the same pathogen associated with a different venue. This enabled the relevant Council to undertake rapid public health action to prevent further illness.

More broadly, I also developed my understanding of the notification requirements for blood-borne viruses, sexually transmitted infections, mycobacterial infections (tubercular and non-tubercular) by assisting with the daily assessment of laboratory

and doctor notifications to determine their priority level for follow-up by public health officers.

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Chapter II:
Analysis of a dataset

Prevalence of aero-allergen sensitisation in infancy, Barwon region, Victoria, Australia, 2011–2015

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Prologue

Preface

During my time at the Murdoch Childrens Research Institute (MCRI) I had the opportunity to contribute to, and work with, data from the Barwon Infant Study (BIS). BIS is a prospective cohort study conducted by Barwon Health in collaboration with MRCI and Deakin University which commenced recruitment in June 2010. It is designed to investigate the relationship between early life environmental exposure and non-communicable disease including allergy, neurodevelopment and cardiovascular health. While working on the study I took a particular interest in aero-allergen sensitisation, an area which has commanded less attention than food allergy in recent years but has become more prominent since the thunderstorm-related asthma incident in Melbourne and surrounding areas in November 2016.

This chapter describes an analysis of the aero-allergen data collected in the Barwon Infant Study in order to determine the prevalence of sensitisation in 12-month-old infants.

Project role

Skin-prick-tests for food and aero-allergens had already been carried out on 12-month-old infants enrolled in BIS. Data on food allergens had already been cleaned, analysed and reported as part of a case cohort study on vitamin D insufficiency and challenge-proven food allergy, however, the aero-allergen data had not yet been addressed.

As the lead investigator on this project, I cleaned the raw aero-allergen skin-prick-test data, researched and set criteria for defining aero-allergen sensitisation, and carried out the data analysis.

Lessons learnt

Working with data from BIS gave me the opportunity to learn about the collection of data in longitudinal studies and some of the challenges associated with this type of study such as the development of well-designed questionnaires, maintaining consistency in questions across time points, the management of large datasets, and attracting the grant funding needed to continue studies.

Analysis of the aero-allergen dataset in particular gave me experience in cleaning data, developing and applying case definitions and calculating prevalence rates. I also learnt

about different approaches to dealing with missing data including inverse probability weighting which I applied in this data analysis project.

Public health impact

While a number of Australian population-derived studies have reported the prevalence of food sensitisation in infants, little data are available on the prevalence of aero-allergen sensitisation. Existing data in the Australian context comes from a study of infants who are at high-risk of allergy. This data analysis fills a gap in data on the prevalence of aero-allergen sensitisation in infants using data from a population-derived birth cohort.

Data from the study will also be used in future BIS studies investigating the increase in aero-allergen sensitisation in infants from the first year of life to pre-school, and the relationship between aero-allergen sensitisation in early life and lung function.

Communication

I presented the initial findings of this data analysis as an oral 'iPoster' at the 9th Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET) Global Scientific Conference in Chiang Mai, Thailand, 2017; and the Australasian Epidemiological Association (AEA) Annual Scientific Meeting, Sydney, Australia, 2017 (Appendix II.A and 11.B respectively).

Master of Applied Epidemiology core requirement

This chapter is written in fulfilment of the field placement core activity to undertake an analysis of a public health dataset.

Acknowledgments

This analysis could not have been completed without assistance from Angela Pezic, who spent copious amounts of time introducing me to BIS and data analysis in Stata, and Mari Sasaki, who was also conducting an allergy prevalence study at MCRI and provided me with a practical example of inverse probability weighting.

Abstract

Background: Aero-allergens are airborne substances which can trigger flares of asthma, hay-fever and eczema in sensitised individuals, although sensitisation to aero-allergens in infants is considered to be rare. As a result, few population-derived studies report the prevalence of aero-allergen sensitisation in infancy. The objective of this study was to describe the prevalence of sensitisation to aero-allergens in 12-month-old infants in the Barwon region, Victoria.

Methods: Skin-prick-test data for 12-month-old infants were collected between 2011–2015 from a population-derived birth cohort in the Barwon region, Victoria, and analysed to determine the prevalence of aero-allergen sensitisation. Infants were defined as sensitised if they had a wheal size of ≥ 2mm to any of aero-allergens tested. Inverse probability weighting was applied to adjust for the distribution of risk factors for allergy between participants who underwent skin-prick-testing compared with non-participants combined with infants who participated in the study but did not undergo skin-prick-testing.

Results: Of those invited to participate in the study, 1074 infants were recruited into the study and a further 2869 mothers did not agree to participate. Among infants who participated in the study, 78.7% (845/1074) underwent skin-prick-testing. The adjusted prevalence of sensitisation to at least one aero-allergen tested after application of inverse probability weighting was 4.1% (95% CI 2.8–5.9). The prevalence of sensitisation to cat was 1.8% (95% CI 1.0–3.2); dust mite 1.5% (95% CI 0.8–2.7); rye grass 0.8% (95% CI, 0.4–1.8); dog 0.5% (95% CI 0.1–1.6); and mould 0.4% (95% CI 0.1–1.4).

Conclusion: The estimated prevalence of aero-allergen sensitisation in 12-month-old infants in the Barwon region of Victoria was 4.1%. This is lower than the prevalence of food sensitisation at the same age as reported in a previous study of data from the same cohort, but not negligible. The prevalence of aero-allergen sensitisation is lower than that reported in a previous Australian cohort study of children at high-risk for allergy. Data from this population-derived study fills a gap in Australian data from population-derived studies reporting the prevalence of sensitisation to aero-allergens in infants and may help inform testing practices.

Background

Allergy and sensitisation

Allergens are substances which can cause an allergic reaction by triggering an immune response.[1] Allergens can be broadly categorised into inhalant (aero) allergens such as pollen and dust mites, ingestion allergens such as foods or drugs, and contact allergens such as nickel, although some allergens may act through multiple routes. For example, food allergens are primarily ingested but may be inhaled if aerosolised, and aero-allergens may exacerbate eczema through inhalation or through direct skin contact.[2] Aero-allergens can be further categorised into indoor allergens such as dust mites and cat and dog dander, and outdoor allergens including grass pollens such as rye grass. Other aero-allergens such as specific species of mould can commonly occur both indoors and outdoors.[3]

Allergen-induced allergic reactions can be classified by their immune mechanism into those mediated by immunoglobulin E (IgE) antibodies, which are more common, non-IgE-mediated allergy such as in Coeliac disease, and mixed IgE and non-IgE-mediated allergy which can involve both of these mechanisms.[4, 5] IgE-mediated reactions occur when IgE antibodies bind to allergens and then mast-cells, triggering the release of inflammatory mediators including histamines, a process referred to as sensitisation.[5] Once sensitised, individuals are primed to react to allergens to which they are sensitised. Onset of symptoms is usually rapid and includes eczema and rashes; hives; abdominal pain; vomiting; swelling of the lips, eyes and face; and in severe cases anaphylaxis.[5] The study described in this chapter focuses on IgE-mediated sensitisation to aero-allergens.

Skin-prick-testing and allergen specific serum IgE tests indicate whether a person has an IgE-mediated sensitisation to a specific allergen. However, sensitisation may occur without triggering allergic symptoms[4] in individuals. As a result, these tests indicate whether individuals are sensitised to allergens rather than having confirmed allergy.

Skin-prick-testing is a convenient and rapid method of allergy testing. Test results are available within 20 minutes.[6] Skin-prick-tests only cause mild discomfort and are well tolerated even by infants, but must be performed by health professionals who are able to respond to allergic reactions which may result from testing.[6] Where skin-prick-testing is not available, or is not suitable in the case of severe skin conditions or use of

antihistamines, blood tests for allergen specific serum IgE may be undertaken, however, skin-prick-testing is more sensitive and is considered the gold standard for diagnosis of aero-allergen sensitisation.[6, 7]

Public health importance

Aero-allergens can trigger flares of eczema[2], allergic rhinitis or allergic asthma[8] in sensitised individuals. Allergic diseases are estimated to cost $7.8 billion per year in direct and indirect medical costs and lost productivity in Australia.[9]

Allergic reactions in sensitised individuals vary in severity but can be fatal as demonstrated in the thunderstorm-related asthma incident in Melbourne and surrounding areas in November 2016. Nine deaths resulted from this incident and around 10,000 people presented at emergency departments in metropolitan Melbourne and Geelong.[10] Thunderstorm-related asthma is thought to occur when weather changes cause a large amount of pollens, likely from rye grass, to rupture and be inhaled, causing asthma attacks in people who are sensitised to rye grass or who have propensity to asthma and are affected by the particulate matter.[10-12]

Identification of sensitisation to aero-allergens is important to allow sensitised individuals to avoid exposure to triggers, or seek immunotherapy to reduce sensitisation to specific allergens where available. However, there are few studies reporting aero-allergen sensitisation rates in infants as sensitisation to aero-allergens is generally accepted to be rare in early childhood and to develop later than food allergen sensitisation.[13-15] Recent studies of infants as young as 12 months of age have reported a high prevalence of aero-allergen sensitisation and have challenged the acceptance that aero-allergens are rare in in early childhood.[16, 17] However, these studies are based on data from cohorts of children at high-risk of allergy such as the Melbourne Atopy Cohort Study (MACS).[16, 18] As a result, there is a gap in the literature data on the prevalence of aero-allergen sensitisation in infancy using population-derived cohort studies in Australia.

Objective

The objective of this study was to describe the prevalence of sensitisation to aero-allergens in 12-month-old infants in the Barwon region, Victoria.

Methods

BIS is a prospective population-derived cohort study (n=1074 infants) with antenatal recruitment conducted in the Barwon region in Victoria, designed to investigate the relationship between early life environmental exposures and non-communicable diseases including allergy.[19] The Barwon region is a Statistical Division (a geographical area defined under the Australian Standard Geographical Classification) in Victoria that encompasses Geelong and includes metropolitan, rural and coastal areas (Figure 1).[19]

There are approximately 3000 live births each year in the Barwon region.[19] Pregnant women attending antenatal appointments held at approximately 15 weeks of pregnancy at hospitals where 90% of these births occur were invited to participate in the study.[19] Recruitment occurred over a three-year period, commencing in June 2010 and ending in June 2013.[19] At baseline (the starting point at which the data collection commenced for infants), 1074 infants were recruited into the cohort (participants). A further 2869 mothers did not agree to their infants' participation in the study (non-participants).[19] Mothers who declined to participate were asked questions related to risk factors for allergy including family history of asthma and eczema, and household size.[19] Residential postcode was also collected in order to ascertain socio-economic status and remoteness by area. The cohort including eligibility criteria, full baseline characteristics, schedule of participant questionnaires and physical reviews, has been previously described in detail.[19]

Figure 1: Map of Victoria highlighting the Barwon region*

* Map adapted from the Australian Bureau of Statistics (ABS)[20]

Skin-prick-testing

Skin-prick-tests were carried out on 12-month-old infants, with infants undergoing testing for five aero-allergens, dust mites (*Dermatophagoides pteronyssinus*), cat, dog, rye grass and mould (*Alternaria tenuis*). Infants also underwent skin-prick-tests for five food allergens, raw egg, cow's milk, peanut, cashew and sesame, the results of which have already been reported.[21, 22] A positive (10mg/ml histamine) and negative control (saline) was also administered. Skin-prick Quintip® lancets were used to administer the allergen on the backs of infants.[21] After 15 minutes the results were read using a ruler to measure the mean diameter of the wheal (a raised inflamed area of the skin at the test site).

Case definition

Infants with an aero-allergen wheal size of at least 2mm greater than the negative control in the presence of a positive histamine control were defined as being sensitised to an aero-allergen.

The absence of development of a wheal in response to the positive control indicates that an infant may have been given antihistamines prior to testing or have non-reactive skin which invalidates testing. Infants without a wheal for the positive control

were considered to have an invalid test and their results were excluded. The negative control was used as some infants develop a small wheal in reaction to the skin-prick itself. Therefore, a wheal of at least 2mm greater than the negative control was required in order to be considered positive.

Statistical analysis

Data management and analysis was performed using Stata 14.1 for Windows (StataCorp LP, College Station, TX, USA). The observed prevalence of sensitisation to aero-allergens was calculated as the observed proportion with confidence intervals (CI) on the basis of a binomial sampling distribution.

Differences between participants who underwent skin-prick-testing as compared with the combined group of non-participants and participants who did not undergo skin-prick-testing were investigated using the chi-squared test for binary or categorical variables and the Wilcoxon rank sum test for continuous variables. A sensitivity analysis was conducted to determine if the differences in the distribution of risk factors between participants and the combined group of non-participants and participants who did not undergo skin-prick-testing influenced the prevalence estimates using an inverse probability approach.[23] Weights were used to adjust the prevalence estimates to reflect the distribution of risk factors. The weights were the inverse of the probability of participation, obtained after fitting a logistic regression model with participation as the outcome and risk factors available for both groups as covariates.

Ethics

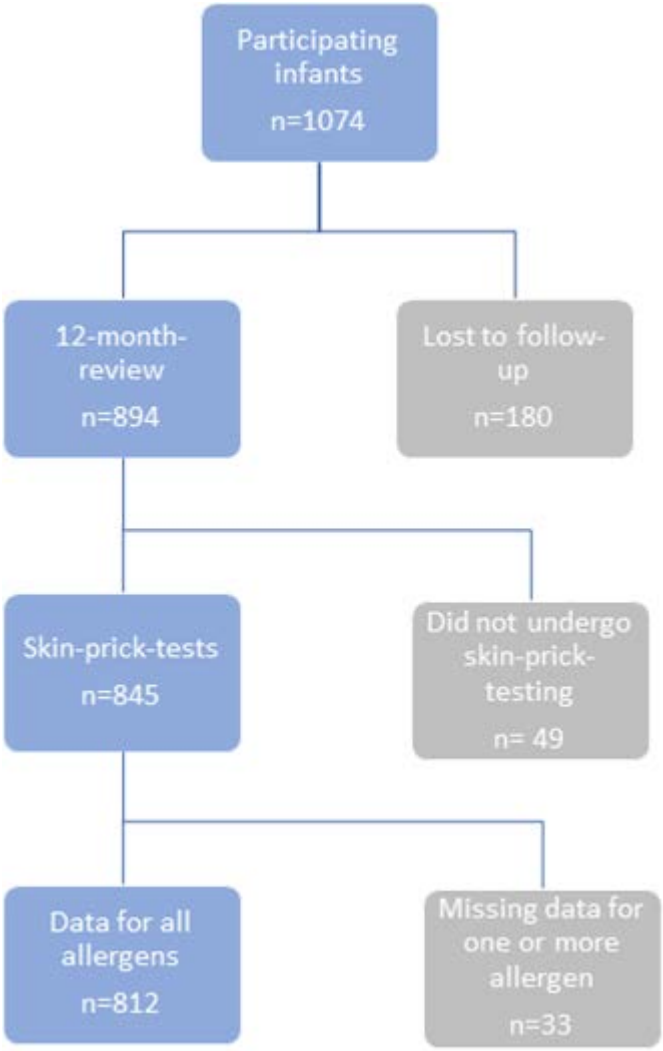
All mothers provided written informed consent. Ethics approval for BIS was obtained from the Barwon Health Human Research Ethics Committee (HREC, reference number 10/24) and ethics approval for this particular data analysis was obtained from the Australian National University HREC (reference number 2016/535).

Results

Participation

The cohort consisted of 1074 infants and as reported in previous publications, 894 of these infants completed the 12-month review[19, 21] and 845 underwent skin-prick-testing. Of those infants who underwent skin-prick-testing, 817 had a skin-prick-test result for at least one of the aero-allergens tested and 812 had a result for all aero-allergens (Figure 1).

Figure 2: Flow chart of the cohort participation



The majority of infants participating in the study at baseline were full-term (i.e. born between 37 and 42 weeks of gestation), had Australian born parents, and resided in major cities. The characteristics of the cohort at baseline and infants who underwent skin-prick-testing are described in Table 1.

Table 1: Characteristics of cohort at baseline and those undergoing skin prick testing

Characteristic	Skin-prick-test participants (n=845) No. (%)*	Baseline cohort (n=1074) No.(%)*
Sex of child		
Male	435 (51.5)	557 (51.9)
Female	410 (48.5)	517 (48.1)
Maternal age		
Mean (SD)	31.9 (4.5)	31.3 (4.8)
Maternal education		
Less than year 10 of high school	6 (0.7)	12 (1.1)
Year 10 of high school or equivalent	39 (4.6)	80 (7.5)
Year 12 of high school or equivalent	121 (14.3)	162 (15.1)
Trade, certificate or diploma	212 (25.1)	266 (24.8)
Bachelor degree	306 (36.2)	354 (33.0)
Postgraduate degree	158 (18.7)	194 (18.1)
Other	3 (0.4)	6 (0.6)
Maternal country of birth		
Australia	760 (89.9)	961 (89.50
Other	83 (10.1)	110 (10.2)
Unknown	2 (0.2)	3 (0.3)
Paternal country of birth		
Australia	726 (85.9)	915 (85.2)
Other	80 (9.5)	108 (10.1)
Unknown	39 (4.6)	51 (4.8)
Maternal smoking during pregnancy (any)		
No	732 (86.6)	892 (83.1)
Yes	106 (12.5)	169 (15.7)
Unknown	7 (0.8)	13 (1.2)
Number of people living in the family home		
Median (IQR)†	3 (1)	3 (2)
Family history of eczema		
Yes	389 (46.0)	480 (44.7)
No	435 (51.5)	568 (52.9)
Unknown	21 (2.5)	26 (2.4)
Family history of asthma		
Yes	420 (49.7)	542 (50.5))
No	412 (48.8)	512 (47.7)
Unknown	13 (1.5)	20 (1.9)
SEIFA tertile‡		
1 (most disadvantaged)	269 (31.8)	375 (34.9)
2	340 (40.3)	413 (38.5)
3 (least disadvantaged)	233 (27.6)	279 (26.0)
Unknown	3 (0.4)	7 (0.7)
Remoteness classification§		
Major cities	603 (71.4)	777 (72.4)

Inner/outer regional	241 (28.5)	294 (27.4)
Unknown	1 (0.1)	3 (0.3)
Gestational age at birth		
32 to 36 weeks	37 (4.4)	47 (4.4)
37 to 42 weeks	808 (95.6)	1027 (95.6)
Birthweight (kg)		
Mean (SD)	3.5 (0.5)	3.5 (0.5)

* Number and percentage unless otherwise specified
† Other than the infant
‡ ABS Index of Relative Socio-Economic Disadvantage for Areas[24]
§ ABS Remoteness Area[25]

Risk factors for allergy among the participating infants who underwent skin-prick-testing (n=845) were compared with those of non-participants (n=2869) combined with participants who did not undergo skin-prick-testing (n=229) (Table 2). Participating infants who underwent skin-prick-testing were more likely than non-participants and participants who did not undergo skin-prick-testing to have a family history of asthma or eczema. They were also less likely to reside in areas classified as major cities, and more likely to reside in areas of least socio-economic disadvantage. There was no significant difference in the number of people living in the family home.

Table 2: Comparison of risk factors for allergy of participants who underwent skin-prick-testing and non-participants and participants who did not undergo skin-prick-testing

Characteristic	Skin-prick-test participants (n=845) No. (%)*†	Non-participants and participants not undergoing skin-prick-tests (n=3018) No. (%)*†	*P* value
Family history of eczema			<0.001
Yes	389 (47.2)	453 (19.5)	
No	435 (52.8)	1865 (80.5)	
Family history of asthma			<0.001
Yes	420 (50.5)	628 (27.0)	
No	412 (49.5)	1694 (80.0)	
SEIFA tertile‡			<0.001
1 (most disadvantaged)	269 (31.9)	1055 (40.3)	
2	340 (40.4)	982 (37.5)	
3 (least disadvantaged)	233 (27.7)	580 (22.2)	
Remoteness classification§			0.05
Major cities	603 (71.4)	1972 (74.9)	
Inner/outer regional	241 (28.6)	661 (25.1)	
Number of people living in the family home¶			0.15
Median (IQR)	3 (1)	3 (2)	

* Percentages may differ from Table 1 due to the exclusion of missing data
† Number and percentage unless otherwise specified
‡ ABS Index of Relative Socio-Economic Disadvantage for Area[24]
§ ABS Remotes Area[25]
¶ Other than the infant

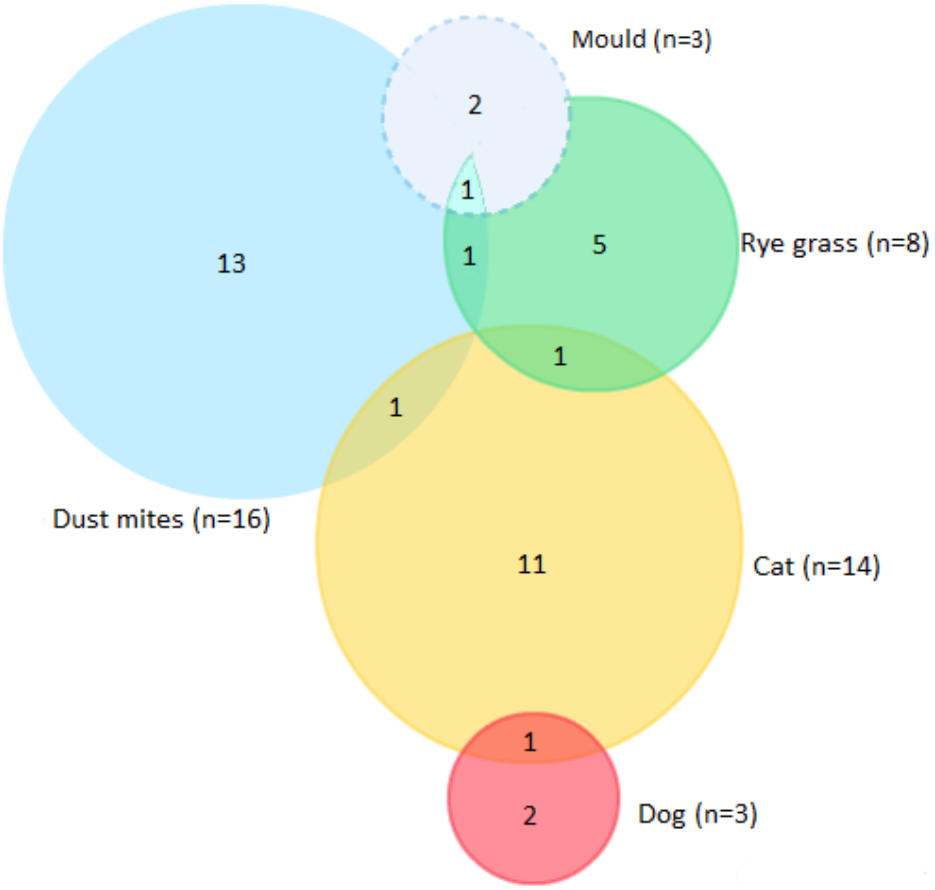
Prevalence of aero-allergen sensitisation

Skin-prick-test results for all the aero-allergens tested were available for 75.6% (812/1074) of infants participating in the study. Overall, 38 infants were sensitised to one or more of the aero-allergens tested and the observed prevalence was 4.7% (95% CI 3.4–6.4). House dust mites were the most common aero-allergen to which infants were sensitised (2.0%, 95% CI 1.2–3.2), followed by cat (1.7%, 95% CI 1.0–2.9) and rye grass (1.0%, 95% CI 0.5–2.0). Sensitisation to dog and mould were equally the least common allergens (0.4%, 95% CI 0.1–1.1; Table 3).

Among sensitised infants, 33 (86.8%) were sensitised to only one aero-allergen (mono-sensitised) and 5 (13.2%) were sensitised to two or more aero-allergens (poly-sensitised) as illustrated in Figure 3. The majority of poly-sensitised infants (4/5) were

only sensitised to one additional allergen. Two infants were sensitised to both dust mites and rye grass, and one of these infants was also sensitised to mould. No infants were sensitised to mould and rye grass or mould and dust mites alone.

Figure 3: Mono and poly-sensitisation to aero-allergens* (n=38)



* The number within the centre of the circles reflects the number of infants sensitised to that aero-allergen alone (mono-sensitised). The area where circles overlap reflects the number of infants who were sensitised to additional allergens (poly-sensitised).

Sensitivity analysis

As the comparison of infants who underwent skin-prick-testing and the combined group of non-participants and participants who did not undergo skin-prick testing indicated significant differences in the distribution of risk factors for allergy (Table 2), I conducted a sensitivity analysis using an inverse probability weighting approach.[23] Weighting was used to adjust for differences in the distribution of socio-economic status by area, family history of eczema and allergy, and remoteness area. This decreased the estimated prevalence of sensitisation to any aero-allergen from 4.7%

(95% CI 3.4–6.4) to 4.1% (95% CI 2.8-5.9). After inverse probability weighting was applied, cat became the most common aero-allergen to which infants were sensitised (1.8%, 95% CI 1.0–3.2), followed by dust mites (1.5%, 95% CI 0.8–2.7). Results for the observed and adjusted prevalence of all aero-allergens tested are in Table 3.

Table 3: Prevalence of allergen sensitisation

Aero-allergen tested	Number sensitised*	Observed prevalence % (95% CI)	Adjusted prevalence % (95% CI) †
House dust mite (*Dermatophagoides pteronyssinus*)	16/817	2.0 (1.2–3.2)	1.5 (0.8–2.7)
Cat	14/817	1.7 (1.0–2.9)	1.8 (1.0–3.2)
Rye grass	8/814	1.0 (0.5–2.0)	0.8 (0.4–1.8)
Dog	3/814	0.4 (0.1–1.1)	0.5 (0.1–1.6)
Mould (*Alternaria tenuis*)	3/812	0.4 (0.1–1.1)	0.4 (0.1–1.4)
Any aero-allergen	38/812	4.7 (3.4–6.4)	4.1 (2.8–5.9)

* Denominators differ for each specific aero-allergen tested as some allergens were not available for testing on all participants

† Weighted to adjust for differences between participants who underwent skin-prick-testing and non-participants combined with participants did not undergo skin-prick-testing on the following risk factors: socio-economic status by area, family history of eczema and allergy, and remoteness area

Prevalence of aero-allergen and food sensitisation

As already reported in BIS, 93 infants of the 803 infants tested for all food allergens were sensitised to at least one of the foods tested and the observed prevalence of sensitisation was 11.6% (95% CI 9.5–14.0).[21, 22] After applying inverse probability weighting to adjust for differences in risk factors between participants who underwent skin-prick-testing and non-participants combined with participants who did not undergo skin-prick-testing, the adjusted prevalence of food sensitisation was 10.2% (95% CI 8.1–12.7).

Among the 800 infants for whom data for both food and aero-allergen data was available, a total of 113 infants were sensitised to at least one of the foods or aero-allergens tested and the observed and adjusted prevalence was 14.2% (95% CI 11.9–16.7) and 12.5% (95% CI 10.2–15.2) respectively.

Discussion

This study describes the prevalence of sensitisation to aero-allergens in 12-month-old infants in BIS. The results support the finding of previous studies that aero-allergen sensitisation is less common in young children than sensitisation to foods, with a

weighted prevalence of sensitisation to any aero-allergen of 4.1% (95% CI 2.85-5.89), compared to 10.2% (95% CI 8.1–12.7) for sensitisation to any of the foods tested as calculated using previously reported data.[21, 22]

Cat was the most common aero-allergen to which infants were sensitised (1.8%, 95% CI 1.0–3.2), followed by dust mites (1.5%, 95% CI 0.8–2.7). Cat rather than dust-mites became the most common aero-allergen to which infants were sensitised after inverse probability weighting was applied, however, it should be noted that the confidence intervals overlap.

There are few relevant studies describing the prevalence of aero-allergen sensitisation in infancy to which the findings of this study can be compared. A higher prevalence of aero-allergen sensitisation in 12-month-old infants (18.5%) was reported in MACS despite testing for only three aero-allergens (cat, dust mites and rye grass) as compared to the five tested for in BIS.[26] However, MACS restricted eligibility to children with first degree relatives with allergic disease.[26] This is a risk factor for sensitisation to aero-allergens[27] and accordingly MACS could reasonably be expected to find a higher prevalence of sensitisation than a population-derived study such as BIS. While BIS participants were more likely than non-participants to have a family history of allergy, an allergic family history was not an eligibility requirement and, in anticipation of this bias, information was collected from non-participants in order to enable a sensitivity analysis.

Internationally, the German Multicenter Atopic Study (MAS) also found a higher prevalence of any aero-allergen sensitisation in 12-month-old infants (16%).[28] This may be due in part to the wider range of aero-allergens tested for (nine in total). Additionally, the MAS cohort included a high-proportion of children at high-risk of allergic disease.[28] However, of the specific aero-allergens also tested for in this study, a similar prevalence of sensitisation to cat (2.2%), house dust mite (0.8%) and dog (0.1%)[28] was found. The Pollution and Asthma Risk Infant Study (PARIS), a population-derived cohort study of 18-month-old infants in Paris and surrounding suburbs, also found similar rates of sensitisation to house dust mites (1.1%) and cat (1.1%) as found in this study.[29]

Differences in the prevalence of sensitisation to aero-allergen in this study compared to other studies are likely to be due to multiple factors. These include methodological

differences between studies such as the number of, and specific allergens tested for; the study population, such as selecting participants with a family history of allergy;[27] the method of testing, such as skin-prick-test or allergen specific serum IgE; and definitions of sensitisation such as wheal size or IgE antibody levels. Environmental and geographic differences between study sites may also influence the prevalence estimates. For example, a recent Australian study found that patterns of sensitisation to aero-allergens varied by coastal proximity, climate and urban versus rural location.[27] Demographic factors may also influence allergy. For example, studies found that children born in Australia to parents who were born in East Asia had an increased risk of peanut allergy and egg allergy.[30, 31] Similarly, a study of patients presenting to two emergency departments in Melbourne during the 2016 thunder-related asthma incident found that individuals with Asian and Indian ethnicity had higher rates of hay fever and were more likely to be affected by thunderstorm-related asthma.[32] Socioeconomic status has also been suggested as a risk factor for sensitisation to foods and aero-allergens.[33, 34] These methodological, environmental, geographic and demographic factors need to be considered when comparing the findings of different studies.

Strengths and limitations

In this study an aero-allergen skin-prick-test wheal size of at least 2mm greater than the negative (saline) control in the presence of a positive (histamine) was used to define aero-allergen sensitisation. In clinical practice a wheal size of at least 3mm greater than the negative control is commonly used, however studies have shown that reactions to skin-prick-tests are smaller in infants.[35] Therefore, 2mm was used in this study. This is consistent with recent Australia studies of both food and aero-allergen sensitisation in infants.[21, 26, 35]

A key strength of this study is the use of data from a population-derived cohort study based in the Barwon region. This region encompasses areas classified as major cities and regional or rural areas, as well as coastal and inland areas, which have been found to affect patterns of sensitisation to aero-allergens.[34] However, the study site was restricted to temperate areas and further studies which cover a variety of different climatic regions may produce different findings.[36] Additionally, compared to the Victorian population, the Barwon region has a lower proportion of residents who were

born overseas (26.2%[37] and 20.5%[38] respectively in 2011), which may somewhat limit the generalisability of the findings of this study given research which suggests that parental country of birth and ethnicity influence the risk of food allergy and aero-allergen sensitisation.[30-32]

A further potential limitation of this study is the low recruitment rate and loss of participants to follow up. Participants undergoing skin-prick-testing were more likely to have a family history of eczema and asthma, more likely to reside in areas of least socioeconomic disadvantage, and less likely to reside in major cities than non-participants and those not undergoing skin-prick-testings. These factors have been found to influence the risk of sensitisation to aero-allergens.[20, 27, 33]

On the basis of these differences I conducted a sensitivity analysis using an inverse probability weighting approach. The prevalence of sensitisation to aero-allergens was weighted on the basis of the distribution of risk factors for allergy in participants who underwent skin-prick-testing and non-participants combined with participants who did not undergo skin-prick-testing. This decreased the estimated prevalence slightly to 4.1%. Inverse probability weighting is a commonly used method to address bias induced by restricting analysis to available cases[39] and has been used in recent studies of the prevalence of food allergy in Australia.[21, 40, 41] Notwithstanding this, I could only include risk factors in the logistic model that had been collected from both groups, and further unmeasured differences may exist and influence the findings.

Repeat skin-prick-testing on 4-year-old BIS participants is currently being carried out. This will allow the investigation of the increase in aero-allergen sensitisation with age, and the relationship between aero-allergen sensitisation in early life and lung function.

Conclusions

This study estimates that the prevalence of sensitisation to aero-allergens in 12-month-old infants in the Barwon region is 4.1%. Consistent with the findings of a previous study of both food and aero-allergens in Australia,[26] the prevalence of sensitisation to aero-allergens found in this study is lower than the already reported prevalence of food sensitisation,[21, 22] but not negligible.

The findings of this study indicate a lower prevalence of sensitisation in 12-month-old infants than that reported in MACS, a cohort of children in Melbourne at high-risk of allergic disease.[26] Notwithstanding the lower prevalence of sensitisation to aero-

allergens found in this study, testing of infants with symptoms of allergic disease such as eczema, one of the most common manifestations of allergy in early childhood,[42] should be considered as informed by clinical history in order to allow the avoidance of allergens which may worsen symptoms. Exposure to cat, the most common allergen to which infants were sensitised (after the application of inverse probability weighting) can largely be avoided in the family home and measures to reduce exposure to other allergens such as dust mites can be taken.

The population-derived nature of BIS, and the selection of a study site that includes major cities and regional or rural areas, and coastal and inland areas, makes BIS a valuable source of information on the prevalence of aero-allergen sensitisation in infancy. Further studies which cover a range of climatic regions and areas with a higher proportion of individuals born overseas will further add to the understanding of the prevalence of aero-allergen sensitisation in infants.

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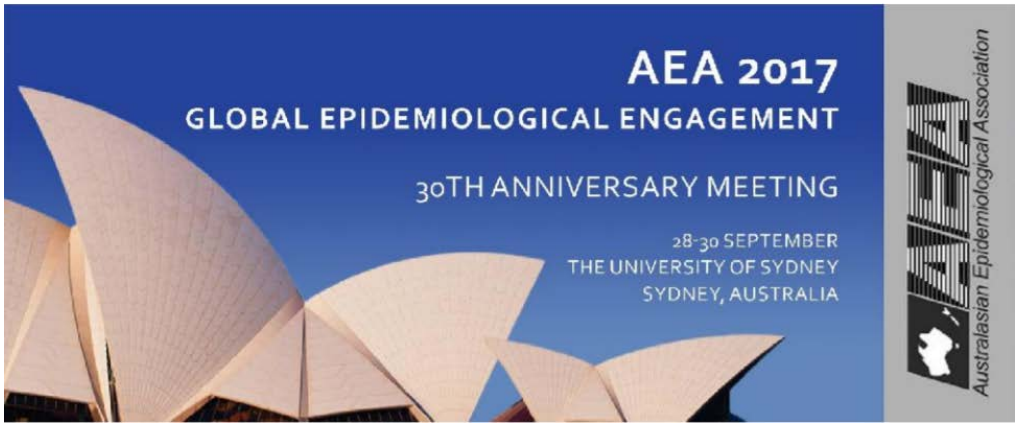
Appendices

Appendix II.A: Oral iPoster presented at the TEPHINET Global Scientific Conference, Chiang Mai, Thailand, 2017

Appendix II.B: Abstract of an oral presentation given at the AEA Annual Scientific Meeting, Sydney, Australia, 2017



Prevalence of aero-allergen sensitisation in infancy, Barwon Region, Victoria, 2011-2015

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Background: Aero-allergens can trigger flares of asthma, hay-fever and eczema in sensitised individuals, though sensitisation in infants is considered to be rare. As a result, few cohort studies report the prevalence of aero-allergen sensitisation in infancy. The recent thunderstorm-related asthma incident in Melbourne highlights the importance of identifying sensitised individuals. The objectives of this study were to describe the prevalence of sensitisation to aero-allergens and the association with eczema in 12-month-old infants in the Barwon Region, Victoria.

Methods: Skin-prick-test (SPT) data for 12-month-old infants were collected between 2011–2015 from a population-derived birth cohort in the Barwon Region, Victoria, and analysed to determine the prevalence of aero-allergen sensitisation. Infants were defined as sensitised if they had a wheal size of ≥2mm to the aero-allergens tested. Inverse probability weighting was applied to adjust for the distribution of risk factors for allergy between participants and non-responders. Eczema status was assessed at the 12-month physical review.

Results: SPT data were available for 817 of 1074 participating infants (76.1%). The adjusted prevalence of sensitisation to at least one aero-allergen was 4.2% (95% CI 2.9–6.0); cat 1.9% (95% CI 1.0–3.6); dust-mite 1.5% (95% CI, 0.8–2.6); rye grass 0.8% (95% CI 0.4–1.8); dog 0.4% (95% CI 0.1–1.4); and mould 0.4% (95% CI 0.1–1.4). The observed prevalence of eczema was higher among those sensitised to aero-allergens (39.5%) than infants overall (8.3%).

Conclusion: Our results indicate that aero-allergen sensitisation among infants is more common than widely held. Consideration should be given to testing infants with eczema or known risk factors.

Chapter III:

Evaluation of a surveillance system

Evaluation of Australia's Influenza Complications Alert Network

Table of contents

Prologue

Preface

Australia's Influenza Complications Alert Network (FluCAN), is a sentinel surveillance system which was established in 2009 as part of Australia's response to the A(H1N1/09) pandemic. The Centers for Disease Control and Prevention (CDC) recommends that public health surveillance systems be evaluated periodically in order to ensure that objectives are being met and that they are functioning efficiently and effectively.[1] While some aspects of FluCAN have been evaluated since it was established, to date no comprehensive stakeholder consultation has been undertaken. This chapter describes an evaluation of FluCAN, which aims to build on and supplement previous evaluations.

Project role

This evaluation of FluCAN was initiated by Prof Allen Cheng, Director of FluCAN, who identified the need for a stakeholder consultation of the surveillance system, and Lucinda Franklin, Victorian Government Department of Health and Human Services (DHHS) Vaccine Preventable Disease Epidemiologist, who identified the need to assess the representativeness of Victorian FluCAN data.

As two recent evaluations of FluCAN conducted in 2016 had covered the timeliness of data entry, validity of data and completeness of data fields, I did not seek to repeat these analyses but instead sought to complement them through a stakeholder evaluation and targeted analysis of the representativeness of Victorian data.

As the lead investigator on this evaluation, I developed the evaluation plan, reviewed system protocols and previous evaluations, undertook interviews with key informants, developed and administered an online survey for stakeholders and analysed data from the surveillance system. I also prepared the final report and developed recommendations to improve the usefulness and operation of the system.

I consulted with Allen Cheng and Lucinda Franklin throughout the evaluation with respect to the design of the evaluation and for context around my findings.

Lesson learnt

This evaluation was conducted during my second year MAE placement at DHHS. In the early stages of this investigation I struggled to balance my desire to fully understand the system and how it fits into influenza surveillance in Australia more broadly, with

the need to launch quickly into the stakeholder consultation. Normally I would prefer to explore the data to get a 'hands on' understanding of the epidemiology of disease under surveillance and fully understand the structure of the surveillance system in order to inform the stakeholder consultation. In this project, many of the attributes of the surveillance system suitable for data analysis had already been covered by previous evaluations, so I relied on these for context. I reviewed previous evaluations and system protocols, and interviewed key informants to identify outstanding issues that should be explored in the stakeholder consultation. This was a valuable experience for me as it involved stepping outside my preferred learning and working style.

I also experienced some challenges in the data analysis component of the evaluation. When I started working on the evaluation, a previous MAE Scholar had already requested an extract of data from the Victorian Admitted Episodes Dataset (VAED) that they intended to use in their own evaluation of influenza surveillance systems in Victoria. This was received after they completed their placement and I inherited the data for my own analysis. In my timeline I had scheduled the data analysis around the stakeholder evaluation, however when I finally started to analyse the data in May 2017 I quickly realised that there were several problems with the dataset that had been provided. Firstly, the VAED extract reported hospital separations while FluCAN reports hospital admissions and the extract only included month of separation. This disparity meant I could not easily calculate month of admission from the length of hospital stay. As soon as I had developed a way around for this issue I encountered a new problem: the numbers of influenza-related hospitalisations in the dataset were much lower than expected (based on other evidence). Eventually, I discovered that the dataset only contained influenza-related deaths in hospitals, rather than all influenza-related hospitalisations. A new request for data (this time with month of admission and all influenza-related hospitalisations) had to be submitted and luckily the new dataset was received towards the end of the timeframe for completion of this evaluation. In hindsight, I should have reviewed the content of the dataset at an earlier stage of the evaluation, however, this is easier said than done when managing multiple projects at once.

Overall, I found that this project allowed me to gain a better understanding of the influenza surveillance in Australia.

Public health impact

My evaluation identified a number of recommendations to improve the operation and usefulness of FluCAN. Some of the minor recommendations relating to the reporting of, and access to data from the surveillance system are already being implemented. The major recommendations arising out of this evaluation highlight the need to increase the funding for the surveillance system to improve the timeliness and representativeness of data, and the need for subtyping of a greater number of influenza samples which is a challenge for influenza surveillance in Australia broadly.

Communication

A summary report outlining key findings and recommendation for improving the usefulness and operation of FluCAN has been provided to members of the National Influenza Surveillance Committee (NISC) which oversees the improvement of influenza surveillance in Australia. The findings and recommendations were also presented at the NISC face-to-face meeting in mid-December 2017.

Master of Applied Epidemiology core requirement

This chapter is written in fulfilment of the field placement core activity to evaluate a surveillance system.

Acknowledgements

This evaluation would not have been possible without the assistance of Allen Cheng, Jill Gallick and Janine Roney who answered my questions about the surveillance system and who piloted my stakeholder survey.

I also acknowledge the contribution of:

- Katrina Roper and Lucinda Franklin for their input as my supervisors during the design of the evaluation and the ethics application process, especially Lucinda who tirelessly reviewed my work and made valuable suggestions throughout the evaluation.
- NISC members and FluCAN investigators and data collection/coordination staff for contributing to the stakeholder evaluation.

- Tanyth de Gooyer, Siobhan St George and Lucinda (again) for also piloting the stakeholder survey.

Abstract

Background: The Influenza Complications Alert Network (FluCAN) was established in 2009 as part of Australia's response to the A(H1N1/09) pandemic in order to provide reliable, comprehensive and consistent data on influenza severity. The aims of this evaluation were to determine the effectiveness of the surveillance system in achieving its aims, to determine the usefulness and performance of the system, and to make recommendations to improve the operation and usefulness of the system.

Methods: The evaluation followed the United States' Centers for Disease Control and Prevention's (CDC) Updated Guidance for Evaluation and Public Health Surveillance Systems. The evaluation included a review of key documentation, key informant interviews, an online survey of system stakeholders, and analysis of the representativeness of Victorian FluCAN data with respect to the capture of influenza-related hospitalisations. In addition to the overall usefulness and achievement of the system's aims, the attributes of simplicity, acceptability, data quality, sensitivity, representativeness, flexibility, timeliness and stability were assessed.

Results: Overall, this evaluation found FluCAN to be an important, effective and useful surveillance system. The majority of respondents rated the system highly and reported using outputs of the system. Stakeholders reported that FluCAN filled gaps in influenza surveillance and complemented other systems with particular regard to the provision of timely data on influenza severity. Since its establishment the number of sentinel sites participating in FluCAN and the number of influenza-related hospitalisations recorded by the sentinel sites system have increased. This has increased the volume of work undertaken by staff at sentinel sites and increased the burden on the system's resources.

Discussion: This evaluation generated 13 recommendations to improve the operation and usefulness of FluCAN. This includes recommendations for the FluCAN Director who has overall responsibility for coordinating the system, the National Influenza Surveillance Committee (NISC) which has responsibilities for improving the effectiveness of influenza surveillance in Australia, the Australian Government Department of Health which currently provides funding for FluCAN, and state and territory health departments which have previously contributed to FluCAN funding. Recommendations range from minor changes to reporting of, and access to, data, to

major recommendations such increasing the funding for the surveillance system which is expected to improve the timeliness and representativeness of data, and exploring barriers and options to increase the number of influenza samples that are subtyped.

Introduction

Public health importance of influenza

Influenza is an acute viral illness of the respiratory tract characterised by fever, cough, sore throat, muscle and joint aches, headache, fatigue and in some cases gastrointestinal symptoms (more common in children).[2] Complications of influenza vary in severity from sinus and ear infections, to viral and bacterial pneumonia, inflammation of the heart, brain or muscle, multi-organ failure, and death.[2] Exacerbation of pre-existing conditions such as asthma or chronic heart disease is common.[2] Certain groups are considered to be at higher risk of complications of influenza including children aged under five years and older adults (over 65 years); pregnant women; individuals with certain chronic medical conditions; and Aboriginal and Torres Strait Islander people aged six months to five years or 15 years and older.[3, 4]

There are three recognised types of influenza virus known to cause illness in humans, A, B, and C. Compared with types A and B, type C is of less public health significance as it causes less severe illness. Influenza type A viruses are classified into subtypes based on the combination of the proteins, haemagglutinin (H) and neuraminidase (N), located on the surface of the virus, and further classified into strains.[3] Influenza type B viruses are divided into lineages and strains rather than subtypes.[3] The nomenclature for influenza viruses includes the antigenic type (A, B or C); host or material of origin if non-human (e.g. swine); geographical origin; strain number; year of isolation; and for influenza A viruses the H and N description in brackets (e.g. H1N1).[5] For example, A/California/7/2009 (H1N1) or B/Brisbane/60/2008.[5] While only influenza A viruses have been known to cause pandemics, both influenza A and B viruses are included in seasonal influenza vaccines as they circulate and cause outbreaks and epidemics.[3] Both influenza A and B viruses undergo continuous albeit gradual changes in their H and N protein antigens, a process referred to as antigenic drift.[6] This means that previous vaccination or infection may only provide partial or even no protection against circulating viruses. Influenza A viruses can also undergo a more abrupt process known as antigenic shift, which occurs when viruses in animal reservoirs with novel H or N proteins infect humans and may lead to pandemics.[6]

Seasonal epidemics occur generally in winter in temperate climates (May to October in the southern hemisphere and November to April in the northern hemisphere), and

throughout the year in tropical regions.[3] Worldwide, annual influenza epidemics result in an estimated 3 to 5 million cases of severe illness, and approximately 250,000 to 500,000 deaths.[3] In Australia, it is estimated that annually there are between 1,500 and 3,500 influenza-related deaths,[7] 18,000 influenza-related hospital admissions, and 310,000 influenza-related general practitioner (GP) consultations.[8] The annual cost to the Australian health care system from the direct costs for hospitalisation and GP consultations alone was estimated at $85 million in 2007.[8] Other direct costs include diagnostic testing and antivirals for influenza, and indirect costs include lost productivity through workplace absences.

The continually evolving nature of influenza, and the burden of disease with regard to mortality, morbidity and health system costs, means that it necessary to undertake ongoing surveillance of influenza.

Influenza surveillance in Australia

According to the World Health Organization (WHO), the overarching goal of influenza surveillance is to "minimize the impact of the disease by providing useful information to public health authorities so they may better plan appropriate control and intervention measures, allocate health resources, and make case management recommendations".[9]

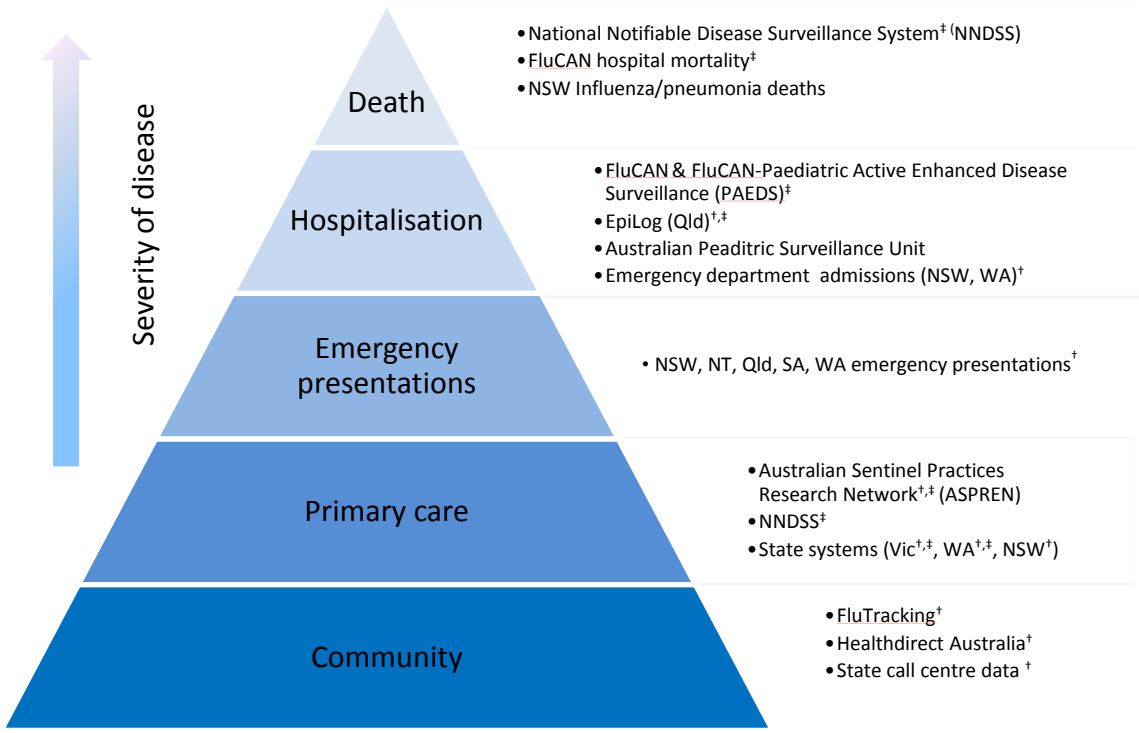
In Australia, the National Influenza Surveillance Scheme was established in 1994, bringing together information from existing influenza surveillance systems with the following objectives, to:

- ensure the early detection of influenza epidemics;
- trigger public health prevention and control activities;
- characterise the epidemic, especially identification of risk groups and disease severity;
- estimate the impact of the epidemic;
- characterise the circulating viruses to inform vaccine virus selection and assess the effectiveness of antiviral medications; and
- ensure flexibility to enable adaptability for responding to additional surveillance requirements during a pandemic or particularly severe season.[10]

This is achieved through a range of influenza surveillance systems as not all of these objectives are achieved by every system operating in Australia. For example,

community-based systems that collect data on influenza-like-illness are useful for measuring the magnitude of influenza seasons as they are not influenced by the number of tests performed, while hospital surveillance systems can provide information about the severity of influenza seasons. As a result, there are a range of surveillance systems in place in Australia which capture both influenza-like-illness and laboratory confirmed influenza across the community, and in GP clinics, emergency departments, and hospitals (Figure 1).

Figure 1: Influenza surveillance systems operating in Australia, 2017*



* Adapted from sources as referenced[10-12]
† Influenza-like illness (ILI)
‡ Laboratory confirmed influenza

The Australian Government Department of Health collates data from each of the surveillance systems contributing to the National Influenza Surveillance Scheme, along with state and territory datasets and international surveillance data, and publishes these data in the fortnightly Australian Influenza Surveillance Report during the influenza season.[13]

The National Influenza Surveillance Committee (NISC), a sub-committee of the Communicable Disease Network Australia (CDNA), has responsibilities for improving the effectiveness of influenza surveillance systems in Australia. NISC membership comprises influenza epidemiologists and surveillance officers from the Australian

Government, state and territory health departments, and the New Zealand Ministry of Health; coordinators and managers of other influenza surveillance systems (e.g. FluCAN); and representatives from the Victorian Infectious Disease Reference Laboratory (VIDRL), the Public Health Laboratory Network (PHLN), the World Health Organization Collaborating Centre for Reference and Research on Influenza (WHO CCRI), and National Influenza Centres based in Australia.

FluCAN description

The emergence of pandemic A(H1N1) influenza in 2009 revealed that many countries, including Australia, lacked established surveillance for severe disease and as a result had limited ability to evaluate the pandemic in the context of historical severity data.[9] Information on the severity of influenza is important to identify changes in virulence, clinical characteristics and complications, risk factors for severe illness, and the effectiveness of control measures such as the effectiveness of vaccination in protecting against hospitalisation with influenza.[9, 14, 15]

FluCAN was established in 2009 in response to the need for rapid, reliable, comprehensive and consistent data on influenza severity, specifically collecting data on adult acute respiratory hospitalisations.[15] FluCAN is a sentinel surveillance system which collects data on patients hospitalised with laboratory confirmed influenza and test-negative controls with acute respiratory infections. Initially FluCAN operated in 9 hospital sites in Australia and, in 2017, has grown to 20 sites including five specialist paediatric sites. FluCAN now operates in all Australian states and territories, predominately in hospitals in major cities but also in remote and inner and outer regional areas, as well as across a variety of Australian climatic regions (Table 1) in consideration of the differences in transmission patterns and severity of illness across geographical locations and demographic groups.[9]

Table 1: FluCAN sentinel hospital sites by jurisdiction, remoteness and climate, 2017

Sentinel site	Climate[16]	Remoteness area	Location
The Canberra Hospital*	Temperate	Major city	ACT
Calvary Hospital	Temperate	Major city	
Westmead Hospital	Temperate	Major city	NSW
The Children's Hospital at Westmead†	Temperate	Major city	
John Hunter Hospital	Temperate	Major city	
Alice Springs Hospital*	Grassland	Remote	NT
Royal Darwin Hospital†	Tropical	Outer regional	
The Mater Hospital	Subtropical	Major city	Qld
Lady Cilento Children's Hospital†	Subtropical	Major city	
Princess Alexandra	Subtropical	Major city	
Cairns Base Hospital*	Tropical	Major city	
Women's and Children's Hospital Adelaide†	Temperate	Major city	SA
Royal Adelaide Hospital	Temperate	Major city	
Royal Hobart Hospital	Temperate	Inner regional	Tas
Royal Melbourne Hospital	Temperate	Major city	Vic
The Alfred Hospital	Temperate	Major city	
Monash Medical Centre	Temperate	Major city	
University Hospital Geelong*	Temperate	Major city	
Royal Perth Hospital	Subtropical	Major city	WA
Princess Margaret Hospital for Children†	Subtropical	Major city	

* Community-based hospitals which collect data on both adult and paediatric cases.
† Specialist paediatric hospitals collecting data on paediatric cases only.

Aims of FluCAN

The aims of FluCAN have undergone revision since it was established. The current aims as reported in the 2016 FluCAN Study Protocol[17] are to:

A) Collect real-time sentinel surveillance for influenza requiring hospitalisation, to provide a reliable and timely source of information to inform public health policy.

B) Collect detailed clinical and laboratory information from all patients hospitalised within the network with a laboratory confirmed diagnosis of influenza to determine the burden of disease requiring hospitalisation associated with influenza.

C) Estimate the effectiveness of influenza vaccine against hospitalisation with influenza by comparing influenza vaccine status in patients with influenza and test-negative controls.

Stakeholders

Stakeholders of surveillance systems are persons and organisations who contribute to, and use, information from the system.[1] The primary stakeholders of FluCAN include:

- the FluCAN Director, Prof Allen Cheng, who coordinates the surveillance system, liaises with stakeholders, analyses data, develops reports and publications, and manages funding;
- Research Coordinators at the Alfred hospital who under the direction of the FluCAN Director coordinate ethics approvals, and collate and manage information;
- FluCAN contributors including investigators who have responsibilities for overseeing data collection at sentinel sites, performing quality audits and reporting; and data collectors/coordinators who collect and coordinate data collection at sentinel sites;
- the Health Protection Policy Branch (represented on NISC) in the Australian Government Department of Health, which provides funding for FluCAN and compiles data from the system into national influenza reporting; and
- members of NISC (see Introduction for membership) who are provided with weekly reports from FluCAN during the influenza season and oversee the improvement of the effectiveness of influenza surveillance systems in Australia.

Specific recommendations for these stakeholders are included in the Discussion section.

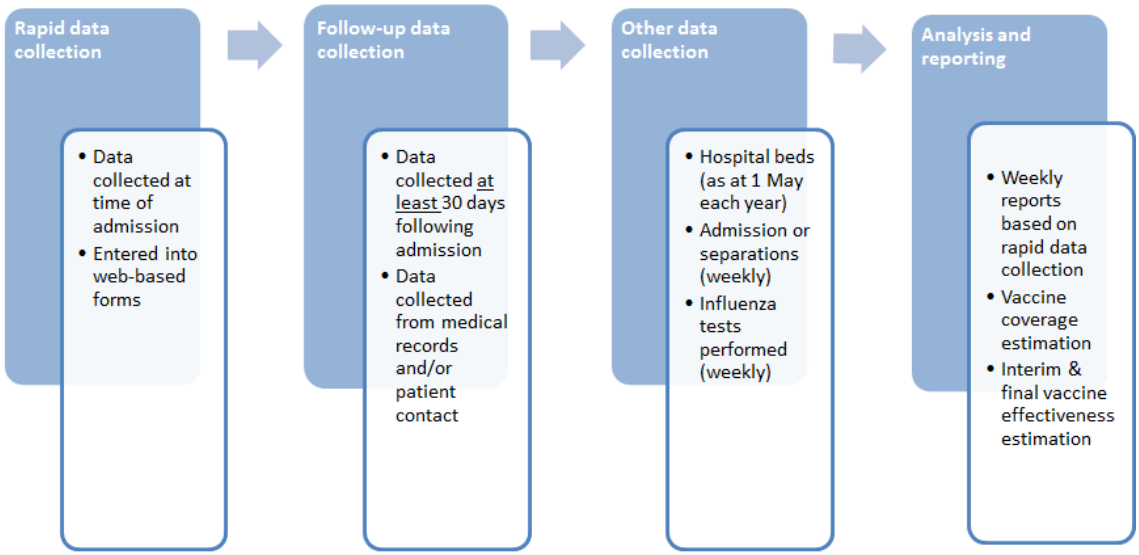
Operation and resources

FluCAN collects data on both patients hospitalised with confirmed influenza and influenza test-negative controls in order to enable estimation of vaccine effectiveness. Cases are defined as patients admitted to a sentinel hospital with suspected influenza, who test positive for influenza using polymerase chain reaction (PCR) testing. Controls are defined as patients admitted to a sentinel hospital with suspected influenza, who test negative for influenza using PCR.

The flow of FluCAN data collection, analysis and reporting is summarised in Figure 2. Data is collected for both cases and controls in two phases: rapid collection and reporting of essential data, and detailed follow-up data collection performed at least 30 days after admission. Data is stored in REDCap (Research Electronic Data Capture),

a secure web application for managing databases. This database can be accessed by jurisdictions and other stakeholders wishing to extract or view data who have been given a login and password.

Figure 2: Flow chart summarising FluCAN data collection, analysis and reporting



Data collected in the rapid collection phase includes:

- hospital site
- date of birth
- sex
- Indigenous status
- influenza test result
- date of influenza specimen collection
- admission date
- clinical presentation – i.e. influenza-like-illness, other presentation, pneumonia
- risk factors
- ward of admission – i.e. general or respiratory ward, ICU
- postcode.

Detailed data collected in the follow-up phase is gathered from medical records and/or patient contact and includes:

- mortality (where possible, determined from hospital records)
- discharge data from ICU where applicable
- discharge data from hospital
- discharge destination – e.g. home, nursing home, rehabilitation hospital

- re-admission to the same site – including the date and cause
- final diagnosis – consistent with influenza or pneumonia
- vaccination status – influenza vaccination (current and previous season).

Other information is also collected by FluCAN and is used as denominator data to allow the comparison of influenza severity between years. This data includes the number of hospital beds (as at 1 May each year); number of hospital admissions or separations excluding day-stay admission (weekly); and number of influenza tests performed (weekly).

Data collection commences in April and concludes at the end of October consistent with the influenza season. The data are analysed and are:

1. reported in a weekly summary for sentinel sites, the Australian Government and state and territory health departments;
2. reported as an interim analysis in September for the WHO influenza vaccine strain selection meeting and the Australian Vaccine Committee; and
3. reported as an end of season analysis for the WHO influenza vaccine strain selection meeting.

When FluCAN was initially established it was funded by a NHMRC grants and since then has received funding from the Australian Government Department of Health and the state and territories. FluCAN is currently funded by the Australian Government Department of Health and is coordinated by Monash University. Individual sentinel hospitals employ local coordinators and data collection staff and invoice Monash University for the cost of study staff (within allocated budgets).

Evaluation objectives

The specific objectives of this surveillance system evaluation were to:

- determine the achievement of FluCAN aims and their importance in relation to influenza surveillance;
- determine the overall usefulness of FluCAN and its performance against system attributes; and
- make recommendations to improve the usefulness and operation of FluCAN.

Methods

For the purposes of this evaluation, I followed the framework as outlined in the CDC in the *Updated Guidelines for Evaluating Public Health Surveillance Systems*.[1] The guidelines include engaging stakeholders in the evaluation; describing the system under evaluation; collecting and assessing information regarding its overall usefulness, achievement of aims, and performance against the attributes of simplicity, flexibility, acceptability, data quality, sensitivity, representativeness, timeliness and stability. Positive predictive value (PPV), the proportion of reported cases that actually have the condition under surveillance,[1] was not included in this evaluation as it was not considered suitable for evaluation by stakeholder consultation.

Two evaluations of FluCAN[18] in 2016 have focused on timeliness of data entry, validity of data (comparing data FluCAN against other data sources with respect to the weekly case count; start and peak of the influenza season; percentage of cases due to influenza A; and percentage of cases in broad age groups), as well as completeness of data fields. However, to date, no comprehensive stakeholder consultation has been conducted. Accordingly, stakeholder consultation was the primary focus of this evaluation.

As part of the surveillance evaluation, I conducted:

- a document review of the FluCAN study protocol[17], weekly reports, publications, a thesis chapter on the establishment of FluCAN[19] and recent evaluations of selected attributes of FluCAN[18];
- key informant interviews with the Victorian Government Department of Health and Human Services (DHHS) Vaccine Preventable Disease Epidemiologist, officers in the Australian Government Department of Health Protection Policy Branch, and the FluCAN Director and Research Coordinators in order to describe the system and to inform the online stakeholder survey;
- an online stakeholder survey of NISC members, system stakeholders and contributors in order to gather information on, and assess performance of the system; and
- an analysis of the representativeness of Victorian FluCAN data with respect to the capture of influenza-related hospitalisations.

In addition, I attended the Communicable Disease Epidemiology and Surveillance Unit's weekly surveillance meetings and monthly NISC teleconferences, where data from influenza surveillance systems including FluCAN were reviewed and interpreted. These opportunities allowed me to observe how FluCAN data was used, reported and interpreted in the Victorian and national context respectively.

Stakeholder consultation

An online stakeholder survey comprising both quantitative and short and open-ended response questions exploring the attributes of FluCAN was distributed by email to 18 NISC members and 29 FluCAN contributors (study investigators and data collectors/coordinators) using the online survey tool *Qualtrics* on 13 June 2017. The FluCAN Director was excluded from the online stakeholder survey but was included in the key informant interviews.

A deadline for responses was set at 27 June 2017 and two reminder emails were sent, one the day before the closing date for responses and a second reminder was sent on the day the survey closed. An extension of time to complete the survey was granted for one participant.

Surveys distributed to NISC members, investigators and data collectors/coordinators covered different attributes of the surveillance system as listed in Table 2. Where NISC members also had a role on FluCAN (two members) they were asked to complete the more in-depth FluCAN contributor survey. Respondents were asked to indicate their affiliation or role on FluCAN, however, no further identifying information such as name or state or territory was collected in order to encourage open responses.

As an alternative to the online survey, participants were also offered a telephone interview using the same questionnaire. This was chosen by one participant and allowed a more in-depth exploration of the themes covered by the survey.

Survey respondents were analysed using a mixed methods approach in which closed-ended responses were analysed quantitatively and open-ended responses were analysed qualitatively using a thematic analysis.

A copy of the survey tools distributed to stakeholders is included as Appendix III.a and III.b at the end of this chapter.

Table 2: FluCAN attributes evaluated in stakeholder consultation

Attribute	NISC member	FluCAN contributors by role	
		Investigators	Data collector/coordinator
Importance & achievement of FluCAN aims	✓	✓	✓
Overall usefulness	✓	✓	
System resourcing		✓	✓
Simplicity – ease of operation		✓	✓
Acceptability – willingness of persons and organisations to use outputs of the system	✓	✓	✓
Data quality	✓	✓	✓
Sensitivity – portion of cases that truly have influenza		✓	✓
Representativeness – ability to accurately describe the health event over time	✓		
Flexibility		✓	✓
Timeliness	✓	✓	✓
Stability		✓	✓

Data analysis

The representativeness of Victorian FluCAN data was assessed by comparing the capture of influenza-related hospitalisations in the system with data from the Victorian Admitted Episodes Dataset (VAED).

This analysis was requested by my second field placement (DHHS) as the system includes four Victorian sites, whereas most other jurisdictions include between one and three sites. DHHS Vic wanted a better understanding of the representativeness of the data and how it should be interpreted, as well as building a 'level of confidence' in the system. An extract of VAED data was analysed in Stata IC 14 (StataCorp LP, College Station, TX, USA) to identify patients with ICD-10-AM[1] codes for influenza (J09 and J10 including all sub-codes) in any of the 40 possible diagnosis code fields, by hospital site, broad age-group (0 to ≤19, 20 to ≤59, and 60+), and month and year of admission. The case count from the Victorian sites in the FluCAN database was then compared against the VAED data for corresponding hospitals, and the percentage of cases 'captured' was calculated.

[1] International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification

Ethics

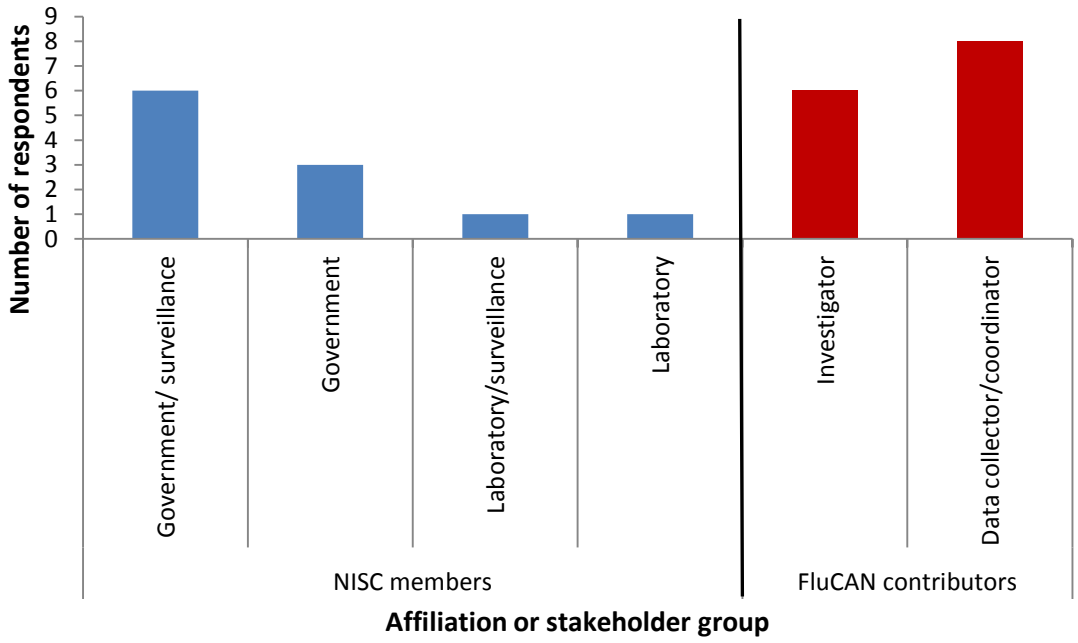
This study received ethical approval from the Australian National University's Human Research Ethics Committee (ref no. 2017/438).

Results

In this section I present the findings of the stakeholder evaluation and the data analysis in relation to the achievement of the aims of the system and their importance with respect to influenza surveillance; the usefulness of the system; and its performance against system attributes.

Eleven (61%) National Influenza Surveillance Committee (NISC) members and 14 (48%) FluCAN contributors completed the survey between 13 June and 29 June 2017. The overall response rate was 53% (25/47). NISC and FluCAN members indicated their affiliation or role as shown in Figure 3.

Figure 3: Affiliation or role of survey respondents (n=25)



Achievement and importance of aims

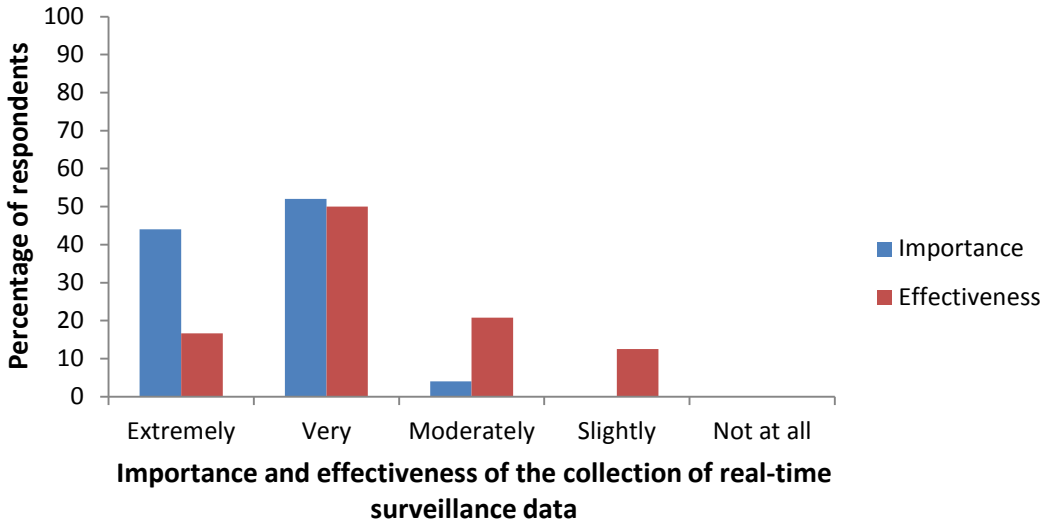
The aims of FluCAN have undergone revision since it was established. The current aims as reported in the 2016 FluCAN Study Protocol are provided in full on page 12.

Aim A: Collection of real-time sentinel surveillance for influenza requiring hospitalisation

Real-time or near real-time collection and reporting of influenza requiring hospitalisation is important to determine the severity of influenza as the influenza season progresses and can inform rapid public health action as required.

The majority of respondents (24/25, 96%) rated the importance of the collection of real-time sentinel surveillance for influenza requiring hospitalisation (Aim A) as either 'extremely' or 'very' important (Figure 3). The remainder (1/25, 4%) of participants rated the importance as 'moderately' or 'slightly' important. With respect to achievement of this aim 87% (20/23) of respondents thought that FluCAN was either 'extremely' or 'very' effective, and 13% thought it was 'moderately' or 'slightly' effective (Figure 4). No respondents rated FluCAN as being not effective in achieving this aim.

Figure 4: Stakeholder ratings of the importance (n=25) and effectiveness (n=23) of the collection of real-time surveillance data for influenza requiring hospitalisation



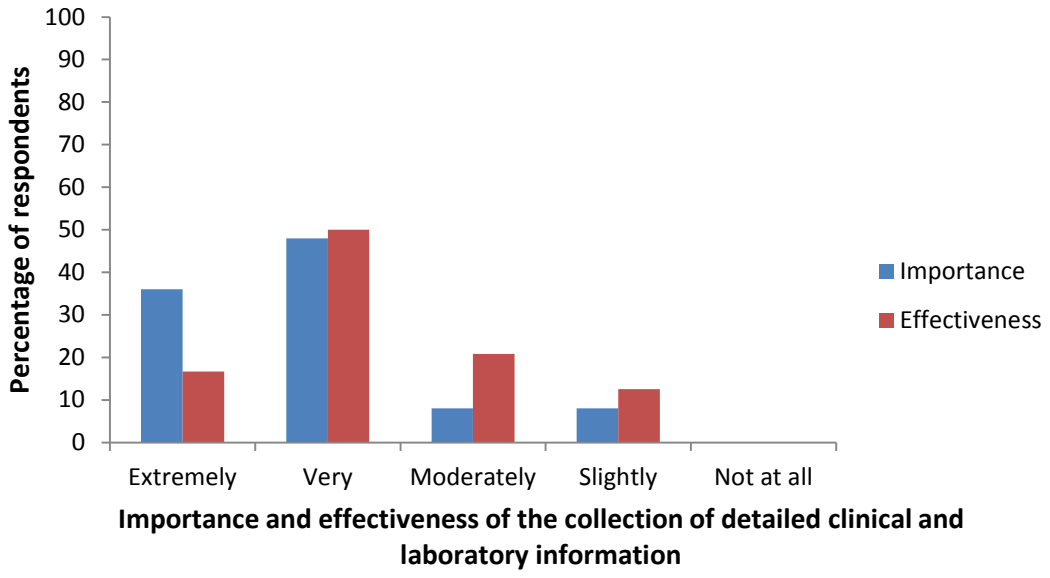
The respondent who rated the effectiveness of FluCAN in achieving this aim as 'slightly' effective commented that the data wasn't actually in 'real-time' and that they were unsure whether the system informs policy. Others described FluCAN as collecting the closest to 'real-time data' as possible and the majority of respondents reported having used outputs from FluCAN, including two respondents who reported using the data for policy/program development or management (see section on Acceptability).

Aim B: Collection of detailed clinical and laboratory data

Collection of detailed clinical and laboratory data from hospitalised patients is important to determine the burden of disease of influenza seasons or particular strains and subtypes. The provision of these data can assist policy makers in evaluating the costs and benefits of interventions.[9]

The majority of respondents (21/25, 84%) rated the importance of the collection of detailed clinical and laboratory data (Aim B) as either 'extremely' or 'very' important (Figure 4). The remainder (4/25, 16%) of participants rated the importance as 'moderately' or 'slightly' important. With respect to achievement of this aim, two-thirds of respondents (16/24, 67%) indicated that FluCAN was either 'extremely' or 'very' effective, and 33% (8/24) thought it was 'moderately' or 'slightly' effective (Figure 5). No respondents rated FluCAN as not effective in achieving this aim.

Figure 5: Stakeholder ratings of the importance (n=25) and effectiveness (n=24) of the collection of detailed clinical and laboratory information



Those that rated FluCAN as 'slightly' effective in collecting detailed clinical and laboratory information to determine the burden of influenza requiring hospitalisation commented that the burden of influenza was difficult to determine without population denominator data. This is a common limitation of sentinel surveillance systems since the population covered or catchment area is often unknown and as such, 'burden' statistics such as population-based rates (e.g. the number of hospitalisations per 100,000 population) cannot be calculated.[20] However, where population

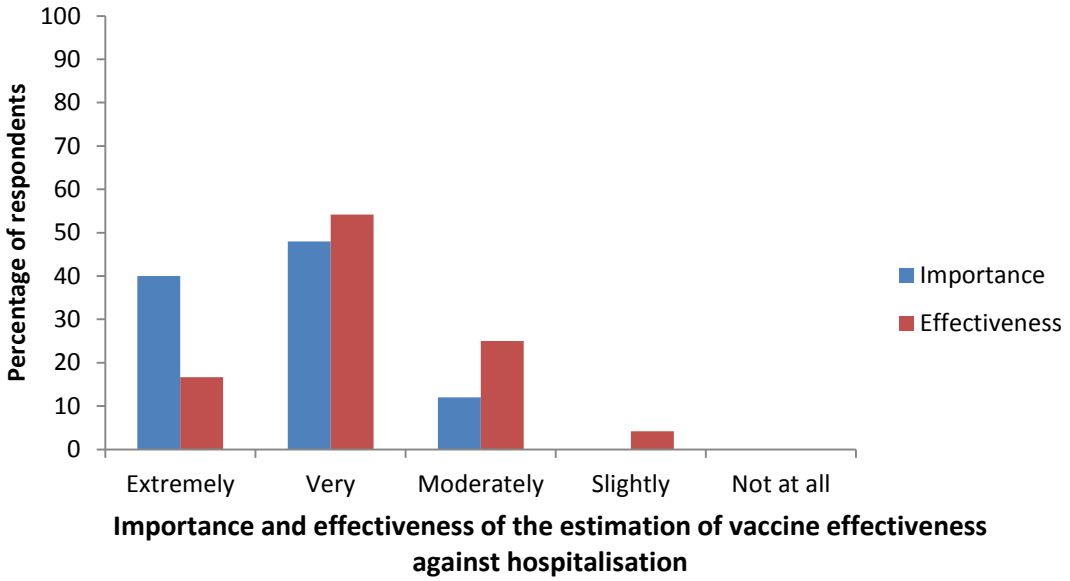
denominators are not available, the proportion of all admissions to a sentinel site due to laboratory confirmed influenza can be used to indicate the burden of influenza on the hospital system as well as allowing comparisons between seasons.[9] FluCAN does collect the number of hospital beds and hospital admissions at sentinel sites and this information could be provided in reports in addition to the proportion of hospitalised cases admitted to ICU which is currently reported.

Aim C: Estimation of the effectiveness of influenza vaccination against hospitalisation

The estimation of the effectiveness of influenza vaccination is important to inform the review of influenza vaccines.

The majority of respondents (22/25, 88%) rated the importance of the estimation of the effectiveness of influenza vaccination against hospitalisation (Aim C) as either 'extremely' or 'very' important (Figure 4). The remainder (3/25, 12%) of participants rated the importance as 'moderately' or 'slightly' important. With respect to achievement of this aim, the majority (17/24, 71%) of respondents thought that FluCAN was either 'extremely' or 'very' effective, and 29% (7/24) thought it was 'moderately' or 'slightly' effective (Figure 6). No respondents rated FluCAN as ineffective in achieving this aim.

Figure 6: Stakeholder ratings of the importance (n=25) and effectiveness (n=24) of the estimation of vaccine effectiveness against hospitalisation



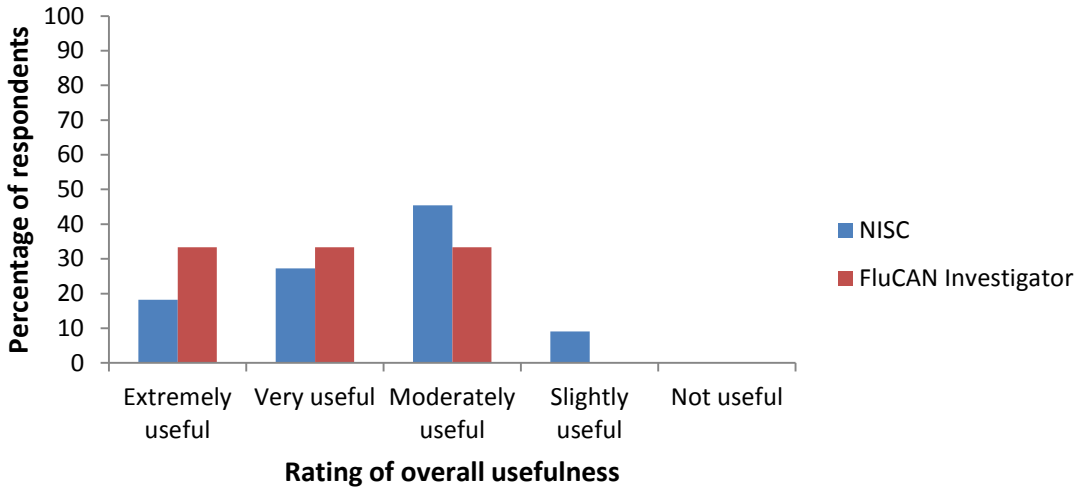
Respondents who rated FluCAN as 'slightly' effective in estimating vaccine effectiveness cited the need for more influenza subtyping information to provide more

granular vaccine effectiveness by subtype and stated that consideration should be given to whether the samples that are being subtyped are representative as only some laboratories in sentinel sites undertake, or forward on swabs for subtyping. One respondent cited that around 20 to 30% of FluCAN specimens were currently subtyped. While more FluCAN swabs could potentially be forwarded on for subtyping, this involves a substantial amount of work for FluCAN contributors as it would require manual processing to link specimen identifiers and integrate subtype information back into the FluCAN database. Additionally, there would be costs for the hospital laboratories associated with the preparation and transport of samples for subtyping. Given that the need for more subtyping of influenza samples is a challenge for influenza surveillance in Australia more broadly (with some exceptions such as VICSPIN which subtypes all influenza A samples), options to address this both through FluCAN and other means should be considered by NISC.

Usefulness

The majority of respondents (9/17, 53%) rated the overall usefulness of FluCAN as either 'extremely' or 'very' useful, with the remainder rating it as 'moderately' (8/17, 41%) or 'slightly' useful (1/17, 6%). No respondents rated FluCAN as not useful (Figure 7).

Figure 7: NISC (n=11) and FluCAN investigators (n=6) ratings of the overall usefulness of FluCAN



Respondents who rated the usefulness of FluCAN as either 'extremely' or 'very' useful described the system's ability to provide: timely information about influenza-related

hospitalisation; vaccine effectiveness against influenza-related hospitalisation; and information about severity of illness overall and for high risk groups (Box 1).

Box 1: Selected respondent comments related to the usefulness of FluCAN

FluCAN provides real time influenza surveillance which is invaluable in developing public health policies and alerting department of health and aging of any major outbreaks or issues with vaccine coverage.

It provides timely information about hospitalisations for flu which most States are not able to provide.

It is the only (close to) national data source that captures hospitalisation data in a timely way, and estimates vaccine effectiveness against hospitalisation.

Provides enhanced data on hospitalised cases, which other surveillance systems do not achieve at all or well.

[Other] hospitalisation data is not timely enough to inform the seasonal and pandemic response to influenza. Therefore, FluCAN provides efficient insights into the severity of influenza, particularly for 'at risk' populations.

Essential to detect the severe end of Influenza morbidity - no other obvious way of achieving this.

Respondents who considered FluCAN to be 'moderately' or 'slightly' useful cited: the need for denominator data to allow comparison of the relative severity of each season; the need for more subtyping of influenza specimens to inform vaccine effectiveness; and lack of evidence that FluCAN is influencing policy (Box 2), however others suggested that it does provide valuable information for policy development (Box 1). These issues are discussed in more detail in *Achievement and importance of aims*.

Box 2: Selected respondent comments related to the usefulness of FluCAN

Not having reliable denominator data makes assessment and comparison of relative severity of each season difficult.

The subtyping information from FluCAN does not appear to be representative. Without representative influenza subtyping information FluCAN is only slightly effective when estimating the effectiveness of influenza vaccine by subtype.

It is unclear if FluCAN is having an influence on policy.

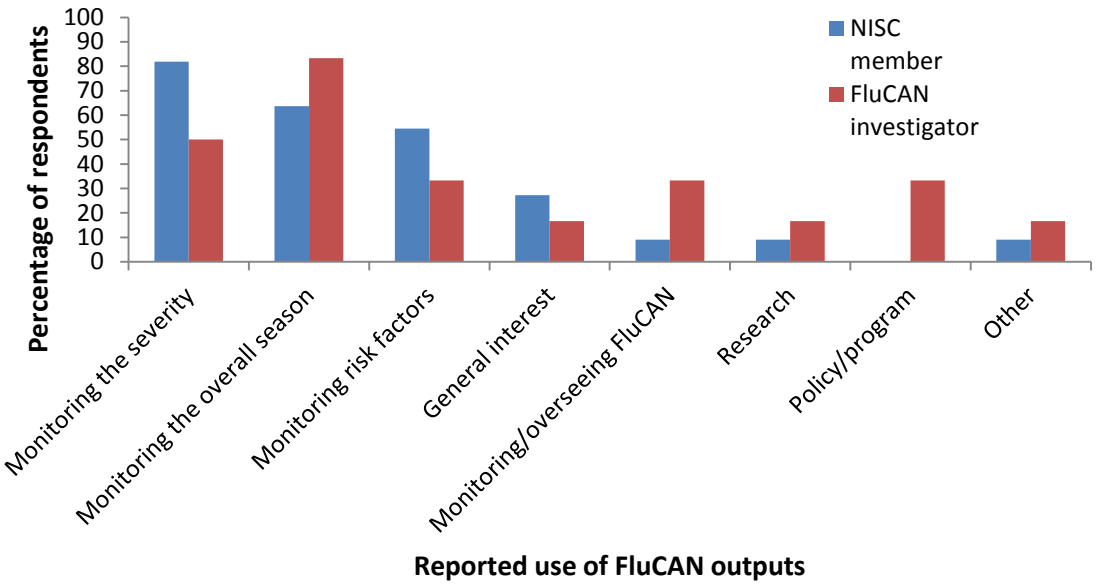
Unsure how it has changed policy nationally.

Acceptability

In this evaluation, 'acceptability' was assessed as the willingness of users and organisations to use outputs of the system. Overall, the majority of respondents (16/23, 70%) reported using data, reports or other outputs from FluCAN. When participant responses were categorised by role or affiliation, the majority of NISC members and FluCAN investigators reported using information from FluCAN (16/17, 94%), while none of the FluCAN data collectors reported using the data, reports or outputs, which they stated was because they were not relevant to their work or roles.

The most common use of information from the surveillance system cited by respondents was to monitor the overall 'picture' of the influenza season, and to monitor the severity of the influenza seasons or strains, closely followed by monitoring risk factors for influenza-related hospitalisations (Figure 8). Under 'other' uses of information from the system, one respondent cited use of the information for developing briefings and responding to media inquiries about the influenza season. It is expected that more respondents would have cited this reason if it had been provided as a specific category in the survey. Two respondents who identified as FluCAN investigators, noting that this category of responder may also identify as members of NISC or may have other government roles in public health, reported using information from FluCAN for policy or program development/management. This may indicate that individuals who are more involved in the surveillance system were more likely to use outputs from the surveillance system data for policy or program purposes.

Figure 8: Reported uses of FluCAN outputs by NISC members (n=11) and FluCAN investigators (n=6)



Respondents who reported using outputs of the surveillance system were also asked which outputs they used and how (if at all) these could be improved. Most respondents reported using the weekly national FluCAN report circulated by the FluCAN Director. Use of FluCAN data incorporated in the fortnightly Australian Influenza Surveillance Report prepared by the Australian Government Department of Health, and data directly assessed from the REDCap database was also common. Use of information in the annual FluCAN report prepared on conclusion of the season, publications based on FluCAN data, influenza strain data, and influenza samples provided by FluCAN hospitals were reported.

Weekly reports

Respondents reported that some improvements could be made to the charts included in the weekly national FluCAN report in order to improve the ease of interpretation. Specific suggestions included reducing the use of stacked histograms (for influenza subtype and ICU admission) and/or possible separation of data into more than one chart. Some respondents also suggested not including space on the horizontal axis of charts reflecting epidemiological weeks before data collection commenced. Some respondents found the dot plot chart difficult to interpret and suggested use of a histogram instead, alternatively increasing the size of the chart is also likely to increase interpretability as the dotted guidelines display more clearly in larger sizes.

REDCap database

Overall, just under half of NISC members (5/11, 45%) reporting having problems or difficulty in accessing FluCAN. Respondents indicated that these problems related to the REDCap database, particularly with regard to navigating the database and the frequent password resets which made it difficult for irregular users to access data quickly (Box 3).

Others commented that they would like access to line listed data for their jurisdiction. This can currently be accessed through REDCap by exporting data for all jurisdictions and then using pivot tables in Excel or other software packages to extract data for the relevant jurisdiction. However, development of reports by jurisdiction that can be easily exported by stakeholders would be highly desirable. Access to consolidated historical data was also requested by respondents who noted that these used to be available in the previous database platform.

Respondents also commented that a 'how to' guide would assist stakeholders in accessing detailed data in REDCap.

Box 3: Selected respondent comments on the use of FluCAN outputs

I used to export the data on a weekly basis from the database, which was fantastic. We used it to check that notifications were coming through, and use them to update the notified cases. In recent years though I've found the system less simple to negotiate […] and I keep losing my password.

In the past [we] were able to access line-listed data for admissions in my State. That website ceased to operate and/or present data.

The reports are ok, but it would be great to be able to [have] access to more detailed (i.e. line listed) jurisdictional data for internal use within the jurisdiction in which it is collected.

Would like to be able to access data for previous years in Redcap.

Perhaps a 'How to' guide on exporting your state's data [would be an improvement].

<u>Other</u>

Some respondents questioned differences in the data compared to that from other sources, which they suggested might be due to delays in data entry or reporting. The provision of background information or caveats for stakeholders, for example about where there may be lags in data, and differences in data collection methodologies between FluCAN sites, would likely build stakeholder confidence in the data. Some

respondents noted that they would like to see more reporting of, or access to, more of the detailed data collected in FluCAN such as, but not limited to, comorbidity data.

Sensitivity

Sensitivity was assessed with respect to the proportion of cases of a disease detected by the system. This also has relevance to the representativeness of the system which is discussed in further detail in the section on *Representativeness*. FluCAN contributors were asked whether, in their view, FluCAN was capturing all true cases of influenza in patients presenting with influenza-like-illness at their site. The majority of respondents (10/12, 83%) responded in the affirmative. The remaining 17% (2/12) did not believe that all cases were being captured, citing that not all cases presenting at sentinel sites would be admitted, and that some cases who were admitted may be discharged and not enrolled in FluCAN because of delays in obtaining laboratory results. As FluCAN is a passive surveillance in that influenza testing is undertaken as part of routine clinical care, true cases of influenza may also be missed where testing is not performed.

Representativeness

The CDC describes public health surveillance systems as being representative if they accurately describe the occurrence of a health-related event over time and its distribution in the population by place and person.[1] This was investigated both through data analysis and stakeholder consultation.

Data analysis of representativeness

The representativeness of influenza-related hospitalisations recorded by FluCAN was assessed by comparing the capture of influenza-related hospitalisations in the system with data from VAED, Victoria's administrative hospitalisations dataset between April and October (the months in which FluCAN operates).

In 2016, Victorian FluCAN sites captured 82% (484/592) of influenza-related hospitalisations recorded in VAED for corresponding sentinel sites (Table 23). The Alfred Hospital had the highest proportion of cases captured (132/144, 92%) and Monash Medical Centre had the lowest (127/185, 69%). As a proportion of all Victorian influenza-related hospitalisations (including hospitals not participating in FluCAN) Victorian sentinel sites captured 18% (484/2742) of all influenza-related hospitalisations recorded by VAED.

The proportion of cases captured by FluCAN varied by year (Table 2). Across Victorian sentinel sites, the proportion of cases captured was highest in 2012 (390/440, 89%) and lowest in 2013 (202/974, 72%). The proportion of cases captured by FluCAN also varied across Victorian sentinel sites (Table 2). In some years FluCAN sites recorded an over-capture of influenza-related hospitalisations (i.e. FluCAN recorded more cases than VAED). While it is possible than FluCAN may have included false positive results, it is likely that the over-capture is due to operational differences between FluCAN and VAED. Discussions with the FluCAN Director suggest that such over-capture may result from coding errors in either dataset, diagnosis not being recorded in medical records or being made after completion of the discharge summary but otherwise ascertained by FluCAN staff through active surveillance. The University Hospital Geelong had the greatest number of years in which an over-capture of cases was identified (2012–2014), while the Royal Melbourne Hospital and the Alfred Hospital only recorded one year of over-capture (2011 and 2012 respectively). This has not occurred since 2015, however, it was not possible to ascertain whether the circumstance that led to this over-capture are still occurring.

All Victorian sentinel sites had an under-capture of VAED data (i.e. FluCAN recorded fewer cases than VAED) in some years (Table 3). Under-capture may result from: tertiary sentinel sites not collecting data on non-adult cases; use of diagnostic tests other than PCR such as influenza antigen and serology which do not meet the definition for inclusion in FluCAN; coding errors in either dataset or poor medical documentation; diagnosis of influenza prior to hospitalisation or in another hospital prior to transfer to a sentinel site; and cases being missed by data collectors. Of all Victorian sites Monash Medical Centre consistently had the greatest under-capture of cases. This site also had the highest number of influenza-related hospitalisations (as recorded by VAED) which may indicate that the volume number of cases is difficult to record, however, it was hypothesised that the key reason for under-capture was related to Monash Medical Centre not collecting data on non-adult cases.

Table 3: Number and proportion of cases of influenza-related hospitalisations captured by FluCAN in Victoria, during April to October 2010-2016

Year	Source	Alfred	Monash	Geelong	Royal Melbourne	Victorian sentinel sites	Victoria (all hospitalisations)
2016	FluCAN	132	127	90	135	484	484
	VAED	144	185	111	152	592	2742
	%	92%	69%	81%	89%	82%	18%
2015	FluCAN	164	189	88	164	605	605
	VAED	170	276	104	174	724	2978
	%	97%	68%	85%	94%	84%	20%
2014	FluCAN	119	112	77	106	414	414
	VAED	143	163	63	106	475	2093
	%	83%	69%	122%	100%	74%	20%
2013	FluCAN	63	38	47	54	202	202
	VAED	70	116	38	58	282	974
	%	90%	33%	124%	93%	72%	21%
2012	FluCAN	64	86	124	116	390	390
	VAED	53	145	113	129	440	1374
	%	121%	59%	110%	90%	89%	28%
2011	FluCAN	32	41	11	52	136	136
	VAED	44	69	17	41	171	582
	%	73%	59%	65%	127%	80%	23%
2010	FluCAN	30	53	n/a	34	117	117
	VAED	28	76	n/a	35	139	523
	%	107%	70%	n/a	97%	84%	22%

Analysis of data for 2016 by broad age groups (0 to ≤19, 20 to ≤59, and 60+ years) provided further information about the under-capture of cases. While it would have been more desirable to have 0 to ≤ 18 years as the youngest age group in order to better reflect whether cases were children/adolescents or adults, we were limited by the age groups reported in the extract of data from VAED. Analysis of the proportion of cases captured by broad age-group confirmed that Monash Medical Centre had lower overall capture of influenza cases as it did not collect data on non-adult cases (Table 4). When non-adult cases (i.e. those less than 20 years of age) were excluded from the analysis, Monash Medical Centre was found to have captured 85% of adult cases recorded in VAED. Other tertiary sentinel hospitals in Victoria had a lower number of admitted cases who were aged less than 20 years and were estimated to have captured between 67% (2/3, Royal Melbourne Hospital) of these cases and 100% (2/2, Alfred Hospital). University Hospital Geelong, a community-based hospital which collects data on both adult and paediatric cases, captured 92% (24/26) of cases aged

less than 20 years. FluCAN is under-representative of cases aged less than 20 years in Victorian sentinel sites and all Victorian hospitals as whole, capturing 42% (28/66) and 10% (28/279) of cases respectively. However, this is not surprising given that Victorian sentinel sites only include one community hospital which collects data on both adult and paediatric cases and no speciality paediatric sites.

Table 4: Capture of influenza-related hospitalisations (J09-J10 and sub categories in any diagnosis field) in Victoria, by age group, 2016

	FluCAN	VAED	%	FluCAN	VAED	%
	Alfred			Monash		
0 ≤ 19	2	2	100%	0	35	0%
20 ≤ 59	52	62	84%	27	41	66%
60+	78	80	98%	100	109	92%
	Geelong			Royal Melbourne		
0 ≤ 19	24	26	92%	2	3	67%
20 ≤ 59	33	39	85%	51	48	106%
60+	33	46	72%	82	101	81%
	Victorian sentinel sites			Victoria (all hospitalisations)		
0 ≤ 19	28	66	42%	28	279	10%
20 ≤ 59	163	190	86%	163	705	23%
60+	293	336	87%	293	1758	17%

When broken down by month of admission the proportion of data captured by FluCAN was generally lower at the start of the season (Table 5) when contracts may not have been in place for data collection staff at some sentinel sites (see section on *Timeliness*) and again at the end of season when staffing may be low due to lack of funding (see section on *Resources)*. An over-capture of cases was recorded by the Royal Melbourne Hospital in July and August 2016. It is possible that this may be due to differences in the recording of admission month between FluCAN and VAED as there was no over-capture in the total number of cases recorded in 2016.

Table 5: Capture of influenza-related hospitalisations (J09-J10 and sub categories in any diagnosis field) in Victoria, by month, 2016

	Apr	May	Jun	Jul	Aug	Sep	Oct
Alfred							
FluCAN	2	3	2	13	58	41	13
VAED	3	4	5	13	56	47	16
%	67%	75%	40%	100%	104%	87%	81%
Monash							
FluCAN	4	2	3	12	57	37	12
VAED	5	5	3	25	74	48	25
%	80%	40%	100%	48%	77%	77%	48%
Geelong							
FluCAN	2	5	4	9	26	34	10
VAED	5	5	6	8	32	38	17
%	40%	100%	67%	113%	81%	89%	59%
Royal Melbourne							
FluCAN	4	1	3	20	43	43	21
VAED	5	1	4	17	37	57	31
%	80%	100%	75%	118%	116%	75%	68%
Victorian sentinel sites							
FluCAN	12	11	12	54	184	155	56
VAED	18	15	18	63	199	190	89
%	67%	73%	67%	86%	92%	82%	63%
Victoria (all hospitals)							
	April	**May**	**June**	**July**	**August**	**Sept**	**Oct**
FluCAN	12	11	12	54	184	155	56
VAED	88	70	93	251	854	976	410
%	14%	16%	13%	22%	22%	16%	14%

Overall, the representativeness of FluCAN data in Victoria was good with respect to its capture of influenza-related hospitalisations in cases aged 20 years and older, and across all age groups at University Hospital Geelong which is a community hospital that collects data on paediatric cases.

Stakeholder consultation

The selection of sites in sentinel surveillance systems is important to ensure the representativeness of data. When selecting sentinel sites attention should be paid to the inclusion of sites across target age groups, climate zones and both urban and remote locations (all of which may have different patterns in transmission and severity of illness[9]). FluCAN sentinel sites encompass different climatic zones and remoteness areas (Table 1). In order to investigate stakeholder views on the selection of FluCAN sentinel sites, NISC members were asked whether the representativeness of FluCAN was adequate with reference to the geographical distribution of hospital sites and the demographic characteristics of cases. Of the NISC members who responded to this question, 71% (5/7) of respondents agreed that it was representative. Two respondents commented that addition of more hospitals across different regions in their state would be useful.

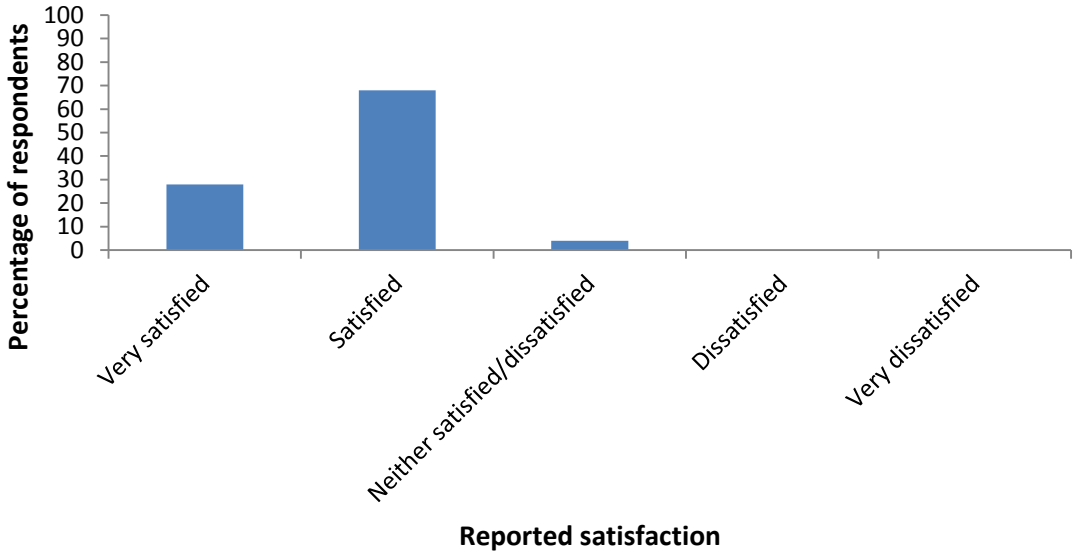
Data quality

Data quality reflects the completeness and validity of the data recorded.[1] These attributes were reviewed as part of a previous evaluation of FluCAN[18], which found Queensland FluCAN data provided similar influenza activity (based on case counts) to data derived from the Queensland EpiLog surveillance system (an influenza surveillance system which links all public hospital admissions with laboratory test results). Comparison of national FluCAN data to that derived from the NNDSS and ASPREN (community-based system of laboratory confirmed influenza) showed variability in the number of cases over time, and the season start and peak of seasons varied across all systems.[18] These differences could be reasonably expected when comparing data from community and hospital-based systems.

The previous evaluation found that, between 2010–2015, all key data fields (excluding vaccination status, influenza subtype, discharge date, mortality status) were complete in 97% of cases, while detailed data fields had at least 80% completeness (excluding smoking status, obesity and vaccination status).[18] Current vaccination status had among the lowest completion at 60% in this period[18], however my own analysis found that completeness of current vaccination status had increased to 82% (1599/1952) in 2016. Factors affecting the completeness of vaccination status are explored in the section on *Simplicity*.

In this evaluation, stakeholders were asked how satisfied they were with the data collected and reported by FluCAN. Ninety-six percent (24/25) reported that they were 'very satisfied' or 'satisfied', and the remaining 4% (1/25) were 'neither satisfied nor dissatisfied (Figure 9). None of the respondents reported being dissatisfied.

Figure 9: Stakeholder reported satisfaction with the quality of FluCAN data (n=25)



Timeliness

Timeliness reflects the time taken between steps in a public health surveillance system.[1] A previous evaluation of FluCAN assessed timeliness of data entry between 2010–2015 and found that the entry of data was timely with 50% of data entered within one week of admission and 75% entered with two weeks of admission.[18] The same evaluation also found that timeliness was reduced early in the season, which the authors attributed to staffing and contracting problems.[18]

As this is a somewhat arbitrary definition of timeliness, I included timeliness in the stakeholder consultation. Five data collectors/coordinators indicated that their site had defined protocols for the timelines of data entry, and four indicated that they would be entered within around 24 hours of identifying a positive case. However, the time from data entry to admission to hospital could vary between sites depending on their processes. For example, two respondents reported that their sentinel site sent samples offsite for testing which led to delays receiving the results over the weekend or were results that were received in a 'batched report'.

I further explored timeliness by specifically asking FluCAN contributors what factors contributed to reduced timeliness, where the entry of initial data into FluCAN for

influenza positive cases takes greater than 7 days or was outside their site's protocol. The most common factor reported was the high number of influenza-related hospitalisations for entry, and project staff capacity (including administrative issues with staff contracts at the start of the season). Delays in the availability of laboratory results for some patients were also cited as an issue for some sites, especially where specimens were sent elsewhere for testing.

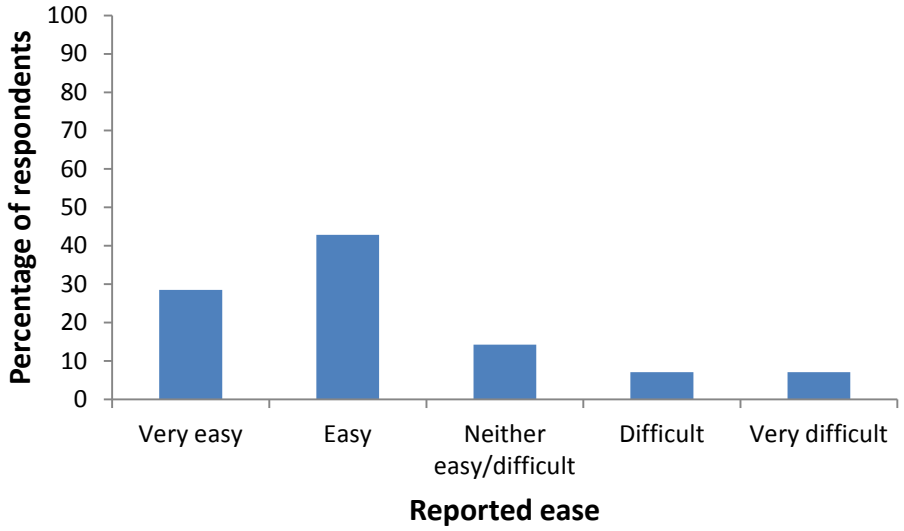
Almost all NISC members and FluCAN investigators (15/16, 94%) agreed that FluCAN provided timely information on influenza hospitalisation that would not otherwise be readily available.

Simplicity

Simplicity was assessed through the stakeholder evaluation with regard to the structure of the system and ease of operation.

Overall, 75% (6/8) of FluCAN contributors and 67% (4/6) of investigators found the ease of contributing to, or overseeing of FluCAN (respectively), either 'very easy' or 'easy' (Figure 10). Those that rated the ease as either 'neither easy nor difficult', 'difficult' or 'very difficult' cited problems with missing data in medical records and difficulty following-up missing data.

Figure 10: FluCAN contributor reported ease of contributing to or overseeing FluCAN (n=14)



Some specific data fields were noted to be particularly difficult to collect. This included vaccination data, risk factors, smoking history and smoking pack-years (calculated by multiplying the number of standard packs of cigarettes smoked per day by the number

of years a person has smoked). Some FluCAN contributors commented that where vaccination status was not available in medical records, follow up with patients to ascertain their vaccination was difficult if a patient's influenza test result came back after the patient was discharged. This was because data collection officers did not feel comfortable in informing patients that they had tested positive for influenza. Data contributors commented that access to data from Australian Immunisation Register (AIR), which in addition to recording childhood vaccination has recently been expanded to include vaccination history for adolescents and adults as provided by vaccination providers who register with AIR, would make data collection of vaccination status easier.

FluCAN contributors also commented that the differences in data collection methods between sites made it difficult to comment on improvements to FluCAN processes. It was noted that some sites collect data in real-time (during patient stay) and others collect data retrospectively by cross referencing laboratory results with other electronic databases and medical records. While this introduces some complexity into the overall collection of data, it also allows flexibility in the collection of data and reflects underlying differences in the way contributing sentinel sites routinely collect and record data.

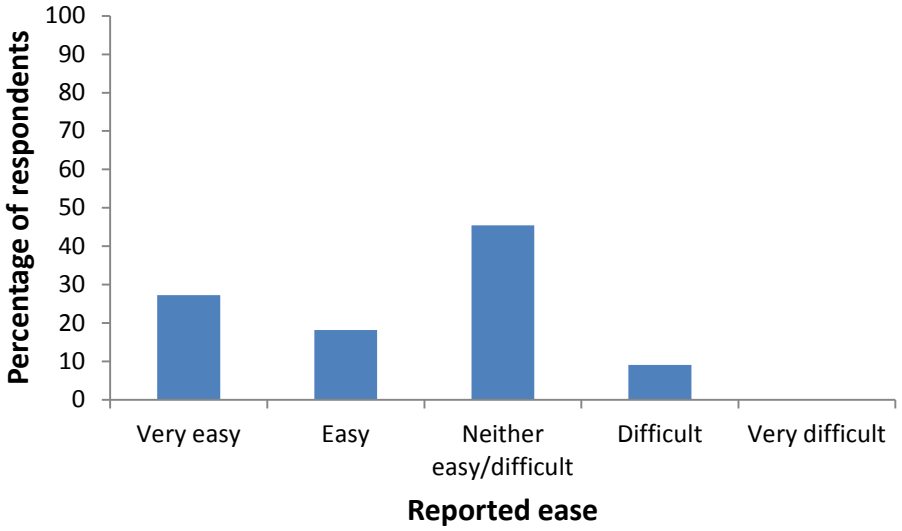
Flexibility

A flexible public health surveillance system can adapt to changing information needs or operating conditions with little additional time, personnel, or allocated funds.[1] FluCAN contributors were asked how easy it would be for their site to adapt to collecting data for other respiratory conditions assuming similar fields were being collected. Responses were divided on this point; 45% (5/11) answered that it would be 'very easy' or 'easy'. A further 45% (5/11) felt that it would be 'neither easy nor difficult' and 10% (1/11) said that it would be 'difficult' (Figure 11). One respondent also commented that it would depend on how much data would need to be collected via patient interview rather than by using existing records.

NISC members also made comments relevant to the surveillance systems' flexibility noting that the addition of new conditions such as respiratory syncytial virus or the varicella-zoster virus would require year-round data collection. Currently FluCAN

collects data from April to the end of October which limits its ability to collect data on other conditions without the addition of more personnel and funding.

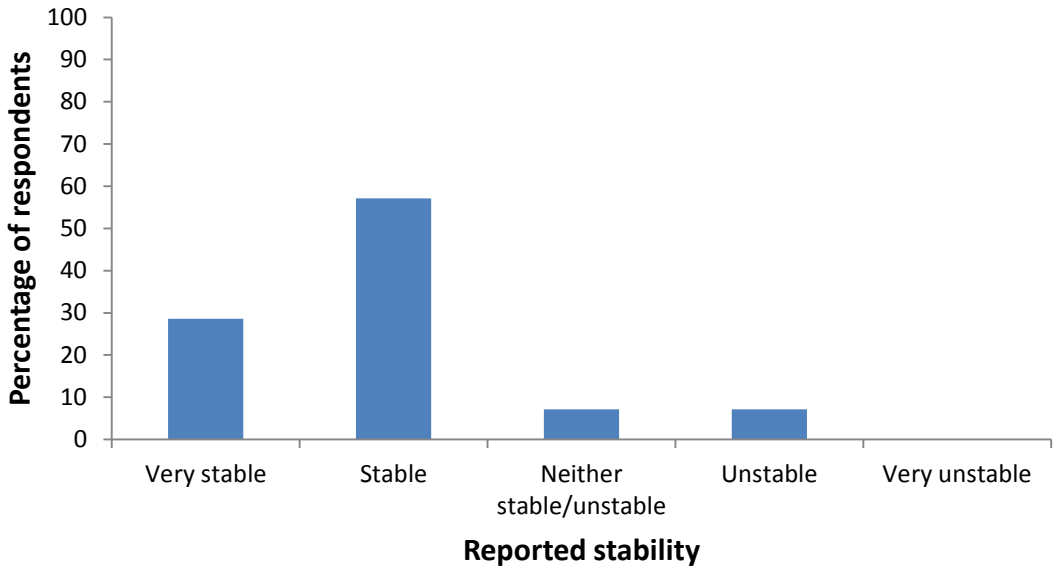
Figure 11: FluCAN contributor reported ease for sites to adapt to collecting data for other respiratory conditions (n=11)



Stability

The stability of a surveillance system relates to its "reliability (i.e., the ability to collect, manage, and provide data properly without failure) and availability (the ability to be operational when it is needed)".[1] FluCAN contributors were asked their views on the stability of FluCAN and the majority (12/14, 86%) responded that it was 'very stable' or 'stable' (Figure 12). The minority (2/14, 14%) who rated it as 'neither stable nor unstable' or 'unstable' commented that the stability of the system relied on the goodwill of sites to collect the data, particularly in seasons with more cases.

Figure 12: FluCAN contributor reported stability of FluCAN with regard to collecting, managing and providing data without failure (n=14)



FluCAN contributors were also asked whether the system's 'site stress' measures, which are implemented when the number of cases reported by sentinel sites reaches a particular pre-defined 'stress limit', are adequate to reduce workload on staff during peak periods. In 2016, the 'site stress' limit was set at 33% above the average number of cases reported by the site in the proceeding four seasons. When the 'site stress' limit is reached workload is reduced by: ceasing to collect data about controls; assessing the need for further funding; and ceasing follow-up of data not available in medical records. Responses to this question were again divided, with 55% (6/11) responding that the measures were adequate and 45% (5/11) that they were inadequate as there remained a large workload in reviewing records and laboratory results (Box 4). Other comments related to resourcing issues which are described in the following section.

Box 4. Selected respondent comments related to 'site stress' measures

In the lead up to the [triggering of the] site stress condition the workload can be very high.

Even the new ['site stress'] measures in place do not fully compensate sites for work done.

System resourcing

FluCAN contributors were asked whether their site was sufficiently resourced. Responses were divided with 57% (8/14) reporting that they were adequately resourced and 43% (6/14) reporting that they were not. As potentially identifying

information was not collected on the contributors' sentinel site it was not possible to ascertain whether differences in views on resourcing were affected by variables such as they length of time a site had been participating in FluCAN. One respondent stated that funding had not increased significantly for many years despite the cost of salaries increasing. Suggestions to improve the resourcing included capitation based on the number of patients enrolled, and consideration of the work involved in data collection. The provision of funding for influenza subtyping was also suggested.

NISC members also commented on the resourcing of FluCAN, including that a full time FluCAN Project Manager would be useful.

Box 5. Selected respondent comments related to system resourcing

Funding does not cover the amount of work involved in the collection of the data. An increase in budget is required. There has been no significant increase in funding for many years but the cost of -salaries continues to increase.

Need greater financial support to continue with this type of research we have tried to embed into our work but the number of flu cases admitted has increased to large numbers over the years

When in full influenza season, keeping up with the numbers of flu cases and trying to get enough appropriate controls can be challenging.

Currently due to the numbers [of cases and controls] this really takes a person 4 days [a week] to collect and enter and we are only funded for around 1 day per week.

Capitation based on number of patients admitted/enrolled [should be considered to improve resourcing].

Funding for influenza typing, and for lab diagnosis of other causes of hospitalisation [is needed].

Discussion

Influenza is a continually evolving disease which requires ongoing surveillance in order to inform public health action. FluCAN has been undertaking surveillance of influenza-related hospitalisations since the 2009 influenza pandemic highlighted a gap in the availability of reliable, comprehensive and consistent data on influenza severity

The purpose of this evaluation was to determine the usefulness and performance of FluCAN and to make recommendations to improve the system.

Overall, this evaluation found FluCAN to be an important, effective and useful surveillance system with the majority of respondents rating the system highly against these key factors. Stakeholders viewed FluCAN as filling gaps and complementing other influenza surveillance systems in Australia with particular regard to the provision of timely data on influenza requiring hospitalisation and illness severity, the provision of enhanced data, and the estimation of vaccine effectiveness. Notwithstanding the overall achievements of FluCAN, this evaluation identified areas in which the usefulness and operation of the system had potential for improvement.

Acceptability of the surveillance system was found to be high with 94% of NISC members and FluCAN investigators reporting that they used at least some of the outputs of the system. Information from FluCAN was used for a variety of purposes including monitoring the influenza season, its severity and risk factors associated with hospitalisation. Respondents also reported using the information for policy/program development or management and for responding to the media. However, several suggestions were identified that would improve access to, and use of, outputs of the system including access to line listed reports by jurisdiction, detailed datasets, consolidated historical data (Recommendation 1.f), and a reduction in the frequency of REDCap password changes (Recommendation 1.i); a 'how to' guide for the REDCap database (Recommendation 1.g); and minor amendments to some of the graphs contained in FluCAN reports (Recommendation 1.h). As a result of early feedback on the results of the stakeholder evaluation to the FluCAN Director, changes to the graphs have already been implemented.

Others reported that they would like more context around the data that would help explain any differences between other sources of hospitalisation data (Recommendation 1.j). Additionally, in the absence of population denominators, it

would be useful to include the proportion of all admissions to sentinel sites that are due to laboratory-confirmed influenza to reflect the burden on the hospital system due to influenza and to allow comparisons between years (Recommendation 1.a).

Overall, comparison of data from Victorian FluCAN sentinel sites to VAED found that the surveillance system was representative with respect to its ability to describe the occurrence of influenza. While there was an under-representation of cases aged less than 20 years in Victoria, this is a known limitation of FluCAN which has been addressed in other jurisdictions by the inclusion of several paediatric sites in partnership with the Paediatric Active Enhanced Disease Surveillance system (PAEDS). As a result, it is expected that the representation of the influenza-related hospitalisations in those aged less than 20 years would be higher in most other states as compared with Victoria. Consideration could be given to adding a specialist paediatric site in Victoria in order to address the under-representation of paediatric cases, however, this would require additional funding and a site would need to be identified that could commit to ongoing surveillance (Recommendation 1.d). Addressing contractual issues that delay hiring of staff at the start of the season and increasing funding to sites may improve the proportion of cases captured in Victoria at the start and end of the seasons (Recommendation 1.c). The representativeness of data collected in other states and territories was not assessed, however, it is expected that these sites would have similar patterns.

This evaluation found that while completeness of vaccination status had increased to 82% in 2016, this could be further improved by addressing the concerns reflected by data collection staff about contacting patients after discharge to ascertain their vaccination status where the patient was not aware of their influenza test result. Options to address this include exploring whether access to AIR could be given to FluCAN staff at sentinel sites, development of interview scripts covering test results for data collection staff conducting patient follow-up, or letters to discharged patients informing of their test result and advising that they will be contacted by a FluCAN staff member (Recommendation 1.e).

The need to improve resourcing for FluCAN was a common theme in the stakeholder consultation. The number of cases of hospitalisation due to influenza recorded by FluCAN has increased from 368 in 2010[18] to 1,212 in 2016. This reflects both the

addition of more sentinel sites and a substantial increase in the number of influenza-related hospitalisations at individual sentinel sites. For example, the number of influenza-related hospitalisations recorded by the four Victorian sentinel sites has more than tripled from 136 in 2011 (the first year all four sites participated in FluCAN) to 486 in 2016. One FluCAN contributor noted that there had been no significant increase in funding for many years but the cost of salaries had increased. Increasing FluCAN funding is likely to improve the proportion of cases captured by FluCAN at the end of the season when funding may have been exhausted, and the timeliness of data collection. Funding could also be allocated to increasing the hours of Research Coordinators, or to engage a Project Manager to assist the FluCAN Director in providing access to line listed data for jurisdictions and responding to queries about the data. Currently, FluCAN funding is provided by the Australian Government Department of Health but in previous years state and territory health departments have also contributed to funding. As the outputs of FluCAN are used by the Australian Government and state and territory departments of health, consideration should be given to the Australian Government increasing funding, and to the states and territories also providing funding (Recommendation 3.a). Changes to the model for allocation of funding to sites should also be considered to better reflect the volume of cases at sentinel sites and the methods used to collect data (Recommendation 1.b).

The need for more subtyping of influenza samples was also a common theme in the stakeholder consultation. In particular, it was noted that not all hospitals undertake subtyping of influenza samples which may affect the representativeness of the samples that are subtyped. Increasing the number of influenza samples that are subtyped would improve the estimation of vaccine effectiveness by subtype however this presents a major challenge for FluCAN. This surveillance system is largely a passive system in that influenza testing is undertaken as part of routine clinical care. The subtyping of more samples would require more funding even if samples were sent on elsewhere for subtyping due to the time-consuming process required to link the different laboratory identifiers back to samples and to integrate this information back into FluCAN (Recommendation 3.b). As the subtyping of influenza samples is a challenge for influenza surveillance in Australia generally, options to address this both through FluCAN and other systems should be considered by NISC (Recommendation 2.a).

The key findings of this evaluation are reflected in the following recommendations.

Recommendations

1. Recommendations for the FluCAN Director and Research Coordinators:

a) Include additional denominator data in FluCAN reports, such as the proportion of all admissions to sentinel sites that are due to laboratory confirmed influenza, in order to indicate the burden of influenza on the hospital system and improve comparability between seasons.

b) Explore funding allocation models that reflect site workload both in terms of numbers of cases and processes used by sentinel sites to collect data.

c) Examine administrative challenges related to staff contacts at sentinel sites in order to improve the timeliness and representativeness of cases early in the system.

d) Explore the inclusion of a paediatric specific sentinel site in Victoria in order to address the under-representation of paediatric cases in Victoria.

e) Explore options to improve the completion of the vaccination status field including:

   i. whether project staff could be given access to AIR;

   ii. development of interview scripts for data collection staff conducting follow-up with discharged patients to ascertain vaccination status; or

   iii. letters to discharged patients advising of their influenza test result and advising that they will be contacted regarding their vaccination status.

f) Provide stakeholders with access to consolidated historical FluCAN data and line listed reporting by jurisdiction in REDCap.

g) Develop a user guide for extraction of data from REDCap.

h) Trial alternative presentation of graphs (specifically the use of stacked bar graphs and dot plots) in the weekly national FluCAN report.

i) Explore whether the frequency of required password changes in the Monash University REDCap database server can be reduced.

j) Provide an overview of factors that may affect the comparability of data from FluCAN with other sources of hospitalisation data and approximate lag times in data entry to build stakeholder confidence.

2. Recommendations for NISC

a) Explore barriers to influenza subtyping across jurisdictions generally and options to increasing influenza subtyping through FluCAN or other systems.

3. Recommendations for the Australian Government and state and territory health departments

a) Increase funding for FluCAN to reflect the increasing cost of salaries and volume of work that has arisen from the increasing number of influenza-related hospitalisations.
b) Subject to NISC consideration of options to increase influenza subtyping, consider: increasing FluCAN funding for:
   i. additional subtyping of influenza samples by sentinel site laboratories; or
   ii. coordination and referral of influenza samples to reference laboratories for subtyping, and cross referencing and entry of results back into FluCAN.

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Appendices

Appendix III.a Survey for NISC Members

1. Affiliation or stakeholder group

Q1 1. Please indicate your affiliation or stakeholder group. You may select more than one option:

- ☐ Government (1)
- ☐ Laboratory (2)
- ☐ Surveillance system (3)
- ☐ Other, please specify (4) _____

End of Block

2. Aims of FluCAN

2. a) With reference to the aims of FluCAN (listed in the table on the left), how would you rate the **importance** of each aim in relation to influenza surveillance in Australia?

	Extremely important	Very important	Moderately important	Slightly important	Not at all important	Don't know
A. To collect real-time sentinel surveillance for influenza requiring hospitalisation, to provide a reliable and timely source of information to inform public health policy.	O	O	O	O	O	O
B. To collect detailed clinical and laboratory information from all patients hospitalised within the network with a laboratory confirmed diagnosis of influenza to determine the burden of disease requiring hospitalisation associated with influenza.	O	O	O	O	O	O
C. To estimate the effectiveness of influenza vaccine against hospitalisation against influenza by comparing influenza vaccine status in patients with influenza and test-negative controls. (3)	O	O	O	O	O	O

2.b) With reference to the aims of FluCAN (listed in the table on the left), how **effective** do you think FluCAN is in achieving these aims?

	Extremely effective	Very effective	Moderately effective	Slightly effective	Not at all effective	Don't know
A. To collect real-time sentinel surveillance for influenza requiring hospitalisation, to provide a reliable and timely source of information to inform public health policy.	O	O	O	O	O	O
B. To collect detailed clinical and laboratory information from all patients hospitalised within the network with a laboratory confirmed diagnosis of influenza to determine the burden of disease requiring hospitalisation associated with influenza.	O	O	O	O	O	O
C. To estimate the effectiveness of influenza vaccine against hospitalisation against influenza by comparing influenza vaccine status in patients with influenza and test-negative controls.	O	O	O	O	O	O

2.c) If you rated FluCAN as being 'Slightly effective' or 'Not effective at all' in achieving any of the aims listed, please explain the reason for your response, citing the aim(s) to which you are referring.

_____

2.d) Do you think that any other aims should be added?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: End of Block If Q5 != Yes (1)

2.e) If you answered '**yes**' to **2e**, what aim(s) do you think should be added and why?

_____

_____
_____

End of Block

3. Usefulness

3. a) How would you rate the overall usefulness of FluCAN in terms of contributing to the prevention and control of influenza, including improving our understanding of the public health implications of influenza?

O Extremely useful (1)

O Very useful (2)

O Moderately useful (3)

O Slightly useful (4)

O Not useful (5)

O Don't know (6)

Skip To: Q9 If Q7 = Don't know (6)

3.b) Why did you give the above rating for usefulness and how might this be improved (if applicable)?

_____
_____
_____

3. c) What gaps does FluCAN fill that are not filled by any other surveillance system in Australia? Please provide detail.

_____
_____
_____

End of Block

4. Acceptability and simplicity

4. a) Do you use data from or reports/outputs from FluCAN?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: Q11 If Q10 = No (2)
Skip To: Q13 If Q10 = Yes (1)
Skip To: End of Block If Q10 = Don't know (3)

4. b) If you answered '**no'** to **4a**, why don't you use these data or reports/outputs? Please select all that apply.

- ☐ Difficult to access (1)
- ☐ Data or reports are not relevant to my work (2)
- ☐ Other, please specify (3) _____

Skip To: Q12 If Q11 = Difficult to access (1)
Skip To: End of Block If Q11 != Difficult to access (1)

Q12 4.c) If you answered 'difficult to access' to question 4b, please provide detail.

_____
_____
_____
_____
_____

Skip To: End of Block If
Skip To: End of Block If

4. d) If you answered '**yes'** to **4a** what do you use these data or reports/outputs for? Please select all that apply.

- ☐ Monitoring/overseeing the operation of FluCAN (1)
- ☐ Monitoring the overall picture of the influenza season (2)
- ☐ Monitoring the severity of influenza seasons or strains (3)
- ☐ Monitoring risk factors associated with influenza-related hospitalisations (4)
- ☐ Monitoring vaccine effectiveness (5)
- ☐ Policy development (6)
- ☐ Program development or management (7)
- ☐ Research (8)
- ☐ General interest (9)
- ☐ Other, please specify (10) _____

4. e) Please specify which data, reports or outputs you use.

_____
_____
_____

4.f) Do you have any comments or suggestions for improvement regarding the data, reports or outputs that you indicated using? Please provide detail.

_____
_____
_____

4. g) Have you experienced any problems or barriers in accessing or using FluCAN data?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: End of Block If Q16 != Yes (1)

4.h) If you answered to 'yes' to 4g, please expand upon these problems or barriers and how they might be addressed.

_____
_____
_____

End of Block

5. Sensitivity

5.a) Do you think that FluCAN is able to effectively detect outbreaks of influenza or changes in influenza trends?

	A. Outbreaks of influenza (1)	B. Changes in influenza trends (2)
Yes (1)	☐	☐
No (2)	☐	☐
Don't know (3)	☐	☐

5.b) If you answered to 'no' to one or more of the sub-questions in 5a, please explain the reason for your response.

_____
_____
_____

End of Block

6. Timeliness

6. a) Do you think that FluCAN provides timely information about influenza hospitalisations that would not otherwise be readily available?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: End of Block If Q20 != No (2)

6.b) If you answered '**No**' to **6a**, please explain the reason for your response.

_____
_____
_____

End of Block

7. Data quality

7.a) How satisfied are you with the data collected and reported by FluCAN?

O Very satisfied (9)

O Satisfied (10)

O Neither satisfied nor dissatisfied (11)

O Dissatisfied (12)

O Very dissatisfied (13)

O Don't know (14)

Skip To: End of Block If Q22 = Very satisfied (9)
Skip To: End of Block If Q22 = Satisfied (10)
Skip To: End of Block If Q22 = Neither satisfied nor dissatisfied (11)
Skip To: End of Block If Q22 = Don't know (14)

7.b) If you answered 'Dissatisfied' or 'Very dissatisfied' to 7a, please explain the reason for your response.

_____
_____
_____

End of Block

8. Representativeness

8.a) Noting that FluCAN is a sentinel surveillance system, do you think the representativeness of FluCAN data is adequate with reference to geographical distribution of hospital sites and the demographic characteristics of cases?

O Yes (13)

O No (14)

O Don't know (15)

Skip To: End of Block If Q24 != No (14)

8.b) If you answered '**No**' to **8a**, please explain the reason for your response.

_____

End of Block

9. Strengths and weaknesses

9.a) In your view, what are the strengths of FluCAN? Please provide detail.

_____
_____
_____

9.b) In your view, what are the weaknesses of FluCAN? Please provide detail.

_____
_____
_____

End of Block

10. Other comments or suggestions for improvements

10. Do you have any other comments or suggestions for how FluCAN might be improved? Please provide detail.

_____
_____
_____

End of Block

Appendix III.b Survey for FluCAN contributors

1. Role

Q1 1. Please indicate your **primary** role in FluCAN.

- O Data collection including the coordination of data collection (1)
- O Investigator (2)

End of Block

2. Aims of FluCAN (all respondents)

2. a) With reference to the aims of FluCAN (listed in the table on the left), how would you rate the **importance** of each aim in relation to influenza surveillance in Australia?

	Extremely important	Very important	Moderately important	Slightly important	Not at all important	Don't know
A. To collect real-time sentinel surveillance for influenza requiring hospitalisation, to provide a reliable and timely source of information to inform public health policy.	o	o	o	o	o	o
B. To collect detailed clinical and laboratory information from all patients hospitalised within the network with a laboratory confirmed diagnosis of influenza to determine the burden of disease requiring hospitalisation associated with influenza.	o	o	o	o	o	o
C. To estimate the effectiveness of influenza vaccine against hospitalisation against influenza by comparing influenza vaccine status in patients with influenza and test-negative controls.	o	o	o	o	o	o

2.b) With reference to the aims of FluCAN (listed in the table on the left), how **effective** do you think FluCAN is in achieving these aims?

	Extremely effective	Very effective	Moderately effective	Slightly effective	Not effective at all	Don't know
A. To collect real-time sentinel surveillance for influenza requiring hospitalisation, to provide a reliable and timely source of information to inform public health policy.	o	o	o	o	o	o
B. To collect detailed clinical and laboratory information from all patients hospitalised within the network with a laboratory confirmed diagnosis of influenza to determine the burden of disease requiring hospitalisation associated with influenza.	o	o	o	o	o	o
C. To estimate the effectiveness of influenza vaccine against hospitalisation against influenza by comparing influenza vaccine status in patients with influenza and test-negative controls.	o	o	o	o	o	o

2.c) If you rated FluCAN as being 'Slightly effective' or 'Not effective at all' in achieving any of the aims listed, please explain the reason for your response citing the aim(s) to which you are referring.

_____
_____
_____

2.d) Do you think that there are any other aims that FluCAN could or should be trying to achieve?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: End of Block If Q5 != Yes (1)

2.e) If you answered 'yes' to 2e, what aim(s) do you think should be added and why?

_____
_____
_____

End of Block

3. Usefulness (investigator only)

a) How would you rate the overall usefulness of FluCAN in terms of contributing to the prevention and control of influenza, including improving our understanding of the public health implications of influenza?

Extremely useful (1)

O Very useful (2)

O Moderately useful (3)

O Slightly useful (4)

O Not useful (5)

O Don't know (6)

Skip To: Q9 If Q7 = Don't know (6)

3.b) Why did you give the above rating for usefulness and how might this be improved (if applicable)?

_____
_____
_____

3.c) What gaps does FluCAN fill that are not filled by any other surveillance system in Australia? Please provide detail.

_____
_____
_____

End of Block

4. Resources (investigator only)

4.a) Do you believe that your unit is sufficiently resourced for FluCAN activities in terms of funding, training and other resources?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: Q12 If Q10 != No (2)

4.b) If you answered 'no' to question 4a, how could FluCAN resourcing could be improved?

_____
_____
_____

4.c) Approximately, how many **full-time equivalent (FTE) staff** are employed at your site to work on FluCAN related Investigator and on data collection/coordination activities during the following phases? If unknown, please enter an X in the 'Don't know column'.

	Investigator activities		Data collection/coordination activities	
	FTE staff (1)	Don't know (2)	FTE staff (1)	Don't know (2)
Pre-season (April to end of May) (1)				
Flu-season (June to end of Oct) (2)				
Post and inter-season (Nov to end of March) (3)				

4.d) Approximately how many **hours per week** are spent at your site on FluCAN related Investigator and on data collection/coordination activities during the following phases? If unknown, please enter an X in the 'Don't know column'.

	Investigator activities		Data collection/coordination activities	
	Hours per week (1)	Don't know (2)	Hours per week (1)	Don't know (2)
Pre-season (April to end of May) (1)				
Flu-season (June to end of Oct) (2)				
Post and inter-season (Nov to end of March) (3)				

End of Block

4. Resources (data collection only)

4.a) Do you believe that your unit is sufficiently resourced for FluCAN activities in terms of funding, training and other resources?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: Q48 If Q46 != No (2)

4.b) If you answered 'no' to question 4a, how could FluCAN resourcing could be improved?

_____
_____
_____

4.c) Approximately, how many **full-time equivalent (FTE) staff** are employed at your site to work on FluCAN related data collection/coordination activities during the following phases? If unknown, please enter an X in the 'Don't know' column'.

	Data collection/coordination activities	
	FTE staff (1)	Don't know (2)
Pre-season (April to end of May) (1)		
Flu-season (June to end of Oct) (2)		
Post and inter-season (Nov to end of March) (3)		

4.d) Approximately how many **hours per week** are spent at your site on FluCAN related data collection/coordination activities at your site during the following phases? If unknown, please enter an X in the 'Don't know' column.

	Data collection/coordination activities	
	Hours per week (1)	Don't know (2)
Pre-season (April to end of May) (1)		
Flu-season (June to end of Oct) (2)		
Post and inter-season (Nov to end of March) (3)		

End of Block

5. Simplicity and acceptability (investigator only)

5.a) With reference to the questions on the left in the table below, how would you rate the ease of FluCAN processes (if applicable to your role)?

	Very easy (1)	Easy (2)	Neither easy or difficult (3)	Difficult (4)	Very difficult (5)	Not applicable (6)
How easy is it to audit and identify/address errors in FluCAN? (2)	O	O	O	O	O	O
How easy is it to extract data from FluCAN for analysis and reporting? (3)	O	O	O	O	O	O
How easy is it to generate routine FluCAN reports? (4)	O	O	O	O	O	O
Overall, how easy is it to oversee the FluCAN surveillance system at your site? (1)	O	O	O	O	O	O

5.b) If you answered 'Difficult' or 'Very difficult' to any of the questions in 5a above please explain the reason for your response.

_____
_____
_____

5.c) Are there any improvements that could be made to improve the efficiency and ease of FluCAN processes? Please provide detail.

_____
_____
_____

5.d) Do you use data from or reports/outputs from FluCAN?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: Q18 If Q17 = No (2)
Skip To: Q20 If Q17 = Yes (1)
Skip To: End of Block If Q17 = Don't know (3)

5.e) If you answered 'no' to 5d, why don't you use these data or reports/outputs? Please select all that apply.

- ☐ Difficult to access (1)
- ☐ Data or reports are not relevant to my work (2)
- ☐ Other, please specify (3) _____

Skip To: End of Block If Q18 != Difficult to access (1)

5.f) If you answered 'difficult to access' to question 5e, please provide detail.

_____
_____
_____

Skip To: End of Block If
Skip To: End of Block If

5.g) If you answered '**yes'** to **5d** what do you use these data or reports/outputs for? Please select all that apply.

- ☐ Monitoring/overseeing the operation of FluCAN (1)
- ☐ Monitoring the overall picture of the influenza season (2)
- ☐ Monitoring the severity of influenza seasons or strains (3)
- ☐ Monitoring risk factors associated with influenza-related hospitalisations (4)
- ☐ Monitoring vaccine effectiveness (5)
- ☐ Policy development (6)
- ☐ Program development or management (7)
- ☐ Research (8)
- ☐ General interest (9)
- ☐ Other, please specify (10) _____

5.h) Please specify which data, reports or outputs you use.

_____
_____
_____

5.h) Do you have any comments or suggestions for improvements regarding the data or reports that you indicated using? Please provide detail.

_____
_____
_____

5.i) Have you experienced any problems or barriers in accessing or using FluCAN data?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: End of Block If Q23 != Yes (1)

5.j) If you answered to 'yes' to 5i please expand upon these problems or barriers and how they might be addressed.

_____
_____
_____

End of Block

5. Simplicity and acceptability (data collection only)

5.a) With reference to the questions on the left in the table below, how would you rate the ease of FluCAN processes (if applicable to your role)?

	Very easy (1)	Easy (2)	Neither easy or difficult (3)	Difficult (4)	Very difficult (5)	Not applicable (6)
How easy is it to identify and recruit cases and controls? (2)	O	O	O	O	O	O
How easy is it to extract or collect the **initial or summary data** required for cases and controls? (3)	O	O	O	O	O	O
How easy is it to extract or collect the **follow up data** required for cases and controls? (4)	O	O	O	O	O	O
How easy is it to enter data in the Redcap data base? (5)	O	O	O	O	O	O
Overall, how easy is it to use or contribute to the FluCAN surveillance system? (1)	O	O	O	O	O	O

5.b) If you answered '**Difficult'** or **'Very difficult**' to any of the questions in **5a** above please explain the reason for your response.

_____
_____
_____

5.c) Are there are specific fields of data that are difficult to collect or record (e.g. smoking or vaccination status)? Please provide detail.

_____
_____
_____

5.d) Are there any improvements that could be made to improve the efficiency and ease of FluCAN processes? Please provide detail.

_____
_____
_____
_____
_____

5.e) Do you use data from or reports/outputs from FluCAN?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: Q56 If Q53 = Yes (1)
Skip To: Q54 If Q53 = No (2)
Skip To: End of Block If Q53 = Don't know (3)

5.f) If you answered 'no' to 5e, why don't you use these data or reports/outputs? Please select all that apply.

☐ Difficult to access (1)

☐ Data or reports are not relevant to my work (2)

☐ Other, please specify (3) _____

Skip To: End of Block If Q54 != Difficult to access (1)

5.g) If you answered 'difficult to access' to question 5e, please provide detail.

_____
_____
_____

Skip To: End of Block If
Skip To: End of Block If

5.h) If you answered **'yes'** to **5e** what do you use these data or reports/outputs for? Please select all that apply.

- ☐ Monitoring or overseeing the operation of FluCAN (1)
- ☐ Monitoring the overall picture of the influenza season (2)
- ☐ Monitoring the severity of influenza seasons or strains (3)
- ☐ Monitoring risk factors associated with influenza-related hospitalisations (4)
- ☐ Monitoring vaccine effectiveness (5)
- ☐ Policy development (6)
- ☐ Program development or management (7)
- ☐ Research (8)
- ☐ General interest (9)
- ☐ Other, please specify (10) _____

5.i) Please specify which data, reports or outputs you use.

_____
_____
_____

5.j) Do you have any comments or suggestions for improvement regarding the data or reports that you indicated using? Please provide detail.

_____
_____
_____
_____
_____

5.k) Have you experienced any problems or barriers in accessing or using FluCAN data?

- O Yes (1)
- O No (2)
- O Don't know (3)

Skip To: End of Block If Q59 != Yes (1)

5.l) If you answered to 'yes' to 5k please expand upon these problems or barriers and how they might be addressed?

_____
_____
_____
_____
_____

End of Block

6. Flexibility (all respondents)

6.a) In the event of data needing to be collected for a new respiratory disease, how easy would it be for your site to adapt to collecting data for this respiratory disease assuming similar fields of data were being collected?

O Very easy (1)

O Easy (2)

O Neither easy nor difficult (3)

O Difficult (4)

O Very difficult (5)

O Don't know (6)

Skip To: End of Block If Q25 = Very easy (1)
Skip To: End of Block If Q25 = Easy (2)
Skip To: End of Block If Q25 = Neither easy nor difficult (3)
Skip To: End of Block If Q25 = Don't know (6)

6.b) If you answered 'Difficult' or 'Very Difficult' to 6a, please explain the reason for your response.

_____
_____
_____

End of Block

7. Sensitivity (investigator only)

7.a) Do you think that FluCAN is able to effectively detect outbreaks of influenza or changes in influenza trends?

	A. Outbreaks of influenza (1)	B. Changes in influenza trends (2)
Yes (1)	☐	☐
No (2)	☐	☐
Don't know (3)	☐	☐

7.b) If you answered to 'no' to one or more of the sub-questions in 7a, please explain the reason for your response.

_____
_____
_____

7.c) Do you think that FluCAN is capturing all true cases of influenza in patients presenting with influenza-like-illness at your site?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: End of Block If Q29 = Yes (1)
Skip To: End of Block If Q29 = Don't know (3)

7.d) If you answered to 'No to 7c, please explain the reason for your response.

_____
_____
_____

End of Block

7. Sensitivity (data collection only)
7.a) Do you think that FluCAN is capturing all true cases of influenza in patients presenting with influenza-like-illness at your site?
Yes (1)

O No (2)

O Don't know (3)

Skip To: End of Block If Q61 != No (2)

7.b) If you answered to 'No to 7a, please explain the reason for your response.

_____
_____
_____

End of Block

8. Timeliness (investigator)

8. a) Do you think that FluCAN provides timely information about influenza hospitalisations that would not otherwise be readily available?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: Q33 If Q31 != No (2)

8.b) If you answered 'No' to 8a, please explain the reason for your response.

_____
_____
_____

8.c) Does you site have defined protocols or indicators for the timeliness of entry of initial data for influenza positive cases into FluCAN?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: Q35 If Q33 = No (2)
Skip To: Q35 If Q33 = Don't know (3)

8.d) If you answered 'yes' to 8c, please describe your site's protocols or indicators for the timeliness of initial data for influenza positive cases into FluCAN.

_____
_____
_____

8.e) During the FluCAN phases listed on the left in the table below, are the initial data for most influenza positive cases (i.e. greater than 75% of cases) entered into FluCAN within:

	7 days of patient admission (1)	8 to 14 days of patient admission (2)	Greater than 14 days of patient admission (3)	Don't know (4)
Pre-season (April to end of May) (1)	O	O	O	O
Flu-season (June to end of Oct) (2)	O	O	O	O

8.f) Where the entry of initial data into FluCAN for influenza positive cases takes greater than 7 days or is outside your sites protocols for timeliness, what factors contribute to this? Please select all that apply.

- ☐ Not enough FluCAN staff (1)
- ☐ New staff being trained (or recently trained) in FluCAN processes (2)
- ☐ Delays in testing of patients (3)
- ☐ Delays in the availability of lab results for patients (4)
- ☐ High number of influenza-associated hospitalisations (7)
- ☐ Don't know (5)
- ☐ Other, please specify (6) _____

End of Block

8. Timeliness (data collection only)

8.a) Does your site have defined protocols or indicators for the timeliness of entry of initial data for influenza positive cases into FluCAN?

- O Yes (1)
- O No (2)
- O Don't know (3)

Skip To: Q67 If Q65 = No (2)
Skip To: Q67 If Q65 = Don't know (3)

8.b) If you answered 'yes' to 8c, please describe your site's protocols or indicators for the timeliness of initial data for influenza positive cases into FluCAN.

_____
_____
_____

8.c) During the FluCAN phases listed on the left in the table below, are the initial data for most influenza positive cases (i.e. greater than 75% of cases) entered into FluCAN within:

	7 days of patient admission (1)	8 to 14 days of patient admission (2)	Greater than 14 days of patient admission (3)	Don't know (4)
Pre-season (April to end of May) (1)	O	O	O	O
Flu-season (June to end of Oct) (2)	O	O	O	O

8.d) Where the entry of initial data into FluCAN for influenza positive cases takes greater than 7 days or is outside your sites protocols for timeliness, what factors contribute to this? Please select all that apply.

- ☐ Not enough FluCAN staff (1)
- ☐ New staff being trained (or recently trained) in FluCAN processes (2)
- ☐ Delays in testing of patients (3)
- ☐ Delays in the availability of lab results for patients (4)
- ☐ High number of influenza-associated hospitalisations (7)
- ☐ Don't know (5)
- ☐ Other, please specify (6) _____

End of Block

9. Data quality (all respondents)

9.a) How satisfied are you with the data collected and reported by FluCAN?

- O Very satisfied (9)
- O Satisfied (10)
- O Neither satisfied nor dissatisfied (11)
- O Dissatisfied (12)
- O Very dissatisfied (13)
- O Don't know (14)

Skip To: End of Block If Q37 = Very satisfied (9)
Skip To: End of Block If Q37 = Satisfied (10)
Skip To: End of Block If Q37 = Neither satisfied nor dissatisfied (11)
Skip To: End of Block If Q37 = Don't know (14)

9.b) If you answered 'Dissatisfied' or 'Very dissatisfied' to 9a, please explain the reason for your response.

_____
_____
_____

End of Block

10. Stability (all respondents)

10.a) In your view or experience, how stable do you think the FluCAN surveillance system is with regard to its ability to collect, manage and provide data without failure?

- O Very stable (1)
- O Stable (2)
- O Neither stable or unstable (3)
- O Unstable (4)
- O Very unstable (5)
- O Don't know (6)

Skip To: Q41 If Q39 = Don't know (6)
Skip To: Q41 If Q39 = Very stable (1)
Skip To: Q41 If Q39 = Stable (2)
Skip To: Q41 If Q39 = Neither stable or unstable (3)

10.b) If you answered 'Unstable' or 'Very unstable' to 10.a please explain the reason for your response.

_____
_____
_____

10.c) n your view, is the “site stress” measure, which is implemented when the number of cases reported by sentinel sites reaches a stress limit, adequate to reduce workload on staff?

O Yes (1)

O No (2)

O Don't know (3)

Skip To: End of Block If Q41 != No (2)

10.d) If you answered ‘No’ to 10c, please explain the reason for your response.

_____
_____
_____

End of Block

11. Strengths and weaknesses (all respondents)

11.a) In your view, what are the strengths of FluCAN? Please provide detail.

_____
_____
_____

11.b) In your view, what are the weaknesses of FluCAN? Please provide detail.

_____
_____
_____

End of Block

12. Other comments or suggestions for improvement (all respondents)

12. Do you have any other comments or suggestions for how FluCAN might be improved? Please provide detail.

_____
_____
_____

End of Block

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Chapter IV:
Epidemiological study

Epidemiology of Shiga toxin producing *Escherichia coli* and exclusion of high-risk cases, Victoria, 2002–2003 to 2016–2017

"The best laid schemes o' mice an' men, / Gang aft a-gley" [The best laid schemes of mice and men / Go often askew]

To a Mouse, on Turning Her Up in Her Nest With the Plough, November, 1785

Robert Burns

Table of contents

Prologue

Preface

This chapter describes an epidemiological study conducted in order to describe the epidemiology of Shiga toxin-producing *Escherichia coli* (STEC) in Victoria and to investigate the implications of testing practices used to determine exclusion of cases in high-risk groups including children attending child care, food handlers, and child and health care workers. The purpose of this study was to inform Victoria's policy regarding the exclusion of cases in these high-risk groups.

Project role

This project was initiated by Zoe Cutcher (OzFoodNet Epidemiologist in the Victorian Government Department of Health and Human Services (DHHS)) who, in collaboration with Rebecca Schack (Public Health Officer, DHHS), had observed a case of extended detection of STEC in faecal samples collected to determine pathogen clearance using polymerase chain reaction (PCR). Both this case and changes in STEC testing practices have highlighted the potential implications for individuals of Victoria's current policy to minimise person-to-person transmission of STEC through the exclusion of cases in high-risk occupations from work until cessation of symptoms and two consecutive faecal samples are negative for STEC. This policy may also extend to the exclusion of children from child care.

As the lead investigator on this project, I developed the project and data analysis plan with input from Zoe Cutcher and Lucinda Franklin (Senior Epidemiologist DHHS) and reviewed exclusion policies of other jurisdictions. I also extracted case and testing information from the surveillance database, cleaned (involving review of hard copy files) and analysed the data, and reported findings back to internal stakeholders.

Lesson learnt

While initially appearing straightforward, this project was the most challenging of the projects I undertook as part of the Master of Applied Epidemiology. Despite being well planned this project threw up unexpected challenges.

I was aware when beginning this project that the number of cases with clearance testing data was only available for a small number of cases, with around 22 cases marked as belonging to high-risk groups (a further three cases were later identified during review of the data). I was therefore careful to scrutinise the clearance testing

results for these cases to see if I would have enough data to complete my planned analysis and to see if there were any other cases I could include. My preliminary review of these results appeared to support my hypothesis that cases took longer to test negative for STEC using PCR based methods as compared to culture, but that the time required to undertake the testing was longer for culture.

Later when reviewing the hardcopy files, I discovered data entry errors which could not be identified as part of data cleaning of the electronic dataset using data analysis software alone. These errors included the duplicate entry of test results where the date the laboratory received the sample had been erroneously entered in place of the date of sample collection making them appear as tests on separate samples. Additionally, results had been entered stating that samples tested 'culture negative' where culture based tests had not been performed. In practice these are merely data entry errors which have no public health significance but for my analysis this led to observation error. This reduced the number of cases which could be included in the study group as having two culture negative results to two.

These challenges with the quality of data were compounded by the short period of time I had to complete this project. This study was initiated as a replacement project after the data required for my originally planned epidemiological study at the Murdoch Childrens Research Institute (MCRI) did not arrive in time. While my study did not have sufficient sample size to enable conclusions about my key hypothesis, the descriptive case series review was useful as I was able to make findings about the overall length of exclusion of high-risk cases and alternative exclusion criteria which could be implemented. These findings will inform a review of the Victorian exclusion policy.

Overall, this project developed my understanding of the epidemiology of STEC and diagnostic methods for the detection, isolation and identification of STEC. It also showed me that some data quality issues cannot be identified through data cleaning in software packages alone. Previously I had used data analysis software to identify potential errors for checking in hardcopy files, which is an approach more suitable for datasets collected specifically for that research purpose. Last, but not least this project taught me that sometimes despite good planning, research projects can go awry.

Public health impact

This study provides important information about the implications of Victoria's exclusion policy for STEC cases, particularly highlighting the need to review the requirement that two consecutive negative faecal samples are provided, in light of changes in testing practices and the length of exclusion of high-risk cases. To inform any future policy review, this study also provides a comparison of STEC exclusion policies from other jurisdictions, and discusses how adopting policies in place in New South Wales, South Australia and the Australian Capital Territory would impact on the length of exclusion of cases.

Additionally, this study describes the epidemiology of STEC in Victoria including regional differences in rates of STEC.

Communication

The key findings of this study have been provided to the Victorian OzFoodNet epidemiologists and will inform a review of Victoria's exclusion policies for cases in high-risk groups. My findings which highlighted discrepancies in STEC laboratory data fields have been communicated to the relevant staff to enable revision and clarification of the STEC data entry guidelines.

Master of Applied Epidemiology core requirement

This chapter is written in fulfilment of the field placement core activity to design and conduct an epidemiological study.

Acknowledgements

I gratefully acknowledge the contribution of:

- Zoe Cutcher, Lucinda Franklin and my academic supervisor Katrina Roper, for their input and support throughout the project
- Mary Valcanis and Nela Subasinghe of the Microbiological Diagnostic Unit Public Health Laboratory for their advice on methods for the detection of STEC and the interpretation of laboratory results
- Rebecca Schack for providing information on the process for follow-up of STEC cases in high-risk groups.

Abstract

Background: Shiga toxin-producing *Escherichia coli* (STEC) is an uncommon but important cause of gastrointestinal illness because of the potential for development of serious complications. In Victoria, in order to prevent person-to-person transmission of STEC, cases in high-risk occupations (food handlers, child care and health care workers) are required to be excluded from work until cessation of symptoms and two consecutive faecal samples taken at least 24 hours apart are negative for STEC. This exclusion policy may also extend to the exclusion of children from child care. Changes in STEC testing methods and the observation of a case of extended detection of STEC by polymerase chain reaction (PCR) have prompted the need for a review of Victoria's exclusion policy. The primary objectives of this project were to inform this review by describing the epidemiology of STEC in Victoria and by comparing the duration of exclusion from work or child care for high-risk cases as determined by PCR versus culture-based methods for the detection and isolation of STEC.

Methods: Notifications of STEC received between 1 July 2002 and 30 June 2017 were extracted from the Victorian Government Department of Health and Human Services (DHHS) Public Health Surveillance System (PHESS). Rates of STEC notifications by year, age group and geographical region were calculated using Australian Bureau of Statistics (ABS) estimated resident population (ERP). For cases in the high-risk groups described above ('high-risk cases') the median and range of exclusion time as determined by PCR and culture was calculated as the time from illness onset to the date that DHHS received the laboratory result for the second consecutive negative test. As the exclusion period is influenced by both the time taken for cases to reach a second negative test ('time to sample clearance') and the time taken for the sample to be tested and for the result to be received in DHHS ('turnaround time'), the exclusion time was broken down into these components. Notified cases of STEC were reviewed in order to identify cases of person-to-person transmission of STEC amongst household contacts of high-risk cases and to identify when transmission may have occurred.

Results: Notifications of STEC in Victoria have increased from a low of 4 notifications (0.1 cases per 100,000 population) in 2003–04 to 37 notifications in 2016–17 (0.6 cases per 100,000 population). An increase in the number of notified case occurred after the Microbiological Diagnostic Unit Public Health Laboratory (MDU) commenced PCR

testing for STEC in 2004–05. A second increase occurred when a public pathology provider commenced testing for STEC as part of an enteric bacteria PCR panel in 2014–15. Notification rates were highest among those aged under 5 years of age. There was geographic variation in STEC incidence with the highest rate in the Barwon-South West region of Victoria. There were 25 high-risk cases in the dataset of which only two had two consecutive negative samples which tested negative by culture-based methods and 12 cases who had two consecutive negative samples by PCR. The exclusion period for the high-risk cases in the culture group (median 49.5 days, range 39–60) was longer than that for those high-risk cases in the PCR group (median 39.5 days, 23–65). This was influenced by the longer 'turnaround time' for culture results, as the 'time to clearance' was similar in both groups. The shortest exclusion period amongst high-risk cases was 23 days. Exclusion of cases until 48 hours after cessation of symptoms as is required for high-risk cases in some jurisdictions would have resulted in shorter exclusion periods (median 7 days, range 5–16). There were no cases of person-to-person transmission identified amongst household contacts of high-risk cases.

Conclusions: The increase in the number and rate of notified cases from 2003–04 to 2016–17 is likely to be at least partially related to changes in STEC testing and recent changes to the national case definition for STEC. Although the number of high-risk cases with two consecutive samples which tested negative by culture-based methods was too small to enable conclusions about the duration of exclusion by diagnostic method, long exclusion periods were identified. This results in a socio-economic burden for cases and their families, especially where they have exhausted their paid sick leave provisions or are employed on a casual basis and are not eligible for paid sick leave. Consideration should be given to reviewing adoption of policies similar to that in place in some jurisdictions that require that high-risk cases wait between 24 and 48 hours after cessation of symptoms to return to work or child care. At the national level, consideration should also be given to developing nationally consistent guidance for the public health response to STEC.

Background

Shiga toxin-producing *Escherichia coli* (STEC) are strains of *Escherichia coli* (*E. coli*) that are capable of producing toxins that can bind to the endothelial cells of the intestines resulting in haemorrhagic colitis (bloody diarrhoea).[1, 2] STEC infections can be asymptomatic, or can manifest from watery diarrhoea and abdominal pain, to haemorrhagic colitis. Occasionally, where damage to the blood vessels of the intestines allows toxins to enter the blood stream and circulate through the body, haemolytic uraemic syndrome (HUS) may occur.[1] HUS is a serious complication of STEC characterised by acute renal failure (where kidneys cannot adequately filter metabolic waste from the body), haemolytic anaemia (the destruction of red blood cells which carry oxygen and remove carbon dioxide from the body) and thrombocytopenia (low blood platelets which are required to stop bleeding).[3] HUS can also develop from infection with other pathogens.[4]

Public health importance

Although STEC is less common than other bacterial causes of gastrointestinal illness such as *Salmonella* it is considered to be of high public health importance due to the potential for development of severe complications such as HUS. In 2016 there were 33 notified cases of STEC in Victoria and 341 in Australia (a rate of 0.5 and 1.4 cases per 100,000 population respectively).[5] However, notifications of STEC are considered to significantly underestimate the true burden of disease due to the fraction of cases notified.[6, 7] The incidence of STEC is highest in children under 5 years of age[6, 8] and in older adults.[6]

HUS develops in approximately 3–7% of cases of STEC[9] and is estimated to result in death in approximately 12% of cases.[6] Additionally, up to 50% of those who develop HUS experience some degree of renal impairment.[10] HUS is more common in those under five years of age[11] and also in those over than 70 years.[10]

A study of Australian hospitalisation data indicated that there were 152 hospital admissions with STEC attributed as a principal diagnosis between 1 July 1999 and 30 June 2008, giving an annual rate of 0.08 admissions per 100,000 population.[6] In the same period there were 670 hospital admissions with HUS attributed as a principal diagnosis, giving an annual rate of 0.37 admissions per 100,000 population.[6]

STEC infections in Australia have been estimated to cost approximately $2.6 million each year but the actual figure may be higher.[12] Direct costs including medications and medical care comprise $1.6 million of estimated costs.[12] This is high considering that STEC is a relatively uncommon cause of gastrointestinal illness but reflects the serious nature of STEC infections.

Transmission

The infectious dose (the amount of a pathogen required to cause infection) of STEC is very low.[13] Transmission of STEC is mainly foodborne causing an estimated 57% of illness in Australia, with the remainder of illness being attributed to environmental pathways including animal contact, waterborne and person-to-person transmission.[14]

Cattle are an important reservoir of STEC and other animals such as sheep and goats may also carry the pathogen.[15] Consuming meat or unpasteurised milk from animals carrying STEC may result in infection, as may consuming fruit or vegetables that have been contaminated with pathogens in water used for irrigation, animal manure used as fertiliser, or by animals defecating in or nearby fields where produce is grown.[16] Food may also be contaminated from infected humans during handling and preparation.

The period of communicability (the time during which an infectious agent may be transferred from person-to-person) is estimated to be one week or less in adults, and up to three weeks in children,[13] however prolonged shedding may occur.[17]

Exclusion of cases in high-risk groups

In order to prevent person-to-person transmission most jurisdictions in Australia have implemented policies regarding the exclusion of cases in high-risk groups such as children attending child care centres, food handlers, and health and child care workers. While symptomatic cases are more likely to transmit STEC, post-symptomatic excretion of the pathogen or 'shedding' can also occur.[18] In Victoria food handlers, child care and health care workers must not work until cessation of symptoms and two consecutive faecal samples taken at least 24 hours apart are negative for STEC,[19] and children may be excluded from child care if deemed necessary.[20] The current policy was written in 2011 and does not specify whether this clearance testing should be based on the detection by PCR or culture based methods and needs to be reviewed and updated in light of changes in STEC testing.

Several factors may influence the time to clearance of STEC including serotype[17] and age, with studies suggesting that younger patients may shed the bacteria for longer periods.[21, 22]

Additionally, the sensitivity of diagnostic methods influences the period of time in which STEC can be detected in samples. PCR is a rapid diagnostic method and is more sensitive than culture for detection of STEC.[23] As a result, PCR may be able to detect STEC for longer periods than culture as bacterial loads decrease from the time of infection and fall below the detection limit of culture based methods.[23] Additionally, as PCR detects the genetic material encoding Shiga toxins it may detect both viable or non-viable organisms. As a result, the public health significance of positive PCR tests in terms of whether, and for how long, a case is at risk of transmitting the STEC to others, is difficult to determine. This poses a challenge for policy makers who need to balance the likelihood of transmission of STEC with the burden of exclusion policies on cases who are in high-risk groups.

Objectives

The primary aim of this project was to inform Victoria's policies regarding the exclusion of high-risk cases with STEC from workplaces and child care. Specifically, I sought to:

- describe the epidemiology of notified cases of STEC in Victoria by person, place and time;
- review and describe STEC exclusion policies in other states and territories;
- determine the median and range of exclusion time as determined by diagnostic method (i.e. PCR or culture) using a case series of notified cases in high-risk groups, broken down into:
  - the time taken to reach the second negative result ('time to clearance'); and
  - the time taken for the sample to be tested and for the result to be received in DHHS ('turnaround time'); and
- identify any instances of person-to-person transmission of STEC amongst household contacts of high-risk cases and describe the time during which transmission most likely occurred.

Specifically, I hypothesised that the median exclusion period as determined by culture would be longer due the longer 'turnaround time' for culture based tests, but that the

'time to sample clearance' by PCR would be longer as PCR is a more sensitive diagnostic method.[23]

Methods

Case definition

The case definition for STEC surveillance in Victoria is adapted from the Communicable Disease Network of Australia's (CDNA) case definition for the National Notifiable Diseases Surveillance System.[24] Confirmed cases that meet the CDNA case definition as defined at the time of notification were included in the analysis (Box 1).

Box 1. CDNA STEC case definition

Case definition as at 1 July 2016

Reporting

Only confirmed cases should be notified. A confirmed case requires laboratory definitive evidence only:

Laboratory definitive evidence

1. Isolation of Shiga toxigenic *Escherichia coli* from faeces; or
2. Detection of the gene(s) encoding the Shiga toxins (stx1 and/or stx2) in faeces or from a clinical isolate of *Escherichia coli*.

Note: Where STEC is isolated or detected in the context of haemolytic uraemic syndrome (HUS), it should be notified as STEC and HUS.

Case definition prior to 1 July 2016

Prior to 1 July 2016 the CDNA case definition included the alternative nomenclature 'vero toxin producing *Escherichia coli*'. This was removed from the updated case definition implemented as of 1 July 2016, as was reference to 'isolation of Shiga toxin or vero toxin from a clinical isolate of *Escherichia coli*' and the specification that identification of genes associated with the production of Shiga toxin be from 'raw bloody diarrhoea'.

Source: CDNA 2016[25]

For the purposes of this study, 'high-risk cases' were defined as cases belonging to the following groups:

- food handlers;
- health care workers;
- child care workers;
- children attending child care; or
- persons living in a healthcare or institutional setting such as an aged care facility.

Data extraction

A line list of all notifications of STEC and corresponding laboratory results received by the Victorian Government Department of Health and Human Services (DHHS) between 1 July 2002 and 30 June 2017 was extracted from the Victorian Public Health Event Surveillance System (PHESS). Notifications with a primary classification of (HUS) were also extracted and merged with STEC data if they had laboratory confirmed STEC.

Notifications for individuals who did not meet the case definition (Box 1) or cases that did not reside in Victoria were excluded from all analyses (n=82).

Data analysis

Data cleaning and analysis for all confirmed cases were completed using Stata IC 14 (StataCorp LP, College Station, TX, USA). Missing data for key fields such as age at illness onset, serotype and region of residence were identified from the case notes in PHESS or hardcopy files.

High-risk cases were identified as noted in PHESS, or through review of case notes in PHESS or hardcopy files for cases which were identified in the dataset as having provided multiple faecal samples for testing. Data cleaning for high-risk cases was initially conducted in Stata, however, after identification of unexpected results (i.e. cases in which culture-based tests were reported to have been performed on samples that tested negative or not detected by PCR) the data was checked against hardcopy laboratory test reports and case notes. The dataset was amended in Excel and then analysed in Stata.

Rate of notifications

The rate of notifications of confirmed STEC and HUS by age, sex, and DHHS regions was calculated using ABS estimated resident population data[26, 27] for relevant years.

States and territory policies for the exclusion of high-risk cases

The websites of state and territory health departments were reviewed to determine their respective exclusion policies. Where no information was publicly available, enquiries were made directly to the relevant jurisdiction.

Exclusion of cases in high-risk groups

For high-risk cases the exclusion period was calculated as the time from illness onset to the date that DHHS received notification of the second consecutive negative on subsequent samples provided for clearance testing (i.e. not including any negative results by culture on initial samples provided for diagnosis of STEC which also tested positive by PCR). The exclusion period is influenced by two key factors, the time taken to reach the second negative result ('time to sample clearance') and the time taken for the sample to be tested and for the result to be received in DHHS ('turnaround time'). Therefore, the exclusion period was broken down into 'time to sample clearance' which was calculated from the time of onset of illness to the date of sample collection for the second consecutive negative sample, and 'turnaround time' as calculated from the date of sample collection for the second consecutive negative sample to the date that DHHS was notified of the laboratory test result.

Where onset date was not available (e.g. for asymptomatic high-risk cases screened due to their connection to a symptomatic high-risk case) the date of sample collection for the first positive sample was used in place of onset date. Where the date DHHS was notified of the result was not available, the date the laboratory issued the test result was used instead.

The median and range of time high-risk cases would be excluded based on their results, as well as the 'time to sample clearance' and 'turnaround time' was calculated separately by diagnostic method (i.e. PCR versus culture).

A secondary analysis was also undertaken to calculate the median and range of time that cases would have been excluded if they were required to wait 48 hours after

cessation of symptoms instead of providing two negative faecal samples where duration of illness was available.

Person-to-person transmission amongst household contacts

I also reviewed notified cases which had been linked to high-risk cases in PHESS or that had the same address in order to identify any instances of person-to-person transmission amongst household contacts of high-risk cases and to describe when transmission may have occurred.

Ethics

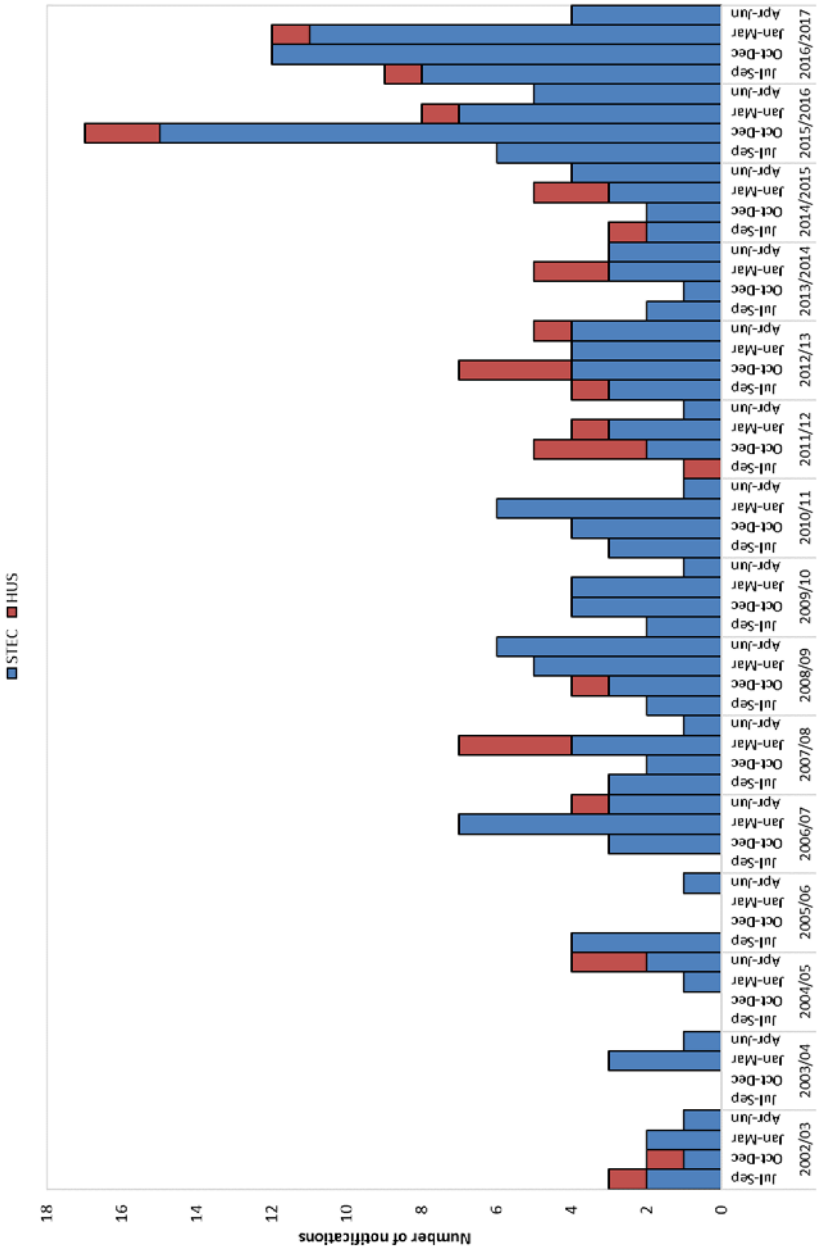
The study received ethical approval from the Australian National University's Human Research Ethics Committee (ref no. 2017/666).

Results

Incidence of STEC

Between 1 July 2002 and 30 June 2017, DHHS received 220 notifications of incident cases of STEC (Figure 1), with an average annual rate of 0.3 cases per 100,000 population. Of these 220 cases, 29 (13%) had a primary notification with HUS. The number and rate of notifications of STEC increased over the 15-year period, from a low of four cases (0.1 cases per 100,000 population) in 2003–04 to 37 cases (0.6 per 100,000 population) in 2016–17.

Figure 1: Confirmed notification of STEC by quarter and year of onset, Victoria, 1 July 2002 to 30 June 2017 (N=220)



Incidence of STEC by age, sex and region of residence

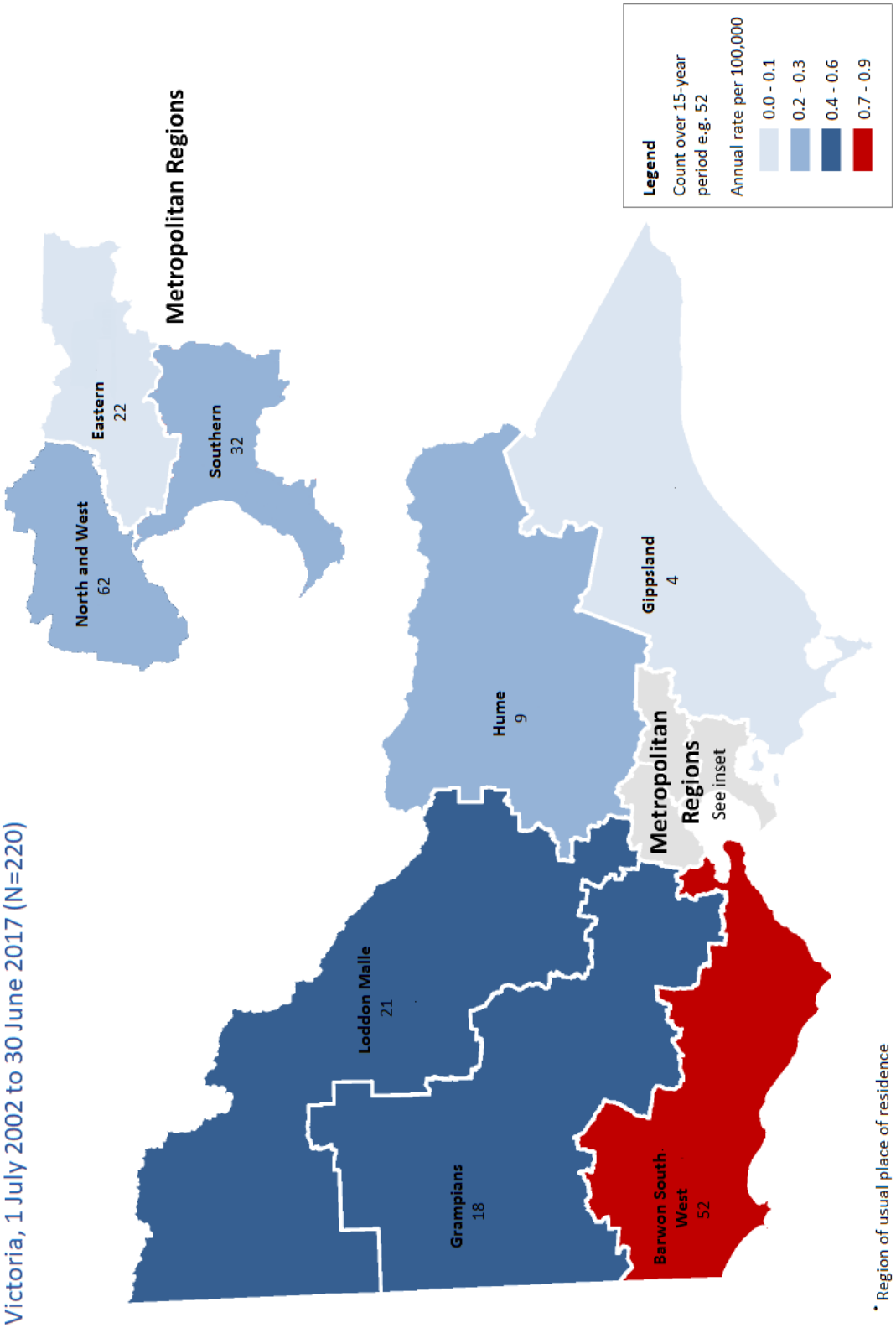
Over the 15-year study period, rates of STEC were highest amongst children under five years of age at 0.6 cases per 100,000 population and adults aged over 65 years of age at 0.5 cases per 100,000 population (Table 1). Overall, females represented 56% of all notifications and had a slightly higher rate of notifications at 0.3 cases per 100,000 population compared to males at 0.2 cases per 100,000 population. HUS was most common in those aged under 5 years representing 38% of cases or 0.2 cases per 100,000 population. HUS was least common in adults aged 15 to 65 years and those over 65 years (0.02 and 0.03 cases per 100,000 population respectively).

Table 1: Rate and number of STEC notifications by age and sex in Victoria, 1 July 2002 to 30 June 2017 (N=220)

	Males	Females	Total	Average annual rate
< 5 years	16	13	29	0.6
5–14 years	13	19	32	0.3
15–64 years	43	54	97	0.2
65+ years	25	37	62	0.5
Total	**97**	**123**	**220**	**0.3**

The number of cases of STEC was almost evenly distributed between metropolitan (53%, 116/220 cases) and rural (47%, 103/220) regions. Figure 2 shows that the average annual rate of STEC notifications was highest in the Barwon South West region (0.9 cases per 100,000 population) and lowest the Eastern Metropolitan and Gippsland regions (both 0.1 cases per 100,000 population).

Figure 2: Total number and average annual rate (per 100,000 population) of notifications of STEC, by DHHS region*, Victoria, 1 July 2002 to 30 June 2017 (N=220)

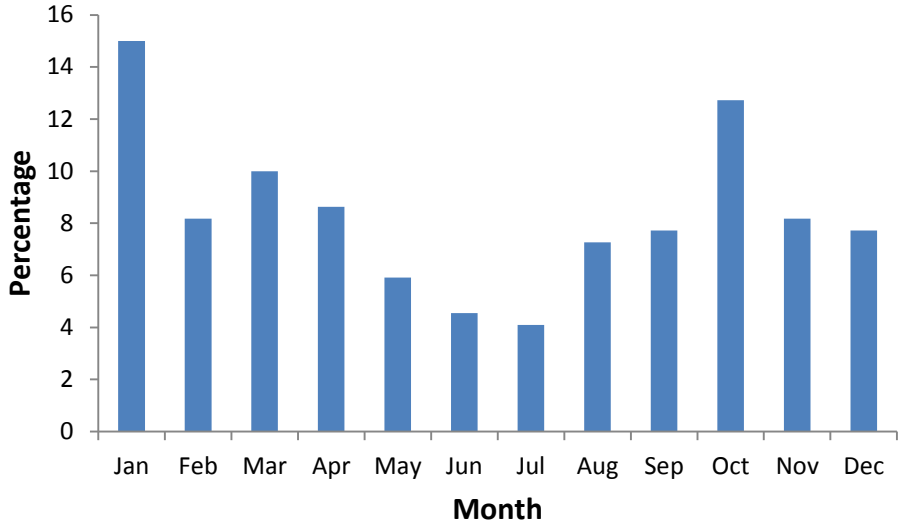


* Region of usual place of residence

Seasonal distribution of STEC

The distribution of STEC was seasonal with a larger proportion of cases occurring in spring and summer (Figure 3). Overall, 60% of cases occurred in spring and summer.

Figure 3: Month of onset* of confirmed STEC cases, Victoria, 1 July 2002 to 30 June 2017 (N=220)

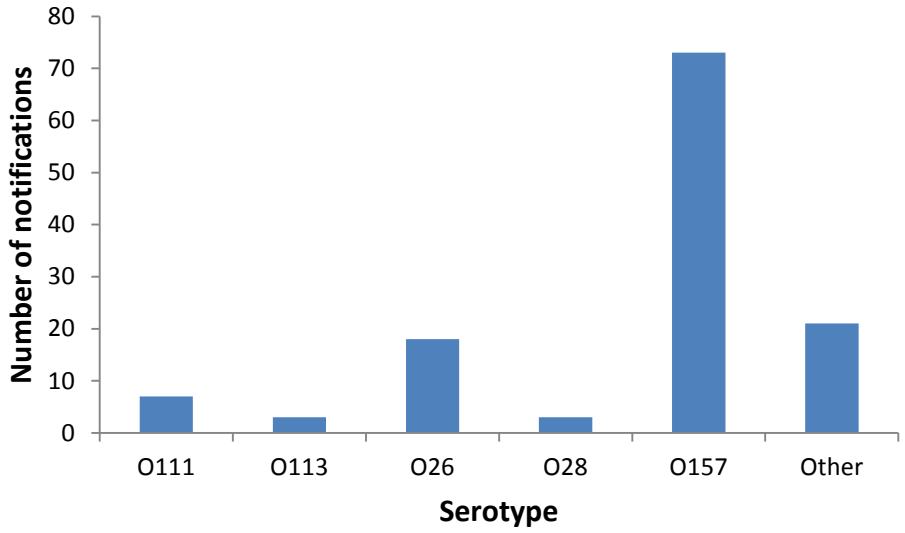


* Month of notification was used for 38 cases for whom month of onset was not available.

Distribution of STEC serotypes

Of the 220 cases of STEC notified between 1 July 2002 to 30 June 2017, 150 cases (68%) underwent serotyping. A serotype was identified for 125 of these cases (83%) and the remaining (17%, n=25) were not-typeable (including rough strains which are not typeable for the O antigen).[28] These not-typeable cases may be O157 or non-O157.[28, 29] The most common serotype was O157 which represented 58% (73/125) of cases where a serotype was identifiable followed by O26 which represented 14% (18/125) of these cases (Figure 4).

Figure 4: Serotype of notified cases, Victoria, 1 July 2002 to 30 June 2017 (n=125*)



* Excludes 95 cases which were not serotyped or not-typeable.

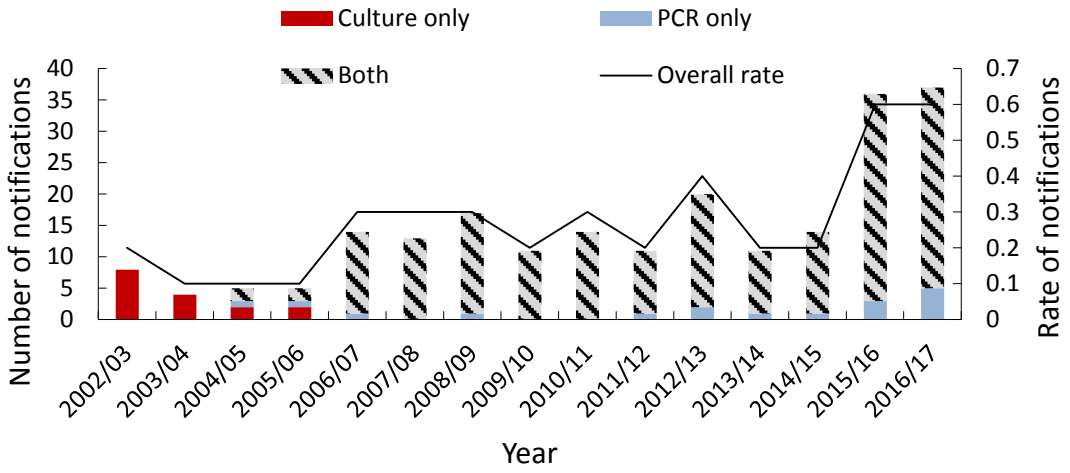
Outbreaks

No outbreak of STEC was identified in Victoria during the study period. One possible outbreak was identified within a health care setting as part of an investigation of a norovirus outbreak. However, the discovery of STEC in faecal samples was considered to be incidental as different serotypes of STEC were identified amongst cases.

Change in laboratory testing methods

The Microbiological Diagnostic Unit Public Health Laboratory (MDU), the reference laboratory providing Victorian public health microbiology services, introduced PCR testing (a more sensitive detection method)[23] for STEC in 2004–05. Prior to this, testing was undertaken using culture based methods and test kits for the detection of toxins. In 2014–15, a private pathology provider in Victoria introduced an enteric bacteria PCR panel which included STEC. This resulted in STEC testing being undertaken by this provider on all samples where the enteric bacterial PCR panel is requested whether STEC is suspected or not. The rate of notifications of STEC increased after both of these changes (Figure 5). Changes to the national STEC case definition also occurred in 2016 (Box 1).

Figure 5: STEC notifications according to laboratory test method*† (and rate per 100,000 population), Victoria, 1 July 2002 to 30 June 2017 (N=220)



* Test performed on initial or subsequent samples
† Tests performed by toxin detection test kit are not reflected in the graph

State and territory policies for exclusion of high-risk cases

Victoria (Vic), Queensland (Qld) and Western Australia (WA) require that high-risk cases are excluded from work until cessation of symptoms and the provision of two consecutive faecal samples taken at least 24 hours apart are negative for STEC (Table 2). New South Wales (NSW), the Australia Capital Territory (ACT), South Australia (SA), Tasmania (Tas) and the Northern Territory (NT) do not require clearance testing but instead require that high-risk cases wait between 24 and 48 hours after cessation of symptoms before returning to work or child care.

More generally, national food standards in Australia require that food handlers who have a foodborne disease report to their supervisor, and that food businesses must exclude employees with foodborne diseases from handling food until a medical practitioner advises the employee no longer has, or is carrying the disease.[30]

Table 2: Policies from the exclusion of cases in high-risk groups by jurisdiction, 2017

Jurisdiction	Exclusion policy
Vic	Food handlers, child care workers and health care workers diagnosed with STEC must not work until cessation of symptoms and two consecutive faecal specimens taken at least 24 hours apart, and not less than 48 hours after taking antibiotics are negative for STEC.[19] Children may be excluded from primary school or children's service centres if required by the Secretary.[20]
Qld	Cases in high-risk groups (children under 5 years of age and other people unable to maintain good hygiene, food handlers, and child and health care workers) should be excluded from work or child care until two successive negative stool samples obtained at least 24 hours apart and not sooner than 48 hours after the last dose of antimicrobials (if administered).[31]
WA	High-risk cases (workers in health care, residential care and child care; food handlers, children in child care; and people who are faecally incontinent) should be excluded until asymptomatic, including normal stools, for 48 hours, then clearance with two consecutive negative faecal specimens collected at least 24 hours apart.[32]
NSW	Cases who are food handlers or care for young children, the elderly or debilitated persons should be advised not to attend work until 48 hours after the resolution of symptoms. Children in child care should not attend until 24 hours after diarrhoea has stopped.[33]
ACT	Children should be excluded from child care, pre-school and school until 24 hours after their last episode of diarrhoea. This also applies to those working in child care, health care settings or with the elderly. Food handlers should remain away from work for 48 hours after their last episode of diarrhoea.[34]
SA	Exclude people with STEC or HUS from child care, preschool, school and work until there has been no diarrhoea for 24 hours. If working as a food handler in a food business, the exclusion period should be until there has been no diarrhoea or vomiting for 48 hours.[35]
NT	STEC is rarely reported in the NT and written guidance has not been published. The exclusion of cases in high-risk settings such as food handlers and health care workers is decided on a case-by-case basis but would likely involve exclusion for 24 hours after cessation of diarrhoea (oral communication, Centre for Disease Control NT, 8 June 2017). Children in child care would also be excluded for 24 hours after cessation of diarrhoea as per standard gastrointestinal illness guidelines.
Tas	STEC is rarely reported in Tas and written guidance has not been published. The exclusion of cases in high-risk settings such as food handlers and health care workers, and children in child care would be decided on a case-by-case basis but would likely involve exclusion for 48 hours after cessation of diarrhoea (email communication, Communicable Disease Prevention Tas, 5 September 2017).

Duration of exclusion of high-risk cases in Victoria

Of the 220 confirmed notifications of STEC in Victoria between 1 July 2002 and 30 June 2017, 11.4% (n=25) were noted in PHESS as belonging to a high-risk group, or were identified as such through visual inspection of cases with repeat testing on subsequent faecal samples (Table). The most common category of high-risk cases was children attending child care who represented 40% (n=10) of cases, followed by food handlers who represented 36% of cases (n=9). The number of notifications of STEC in high-risk cases has increased in recent years and six cases (24%) were identified in 2016–2017 alone.

Table 3: High-risk cases by category, Victoria, 1 July 2002 to 30 June 2017 (n=25)

High-risk cases	Number (%)
Child care worker	1 (4)
Child in child care	10 (40)
Food handler	9 (36)
Health or aged care worker	4 (16)
Other	1 (4)
Total	**25 (100)**

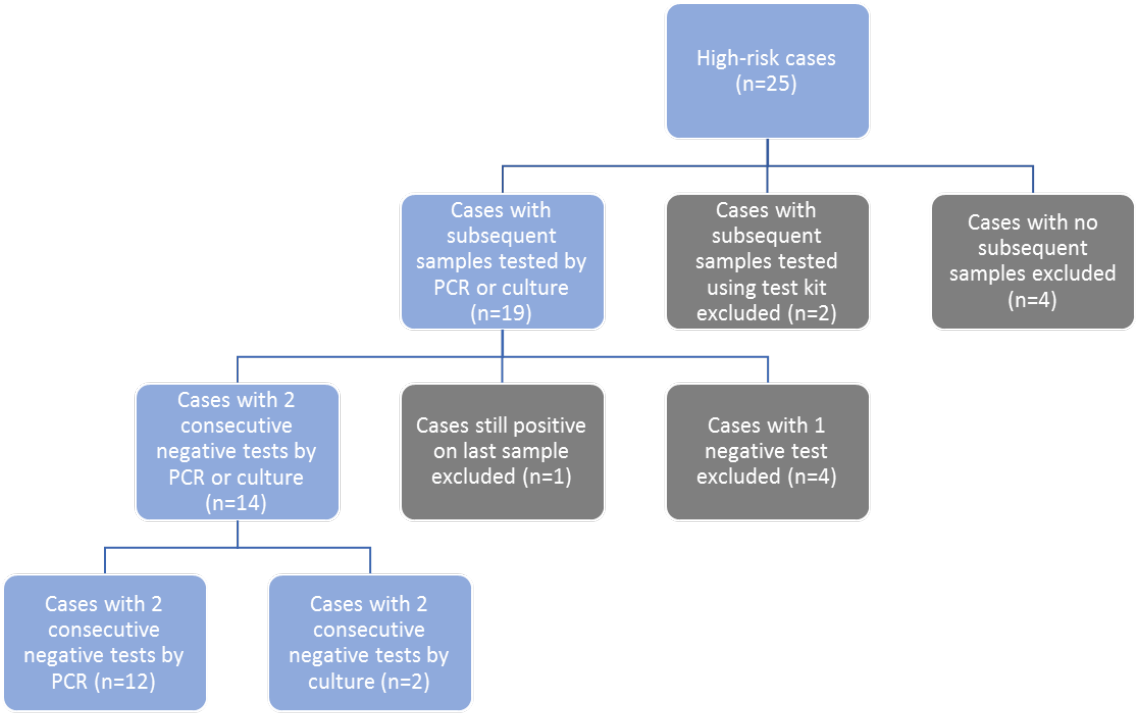
Follow up of high-risk cases

Of the 25 high-risk cases, 19 (76.0%) had PCR or culture performed on subsequent samples and the remaining six cases (24%) either provided no subsequent samples (n=4) or had testing on subsequent samples performed by toxin test kit, i.e. not PCR or culture (n=2) (Figure 6). Of the 19 high-risk cases that did provide subsequent samples for testing by PCR or culture, 14 (73.7%) were followed up until two consecutive negative samples were received in DHHS, four (21.1%) were followed up until one negative sample and one (5.3%) was still positive at last follow-up. The high-risk cases who provided subsequent samples but were not followed up to until the receipt of two consecutive negative samples included children in child care (n=2), an asymptomatic sibling of a case identified through screening of household contacts (n=1), a case who moved to a low risk administrative role (n=1) and a case for whom the reason for further follow-up could not be ascertained from records (n=1).

The 14 high-risk cases who were followed up until receipt of two consecutive negative samples were included in the analysis to determine the median and range of exclusion time. Of these 14 high-risk cases, 12 (85.7%) had two consecutive negative samples as tested by PCR and the remaining two (14.3%) had two consecutive negative samples as

tested by culture. No high-risk cases had two consecutive negative samples as tested by both PCR and culture.

Figure 6: Flow chart showing inclusion and exclusion of high-risk cases in the analysis of exclusion time



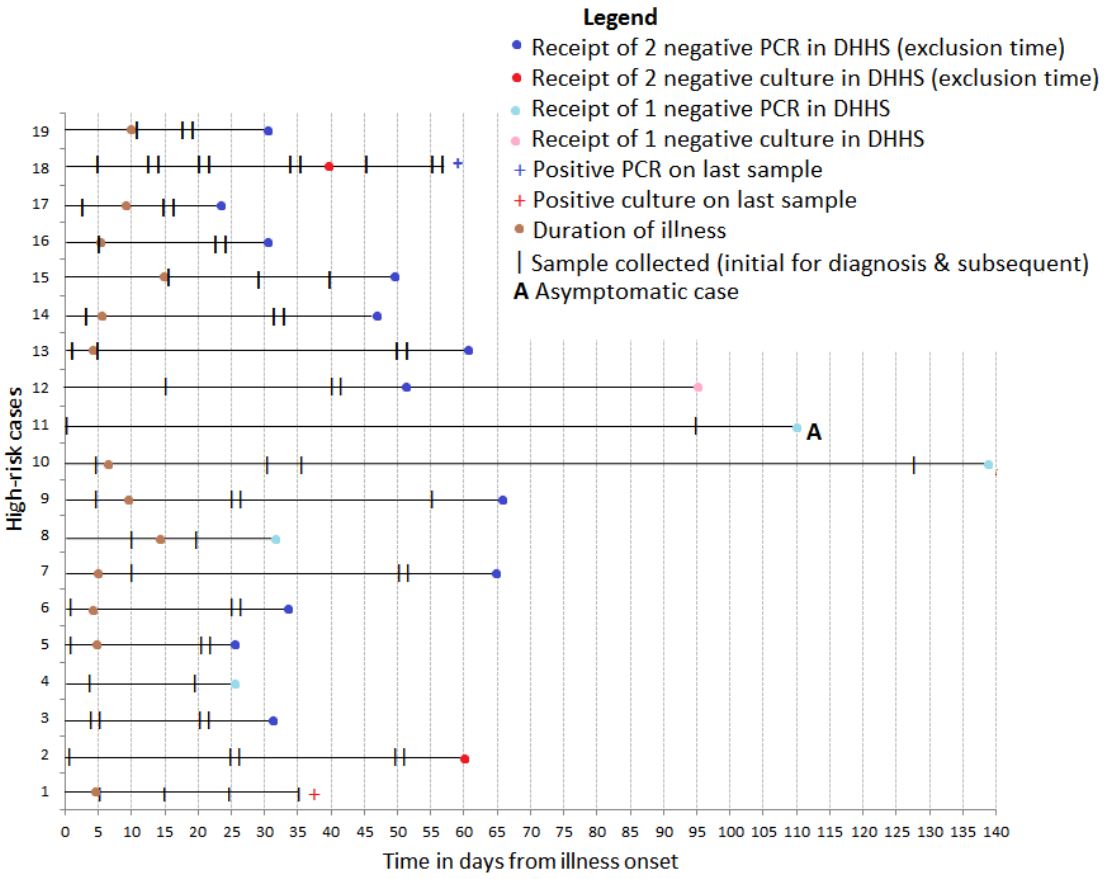
Duration of illness (where known), date of sample collection (including initial diagnosis samples and subsequent follow-up samples), exclusion time by PCR and culture and loss to follow-up for the 19 high-risk cases who provided subsequent samples for testing are illustrated in Figure 6.

Of the 14 cases included in the analysis of the duration of exclusion, illness duration was known for 10 of the 12 cases who provided two consecutive negative samples by PCR (median 5 days, range 3–14 days) and unknown for both of the two cases who provided two consecutive negative samples by culture. The interval between collection of samples was variable and lengthy for some cases (Figure 7).

The twelve cases who provided two consecutive negative samples by PCR were older (median 57 years, range 4–69) than the two cases who provided two consecutive negative samples by culture (median 2, range 0–4 years). Additionally, those in the PCR group were less likely to have HUS (10%) and were almost all female (91%) compared to the culture group of which half had HUS and all were male.

Of the 12 cases who were followed up to the provision of two negative sample as tested by PCR, no cases had a negative PCR result followed by a positive PCR result. Of the two cases who were followed up to the provision of two negative samples as tested by culture, one case was followed up further as they continued to test positive by PCR, and had STEC isolated by culture (i.e. positive result) on samples that were subsequently provided (Figure 7, case 18).

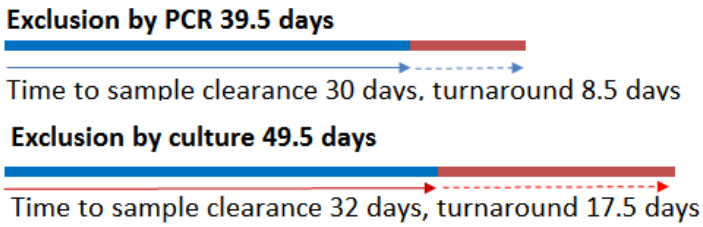
Figure 7: Duration of symptoms, sample collection, exclusion time and loss to follow up of 'high-risk' cases who provided subsequent samples for testing (n=19)



Duration of exclusion based on two negative samples

The median period of exclusion of high-risk cases as calculated on the basis of the time to receipt of two consecutive negative result was 39.5 days (range 23–65) by PCR, compared to a median exclusion period of 49.5 days (range 39–60) by culture (Figure 8). The median 'time to sample clearance' (the period from onset to the collection of the second negative sample) was similar by PCR (30 days, range 16–55) and culture (32 days, 14–50). However, the median 'turnaround time' (the period from collection of the second negative sample to the date the result was received in DHHS) was shorter by PCR (8.5 days, 3–12) compared to culture (17.5 days, range 10–25).

Figure 8: Median exclusion, time to sample clearance and turnaround time, by PCR (n=12) and culture (n=2)



Among cases who were not included in this analysis, one case was still positive by culture 35 days after illness onset (Figure 7, case 1), longer than the median 'time to sample clearance' by culture of 32 days. One case was also still positive by PCR 56 days after illness onset, longer than the median 'time to sample clearance' by PCR but had already provided two consecutive negative samples by culture which were included in the analysis (Figure 7, case 18). Four cases who had provided one negative sample tested by PCR were also excluded from the analysis. Two of these cases (Figure 7, case 4 and 8) had 'time to clearance' periods based on one sample which were shorter than the median 'time to sample clearance' (18 and 20 days respectively). The two remaining cases (Figure 7, case 10 and 11) had 'time to clearance' periods based on one sample which were longer than the median 'time to sample clearance' (128 and 95 days respectively). However, these two cases had long intervals between the collection of their last sample which was positive and their final negative sample.

Duration of exclusion based on cessation of symptoms

For the 10 high-risk cases for whom exclusion time by PCR could be calculated and duration of illness was available, it was calculated that if Victoria's exclusion requirement was that high-risk cases be excluded from work or child care 48 hours after cessation of symptoms, the median exclusion period would be 7 days (range 5–16). Among the same 10 high-risk cases the median exclusion period based on two consecutive negative samples was 39.5 days (range 23–65).

Person-to-person transmission amongst household contacts

No cases of person-to-person transmission amongst household contacts of the 25 high-risk cases could be confirmed. Two asymptomatic siblings of high-risk cases

tested positive for STEC as part of household screening during the period in which their respective siblings were positive for STEC. However, these asymptomatic cases had the same exposures as their siblings.

Discussion

In Victoria, there were 220 notifications of STEC from 1 July 2002 to 30 June 2017, giving an average annual rate of 0.3 cases of STEC per 100,000 population. This is likely to be an underestimation of the true occurrence of STEC in Victoria as for cases to be notified with STEC they must visit a doctor, have a clinician order testing for STEC, provide a stool sample for testing, have a positive laboratory test and have this result notified to the DHHS.[6] Notifications of STEC have increased from a low of four notifications in 2003–2004 (0.1 cases per 100,000 population) to 37 notifications in 2016–2017 (0.6 cases per 100,000 population).

Changes in STEC testing in 2004–05 and 2014–15 have respectively resulted in the introduction of more sensitive methods for detection of STEC and the testing of more samples for STEC. This second change has likely also resulted in the detection of incidental findings in cases who were not clinically suspected to have STEC. Changes to the case definition for confirmed STEC in 2016 removing the requirement that identification of genes associated with the production of Shiga toxin be made from 'raw bloody diarrhoea' sample may have also contributed to the increase in cases.

The rate of STEC notifications was highest in the Barwon South West region (0.9 cases per 100,000 population) and lowest in the Eastern Metropolitan and Gippsland region (0.1 cases per 100, 000 population respectively). The Barwon South West region has a large cattle and wool production industry, as well as coastlines, lakes and waterfalls which attract tourism and outdoor activity.[36] Animal and waterborne transmission from these activities may be associated with higher rate of notified cases in this region, however, the Gippsland region, which has the equal lowest rate of notifications also has a tourist industry based on water and other outdoor activities and has a large dairy production industry.[36] As sources of exposure are difficult to ascertain in sporadic STEC cases they were not explored in this study, however, further research could be undertaken to explore risk factors which may be associated with the higher notification rate in the Barwon South West region.

Consistent with the findings of prior studies,[6, 8] rates of STEC were highest in those aged under 5 and in those over 65 years of age. Rates of HUS attributed to STEC were also highest among those aged under 5, but were lower in those aged over 65 years of age than expected compared to national data.[6]

The occurrence of STEC was highest in warmer months with 60% of cases occurring in spring and summer. This is consistent with the findings of previous studies[6, 37] and may be due to food not being held at appropriately cold temperatures during warmer weather allowing for bacterial growth. Studies of STEC in bovine faeces and farm soil have also indicated that the prevalence of STEC in these samples also increased in warmer months which may result in a corresponding increase in human cases due to foodborne and environmental transmission.[38]

The most common serotype identified during the study period was O157 which represented 58% of cases where the serotype could be identified. This is consistent with national data.[6] A previous Australian study of risk factors for sporadic STEC infection found that O157 infection was associated with consumption of hamburgers, visiting restaurants and occupational exposure to red meat.[39, 40] Non-O157 infection, however, was associated with consumption of chicken, meat or corned beef from a deli, camping in the bush and occupational exposure to animals.[39, 40]

I was unable to draw conclusions about the length of exclusion by PCR compared to culture due to the small number of high-risk cases analysed in this study and the fact that only two of 14 high-risk cases analysed had two consecutive negative samples as tested by culture-based methods. The available data indicated that the length of exclusion as determined by culture-based methods was longer than by PCR. This appeared to be due to the longer 'turnaround time' required to undertake culture-based tests. The 'time to sample clearance' was similar for both PCR and culture despite PCR being a more sensitive method for detection of STEC[23] but this result was based on a small number of cases and may also have been influenced by differences between the demographic and clinical characteristics of those with PCR results available compared to those culture results.

In practice some children in child care may be able to return to child care after shorter periods than calculated in this study as decisions to allow children to return to child care are made on a case-by-case basis. Such decisions are considered when children have ceased being symptomatic and have good hygiene but have extended detection of STEC in faecal samples provided for clearance testing. Additionally, some workers may have been able to return to low risk positions such as administrative roles while undertaking clearance testing.

Notwithstanding this, the results of this study indicate that high-risk cases have been excluded from workplaces and child care for long periods of time with the shortest exclusion period calculated in this study being 23 days. Such lengthy exclusions periods have a significant socioeconomic burden for cases and their families due to costs associated with non-attendance at work and alternative child care arrangements, in particular where cases have exhausted their paid sick leave or are employed on a casual basis and are not eligible for paid sick leave.

A secondary analysis of high-risk cases for whom length of exclusion as determined by PCR and duration of illness was available was undertaken to determine the length of exclusion if the cases were allowed to return to work or child care 48 hours after cessation of symptom (as required in SA, NSW and the ACT). This analysis identified that application of this alternative exclusion criteria would result in a reduced median exclusion time of one week compared to that of over a month under the current policy.

Additionally, among the 12 high-risk cases who had two consecutive negative PCR samples, none returned a negative PCR test followed by a positive result as part of clearance testing. However, of the two cases who provided two consecutive negative culture samples, one case provided subsequent samples which tested positive by culture which may indicate that negative culture results do not necessarily indicate microbial clearance. Analysis of a larger number of cases would be useful to help inform the need for a second negative PCR sample in terms of reducing the risk of person-to-person transmission in high-risk cases. Reducing the number of subsequent negative PCR samples to one sample would marginally reduce exclusion period but would also reduce inconvenience for cases associated with collection of a second sample.

No confirmed case of person-to-person transmission amongst household contacts was identified. While two asymptomatic siblings of high-risk cases were identified positive for STEC during their respective sibling's exclusion period, all siblings were reported as sharing the risk factors. Analysis of a larger sample would be useful to determine the risk of person-to-person transmission

Limitations

A major limitation of this study was the limited number of high-risk cases with data available for analysis, particularly those in the culture group as significantly less samples had negative tests by culture than first thought during the planning phase. The reduction of eligible cases was identified in a review of hardcopy laboratory reports, whereby it was discovered that some high-risk cases had test results which had been entered in the database as PCR and culture negative when no culture had been performed. As a result of this, clarification will be made to data entry guidelines for STEC results which will improve the quality of data. This finding meant that the main hypothesis of this study could not be adequately explored, however, useful information was still gained regarding the length of exclusion periods more generally, and sufficient data was still available to estimate the length of exclusion if alternative criteria (48 hours after cessation of symptoms) was adopted.

A further major limitation was that some high-risk cases were not followed up until the provision of two negative samples. While a secondary analysis which included those with one negative sample and those who were still positive at the end, follow-up would have likely resulted in a longer median exclusion and 'time to sample clearance'. Two of these five cases had lengthy periods between provision of their last positive and first negative sample. As such, it is not possible to determine whether these two cases were truly outliers in terms of their 'time to sample clearance'.

The number of high-risk cases included in the analysis of exclusion time was considered too small to allow statistical comparisons of exclusion time between the PCR and culture group using the Wilcoxon Rank Sum Test or other statistical methods. Likewise, multivariate methods to adjust for differences in the ages, clinical presentation or serotype, or a survival analysis to allow consideration of cases lost to follow-up was not attempted due to the small number of cases. This could be further investigated in a future study using a larger dataset sourced from all states which require clearance testing for high-risk cases.

Ideally, a prospective study of exclusion periods and 'time to sample clearance' or duration of shedding would have been undertaken on outbreak cases. This would allow for the control of the testing methods used and the interval between sample collection. This could be considered if an outbreak were identified in the future

however, STEC outbreaks in Australia have been infrequent and have involved a small number of cases.[6]

Conclusion

While the number and rate of STEC in Victoria have increased this is likely to be at least at least partially related to changes in STEC testing in Victoria and recent changes to the national case definition for STEC. The number of notifications of STEC among high-risk cases has also increased in recent years with 24% of the high-risk cases identified in the 15-year study period occurring in 2016–17 alone.

The findings of this study indicate that high-risk cases are excluded for long periods under the current requirement that they have two consecutive negative faecal samples taken at least 24 hours apart. In practice, the burden associated with Victoria's exclusion policy for high-risk cases may be mitigated for some high-risk cases who are able to return to work in alternative positions such as administrative roles. Additionally, as children in child care are excluded on a case-by-case basis some of these cases may be allowed to return to child care before receipt of two consecutive negative samples. However, for other high-risk cases who cannot be redeployed to other roles, especially those in employed in casual positions who do not have paid leave provisions, the burden of such lengthy exclusions can be high.

The results of this study highlight the need to review Victoria's exclusion policy, with specific consideration of introducing requirements similar to those in place in NSW, ACT and SA which require that high-risk cases wait between 24 and 48 hours after cessation of symptoms to return to work or child care. Alternatively, amending the exclusion policy to require the provision of only one negative sample as tested by PCR would marginally shorten exclusion periods and reduce the inconvenience for cases associated with collection of a second sample. Such a review should be informed in the context of a literature review of the evidence of person-to-person transmission after cessation of symptoms.

At the national level, consideration should be given to developing Series of National Guidelines (SoNG) for STEC in order to provide nationally consistent advice and guidance to states and territories on the exclusion of high-risk cases.

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Chapter V:
Outbreak investigation

An outbreak of salmonellosis with a high proportion of hospitalised cases linked to hollandaise sauce at a Melbourne café

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Prologue

Preface

This chapter describes a case-control study undertaken in March 2017 in response to reports of gastrointestinal illness among café patrons in two unrelated groups who had eaten at the café on the same day. The Communicable Disease Prevention and Control (CDPC) section of the Victorian Government Department of Health and Services (DHHS) became aware of this outbreak after patrons complained to Environmental Health Officers (EHOs) from the relevant Melbourne council. The purpose of this investigation was to identify the source of illness and to implement public health measures to prevent further illness.

I drafted a late draft article describing the outbreak for submission to the *Communicable Disease Intelligence* journal. This draft publication forms the body of this chapter.

Project role

This outbreak was brought to my attention by Nicola Stephens, Manager, Communicable Disease Epidemiology and Surveillance (CDES) section, DHHS, who suggested that it might be a suitable outbreak to meet my field placement requirement to investigate an acute public health event.

I was the co-lead investigator on this outbreak, alongside Shaun Coutts, Public Health Officer (PHO), CDPC, DHHS. Shaun was the main point of contact with council and Regional EHOs, undertook initial contact with patrons on the café booking list and assisted in the interviewing of cases and controls. I developed the menu-based questionnaire with assistance from Siobhan St George, a fellow MAE scholar, Shaun and Joy Gregory, OzFoodNet Epidemiologist, DHHS, and interviewed approximately 75% of patrons including both cases and controls. I entered the data into the Public Health Event Surveillance System (PHESS) with assistance from Shaun and Joy, conducted the statistical analysis, and wrote the investigation report.

Lessons learnt

Leading the outbreak investigation gave me first-hand experience of the challenges involved in investigating foodborne illness and strengthened my interview and data collection skills.

It made me aware of the many groups who play a role in foodborne outbreak investigations in Victoria including the public, the food service industry, epidemiologists, PHOs, EHOs, medical professionals, hospitals, private and hospital laboratories and the Microbiological Diagnostic Unit Public Health Laboratory (MDU). It also emphasised the role of the Department of Economic Development, Jobs, Transport and Resources (DEDJTR) and AgriBio in outbreak investigations and the importance of food safety throughout the supply chain, "from the paddock to the plate".

I gained a great respect for the amount of work that goes into interviewing cases and controls and the incredible skill of the CDPC PHOs in building relationships with all stakeholders and getting the information required to investigate outbreaks in a sensitive manner.

I also learnt the challenges and benefits of working on a high-profile outbreak. This outbreak was picked up by the media, which made cold-calling patrons on the booking list somewhat easier but also resulted in media enquiries that required rapid and accurate responses about the outbreak.

Public health impact

The epidemiological evidence from this study implicated the hollandaise sauce as the likely cause of the outbreak. The local council EHOs had already supervised a precautionary clean-up of the café and advised the café to cease production of raw-egg based hollandaise and aioli sauce. However, the findings of this study informed ongoing action being undertaken by the relevant local council.

During the course of the outbreak investigation, I also identified a separate outbreak while undertaking active case ascertainment using *Salmonella* Typhimurium (STm) laboratory notifications. Specifically, while contacting people who had the same serotype and lived in the same region as those in the café outbreak I was investigating, I identified two people who indicated during interview that they had dined at a separate restaurant in the week before the outbreak I was investigating. On checking our surveillance database, I identified further cases who had been interviewed by different PHOs but had also indicated eating at this separate restaurant during their incubation periods. All cases had earlier onset dates than cases in the outbreak I was investigating and had not indicated eating at the café. As these cases had less severe

illness and had not made complaints to Council, it is unlikely that the outbreak would have been identified if active case ascertainment or cluster investigation had not been undertaken.

Communication

Updates on the outbreak including case numbers were provided to the DHHS Media Unit for use in response to media queries and to the relevant council in order to inform public health action. The outcomes of this outbreak investigation were included in the OzFoodNet quarterly report for Victoria, and will be submitted to the *Communicable Disease Intelligence* journal.

Master of Applied Epidemiology core requirement

This chapter is written in fulfilment of the field placement core activity to undertake an investigation of an acute health event.

Acknowledgments

I acknowledge the contribution of:

- Joy Gregory and Marion Easton, Principal Epidemiologist, Antimicrobial Resistance & Genomic Sequencing, for the guidance on enteric disease, outbreak investigation and case-control studies.
- Shaun Coutts, for his role as co-lead investigator.
- Rebecca Schack and John Whittman, PHOs in CDPC for undertaking additional interviews.
- Sally Atkinson, PHO in CDPC for patiently teaching me how to conduct interviews with cases.
- Siobhan St George, for sharing the learnings for her own outbreak investigation and advice on questionnaire development.
- EHOs from the relevant local Council.
- Mary Valcanis, Section Leader, Enteric Reference Laboratory, MDU.
- Staff at the Food Environment and Outbreak Response Section, MDU.

Late draft article for submission to the *Communicable Disease Intelligence* journal

An outbreak of salmonellosis with a high proportion of hospitalised cases linked to hollandaise sauce at a Melbourne café

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Word count

Abstract: 190

Main article (excluding title, abstract, keywords, figures, tables and footnotes): 2,968

Abstract

Salmonellosis outbreaks related to consumption of raw or minimally-cooked egg products remain an important cause of gastrointestinal illness outbreaks in Australia. In March 2017, an outbreak of salmonellosis occurred among patrons who had eaten at a Melbourne café. We conducted an outbreak investigation, including a case-control study, in order to identify the source and to inform public health action to prevent further illness. This study describes a point source outbreak of *Salmonella* Typhimurium characterised by a short median incubation period (8.75 hours) among cases and a high proportion of hospitalised cases (58.62%). Epidemiological analysis identified a statistically significant association between illness and consumption of hollandaise sauce (OR 494.68, 95% CI 66.18–∞, P < 0.0001). The high proportion of cases hospitalised in this outbreak shows the serious health implications of salmonellosis and potential consequences of deficient storage and food handling processes for potentially hazardous food products. This outbreak, along with evidence of the increasing proportion of outbreaks associated with raw or minimally-cooked egg products, demonstrates the importance of ongoing efforts to educate the food service industry about the risks, and proper storage and handling of such potentially hazardous foods.

Keywords: outbreak, Salmonella, gastroenteritis, case-control study, public health

Introduction

In 2011, *Salmonella* was the most common aetiological agent identified in foodborne outbreaks in Australia.[1] In outbreaks attributed to a single food, raw and minimally-cooked eggs were associated with 53% of outbreaks, all of which were due to *Salmonella* Typhimurium (STm).[1] The proportion of outbreaks associated with the consumption of raw or minimally-cooked eggs has increased significantly between 2001 and 2011.[2]

On 20 March 2017, the Communicable Disease Prevention and Control (CDPC) section of the Victorian Government Department of Health and Human Services (the Department) was notified of an outbreak after a Melbourne council received complaints of gastrointestinal illness among five patrons in two unrelated groups who had eaten at the same café on Saturday 18 March 2017. An outbreak investigation including a case-control study was initiated in order to identify the source of illness and to implement public health measures to prevent further illness. This article details the epidemiological, environmental, laboratory and analytical findings of the outbreak investigation.

Methods

Epidemiological investigation

A case-control study was conducted in order to identify the source of illness. All interviews were conducted via telephone using a structured questionnaire based on the cafe's menu. The questionnaire included demographics, illness onset and duration, symptoms, and foods and beverages consumed at the café. Ethics approval was not sought as this study was conducted as part of a public health investigation under the Victorian *Public Health and Wellbeing Act 2008*. Approval was granted by the Australian National University Human Research Ethics Committee for publication of the results of the investigation (2017/710).

Cases were identified from a number of sources including complaints received by the Council, active case ascertainment using the café booking list for 18 March, and interrogation of Victoria's notifiable diseases surveillance database, the Public Health Event Surveillance System (PHESS). Controls were identified using the booking list, or were nominated by cases or controls during interviews. In addition, patrons on the café booking list for 17, 19 and 20 March were also contacted to ascertain if there was illness among those who had eaten at the café before or after 18 March.

Faecal specimen kits were provided to ill patrons who had contacted the Council and specimens were submitted to the Microbiological Diagnostic Unit Public Health Laboratory (MDU) for analysis.

A probable case was defined as someone who had eaten at the café on 18 March and who had an onset of diarrhoea within 96 hours. A confirmed case was someone who met the probable case definition and had *Salmonella* isolated from a faecal specimen, later refined to *Salmonella* Typhimurium (STm) with the Multiple Locus Variable-number Tandem Repeat Analysis (MLVA) profile 03-24-12/09-11-523. A secondary case was someone who had eaten at the café on 18 March and who had an onset of diarrhoea greater than 94 hours later. A control was defined as someone who had eaten at the café on 18 March and did not develop gastrointestinal illness.

Data were collected in PHESS and analysed using Stata IC® 14 (StataCorp, USA). Demographic details of cases and controls were compared using Fisher's exact and Wilcoxon rank sum tests to identify any significant differences in sex and age respectively. An unmatched univariate analysis was performed to calculate odds ratios

(ORs) and associated 95% confidence intervals (CIs) and *P* values using Fisher's exact test for each menu item consumed by cases and controls. Exact logistic regression was used where odds ratios were infinite due to zero-cells. Variables with a *P* value less than 0.05 were considered significant. The dose-response relationship was investigated using Fisher's exact test to identify whether there was any significant difference in hospitalisation for cases who reported tasting hollandaise compared with those who consumed an entire meal with hollandaise.

Environmental investigation

Environmental Health Officers (EHOs) from the relevant Council inspected the café on 20, 21 and 22 March. EHOs obtained copies of the café booking list for 17 to 20 March, the café menu, as well as supplier details and batch numbers for eggs used at the premises.

Hygiene, cleaning and food handling procedures were reviewed and swabs of the blender were collected. There were no food items leftover from 18 March for testing however samples of eggs, including fresh eggs, scrambled egg mix, hollandaise sauce and aioli were all collected during the inspection on 20 March. These environmental swabs and samples were submitted to the MDU for testing.

As raw and minimally-cooked egg products are considered to pose a potential hazard for gastrointestinal illness the food process information for preparation of hollandaise sauce was obtained from the café's chefs. The egg supplier and farm were traced and an investigation of the farm was carried out by Veterinary Officers for the Department of Economic Development, Jobs, Transport and Resources (DEDJTR). A precautionary clean-up of the kitchen was supervised and the café was directed to discard and cease production of all raw egg products.

Laboratory investigation

Equipment swabs, food samples and faecal samples obtained by Council were tested by the MDU for *Salmonella* species isolation and characterisation. Faecal samples obtained by general practitioners and hospitals were tested by primary and hospital laboratories either by culture or polymerase chain reaction (PCR). Where *Salmonella* was isolated, cultures were forwarded to the MDU for serotyping and MLVA.

Environmental swabs from the farm investigation were cultured by AgriBio, DEDJTR.

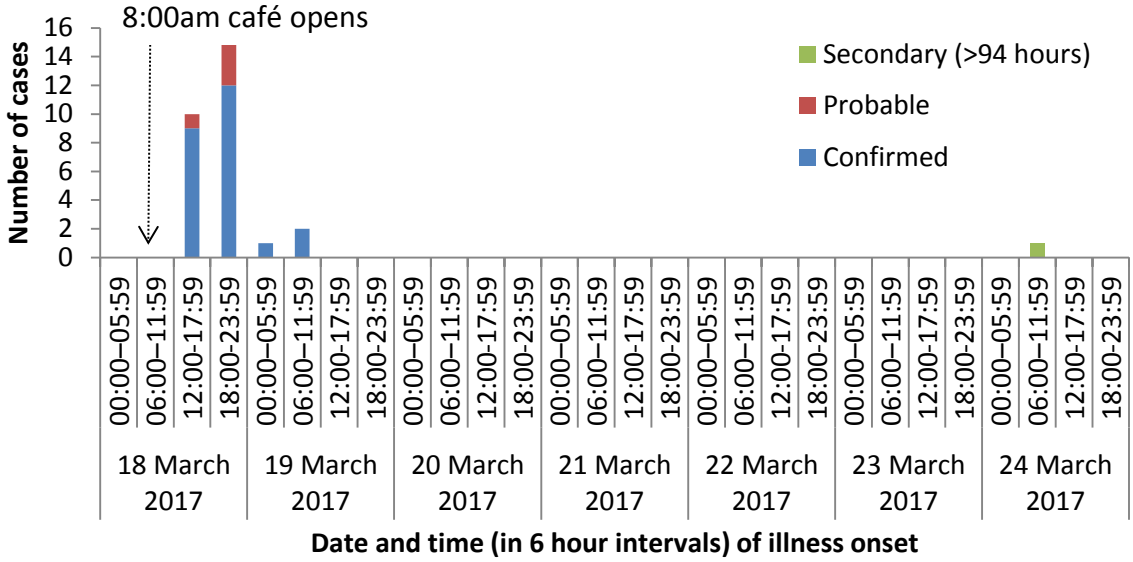
Results

Epidemiology investigation

A total of 26 confirmed cases, 4 probable cases and one secondary case were identified. Of these 31 cases, 29 cases were included in the case-control study and two cases were excluded. One staff member who was a confirmed case was excluded because they were unable to be interviewed. It was unclear what this person's duties were at the café or what foods they had consumed, however the notifying doctor noted this staff member's illness onset as 20 March, after the onset of illness amongst the patrons. The secondary case was also excluded. She had reported being well at the time of the initial interview and was classified as a control, however a specimen for this case was later confirmed as positive for STm. This case was reinterviewed and reported becoming ill five days after eating at the café and had cared for a family member who was a primary laboratory-confirmed case. Based on this second interview the case was reclassified as a secondary case.

All 29 cases included in the case-control study confirmed eating at the café on Saturday 18 March. Calls to patrons on the booking list for 17, 19 and 20 March did not identify any further cases. An incubation period was calculated for 26 of the 29 cases, and was a median of 8.75 hours (range 2–23 hours). The epidemic curve is consistent with a point source salmonellosis outbreak (Figure 1). Duration of illness was available for 17 of the 29 cases, however 12 cases were still unwell at the time of interview which was conducted at least five days after illness onset. For the 17 cases for whom data on duration of illness was available, the median duration was 9 days (range 4–22 days). Of the symptoms reported by cases, abdominal pain and diarrhoea were universal (100%) and 34.48% reported bloody diarrhoea (Table 1). The proportion of cases hospitalised in the outbreak was 58.62%. The median age of cases was 39 years (range 1–87 years), and females represented 68.97% of cases.

Figure 1: Epidemic curve of *Salmonella* Typhimurium cases by date and time of onset after eating at the café (n=30*)



* Includes one secondary case excluded from the case-control study. The staff member excluded from the case-control study is not shown as the time of their illness onset could not be confirmed.

Table 1: Reported symptoms for confirmed primary and probable cases who ate at the café (n=29)

Symptom	n	%*	Unknown
Diarrhoea	29	100.00	
Watery diarrhoea	29	100.00	
Bloody diarrhoea	10	34.48%	1
Abdominal pain	29	100.00	
Fever	28	96.55	
Nausea	27	93.10	
Headache	26	89.66	
Vomiting	21	72.41	

* Includes 'unknown' responses in denominator.

A total of 42 patrons who ate at the café on 18 March were identified through the booking list, or nominated by cases, and included as unmatched controls in the study. The median age for controls was 47 years (range 1–89 years); 71.43% were female. There was no statistically significant difference in the distribution of age ($P = 0.08$) or sex ($P = 0.82$) between cases and controls.

The results of the univariate analysis of selected food items consumed are shown in Table 2. 'Consuming' food items includes patrons who reported tasting or sharing the foods ordered by their dining companions. Consuming eggs benedict which consisted of poached eggs, ham hock and hollandaise sauce on an English muffin (OR 133.81, 95 % CI 20.35–∞, $P<0.0001$), and eggs royale which consisted of poached eggs, smoked

salmon, spinach, dill and hollandaise sauce on an English muffin (OR 8.42, 95% CI 1.01–∞, *P* = 0.05), were both significantly associated with illness. Hollandaise sauce was available to order as a side in addition to being served with the eggs benedict and eggs royale but was only ordered by two cases (OR 3.59, 95% CI 0.27–∞, *P* = 0.33).

Variables for 'any hollandaise' and 'any poached eggs' were constructed in order to further investigate the likely source of illness. Both 'any hollandaise' (OR 494.68, 95% CI 66.18–∞, P<0.0001) and 'any poached eggs' (OR 43.20, 95% CI 7.98–407.40, *P* < 0.0001) were significantly associated with illness. Consumption of 'any hollandaise' was reported by 27 cases (93.10%) and no controls reported this exposure, while 27 cases (93.10%) reported consuming 'any poached eggs' and 10 controls (23.81%) reported this exposure. Multivariate analysis was not performed as no controls reported consuming 'any hollandaise'.

Table 2: Univariate analysis of selected foods consumed by cases (n=29) and controls (n=42) at the café

Foods consumed	Cases		Controls		OR	95% CI	*P* value
	n	%	n	%			
Constructed variables							
Any hollandaise*	27	93.10	0	0.00	494.68	66.18–∞	<0.001†
Any poached eggs	27	93.10	10	23.81	43.20	7.98–407.40	<0.001†
Breakfast menu (available all day)							
Eggs benedict*	21	72.41	0	0.00	133.81	20.35–∞	<0.001†
Eggs Royale*	4	13.79	0	0.00	8.42	1.01–∞	0.05†
Big breakfast	2	6.90	3	7.14	0.96	0.08–9.01	1.00
Eggs curried	0	0.00	2	4.76	0.00	0.00–2.79	0.51
Spinach & ricotta omelette	1	3.45	1	2.38	1.46	0.02–117.70	1.00
Ham & tomato omelette	0	0.00	1	2.38	0.00	0.00–∞	1.00
Shakshouka	2	6.90	3	7.14	0.96	0.08–9.01	1.00
Blueberry pancakes*	1	3.45	0	0.00	1.45	0.04–∞	0.82
Pana cotta	0	0.00	1	2.38	0.00	0.00–∞	1.00
Pastries & muffins	3	10.34	2	4.76	2.31	0.24–29.04	0.39
Smashed avocado	2	6.90	4	9.52	0.70	0.06–5.35	1.00
Breakfast sides							
Eggs a la carte							
All	2	6.90	10	23.81	0.24	0.02–1.28	0.11
Poached	2	6.90	7	16.67	0.37	0.04–2.19	0.29
Scrambled	0	0.00	4	9.52	0.00	0.00–1.33	0.14
Tomato	0	0.00	7	16.67	0.00	0.00–0.70	0.04†
Mushroom	1	3.45	5	11.90	0.26	0.01–2.59	0.39
Spinach	1	3.45	1	2.38	1.46	0.02-111.70	1.00
Potato rosti	4	13.79	2	4.76	3.20	0.42-37.20	0.22
Hollandaise*	2	6.90	0	0.00	3.59	0.27–∞	0.33
Toast	1	3.45	8	19.05	0.15	0.00–1.27	0.07
Lunch menu							
Lamb ragu*	1	3.45	0	0.00	1.45	0.04–∞	0.82
Fish & chips	0	0.00	2	4.76	0.00	0.00–2.79	0.51
Calamari salad with aioli	0	0.00	3	7.14	0.00	0.00-1.82	0.26

* Odds ratio, confidence interval and *P* value calculated using exact logistic regression.
† Statistically significant result between groups at α = 0.05.

There was no statistically significant difference (*P* = 1.00) in hospitalisation status between patrons who reported only tasting meals that contained hollandaise sauce and those who consumed an entire meal containing hollandaise sauce.

Environmental investigation

During inspections by the EHOs, deficiencies in general cleaning, hygiene practices, and food storage and handling procedures were observed. During the initial inspection potentially hazardous foods were observed to be stored for greater than four hours at

temperatures greater than 5°C including hollandaise sauce which measured at 33°C approximately four hours after production.

The café reported making hollandaise sauce every day in one batch at 7:30am in the morning. One bottle was prepared on weekdays using 15–20 eggs, and two bottles on Saturdays and Sundays using 30–40 eggs. The eggs were separated (method unknown) and yolks were either mixed by hand or using a heated food processor. Clarified butter was added, followed by lemon and salt, in a process estimated to take five minutes. The sauce was stored during food service at room temperature. Inconsistent reports from two different chefs were provided as to whether the sauce was discarded four hours after production, or stored all day until the kitchen closed approximately seven and a half hours after production. During the course of a number of interviews conducted over several days with the café proprietor and both chefs, the EHOs were advised that hollandaise sauce produced on 17 March may have either been stored in the refrigerator overnight, or may have been left in the kitchen at room temperature overnight. It was possible that this sauce may have then been served again on Saturday 18 March until it was finished and the café started serving the batch prepared on the morning of 18 March.

The eggs used by the café were delivered twice weekly by a local supplier, and were traced back to the egg wholesaler and egg farm. All eggs were kept stored under refrigeration at the café.

Laboratory findings

All environmental swabs of equipment and samples of food tested by MDU were negative for *Salmonella* although there was no leftover food from service on Saturday 18 March for testing. Eggs sampled from the premises on 20 March were sent for testing however it is likely that they were from a different batch of eggs to those used to make the implicated batch of hollandaise.

Twenty-eight cases submitted faecal specimens for testing, of which 27 were positive for *Salmonella* and typed at the MDU as STm 03-24-12-11-523 (26 cases) or 03-24-09-11-523 (1 case). One case who met the probable case definition provided a faecal specimen to a hospital laboratory for testing but *Salmonella* was unable to be isolated from the specimen. *Salmonella* was also isolated from blood samples of five of the cases who provided positive faecal specimens. One of these isolates showed

resistance to gentamicin however antimicrobial susceptibility testing performed on *Salmonella* isolated from faecal specimens by MDU showed no evidence of antimicrobial resistance.

Environmental samples from the farm investigation were tested by AgriBio. *Salmonella* was isolated from one specimen and referred to the MDU for confirmation and serotyping. However, testing at MDU did not confirm *Salmonella*. A further round of environmental samples was subsequently collected at the farm but all samples were negative for *Salmonella*.

Discussion

The epidemiological evidence from this study implicates the hollandaise sauce as the likely cause of the outbreak. The constructed variable of 'any hollandaise' showed a significant association with illness and was consumed by all but two cases. The two cases who did not consume hollandaise sauce may have consumed food items that were either cross-contaminated in the kitchen or accidentally consumed hollandaise from one of their dining companion's meals. Both of these cases dined with people who consumed hollandaise sauce, and one reported eating food from a dining companion's plate, although they stated that they avoided the hollandaise sauce and poached eggs. Consequently, misclassification of exposure status may have occurred. The constructed variable 'any poached eggs' also showed a significant association with illness. However, 10 controls ate 'any poached eggs' and did not become ill, and no controls reporting consuming hollandaise sauce.

This STm outbreak was characterised by a very short median incubation period (8.75 hours) among cases and resulted in significant illness as shown by the hospitalisation of 56.82% of cases, development of bloody diarrhoea in 34.48% of cases, and invasive disease (cultured from blood) in five cases. The proportion of cases hospitalised was high compared with the estimated 20% reported for *Salmonella* species outbreaks associated with eggs in Australia between 2001 and 2011[2], and 22% in foodborne outbreaks due to STm specifically in 2011[1]. The proportion of cases reporting bloody diarrhoea was also high but not unprecedented based on previous egg related outbreaks of STm in Australia.[3, 4] The severity and short incubation period in this outbreak may be associated with a dose-response relationship between the level of contamination of hollandaise sauce and illness. Previous studies using the amount of food consumed as a proxy for infective dose have found a direct relationship between infective dose, incubation period and severity of illness.[5-7] The level of contamination of the hollandaise sauce could not be ascertained as there was no remaining sauce served on 18 March available for testing. However, the reported length of time that the sauce was kept for serving after production, the possibility that the sauce was kept overnight, possibly at room temperature, and the temperature of a different batch measured during the inspection of the café indicates that the hollandaise sauce may have been kept in conditions conducive to the growth of *Salmonella*.[8] Hollandaise sauce made with unpasteurised eggs is considered to be a 'potentially hazardous' food

and, as it is required to be held at warm temperatures to prevent separation, should be used within four hours of preparation and then disposed.[9]

The dose-response analysis did not show any significant difference in risk of hospitalisation between those who tasted the hollandaise sauce compared to those who consumed it as part of their main meal. Nevertheless, this is a crude estimate of dose and does not take into account the level of contamination of the food itself.

Other factors may also have influenced the severity of this outbreak such as participants with pre-existing medical conditions which may have predisposed them to severe illness. As no data was collected on whether participants had pre-existing health conditions this could not be controlled for in the analysis. Older adults are more likely to have severe illness from *Salmonella* infection however the median age of cases in this outbreak was 39 years.[10] Previous studies of *Salmonella* outbreaks have also shown antimicrobial resistance to be associated with higher hospitalisation rates.[11, 12] This was explored as a possible factor in the high proportion of hospitalisations in this outbreak however testing by the MDU found no evidence of antibiotic resistance in any of the *Salmonella* isolates.

While three different public health officers and an epidemiological registrar conducted the interviews with cases and controls, all interviewers were experienced and a consistent questionnaire based on the café menu was used to minimise measurement bias in this study. The CDPC section was notified of the outbreak two days after the patrons became ill and recall bias was minimised by commencing interviews with cases and controls within five days of exposure at the café.

As the café did not require bookings we were unable to contact all patrons who attended the café on 18 March. This precluded the possibility of conducting a cohort study which would have provided a stronger level of evidence. Nevertheless, we attempted to contact all patrons who were on the booking list in order to reduce selection bias.

A major limitation of this study is that the hollandaise sauce which was served on 18 March was no longer available for testing. STm was not detected in any of the food samples or swabs of equipment taken from the café, or from the farm where the eggs were sourced. Notwithstanding this, there is strong epidemiological evidence suggesting that the hollandaise sauce was the cause of illness in this outbreak and the

environmental investigation undertaken by Council also supports this finding. Laboratory evidence of the outbreak pathogen in leftover sauce or eggs would have further supported this finding.

Conclusion

Hollandaise sauce was the most likely cause of illness in this outbreak. The high proportion of cases hospitalised in this outbreak highlights the potential severity of salmonellosis and the importance of measures to prevent illness. In light of the ongoing public health risks associated with outbreaks related to raw and minimally-cooked egg products, continuing efforts to educate the food service industry about the risks, and proper storage and handling of these products to eliminate/minimise risk are warranted.

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Acknowledgements

The authors wish to acknowledge the following for their assistance with the investigation: Public Health Officers in the Communicable Disease Prevention and Control section at the Victorian Government Department of Health and Human Services; Environmental Health Officers from the relevant Melbourne council; and the Food Environment and Outbreak Response Section at the Microbiological Diagnostic Unit Public Health Laboratory.

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Appendix A:

Late draft of a communication to a lay audience

Improvements to hospital reporting of timeliness of hepatitis B birth dose for all Victorian infants

Background

This project was suggested by Lucinda Franklin, Victorian Government Department of Health and Human Services (DHHS) Vaccine Preventable Disease Epidemiologist, who identified the need to communicate improvements to timeliness of reporting of hepatitis B birth dose vaccination in Victoria. Originally, this draft communication was intended for publication in the DHHS Immunisation Newsletter. However, consideration is currently being given to instead publishing the communication as an introduction to the hepatitis B vaccine coverage data reported on the DHHS website.

Improvements to Hospital Reporting of Timeliness of Hepatitis B Birth Dose for All Victorian Infants

Hepatitis B is a potentially life-threatening infection of the liver caused by the hepatitis B virus. The virus is carried in blood and other bodily fluids such as semen and vaginal fluids.[1] Notably, the virus is very hardy, and can survive outside of the body on surfaces for up to 7 days, which means that if an unvaccinated individual comes into contact with the virus during this time they can become infected.[2] The most common routes of transmission include:

- sexual contact
- sharing injecting equipment
- needlestick injuries in a health care setting
- reuse of unsterilised or inadequately sterilised needles
- child-to-child transmission through contact such as biting
- sharing personal items such as razors, toothbrushes, or hair and nail clippers
- mother-to-baby, particularly where the mother has an undiagnosed infection.[3]

Once a susceptible individual is infected, the average incubation period for the disease is 75 days (range 30 to 180 days).[1] Following an acute infection, up to ten per cent of adults will go on to develop chronic hepatitis B.[1] In infants, up to 90 per cent of infected infants will go on to develop chronic hepatitis B.[1] Chronic infections can lead to liver disease and liver cancer later in life.

Hepatitis B is preventable. A safe and effective vaccine has been available on the Australian market since the 1980s, and a universal infant vaccination program was included on the National Immunisation Schedule in May 2000.[3]

As at 2015, an estimated 232,600 people in Australia were living with chronic hepatitis B infection and over a third have not been diagnosed and are unaware of their infection.[4] For this reason, a birth-dose of the hepatitis B virus vaccine is recommended for all newborns, preferably within 24 hours of birth, to prevent transmission of the hepatitis B virus from mothers, household members, or other close contacts who may be carriers.[3]

In Victoria, data on hepatitis B birth dose administration has been collected since 2009, by the Victorian Perinatal Data Collection (VPDC). In 2016, data for 80,023 births

demonstrated 90.7% of infants received hepatitis B birth dose within 7 days of birth; 0.6% received hepatitis B vaccine more than 7 days after birth; 6.5% had no hepatitis B vaccine given; and for 2.1% vaccination was not stated or was inadequately described.[5] Coverage of birth dose vaccination varies between hospitals.

Importantly 'timely birth dose administration' in these data was defined as within 7 days of birth. This is in contrast to the Australian Immunisation Handbook[3]and the WHO Position Paper on Hepatitis B vaccines[6], both of which define timely birth dose administration as being within 24 hours of birth.

In order to further understand the timeliness of birth dose administration, staff in the Health Protection Branch worked with the VPDC to enable reporting of vaccination within 24 hours of birth to align with the Australian Immunisation Handbook and the WHO Position Paper on hepatitis B vaccines. This change took place on 1 January 2017, which means that we will be able to provide more detailed reports to individual hospitals on their performance by early 2018. Going forward, the Health Protection Branch intends to monitor the timeliness of these data on an annual basis, and will continue to provide individualised reports to hospital CEOs in order to help them continue to improve the timely administration of the birth dose of hepatitis B vaccine to infants, reducing the risk of preventable infection, and thereby contributing to the target of eliminating hepatitis B as a public health concern by 2030.[7]

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Appendix B:

Summary of teaching requirements

First-year MAE cohort teaching exercise

&

Lesson from the field

Background

This appendix summarises activities prepared as part of the teaching requirements of the MAE program.

First-year MAE cohort teaching exercise

MAE Scholars in their second year are required to prepare and conduct a teaching activity for first-year MAE Scholars ('first-years') at their initial course block. I, along with Jonathon Malo, Kath McDermott and Linda Garton, decided to run an activity that would allow the first-years an opportunity to work within teams and build connections with their peers. We had felt that in our own first year what we had really wanted from the previous cohort was an opportunity to get to know them, which is not something that formal teaching activities naturally engender. As such, 'Epi-Cranium' was born.

For 'Epi-Cranium, the first-years were taken outside to the gardens of University House. First-years were asked to split into groups in order to compete in three rounds of fiendishly difficult games related to epidemiological concepts and diseases. In round one, participants had to sculpt, draw or act out in pantomime a series of clues for their own teams to guess such as 'risk ratio', 'Ross River Fever' and 'vaccine preventable disease'. In round 2, first-years participated in a lightning round of questions such as 'What is the term arbovirus an acronym for?' and a nail biting 'What disease am I' (based on Sale of the Century's 'Who am I'). Lastly, first-years filled out a range of table questions with activities including identifying health and epidemiology 'celebrities' from their photos, identifying pathogens from photos of their stylised 'Giant Microbe' plush toys and naming the disease related movie from movie stills. As a prize, all members of the winning team were awarded a plush 'Giant Microbe' of their own, an essential desk item for all epidemiologists.

Feedback from the first-years indicated that 'Epi-Cranium' will be a part of their own teaching activities in 2018 and that it was a great way of building networks between the MAE cohorts.

This activity involved all members of second-year MAE cohort who assisted in trialling the activities that Jonathan, Laura, Kathleen, Linda and I had developed, and also in supervising and keeping score during 'Epi-Cranium'.

Lesson from the field

The 'Lessons from the field' (LFF) activity is a MAE requirement which aims to provide development opportunities for peer-to-peer teaching. I was the first of my teaching group to lead a LFF activity and, after canvassing views as to what teaching activities would be most helpful to my peers, I chose to run a session on data cleaning from a longitudinal cohort study using Stata. This activity drew on my experience at MCRI cleaning data from the Barwon Infant Study (BIS).

The learning objectives of LFF were for participants to:

- be aware of, and understand how to identify some of the issues that commonly arise when cleaning data sets from a longitudinal study;
- understand how to merge data sets from different time points together;
- identify more efficient ways to turn string variables into more useful categorical variables; and
- be able to develop summary variables for use in data analysis projects.

Informal feedback from my peers was that my exercise was timely and useful in teaching participants some useful data cleaning tools. Some of my peers reported referring back to the materials from the activity when cleaning data sets and developing new variables for analyses. The LFF session also provided a valuable opportunity to share alternative methods of undertaking the tasks, which meant that I also learned from my peers.

Developing this exercise was more challenging than I had expected. I had ambitiously decided to build my own datasets including inconsistencies in coding across time points that I had encountered in real life. It was also challenging to develop a scenario that would help to orientate participants and to develop clear instructions that would be suitable for participants with a varying range of experience with data cleaning and Stata.

The instructions and scenario for participants are included on subsequent pages. The data dictionaries and the example answer 'do file' have not been included due to their format and length.

Materials

Instructions and scenarios

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

- identify issues you might come across in cleaning data sets from a longitudinal study;
- merge data sets from different time points together;
- identify more efficient ways to turn a *really annoying* string variable into a useful categorical variable; and
- develop summary measures you can use in a data analysis project.

Useful resources

Before you start this LFF please make sure you review the information on preparing your data set from Day 1 POPH8313 on Wattle.

Files

You should have this question/instruction sheet, 2 data dictionaries and 2 Stata data files.

Scenario

You are working on a longitudinal birth cohort study involving mother-child pairs. Mothers were recruited during the 3rd trimester of pregnancy and their children will be followed up for 18 years. There are 506 children in your study, with the first child born on 3 Jan 2015 and the last on 23 May 2016. So far, questionnaires have been administered during the third trimester of pregnancy, and when the children were 1 and 6 months of age. 12-month clinical exams have commenced for some of the infants and data on some allergic outcomes that you want to investigate in your data analysis are starting to trickle in.

While you are waiting for the outcome data you decide to start cleaning some of the exposure variables that you think might be associated with allergic outcomes, including chemical product exposure such as insect repellent and pets. These variables were collected using hardcopy self-administered questions at the third trimester and 6-month time points. Your end goal is to make summary variables you intend to use as covariates in your data analysis. You have had some training in Stata but have never cleaned 'real' data before.

Your immediate tasks are to:

- clean the individual data sets;
- recode a variable stored as a string variable into a numeric categorical variable;
- merge the data sets together; and
- create summary variables you can use in your data analysis.

You decide to tackle the task in that order. The data manager has helped you out by sending you the relevant data dictionaries, and data sets with all but the variables of interest removed. She has also warned you that due to staff changing between the first time point and the second that there could be some consistency issues. In the interests of being able to review any changes you decide to record your work in a 'do file' rather than directly editing the datasets.

Instructions Part 1

Print out the data dictionaries for both time points and examine the variables and how they are coded.

Question 1

Why is there an additional identification variable in the 6-month dataset? Open the 6-month dataset and enter the command `duplicates report var` for both ID variables. Are there any duplicates and if so, why?

By comparing the data dictionaries for the different time periods can you identify any problems in the consistency of coding of variables across time points?

When you go to merge the two data sets together what problem/s might you have?

Instructions Part 2

Now that you have familiarised yourself with the data dictionaries you can start cleaning the individual data set.

Question 2

Use the `codebook` command to identify any out of range variables. Are there any out of range variables which might be related to problems scanning in the data from the hardcopy data sheet? How might you deal with any out-of-range observations? Make these changes in your do file.

As well as using the `codebook` command, it is a good idea to use the `tab` command with and without labels to help you identify any problems with labels i.e. `tab var, nolabel`. Are there any issues with the values labels in either of the data sets?

In question 1.b) you hopefully identified a problem with the consistency of coding across time points. Have a further look at these variables and apply any necessary fixes for consistency across time points in your do file. Make sure the values labels are correct as well!

Check for inconsistencies across variables and make any necessary changes. As the data was collected in hardcopy there is nothing to stop someone saying 'no' to a one variable and then 'yes' to follow on variables that would have not have been available if the survey was administered in an electronic form. Similarly, participants can say 'yes' to a variable and then not provide a response to a follow-on variable. Make any obvious changes in your do file and list observations to check in hardcopy.

Note the string variable for the 'petothspec' variable. Browse or tab the observations for this variable. Should you make any corrections to the specific pet variables based on the entries in this variable? If so, make the changes.

Instructions Part 3

Once you have completed some basic cleaning you decide to merge the data sets together before you create new variables.

Question 3

Hopefully, you identified in 1.a that there were duplicate identification variables in the 6-month data and guessed that this was because some of the mothers had twins. As a result, when you try to merge the two data sets together you won't be able to merge together on a 1:1 basis. How will you merge them instead?

Before you merge the two data sets, you will want to rename the exposure variables so that you can determine the source of the time point observations. Because aren't many variables you could do this individually for each variable or you could use a 'foreach' loop: http://www.stata.com/manuals13/pforeach.pdf

Merge the two data sets together in your do file. Note what happened to the observations for the twins.

Instructions Part 4

You should now be ready to make some new variables.

Question 4

You want to generate a variable for the age of the mother at the time the child was born. Do this in your do file.

You know that pet exposure is considered to be protective for some allergic outcomes. Your supervisor is particularly keen to look into whether having pet chickens is a protective factor. As there was no specific option for pet chicken you will have to pull this out of the 'petothspec' string variable. You tab 'petothspec' to identify those with pet chickens and in your do file enter the command `gen petchicken=.` and make replacements accordingly.

This wasn't overly difficult as not many people had entered responses for 'petothspec', even though there certainly was a variety of spellings. If there were more responses you could have used a regular expression to make your task easier. Try this for a time point you haven't completed yet. Here is some handy info: http://www.stata.com/support/faqs/data-management/regular-expressions/

We will go through this in the teleconference but here is an example if you are stuck!

`gen petchicken=1 if regexm(petothspec, "^ch.*")` NB. As the spelling or placement of the observations varies you will need to write more than one more regular expression to capture all the responses.

Because of the way the survey was administered you have binary yes/no responses for 'petany' but only yes responses for the specific pets. What observations should be a no and which should be left missing? Please replace the observations accordingly in your do file.

You're done! Send your do files to me for checking along with any questions you have for discussion at the teleconference.

'MAE ANU'

MAE 2016–17 Scholars attending the 9th Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET) Global Scientific Conference in Chiang Mai, Thailand

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