Applied Epidemiology in the ACT

Callum Thirkell

November 2019

Health Protection Service

Population Health, Protection and Regulation

ACT Health

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

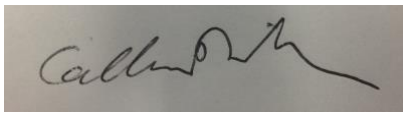
Field Supervisor: Marlena Kaczmarek

NCEPH Supervisor: Ben Polkinghorne

Declaration of work

‘I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at the Australian National University or any other educational institution, except where due acknowledgment is made in the thesis. Any contribution made to the research by others is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project’s design and conception or in style, presentation or linguistic expression is acknowledged’

Callum Evans Thirkell

Signed: 

Date 1/11/2019

Word count: 42,000

Thesis Contents

Acknowledgements

Firstly, I need to thank ACT Health for giving me the opportunity to work in their public health unit and supporting me through my degree.

To my primary supervisors, Ben Polkinghorne and Marlena Kaczmarek, and my surrogate supervisors, Tim Sloan-Gardner and Vanessa Johnston, thank you. Thanks for your honest feedback throughout and providing many comments on my multiple 'early' drafts. My writing and knowledge of public health improved remarkably with all your feedback.

Many thanks to all the CDC staff at ACT Health. Thanks, Rebecca for answering the phone when I rang and taking me on. Milica, Sue, Rachel for answering many questions and requests, always with no fuss or bother. I constantly requested Sam, Romaine and Sandy to ring various people and provide much advice, thanks for always obliging. Thanks, Jodie for providing advice and contributing to my antenatal uptake study. Thanks to all other CDC and immunisation staff who provided assistance and advice.

Thanks to all the NCEPH staff for maintaining and improving the great MAE program. The block courses are a highlight of the program.

Thanks to our cohort for providing such a supportive group. Our Whatsapp group ran hot many days offering advice to each other or generally commiserating with each other.

Lastly and most importantly, thank you Laura for moving 'across the ditch' and living life in this different land, and generally putting up with my crazy idea of starting a new career in a different country with three young children. I greatly appreciate the fact this move wasn't always easy.

Thesis Abstract

This thesis presents four projects along with additional public health experience to meet the competency requirements of the Master of Philosophy in Applied Epidemiology, undertaken at ACT Health in Canberra, working in the Communicable Disease Control section from February 2018 to December 2019.

I undertook a cohort study following a cluster of gastrointestinal illness after a restaurant dinner. *Bacillus cereus* was identified as the likely cause. We identified inadequate hygiene practices and undocumented heating and cooling procedures which were rectified following our investigations. I presented this outbreak to the National Centre for Epidemiology and Population Health and to OzFoodNet at a face-to-face meeting. This outbreak was also published in the *Communicable Disease Intelligence* Journal in September, 2019.

My data analysis project involved a descriptive review of 2009-2018 gonococcal notifications and antibiotic susceptibility test results. This study found that although notification rates have increased 5-fold since 2009, antibiotic resistance has not increased in the ACT. A key finding was a considerable difference in the proportion of notifications receiving a test of culture between sexual health specialists and GPs. I recommended ongoing education of GPs, particularly because heterosexual females have seen the largest rate rise in notifications since 2014 and they are primarily seen by GPs rather than sexual health specialists. This project was presented orally at the PHAA CDCC conference in Canberra in November 2019.

For my epidemiological study I designed and implemented a 12-month study to estimate antenatal pertussis and influenza vaccination uptake in the ACT, and to describe key determinants of uptake. In my chapter I present an analysis of the first 6-months of study data. We found the highest self-reported uptake of antenatal vaccination currently reported in the Australian literature, 95% for pertussis and 74% for influenza. We found that those earning more are more likely to receive influenza vaccines and receive it for free in their workplace. I recommend addressing this access and affordability issue. This study was presented orally at the New Zealand Immunisation conference in September 2019 and as a poster presentation at the PHAA CDCC conference in Canberra in November 2019.

My surveillance project involved developing a surveillance and response plan to control and manage the threat of antimicrobial resistance of *N. gonorrhoea* and *shigella*. Recommendations were made including: what data should be collected, how to capture the data using a new database system (REDCap), response guidelines upon identification of a multi-drug resistant case, and routine reporting.

I also gained significant public health experience in contributing to the public health response for a number of small foodborne outbreaks, as well as measles, hepatitis A, typhoid and many *Salmonella* and *Campylobacter* investigations.

This thesis presents my experiences and documents my competency to fulfil the requirements of the MAE and my contribution to frontline communicable disease control in the ACT and Australia.

Chapter One: Placement experience and MAE competencies

Introduction and overview of field placement

Background

The Australian Capital Territory (ACT) is located in the southeast of Australia and is surrounded by the state of New South Wales. The ACT has an affluent, primarily urban population of approximately 400,000 people.

Placement

ACT Health's vision is '*Your Health – Our Priority*' with the stated values of care, excellence, collaboration and integrity noticeably present in the health protection office.

ACT Health is headed by the Director-General who has responsibility for a number of different departments including policy, innovation, clinical and population health. The Office of the Chief Health Officer (OCHO) operates under the ACT Director-General and is responsible for the Population Health Protection and Prevention Division of ACT Health. The OCHO is responsible for a number of key priority areas including: obesity and injury prevention; medicinal cannabis; asbestos; organ donation; gene technology and health effects of climate change. Two branches operate under the OCHO, namely the Health Protection Service and the Health Improvement Branch.

The Health Protection Service has a more operational focus including:

- Analytical laboratory (environmental)
- Business support services
- Communicable disease control (CDC)
- Environmental health
- Emergency management (HEMU)
- Legal Policy
- Pharmaceutical Services.

My placement was with the CDC whose primary role is to "minimise the harm caused by the spread of communicable diseases." My role was primarily focused on surveillance, outbreak investigation and public health management of notifiable diseases. Other tasks within the CDC remit include: auditing of premises regarding infection control; coordination of the ACT immunisation program; development of communicable disease and immunisation policy; enforcement of public health legislation and information to the public.

Field placement experience

The benefit of being placed in a public health unit is you get to experience the coal-face of public health, talking to patients, clinicians and laboratory staff. Being a small jurisdiction, I had the opportunity to get involved in some capacity in most outbreaks across the breadth of foodborne, STI, and vaccine preventable diseases during my time.

Notification of four seemingly locally acquired *Salmonella* Enteritidis cases resulted in an immediate response involving environmental health, the chief veterinary officer, public health staff and NSW staff. In the context of a large outbreak in NSW but no locally acquired cases in the ACT, this was a significant event. During the second Acute Response Team (ART) meeting we received information that the MLST of the four cases isolates did not match that of the NSW outbreak. All isolates matched the MLST pattern normally found in cases who have travelled to Singapore. Another enteritidis case had been notified on the same day which was related to travel in Singapore. This raised the question of a laboratory error, which was confirmed following further investigations. This was a great learning point highlighting the difficulty of when to act: considering political ramifications, the importance of being cautious with highly unusual and surprising laboratory results, and the swift enaction of a one-health approach.

I took part in contract tracing following two measles cases in 2018 and early-2019. The second case resulted in over 400 follow-ups after prolonged exposure in a clinical facility. Thankfully neither resulted in any secondary cases. This highlighted the very manual process of follow-up required for a measles case. It also showed the quality prevention and surveillance system that Australia has; with good public health action we averted a secondary case. This experience and likelihood that this will occur again led me to complete my learning from the field on the public health response to measles.

I was involved in a small capacity for two other large food premise outbreaks, both were investigated by fellow MAE students. One was a norovirus outbreak located in NSW, just outside of Canberra. More than 160 patrons were contacted and 71 cases of gastroenteritis identified. Norovirus was isolated from four cases. Initially, telephone interviews were carried out; as the numbers grew, an online survey was developed, and invitations to respond were sent by email and text message. I contributed by initiating the response and collaborating with the public health unit to undertake the investigation as no ACT Health epidemiologists were available on the day. I also provided feedback on the survey, including survey design and technical aspects of the software. The second outbreak was associated with a catering service. Over 200 people were contacted and over 100 cases of gastroenteritis identified, norovirus was isolated from one case. Multiple businesses consumed food from the service over one particular day. My

involvement included initial identification of the outbreak, provision of advice to a first-year MAE regarding set-up of a line-list, and feedback regarding survey design.

A cluster of influenza-like-illness (ILI) cases occurred in a school prior to the traditional influenza season. Approximately 30/54 children and a number of staff were absent. The public health concern was, there appeared to be a high attack rate, and no specific diagnosis was initially known. An investigation took place and 17/38 interviewed met our case definition for ILI. We received laboratory results for four cases: two positive for Influenza A, one positive for rhinovirus and one negative for all viral respiratory pathogens. Following this, the public health physician was comfortable that the students and teachers' symptoms were generally mild and that multiple respiratory pathogens were likely to be circulating. Public health messaging was provided to the school, students and parents. A media release was also issued, no further media ensued. The investigation ceased at this point. This was another example of the difficulty in deciding when to investigate. Considerations included: a high attack rate, initially unknown pathogen and likely media interest.

I also managed a number of typhoid cases in people returning from overseas, which involved interviewing the case, determining the risk of transmission, exclusion from work and arranging culture tests of cure. There is a national guideline for the public health management of typhoid cases as part of the Series of National Guidelines (SoNG) produced by Communicable Disease Network Australia (CDNA). CDNA is the peak group who guide public health in Australia. These cases allowed the opportunity to access and interpret the SoNG. Managing these cases highlighted the impact that exclusion from work and clearance testing can have on cases and their contacts. Ensuring appropriate interpretation of the SoNG is important to minimise disruption to individuals while maintaining public health.

I was fortunate to attend three conferences during my MAE and present at two. I attended the inaugural 2019 Global Health Security Conference in Sydney which was a great introduction to global health. Key learnings I took were the importance and value of the International Health Regulations (IHR) and the use of the Joint External Evaluation (JEE) to guide improvement in global health security capacity.

I was also able to attend and present my outbreak at both NCEPH and the Canberra OzFoodNet face to face meeting in 2018. These were good opportunities to gain experience in presenting a scientific paper, to share findings with and receive feedback from experts in the field, and to understand the immense value that the OzFoodNet network provides to public health in Australia.

I attended the NZ immunisation conference and orally presented my epidemiological study, based on the first six months of data. This was a great opportunity to meet public health professionals in a slightly different context in New Zealand.

I will also be presenting my epidemiological study as a poster presentation and data analysis as a short oral report at the Communicable Disease Conference in mid-November 2019.

Summary of MAE course requirements

MAE competencies

Competency	**Thesis Chapter**				
	Chapter One MAE Experience	Chapter Two Outbreak	Chapter Three Data Analysis	Chapter Four Surveillance	Chapter Five Epidemiological Study
Investigation of an acute public health problem		✓			
Analysis of a public health dataset			✓	✓	
Establish a surveillance system				✓	
Design and conduct an epidemiological study					✓
Literature Review				✓	✓
Conference abstract and presentation		✓	✓		✓
Peer-reviewed publication		✓			
Orientation & public health laboratory visit and report	✓				
Field-reports	✓				
Report to a non-scientific audience		✓			
Group teaching & evaluation	✓				
Learning from the field	✓				

Teaching to MAE 2019 cohort

The idea for this teaching session came from Hendrick who is a vet and also grew up in South Africa. He has both professional and personal experience of OneHealth. For me, although I was aware of the concept a lot of learning took place prior to conducting the session.

The rationale for teaching this topic was the immense importance of OneHealth, particularly for antimicrobial resistance, food safety and zoonoses as well as many other topics.

I undertook a coordinator type role within the group. I ensured we had a clear purpose and objectives for the session. There was discussion amongst the group to keep the overall topic hidden and work through the case studies first. We agreed to follow good teaching pedagogy and state the topic and purpose upfront.

Our group of four divided roles and initially planned to present a case study each, however due to a lack of time we decided to only present three case studies. My role became to introduce the session, explain the purpose and objectives and then close with a summary of the OneHealth concept.

Purpose & Objectives of teaching session

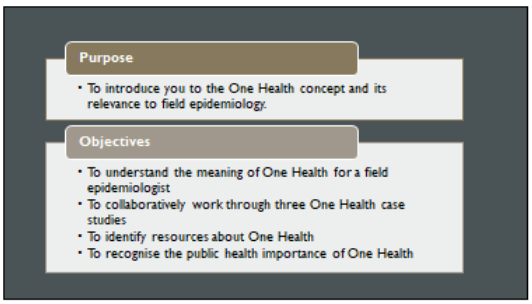
OneHealth
Purpose To introduce students to the OneHealth concept and its relevance to field epidemiology.
Objectives 1. To understand the meaning of OneHealth for a field epidemiologist 2. To collaboratively work through three OneHealth case studies (domestic and international). 3. To identify resources about OneHealth 4. To recognise the public health importance of OneHealth

Evaluation

Most participants seem satisfied with the session and particularly appreciated the engaging style and case study approach. A Likert scale of 1-4 was used for our evaluation questions. A few mentioned the value of more in-depth information, however limited time prevented comprehensive coverage of the topic.

Evaluation Question	Score out of 4
Were the objectives and purpose of the session clear?	3.2
Was the presentation style engaging?	3.8
How did you find the pace of the session?	3.8
How useful was the content?	3.4

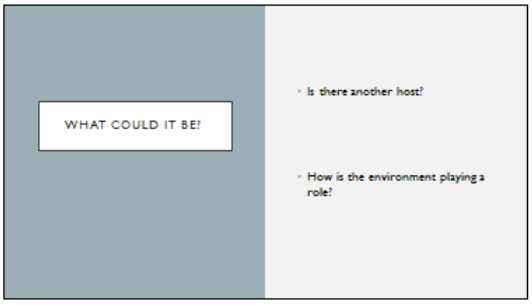

CASE STUDIES OF MYSTERIOUS EVENTS...
Celeste Marsh, Callum Thirkell, Tamara Riley, Hendrik Camphor

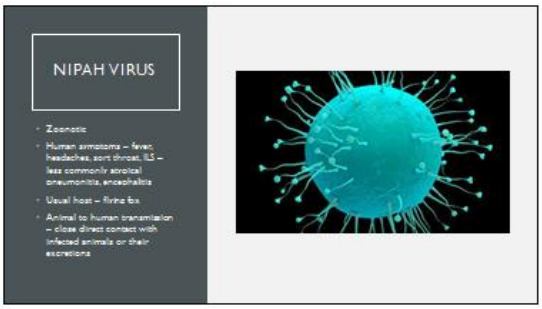

Purpose
• To introduce you to the One Health concept and its relevance to field epidemiology.
Objectives
• To understand the meaning of One Health for a field epidemiologist
• To collaboratively work through three One Health case studies
• To identify resources about One Health
• To recognise the public health importance of One Health

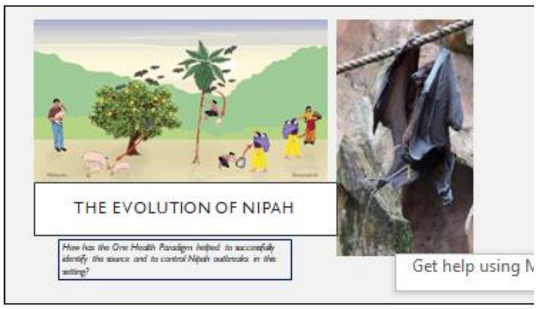

CASE STUDY I
PALM FEVER IN BANGLADESH

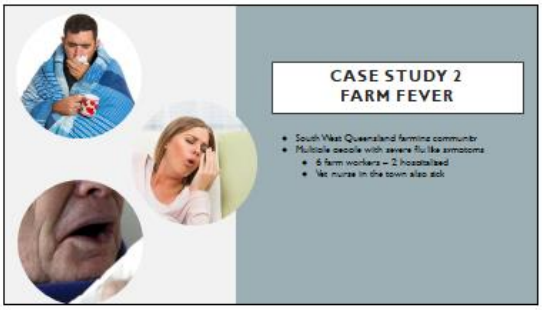

• Rural Bangladesh
• 2001
• Fever, headaches, respiratory symptoms
• CFR of 69%
• Pathogen identified
• But source a mystery

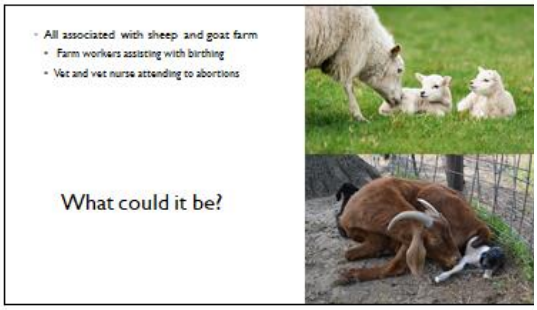

•First identified in 1998 in Malaysia in pig farmers and abbatoir workers – no human to human transmission
•Different picture in Bangladesh
•Risk factors: rural areas, drinking raw palm sap
•Nosocomial transmission = human to human

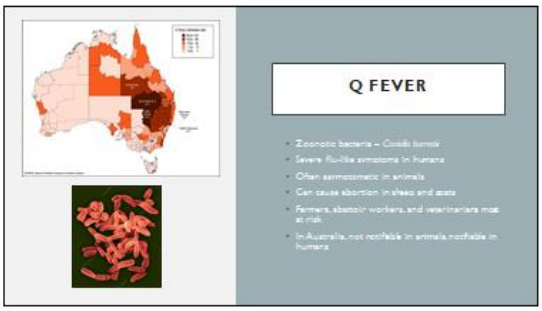

WHAT COULD IT BE?
• Is there another host?
• How is the environment playing a role?

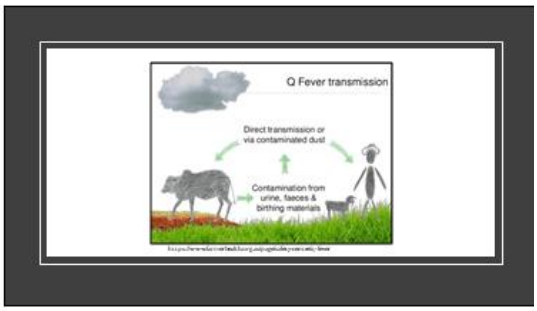

NIPAH VIRUS
Zoonotic
Human symptoms – fever, headaches, sort throat, ILS – less commonly atypical pneumonitis, encephalitis
Usual host – flying fox
Animal to human transmission – close direct contact with infected animals or their excretions


THE EVOLUTION OF NIPAH
How has the One Health Paradigm helped to successfully identify the source and to control Nipah outbreaks in this setting?
Get help using M

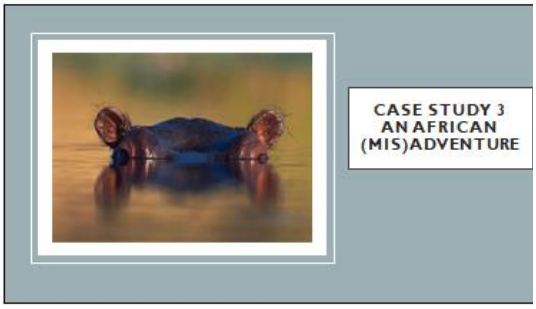

CASE STUDY 2
FARM FEVER
South West Queensland farming community
Multiple people with severe flu like symptoms
6 farm workers – 2 hospitalised
Vet nurse in the town also sick

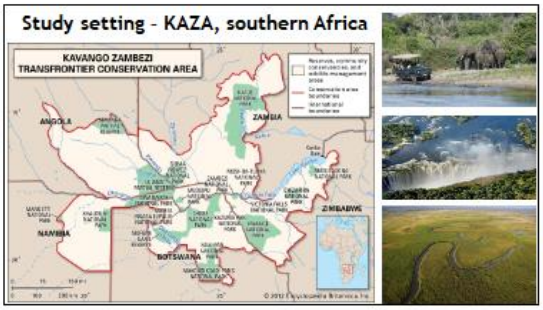

All associated with sheep and goat farm
Farm workers assisting with birthing
Vet and vet nurse attending to abortions
What could it be?

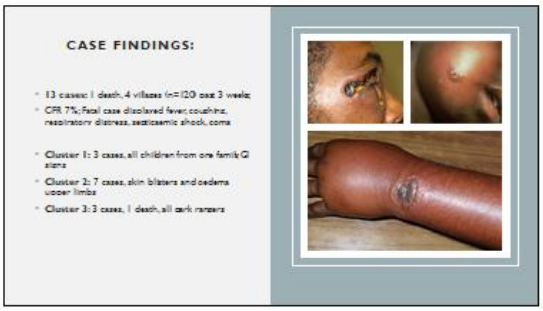

Q FEVER
Zoonotic bacteria – Coxiella burnetii
Severe flu-like symptoms in humans
Often asymptomatic in animals
Can cause abortion in sheep and goats
Farmers, abattoir workers, and veterinarians most at risk
In Australia, not notifiable in animals, notifiable in humans

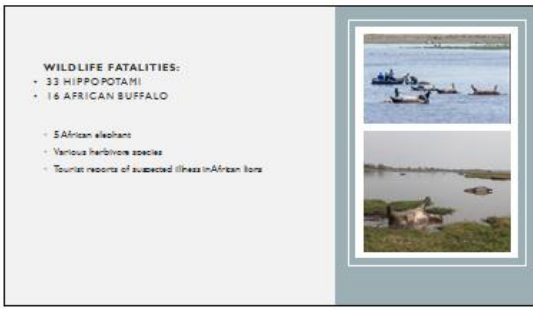

Q Fever transmission
Direct transmission or via contaminated dust
Contamination from urine, faeces & birthing materials

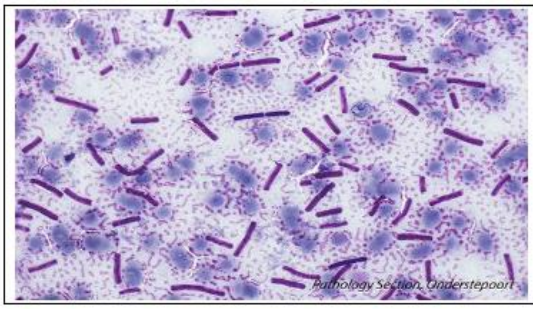

Q FEVER.
SERIOUS.
PREVENTABLE.
PPE
SAFETY
Q FEVER PREVENTION
Personal protective equipment (PPE)
Hygienic on-farm practices
Skin test and/or vaccination for people who work or live in high risk areas

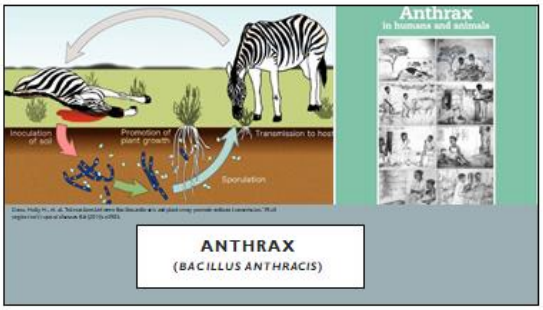

CASE STUDY 3
AN AFRICAN
(MIS)ADVENTURE

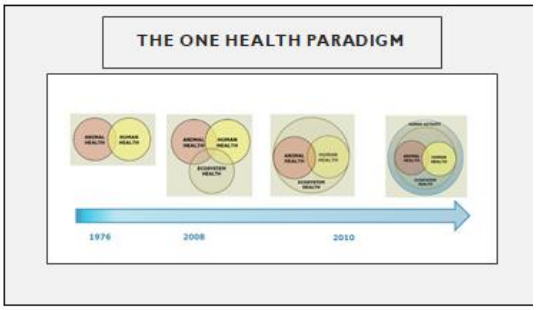

Study setting - KAZA, southern Africa
KAVANGO ZAMBEZI
TRANSFRONTIER CONSERVATION AREA
ANGOLA
ZAMBIA
ZIMBABWE
NAMIBIA
BOTSWANA

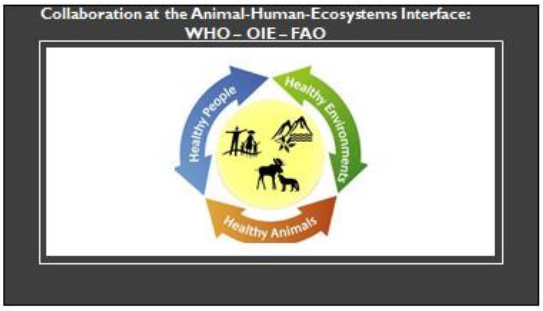

CASE FINDINGS:
13 cases: 1 death, 4 villages (n=120 over 3 weeks
CFR 7%; Fatal case displayed fever, coughing, respiratory distress, septicaemic shock, coma
Cluster 1: 3 cases, all children from one family (2 sisters
Cluster 2: 7 cases, skin blisters and oedema upper limbs
Cluster 3: 3 cases, 1 death, all cattle ranchers

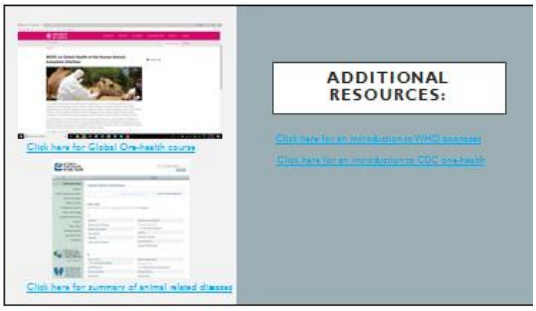

WILDLIFE FATALITIES:
33 HIPPOPOTAMI
16 AFRICAN BUFFALO
5 African elephant
Various herbivore species
Tourist reports of suspected illness in African lions


Pathology Section, Onderstepoort


Anthrax
in humans and animals
Inoculation of soil
Promotion of plant growth
Transmission to host
Sporulation
ANTHRAX
(BACILLUS ANTHRACIS)


THE ONE HEALTH PARADIGM
1976
2008
2010


Collaboration at the Animal-Human-Ecosystems Interface:
WHO – OIE – FAO
Healthy People
Healthy Environments
Healthy Animals


ADDITIONAL RESOURCES:
Click here for Global One-health course
Click here for summary of animal related diseases

Learning from the Field

Our 'lessons from the field' are designed to reflect on a field epidemiology experience and facilitate peer-to-peer teaching based on this experience.

As described earlier in this chapter, one measles case prompted a significant public health response resulting in 475 people being exposed of which 365 were contacted by a small team of approximately a dozen people at ACT Health CDC. A large proportion of these exposures were as a result of two emergency department visits by the case.

This was a valuable learning exercise both for myself and the whole team. A number of learnings were noted following an after-action review which included all the relevant stakeholders:

- Including all stakeholders in Acute Response Team (ART) meetings at the outset of the response.
- Prioritise contacts according to risk of infection during the initial response phase.
- Explore utility of alternative communication methods eg. SMS contact.
- Investigate and simulate use of 'call centre' messaging with a central number for people to ring back on.
- Engage and train more Health Protection Service (HPS) staff for surge capacity.
- Consider creating templates to enable early public health alerts.
- Confirm leadership for incident response and roles/responsibilities of participants.

As a result of these learnings, the increase in cases globally and Australia and significant media interest I decided to undertake my learning from the field on the public health response to measles.

Although the questions seemed somewhat basic, I was the only student placed in an 'operational' public health unit, hence none of the other students have been involved in a public health response to measles. Therefore, gaining an understanding of the epidemiology of measles and what the public health response involves was valued by the other students.

Purpose

To understand the epidemiology of measles and the public health response to a measles case in Australia.

Objectives

1. Understand what measles is, how it presents and the public health importance.
2. Understand the epidemiology of measles in Australia and globally.
3. Understand the public health response in Australia.

Case:

A young 16 month old Indian child has been notified as a potential measles case in the ACT following travel to India; the child was born in Australia. They arrived back from India on the 10th of January.

The case is up up-to-date with their vaccinations and has had one measles vaccine.

The case had a fever from 13th Jan with coryza and cough from the 15th Jan; conjunctivitis and maculopapular rash which started on head and moved down the neck and trunk on the 17th Jan.

The case attended:

1st ED visit on 15th Jan from 0900 – 1200

GP visit on 17th Jan from 1500 – 1545

2nd ED on 18th Jan from 1800 onwards – waiting room until 1900, isolated from 0000.

The on-call CDC were notified late on the 18th Jan. The date now is 19th Jan 0900, 2019.

No laboratory test results are available, the first laboratory test should be available by 1400 on the 19th Jan.

	Contact List	Additional friends/family accompanying contact	
1st ED visit	61 contacts	30 contacts	
GP visit	13 contacts	5 contacts	
2nd ED visit	102 contacts	70 contacts	**Total Contacts 281**

Measles is a highly contagious, acute febrile illness responsible for up to 2 million deaths annually prior to the introduction of the measles vaccine in the 1960's (1). A single measles vaccine was introduced nationally in Australia in 1975 providing 95% protection and a 2nd dose providing 99% protection was funded in 1992 (2).

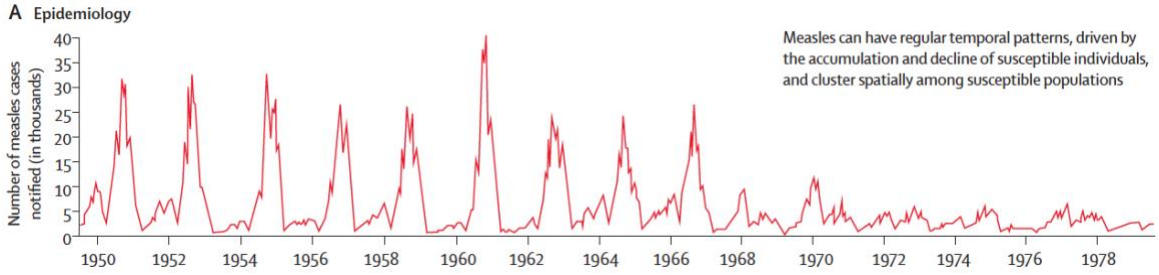


Figure 1: Global epidemiology of Measles 1950 - 1980(1)

Measles has an incubation of 10 days (range 7–18 days) and presents with symptoms including fever and at least one of: cough, coryza or conjunctivitis. Koplik's spots (small white papules) may appear in the mouth 1-2 days before the rash. The rash appears 3-4 days after fever onset and progresses from the face, behind the ears on to the trunk and extremities (1). Cases are normally unwell and miserable. Measles can be spread through respiratory droplets and aerosolised particles and has a reproductive rate of 9–18 people in a non-immune population(1).

The case definition is presented in the measles Series of National Guidelines (SoNG [pg5]) which provides consistent national guidelines for managing a measles case (3). Any suspected case of measles should be notified to the relevant public health jurisdiction, as soon as practical.

A number of groups are at risk and the focus of a public health response. The first measles vaccine is given at 12 months, therefore babies up to this age are potentially at risk if exposed to measles, although transplacental protection is passed to the baby until 6 months if the mother is fully immune. Others at risk include: pregnant women, immunocompromised people, children <5yrs, adults >20 years and anyone not fully vaccinated. Thankfully, vaccination rates remain high in Australia with 93.5% of all children fully vaccinated against measles at 24 months (4).

Resources

- Click here to read the Lancet measles article
- Click here to read the measles SoNG

QUESTIONS

1. Is this a plausible measles case? Why?
2. Is this a confirmed case according to the CDNA guidelines?
3. Would you initiate a public health response without confirmed laboratory evidence?
4. What is the primary purpose of public health follow up in Australia?
5. It is clear a number of days will be required to contact all these people.
    a. Who would you prioritise to contact first?

Although measles elimination was estimated to have occurred between 1999 and 2005 (5) it took until 2014 to provide the required evidence for WHO to officially announce measles elimination in Australia (6). As a result of this measles cases are relatively rare in Australia and each case produces a significant public health response, focused on avoiding the risk of spread

and ensuring people exposed are vaccinated. Cases most commonly occur as a result of not fully/un-vaccinated returning travellers and occasionally result in secondary cases as a result of exposure to the case in Australia.

Resources

- Click on this measles elimination press release
- Click on this article about measles elimination in Australia

Questions

Australia eliminated measles in 2014: bearing this in mind:

6. What is required to eliminate measles?
7. We still get cases and secondary cases so why are we still considered to have eliminated measles?
8. Is measles a candidate for eradication? Why?
9. What is the difference between elimination and eradication?

Resources

- Click here to read the contact interview form
- Click here to read the explanatory notes

Questions

For all of these contacts decide whether to offer them NHIG, vaccination, serology testing or advice only?

10. The male contact was born in 1975 and thinks he had one vaccination but isn't sure about the second. He hasn't had measles and has no medical problems. Exposure was 48 hours ago.
11. The female contact was born in 1984 and is unsure about her vaccination status. She is 14 weeks pregnant but otherwise well. Exposure was four days ago.
12. The female contact was born in April 2018 and has not received her measles immunisation yet. The child is otherwise well and born in Australia. Exposure was 2 days ago.
13. The 50-year old male is unsure about his vaccination status. He is on chemotherapy for lung cancer. Exposure was 5 days ago by the time we contact him.

References

1. Moss WJ. Measles. Lancet [Internet]. 2017;390(10111):2490–502. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673617314630
2. NCIRS. Significant events in measles-mumps-rubella vaccination practice in Australia [Internet]. 2018 [cited 2019 Feb 20]. Available from: http://www.ncirs.org.au/sites/default/files/2018-12/Measles-mumps-rubella-history-Dec-2018.pdf
3. Measles CDNA National Guidelines for Public Health Units [Internet]. [cited 2019 Feb 20]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/BD2AD79FD34BFD14CA257BF0001D3C59/$File/Measles-SoNG-final-April2015.pdf
4. NCIRS. Coverage data and reports | NCIRS [Internet]. 2018 [cited 2019 Feb 20]. Available from: http://www.ncirs.org.au/health-professionals/coverage-data-and-reports
5. Heywood AE, Gidding HF, Riddell MA, Mcintyre PB, Macintyre R, Kelly HA. Elimination of endemic measles transmission in Australia. Bull World Heal Organ [Internet]. 2009 [cited 2019 Feb 20];87:64–71. Available from: http://www.who.int/bulletin/
6. Department AG. Measles – Elimination Achieved in Australia [Internet]. Australian Government Department; 2014 [cited 2019 Feb 20]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-measles-elim-announce-2014.htm

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Chapter Two: Outbreak of *Bacillus cereus* at a Restaurant in Canberra

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Prologue

This chapter fulfils the competencies to respond to an acute public health problem, present to a conference, write a report for a lay-audience, and write a peer-reviewed publication. This publication was published in CDI in September, 2019 (CDI Journal). A report for a lay-audience was also completed (Appendix One).

This was a cohort investigation of a foodborne outbreak in a Canberra restaurant. As noted below, I was intimately involved in every part of the outbreak.

A number of other outbreaks and a summary of my public health experience are discussed in chapter one.

My Role

As part of the outbreak team I worked closely under the guidance of Tim Sloan-Gardner as the OzFoodNet Epidemiologist at ACT Health. Tasks I completed during and after the outbreak included:

- Design of the outbreak questionnaire using a standard template.
- Interviewing cohort (with other members of the surveillance team).
- Creating a data dictionary, completing data entry and undertaking analysis.
- Writing regular epidemiological summaries for ACT Health throughout the investigation.
- Writing an outbreak summary for ACT Health Protection staff.
- Contributing to ACT Acute Response Team meetings (ART).
- Participating in environmental investigation on site.
- Epidemiological study design (under supervision).
- Writing a summary of the outbreak investigation and its conclusions for the restaurant management.
- Writing a peer reviewed paper.

Acknowledgements

Many thanks to Tim Sloan-Gardner for leading the epidemiological investigation, encouraging me to complete various useful tasks for my learning, actively organising restaurant visits and arranging additional laboratory tests. Others involved in the investigation included: William Mude (Environmental Health), Radomir Krsteski (Environmental Health); Victoria Wansink (who patiently talked me through all the tests involved), Vanessa Johnston (leading ART team), Debbie Clark/Rachel Crane (interviews), Ben Polkinghorne (academic supervisor), Marlena Kaczmarek (field supervisor), Amy Jennison and John Bates (laboratory toxin analysis).

Lessons learnt

This was my first outbreak investigation and occurred within one month of my starting at ACT Health. Therefore, while our outbreak course was fresh in my mind, I was still coming to grips with the workplace. Some of the differences for me included working in a government department rather than a clinical organisation and the time-frames required. Time-frames are

more prolonged in public health compared to my pre-hospital emergency experience. While commencement of the investigation was immediate; including inspection and collection of food samples, analysis took place over a number of weeks, interspersed with business as usual tasks. This required on-going prioritisation skills and juggling a number of different tasks over a more extended period. More layers of sign-off can also increase timeframes, although knowing when authorisation is required will come with more experience.

I was fortunate to attend the restaurant to view the premises, visualise their processes and talk with the head chef. This provided a broader perspective on the whole outbreak and I found putting 'boots on the ground' helped to personalise the outbreak and make it more than just an academic exercise. While not always necessary, after my experience I think it is always preferable to visit the premises if appropriate and possible.

Differentiating the academic scenario from real life is something I have taught regularly in a clinical context however, this is the first time I have had to apply this in a public health context. The ten steps worked asynchronously and simultaneously at times, as was taught during our course block. However, this was my first experience of an outbreak; subsequent investigations have differed significantly depending on the pathogen, available resources, the number ill, and public interest amongst many other factors.

This also highlights some of the conditions of field epidemiology which include: "extent of the investigation is likely to be limited because of the imperative for timely intervention and by other situational constraints"(1). For example, we cannot control all aspects of an investigation in the same way an academic research project may aim to do. As a result, we may not be able to interview every attendee and instead rely on internet-based surveys. We may get few or no human or environmental samples, the conditions when the outbreak occurred may be different from those investigated.

During the analysis stage I noted a number of missing values, particularly with regard to food histories from uncontactable cohort members. The importance of information gathering was highlighted for me as you can only analyse the information you have gathered.

We conducted a retrospective cohort study as we were able to interview >80% of attendees. A cohort study allows calculation of attack rates (the denominator is known) and often a risk ratio. In this instance, because of universal exposure we used an exact logistic regression which produces an odds ratio instead. Although I initially thought that universal exposure was unique and interesting, I learnt this is a common occurrence with food-borne outbreaks. While analytical studies may still be beneficial, in this instance no significant results were identified, placing increased importance on describing the data by time, place and frequency of exposures.

In a similar way the importance of individual details gathered is difficult to know at the time but can become very important during analysis. Although exact durations and onsets of illness didn't seem important at the time, this became crucial during the analysis when differentiating *Bacillus* toxins. Accuracy of symptoms is also very important in this regard. Clinically, the difference between diarrhoea and vomiting is not significant in an acute situation. However, this difference was again very important in distinguishing between two toxins and is critical for differential diagnosis in the absence of human microbiological evidence.

The laboratory is a critical component of most outbreaks and this outbreak was no exception. Without their involvement we would not have identified the likely cause and our conclusion would have been a gastrointestinal outbreak with an unknown source. Knowing and befriending the laboratory staff was important and useful. Their assistance in understanding and contextualising results was invaluable for me. If stool samples had been received a multiplex polymerase chain reaction (PCR) test would be requested. These can often test more than twenty enteric pathogens at a time.

A highlight of this outbreak was getting an article published prior to completion of the thesis (Appendix One). Although this was a long, iterative process, the improvement following multiple versions was clear and I could see the clarity of writing improved with each version.

Public Health implications of this work

B. cereus toxin-mediated gastroenteritis is not nationally notifiable in Australia however, "food or water borne disease in 2 or more linked cases" is notifiable in the ACT and all foodborne outbreaks are reported by all state and territory OzFoodNet epidemiologists and captured in the OzFoodNet outbreak register. Very few *Bacillus cereus* outbreaks are detected in Australia due to the mild severity and short duration of symptoms making it less likely for people to report illness and much less likely to submit a stool specimen. Even fewer provide evidence of both emetic and diarrhoeal toxins.

Our investigation detected a striking difference in ill persons based on major symptom, time of onset, and duration with two distinct cohorts emerging one with rapid onset and short duration with vomiting the major symptom (an emetic cohort) and one with later onset, longer duration and diarrhoea the major symptom (a diarrhoeal cohort). As expected with a *B. cereus* outbreak in a relatively healthy population there was no hospitalisation, only two cases presented to a GP and no one submitted a stool specimen.

The environmental investigation detected *Bacillus cereus* in the beef and risotto balls. To further support this evidence, specimens were sent to Queensland Health Molecular Epidemiology for whole genome sequencing which detected identical diarrhoeal toxin genes in the beef and risotto. This provided evidence to support potential cross contamination between the risotto

balls and the beef. This added to our portfolio of evidence as we had no human microbiological evidence and due to near universal exposure because of a set menu we were unable to detect significant analytical result.

Our public health investigation found the *B. cereus* was highly likely to have been introduced by restaurant staff either through poor hygiene practice or temperature abuse. While preparing short rib at this restaurant, deliveries of fresh food (a known source of *B. cereus*) arrived. There was no policy reinforcing hand hygiene following handling of this fresh produce creating the potential for cross contamination.

As a result of this investigation we recommended the following hygiene and food preparation improvements: washing of hands prior to any food preparation, including following handling of raw fruit and vegetables; documentation of a hygiene policy; documentation of beef temperatures over time. The restaurant adopted all recommendations.

Hygiene and sanitation policies were changed with an increase in hand washing required following a change in task. Raw food practices were altered to decrease the risk of contamination in the food when served, while not altering the quality of their product in terms of taste and texture.

A heightened awareness of the potential for staff to introduce pathogens and cause illness led to improved individual practice as a result.

An outbreak of *Bacillus cereus* toxin-mediated emetic and diarrhoeal syndromes at a restaurant in Canberra, Australia 2018

C. E. Thirkell, T. S. Sloan-Gardner, Dr M. C. Kaczmarek, Dr B. G. Polkinghorne

Abstract

A cluster of gastrointestinal illness was detected following receipt of a complaint of becoming ill after a multi-course dinner at a restaurant in Canberra, Australian Capital Territory (ACT), Australia. The complaint led to an investigation by ACT Health.

Food samples retained by the restaurant for microbiological analysis returned an unsatisfactory level of *Bacillus cereus* in beef (19,000 colony forming units/gram [cfu/g]) and a satisfactory level in arancini (50cfu/g). These positive samples underwent whole genome sequencing and genes encoding diarrhoeal toxins were detected with no laboratory evidence of the emetic toxin. No stool specimens were collected.

A cohort study was undertaken and 80% (33/41) of patrons took part in a structured interview. There was no significant difference in age or sex between those ill and not ill. Due to universal exposure most foods were unable to be statistically analysed and no significant results were found from the food history. The ill cohort diverged into two distinct groups based on incubation period and symptoms suggesting this outbreak involved *B. cereus* intoxication with both diarrhoeal and potentially emetic toxins. Some hygiene practices during food preparation were noted to be inadequate and heating and cooling procedures were unverified when questioned.

A combination of the incubation periods and symptom profile, food laboratory evidence, and genomic sequencing of the *B. cereus* diarrhoeal gene suggest a probable aetiology of *B. cereus* intoxication. Public health action included the restaurant rectifying hygiene practices and documenting heating/cooling procedures.

Key words: *Bacillus cereus,* universal exposure, emetic syndrome, diarrhoeal syndrome, genomic sequencing, gastroenteritis, foodborne disease.

Introduction

Four people reported gastrointestinal illness to a restaurant in Canberra, Australian Capital Territory (ACT), Australia the morning after attending a multi-course dinner. The restaurant subsequently self-reported the cluster of illness to ACT Health. The restaurant had three seatings each night during the period of concern; early, middle and late. This report describes the outbreak investigation of *Bacillus cereus* toxin mediated emetic and diarrhoeal syndromes associated with that multi-course dinner, and the first published use of whole genome sequencing (WGS) in a *B. cereus* foodborne outbreak investigation in Australia.

Foodborne illness is estimated to cause 4.1 million cases of gastroenteritis and 3,350 episodes of *B. cereus* each year in Australia, the majority of these are not reported (1). *B. cereus* toxin-

mediated gastroenteritis is not notifiable in Australia however, outbreaks are reported by all states and territories and captured in the OzFoodNet outbreak register (2). A foodborne outbreak is defined as a similar illness in ≥2 people after consuming a common food and epidemiological and/or microbiological evidence implicates food as the source of illness (3). *B. cereus* was officially attributed to just ten outbreaks on the register between 2001 - 2013, likely due to the short duration of illness and relatively mild symptoms limiting reporting (4).

B. cereus is ubiquitous in the environment, particularly in soil and vegetation (5) and can cause two type of illnesses referred to as emetic-type and diarrhoeal-type illness (6). Emetic-type illness occurs from the production of the toxin cereulide. This toxin is pre-formed in the food with a temperature production range of 12 - 37°C. It is heat stable to 100°C for >2 hours and results in emetic illness which typically has an average incubation of 1-6 hours and symptom duration of 6-24 hours (6,7). Foods commonly associated with emetic illness include rice, pasta and pastries and are generally linked to improper surface cleaning, cross contamination or temperature abuse through inadequate heating and cooling (7–9). The infective dose has not been determined for the emetic toxin. However, although it has been reported as low as 10^3 cfu/g, in most cases it is above 10^5 cfu/g (10).

Diarrhoeal-type illness results from one or a number of associated toxins including: enterotoxin FM which is not pathogenic but contributes to the severity of diarrhoeal illness, haemolysin BL (HBL), cytotoxin K (cytK) and non-haemolytic enterotoxin (Nhe) (11). The illness is caused by the ingestion of dormant spores which then germinate and proliferate in the small intestine and then produce the toxins. Diarrhoeal-type illness has an average incubation of 8-16 hours and symptom duration of 12-24 hours (7). Spores should be eliminated by heating to 100°C for 3 minutes when appropriate heating and cooling processes are adhered to. Foods commonly associated with diarrhoeal illness include protein foods such as meat products, soups, vegetables and sauces; and practices linked to contamination including poor heating and cooling in particular (7). The infective dose is generally considered to be between 10^5 – 10^8 cfu (10).

Methods

Epidemiological investigation

A retrospective cohort study was performed using a standard gastrointestinal outbreak questionnaire adapted to the menu used on the implicated night. A contact from each table was obtained from the restaurant and phone interviews were conducted. Non-respondents were called back either until they responded or six attempts to make contact were unsuccessful. A case was defined as someone who ate dinner at the specified restaurant on the implicated date and experienced gastrointestinal symptoms (nausea, vomiting, diarrhoea and abdominal pain) within 24 hours. A line-list was entered into Microsoft Excel 2013 and analysed using STATA 15.0

(12). Univariate analysis included generating odds ratios using logistic regression, and exact logistic regression where this was not possible due to zero cell counts. Age was compared using a two-sample t-test, after confirming a normal distribution. Gender was compared using two-tailed Fisher's exact test. Ethics approval was not sought as this is not required under the ACT *Public Health Act 1997* for the purposes of a public health investigation (13). Australian National University has a waiver of consent for research performed as part of an outbreak investigation under protocol: 2017/909.

Environmental health investigation

An Environmental Health Officer from ACT Health attended the restaurant to perform a routine food premises inspection. Samples of all retained food served on the implicated night were taken for laboratory analysis as required by the *Food Act 2001 (ACT)* (14). Two follow-up visits were conducted with ACT Health staff to discuss food preparation techniques and laboratory results.

Laboratory investigation

No stool specimens were received from cases. Food samples were tested at the ACT Government Analytical laboratory (ACTGAL) for *Staphylococcus aureus, B. cereus* and *Clostridium perfringens* using a spread plate method and standard plate counts. Microbiological results for *B. cereus* are classified as satisfactory (<100 cfu/g), marginal (100 - <1000cfu/g), unsatisfactory (1000 - <100,000cfu/g) and potentially hazardous (>100,000) (15). Further into the investigation WGS was performed by the Queensland Health Molecular Epidemiology Unit utilising the Illumina NextSeq genome sequencing platform to detect enterotoxin genes for all food isolates which grew *B. cereus.*

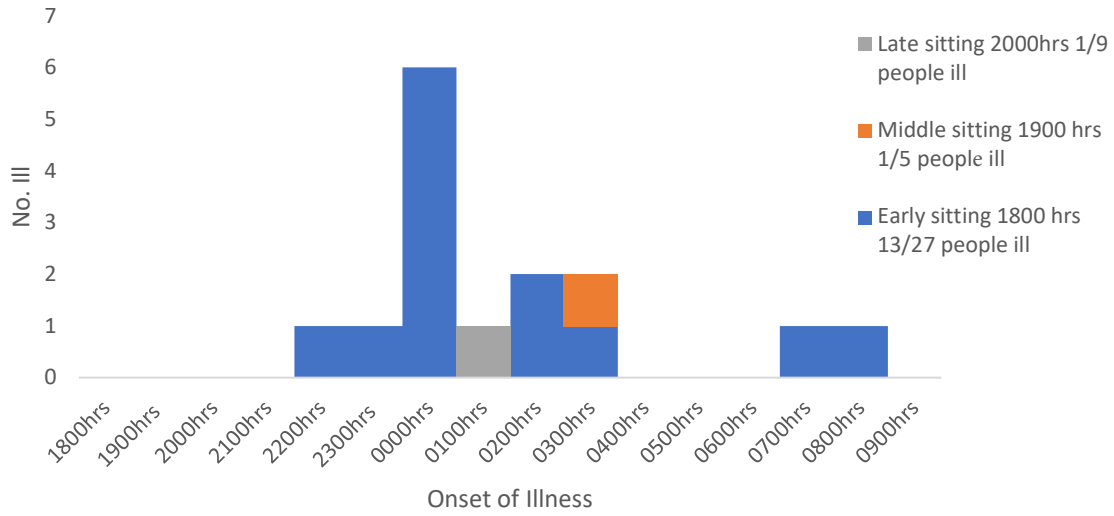
Results

Epidemiological

A total of 45 patrons dined in three separate sittings at the restaurant on the night, across 15 tables. We were able to contact 41 patrons (91%) from 14 tables. Of the 41 who were contacted, an ill status was gathered for all (100%) and a food history was obtained for 33 patrons (80%). The attack rate for those who attended on the night was 37% (15/41) (Figure 1).

There was no statistically significant difference in gender (p=0.51) or age (p=0.93) between those ill and not ill. No cases required treatment in-hospital.

Figure 1: Epidemiological curve of cases by onset of illness time after attending dinner at restaurant (n = 15)



More than eight courses were served, and ten foods were captured during interview (Table 1). Universal exposure was present for four foods (pastry, crocodile, arancini and salmon) and >90% ate another four foods (beef, apple lolly, apple sour and scallops). The two other foods were alternate foods provided for taste or intolerance to menu foods (oysters, raspberry). Statistical analysis of ill status and exposure to foods provided no evidence of a contaminated food source. All confidence intervals crossed one and no odds ratios with significant p-values were produced.

Illness was concentrated in the early sitting (1800 hrs) with an attack rate of 48%, 20% for the middle sitting (1900 hrs), and 11% for the late sitting (2000 hrs). No significant differences ($p>0.05$) were noted in age, sex or general health between those who were ill or not ill in the early sitting.

No clusters among tables were observed with a broad distribution of illness across the 15 tables. Food history was available for 13 of 15 ill patrons and 20 of 26 not ill patrons. No staff were interviewed but all staff were reported to eat the same food on the night prior to opening except for the beef and none were reported to be ill.

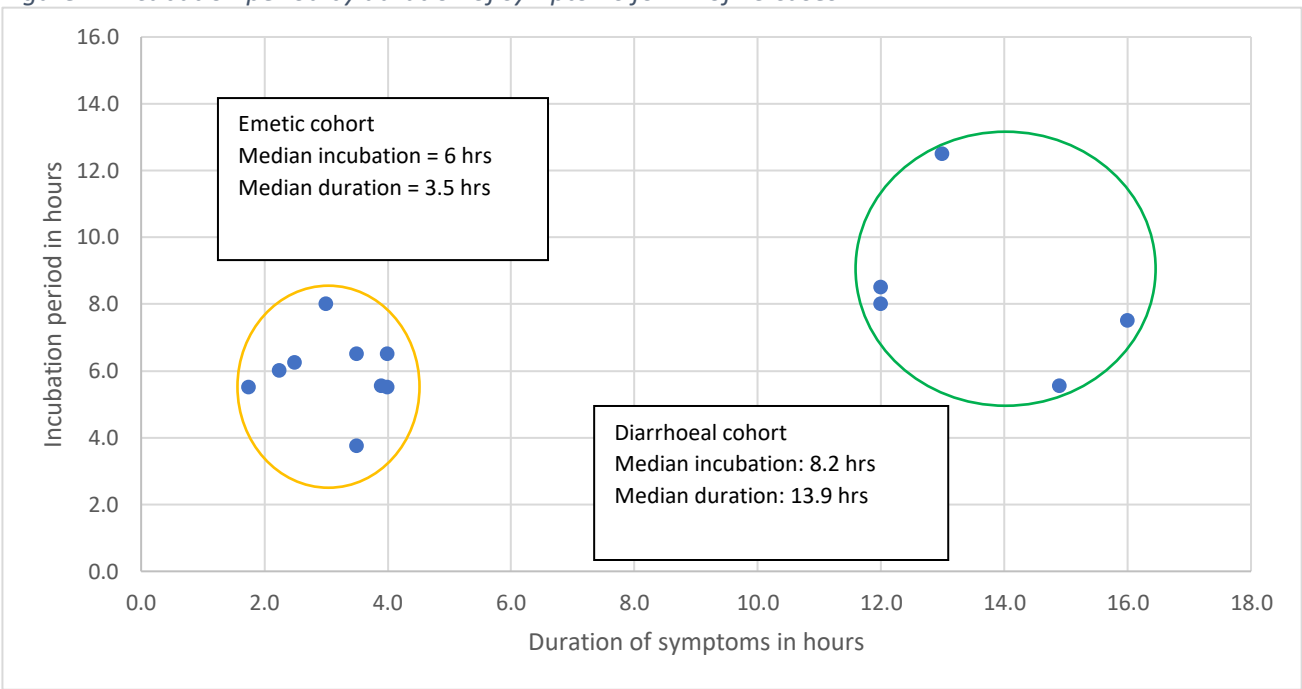
Two distinct ill cohorts emerged based on incubation period and duration of symptoms (Figure 2). All emetic syndrome cases (nine) had vomiting and all diarrhoeal syndrome cases (six) had diarrhoea.

Table 1: Univariate analysis of food exposures (n = 33)

	EXPOSED			NOT EXPOSED				
FOOD	**Ill**	**Not ill**	**AR (%)**	**Ill**	**Not ill**	**AR (%)**	**Odds ratio (95% CI)**	**p value**
OYSTERS	3	4	43	10	15	40	0.76 (0.33 – 1.76)	0.52
PASTRY	13	20	39	0	0	0	*	
CROCODILE	13	20	39	0	0	0	*	
SCALLOPS	13	19	40	0	1	0	0.65 (0.02 - ∞) †	1.0
ARANCINI	13	17	43	0	0	0	0.88 (0 – 1.18) †	0.42
SALMON	13	20	39	0	0	0	*	
BEEF	12	20	38	1	0	100	0.65 (0 – 25.35) †	0.79
APPLE LOLLY	12	18	40	1	2	33	1.3 (0.11-16.39)	0.82
APPLE SOUR	12	18	40	1	2	33	1.3 (0.11-16.39)	0.82
RASPBERRY	2	7	22	4	9	31	1.19 (0.99-1.42)	0.06

** Logistic and exact regression unable to be calculated due to zero cell counts and collinearity*
† Calculated using exact logistic regression
Denominator differs by food due to unknown data

*Figure 2: Incubation period by duration of symptoms for 14 of 15 cases**



**One diarrhoeal syndrome case excluded from graph due to duration of 48hrs (incubation of 14 hrs)*
This case had rice as a starter with no other differences noted (no other cases reported eating rice other than the arancini)

Environmental

The environmental health officer collected three frozen samples each of crocodile, beef and arancini during their first inspection. Following discussions with the restaurant chef, it was discovered that the beef dish was cooked for 12 hours at 85°C before being de-boned. The deboning process was interrupted by the arrival of fresh fruit and vegetables which the staff

unloaded and then returned to meat preparation with no hand hygiene performed. The beef was then spread across large metal trays which were stacked and placed in the cool-room for 25 minutes. The meat was then pressed and placed in the cool-room overnight. The following day, 12 individual servings were placed into 2 kilogram (kg) vacuum sealed bags and then frozen. Prior to serving, the 2kg bag was reportedly thawed in a water bath held at 55°C for 35 minutes, then just prior to serving a single-serving size of beef was added to a *jus* sauce heated to 78°C for <5min. The heating, cooling and re-heating process was not documented or verified with thermometers. Three to four bags were reported to be used on the night, however, the restaurant was unable to confirm whether they were from the same batch of cooking, nor whether the bags were used concurrently or consecutively.

Laboratory

Initial testing of retained food specimens demonstrated growth of *B. cereus* at unsatisfactory levels in the beef dish and at detectable but satisfactory levels in the arancini balls (16). No pathogens were detected in any other samples. The restaurant requested testing of a second sample of the beef dish retained by the laboratory, and another 2kg bag of frozen beef the restaurant had retained. The second beef sample demonstrated growth of *B. cereus* at lower levels than the first sample but still unsatisfactory. No pathogens were detected in the 2kg frozen sample (Table 2). Whole genome sequencing was performed on isolates from the two positive beef samples and one positive arancini sample. The diarrhoeal toxin genes Hbl, Nhe and CytK were detected in both the beef and arancini balls. All three positive isolates had the same multi locus sequence type (MLST) 177. The emetic toxin, cereulide was not detected in any of the three isolates tested. No stool samples were received from cases.

Table 2: Food related laboratory testing and results

Food Tested	Organism or toxin testing for	Test	Result	Interpretation
Beef first sample	*S. aureus*	Spread plate	<50cfu/g	Satisfactory
	B. cereus	Spread plate	19,000cfu/g	Unsatisfactory
	C. perfringens	Pour plate	<50cfu/g	Satisfactory
Crocodile	*S. aureus*	Spread plate	<50cfu/g	Satisfactory
	B. cereus	Spread plate	<50cfu/g	Satisfactory
	C. perfringens	Pour plate	<50cfu/g	Satisfactory
Arancini balls	*S. aureus*	Spread plate	<50cfu/g	Satisfactory
	B. cereus	Spread plate	50cfu/g	Satisfactory
	C. perfringens	Pour plate	<50cfu/g	Satisfactory
Beef second sample	*B. cereus*	Spread plate	3,500cfu/g	Unsatisfactory
2kg Frozen bag of beef	*B. cereus*	Spread plate	<50cfu/g	Satisfactory

Discussion

The food laboratory evidence along with duration, incubation and symptom history provides evidence of a probable outbreak of *B. cereus* intoxication caused by diarrhoeal and potentially emetic toxins. According to OzFoodNet and the US Centers for Disease Control and Prevention (CDC) guidelines, definitive evidence would require case specimens or isolation of at least 100,000 cfu/g from food samples (3,17). The evidence to support this cfu/g threshold is not clear with some variance in other investigation reports (18) and this outbreak suggesting lower levels may be appropriate. Re-heating of the beef for service indicates both emetic-toxin mediated and diarrhoeal toxin-mediated gastroenteritis are biologically plausible because being placed in 55°C water for thirty five minutes followed by briefly being placed in the jus may not destroy either the pre-formed emetic toxin or the diarrhoeal spores. Evidence suggests the risk of meat contamination increases with multiple stages of preparation (19) which is consistent with the complex meat preparation implicated in this outbreak.

Although the majority of illness was concentrated in the early sitting, the reason for this is unknown. Contamination appears to have occurred in batches however, investigations were unable to identify differences in food preparation or plating. The fresh fruit and vegetables arrived during the deboning process following initial cooking and it is postulated that contamination may have occurred at this stage. The process of cooling then involved stacking the trays of beef directly on top of each other in the cool room. It is possible the middle trays were not cooled to the same extent or as quickly resulting in batched contamination.

The MLST identified was last reported in human isolates in Europe in 2003/04 on PubMLST, (a global database for molecular typing). This is the first documented whole genome sequencing of *B. cereus* isolates following an outbreak in Australia. Although the arancini did not produce unsatisfactory levels of *B. cereus*, the isolated genes and MLST type found matched those of the beef. This suggests there was cross contamination between the beef and the arancini and potentially undetected cross contamination with other foods. Beef is one of the predominant food types associated with *B. cereus* diarrhoeal syndrome (6) and therefore biologically plausible and consistent with the cases who presented with diarrhoeal symptoms in this outbreak. The majority were unwell with emetic symptoms suggesting either another source of illness or the beef producing both toxins. Improvement of hygiene policies with increased hand hygiene was a public health action from this investigation which may help prevent the introduction of organisms into the food and also prevent cross-contamination within the kitchen.

Literature has traditionally suggested it is rare to have both forms of illness however, a 2016 review of French *B. cereus* outbreaks has challenged this thought and this outbreak supports this notion (6,20). It was noted that 57% (42/74) of *B. cereus* related outbreaks resulted in both

emetic and diarrhoeal symptoms with variability in incubation periods. The two distinct illness profiles in this outbreak, present as a typical example of emetic and diarrhoeal syndromes although the emetic cases with a median incubation of 6 hours support the suggestion of a longer incubation period because of a low dose of the emetic toxin. Isolating the *B. cereus* diarrhoeal gene in the food provides strong evidence of the cause of the diarrhoeal syndrome even though only 6/15 cases presented with typical diarrhoeal symptoms. Not isolating the *B. cereus* emetic toxin does not rule out its presence – it is still considered the likely cause of the emetic syndrome based on the case profiles and is consistent with recent evidence (20). It is well accepted that the emetic toxin is difficult to isolate in food and stool samples which emphasises the importance of epidemiological evidence (21).

Limitations of this investigation included no stool samples being received, however, nearly all the ill patrons had recovered by the time they were contacted. Steps to minimise this bias included a standard detailed questionnaire. This questionnaire also helped to highlight differences in incubation/duration times. Eight people were unable to be contacted of which two were ill. A variety of food was available on the implicated night with only three foods available for analysis. Near universal exposure hampered statistical testing due to zero cell counts and attack rates were not high. For example, the one person who did not report eating beef, did report being ill, hence a statistically insignificant, protective odds ratio was produced. This highlights the importance of gathering a portfolio of evidence including descriptive epidemiological and microbiological food evidence.

This investigation is a good example of a public health response that combined detailed epidemiological, microbiological, whole genome sequencing and environmental health expertise to provide strong evidence of a likely pathogen and cause of contamination. This led to recommendations regarding hygiene and food preparation practices and no further reports of illness. The restaurant in question was very cooperative and positively engaged in the investigation: self-reporting in a timely manner, retaining specimens for testing and responding to all public health requests.

Conclusion

Following a thorough and rapid investigation, the probable aetiology of this outbreak was *B. cereus* intoxication with diarrhoeal and potentially emetic toxins due to cross contamination of food. This was corroborated by the symptom profile and food sample laboratory evidence, including genome sequencing of the diarrhoeal gene. Although rarely reported in Australia, this outbreak provides evidence of the ongoing risk of *B. cereus* in food produced in restaurants, and highlights the need for continued vigilance in food preparation techniques.

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References

1. Goodman, R. Buehler, J. Koplan J. Defining Field Epidemiology. Am J Epidemiol [Internet]. 1990;132:91–6. Available from: https://www.cdc.gov/eis/field-epi-manual/chapters/Defining-Field-Epi.html
2. Kirk, M. Ford, L. Glass, K. Hall G. Foodborne Illness, Australia, Circa 2000 and Circa 2010. Emerg Infect Dis [Internet]. 2014 [cited 2018 May 22];20(11):1857. Available from: https://wwwnc.cdc.gov/eid/article/20/11/pdfs/13-1315.pdf
3. OzFoodNet Working Group. OzFoodNet Outbreak Register Data Dictionary. 2016.
4. May FJ, Polkinghorne BG, Fearnley EJ. Epidemiology of Bacterial Toxin-mediated Foodborne Gastroenteritis Outbreaks in Australia, 2001 To 2013. CDI [Internet]. 2016 [cited 2018 Apr 19];40(4). Available from: https://www.health.gov.au/internet/main/publishing.nsf/content/cda-cdi4004-pdf-cnt.htm/$FILE/cdi4004c.pdf
5. Food and Drug Administration. Bad Bug Book Handbook of Foodborne Pathogenic Microorganisms and Natural Toxins [Internet]. Second. 2012 [cited 2018 May 21]. 292 p. Available from: https://www.fda.gov/downloads/Food/FoodborneIllnessContaminants/UCM297627.pdf
6. Food Standards Australia New Zealand. Bacillus cereus [Internet]. 2013 [cited 2018 May 21]. Available from: https://www.foodstandards.gov.au/publications/Documents/Bacillus cereus.pdf
7. Granum PE, Lund T. Bacillus cereus and its food poisoning toxins. FEMS Microbiol Lett [Internet]. 2006 Jan 17 [cited 2018 May 30];157(2):223–8. Available from: https://academic.oup.com/femsle/article-lookup/doi/10.1111/j.1574-6968.1997.tb12776.x
8. Ehling-Schulz M, Fricker M, Scherer S. Identification of emetic toxin producing Bacillus cereus strains by a novel molecular assay. FEMS Microbiol Lett. 2004;232(2):189–95.
9. Osimani, A. Aquilanti, L. Clementi F. Bacillus cereus foodborne outbreaks in mass catering. Int J Hosp Manag [Internet]. 2018 [cited 2018 Oct 17];72:145–53. Available from: https://ac-els-cdn-com.virtual.anu.edu.au/S0278431917304486/1-s2.0-S0278431917304486-main.pdf?_tid=c4ff2ddf-06ad-42bc-b4f1-0bc8582e23a0&acdnat=1539747561_53c5b66dc910f36c7d06bb9b76fb5760
10. Stenfors Arnesen LP, Fagerlund A, Granum PE. From soil to gut: *Bacillus cereus* and its food poisoning toxins. FEMS Microbiol Rev [Internet]. 2008 Jul 1 [cited 2018 Nov 19];32(4):579–606. Available from: https://academic.oup.com/femsre/article-lookup/doi/10.1111/j.1574-6976.2008.00112.x
11. Walker-York-Moore L, Moore SC, Fox EM. Characterization of enterotoxigenic bacillus cereus sensu lato and Staphylococcus aureus isolates and associated enterotoxin production dynamics in milk or meat-based broth. Toxins (Basel). 2017;9(7):1–15.
12. StataCorp. Stata Statistical Software: Release 15 [Internet]. College Station; 2017. Available from: https://www.stata.com/support/faqs/resources/citing-software-documentation-faqs/
13. ACT Government. Public Health Act 1997 [Internet]. Australian Capital Territory Public Health Act 1997. Available from: http://www.legislation.act.gov.au/a/1997-69/current/pdf/1997-69.pdf
14. Food Act 2001 [Internet]. 2001. Available from: http://www.legislation.act.gov.au/a/2001-66/20141120-59637/pdf/2001-66.pdf
15. FSANZ (Food Standards Australia New Zealand). Compendium of Microbiological Criteria for Food. 2016 [cited 2018 Jul 10];50. Available from: https://www.foodstandards.gov.au/publications/Documents/Compedium of

Microbiological Criteria/Compendium of Microbiological Criteria.pdf

16. Australian New Zealand Food Authority. A Guide to the Food Safety Standards Safe Food Australia [Internet]. 2001 [cited 2018 May 21]. Available from: https://www.foodstandards.gov.au/publications/documents/complete_safefood.pdf
17. Centers for Disease Control and Prevention. Guide to confirming an Etiology in Foodborne Disease Outbreak [Internet]. 2015. Available from: https://www.cdc.gov/foodsafety/outbreaks/investigating-outbreaks/confirming_diagnosis.html
18. Walker-York-Moore L, Moore SC, Fox EM. Characterization of Enterotoxigenic Bacillus cereus sensu lato and Staphylococcus aureus Isolates and Associated Enterotoxin Production Dynamics in Milk or Meat-Based Broth. Toxins (Basel). 2017;9(7):1–15.
19. Tewari A, Abdullah S. Bacillus cereus food poisoning: international and Indian perspective. J Food Sci Technol [Internet]. 2015 May [cited 2018 Apr 30];52(5):2500–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25892750
20. Glasset B, Herbin S, Guillier L, Cadel-Six S, Vignaud M, Grout J, et al. Bacillus cereus-induced food-borne outbreaks in France, 2007 to 2014: epidemiology and genetic characterisation. [cited 2018 Nov 22];1. Available from: www.eurosurveillance.org
21. Phat C, Kim S, Park J, Lee C. Detection of Emetic Toxin Genes in *Bacillus cereus* Isolated from Food and their Production of Cereulide in Liquid Culture. J Food Saf [Internet]. 2017;37(1):e12293. Available from: http://doi.wiley.com/10.1111/jfs.12293

Appendix One: Publication cover

ACT Government
Health

Health Protection Service

Howard Florey Centenary House, 25 Mulley Street, Holder ACT 2611
Locked Bag 5005, Weston Creek ACT 2611
Phone: (02) 6205 1700 Fax: (02) 6205 1705
Website: www.health.act.gov.au

Dear *** Restaurant,

On 18th April, 2018 ACT Health: Environmental Health received a report from *** Restaurant of multiple patrons experiencing gastrointestinal symptoms following eating dinner at the restaurant on the 17th April 2018.

Environmental Health undertook an inspection noting the premises was clean and compliant with no food handling issues identified. A number of food samples were taken for analysis. ACT Health staff subsequently met with *** staff to clarify preparation and cooking procedures and discuss laboratory results. After contacting almost all of the patrons who dined that night, over a third were ill after consuming food from the restaurant.

The short rib returned unsatisfactory growth of *Bacillus cereus* following laboratory analysis. Confirmatory testing of the B sample confirmed these results. Hand hygiene deficiencies were identified, specifically when food preparation was interrupted by fresh produce arrivals. The heating and cooling process for the short rib was also unverified. A number of raw foods were identified as being served including crocodile and scallops.

*** restaurant have changed their practice of scallop preparation by searing the scallops prior to blending and serving. *** have satisfactorily verified the cooking and cooling process and provided this to ACT Health. *** will amend their hand hygiene and sanitisation procedures when handling produce and receiving goods and provide this to ACT Health.

The incubation period (time from eating to illness), duration of illness and symptom profile suggest *B. cereus* caused two different toxins (vomiting and diarrheal) following the consumption of food at *** restaurant on the 17th April 2018. The results of the investigation suggest that temperature abuse and food handling practices may have resulted in contamination of food served on the night. No further public health action is required.

Regards,

Dr Vanessa Johnston
Public Health Physician

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Chapter Three: Epidemiology and antimicrobial resistance of gonococcal notifications in ACT from 2009 to 2018

Table of Contents

Prologue

My Role

I chose this topic to broaden my experience of public health. A subsequent benefit included providing background context for my surveillance plan. I designed the study, wrote the study proposal, ethics application and data analysis plan. I collected and collated the data from the Notifiable Disease Management System (NDMS), enhanced data Excel spreadsheets, and two extracts of data from the laboratory, as well as paper records. I conducted all the data cleaning and analysis in STATA, used R for some of the graphics and developed the chapter.

Acknowledgements

Marlena Kaczmarek (ACT Health), Ben Polkinghorne (ANU) and Vanessa Johnston for your supervision throughout the process. Sue Reid and Rachel Crane (ACT Health) for patiently answering my endless questions.

Lessons learnt

This project provided a great lesson of seemingly simple data providing plenty of challenges, particularly merging data. I gained a lot of practice in cleaning and merging datasets while becoming more efficient with my code over time. This study was a good example of the benefits of descriptive epidemiological analysis compared with performing complicated statistical analyses.

It is one thing to be told that routine datasets can be difficult to clean and analyse, it is another to actually experience it. This project highlighted the importance of using appropriate validated databases rather than excel spreadsheets and appropriately choosing variables and inputs that are useful for analysis later on. One variable had approximately 53 versions of just three terms due to no validation at the data entry phase. Recoding and manual checking of details was a very time-consuming but useful learning process.

Gonococcal notifications can include infection from multiple sites (eg. urogenital, rectal and oral) which can further complicate analysis. Distinguishing whether you are analysing the number of sites infected, or the number of notifications is important for analysis and writing. Needless to say, the number of sites is higher than the number of notifications. Data was presented as 'wide' data with one notification per row. The majority of analysis was undertaken with wide data. Analysis of antimicrobial resistance (AMR) data by isolate required reshaping the data to 'long' and creating one entry per site of infection. In hindsight much of the research only reports one infection per person and prioritises pharyngeal, rectal and urogenital. This is a pragmatic approach considering a person with multiple sites of infection is likely to have the same antibiotic sensitivities at each site.

Merging data with unique identifications was a relatively simple process. One dataset did not include a unique identifier which resulted in a laborious manual process to enter them. The benefits of a unique identifier were apparent to avoid unnecessary work as well as data entry errors.

Aspects of this data are very well documented on an annual basis by The Kirby Institute and the National Neisseria Network. It was important to try and identify information gaps which neither report on. One of the key gaps included the link between epidemiological and laboratory data which became a focus for this chapter. Another gap was the link between sexual exposure and sites of infection, resistance trends and diagnosing clinician.

Different laboratories use different methods of producing and interpreting antimicrobial resistance results (see chapter 4, page 3 for further information). This caused difficulty in comparing results from the different laboratories. These interpretations are based on minimum inhibitory concentration (MIC) levels which can be compared across laboratories. A useful learning point was understanding that these different methodologies exist, as well as what results can and cannot be compared across organisations.

A variety of terms are used to define sexual exposure in the literature (1). The terms used in this chapter are consistent with the way in which national enhanced data is recorded which focuses on exposure rather than sexual identity. The term men who have sex with men (MSM) is used to capture exposure as sexual practices may not reflect sexual orientation.

Public Health implications of this work

The rationale for completing this project was the rise in gonococcal notifications rates in recent years across Australia including the ACT, alongside increasing concern regarding AMR. Two cases of extremely resistant gonorrhoea notified in Australia during 2018 provided further evidence of the risk of increasing incidence and AMR of gonorrhoea in Australia (2).

A lot of the background work for this project contributed towards my surveillance plan and as a result of many conversations, particularly with the public health nurses, some improvements were made. For example, while analysing the gonococcal AMR data, I identified that receipt of some of the data from the laboratories was inconsistent and untimely. During discussions with the laboratory to resolve these issues, a potential error in interpretation by one of the primary laboratories was identified. This was identified following analysis by the reference laboratory who reported an isolate as resistant, previously reported as sensitive by the primary laboratory. This occurred because the primary laboratory had been classifying isolates with a minimum inhibitory concentration (MIC) of 0.75 mg/L as sensitive when they should have been reported

as resistant (1mg/L). This led to an additional 25 isolates over a number of years being reclassified as resistant, after previously reported as sensitive.

Analysing the process of gonococcal data collection for this project provided insight into what changes and new variables might be useful for the surveillance of gonococcal AMR data. Antimicrobial data from *N. gonorrhoea* notifications has been collected for some time in the ACT. Therefore, aspects of a surveillance system evaluation were documented for gonorrhoea notifications in my surveillance chapter. My gonococcal data analysis informed this evaluation by providing a better understanding of what data is currently collected and what information is useful to collect for public health surveillance.

This study was presented to the ACT Sexual Health Advisory group providing data on the current trends and also presented to the Australian Communicable Disease Conference in November, 2019.

This project helped me to understand the epidemiology of gonorrhoea in the ACT and provided a sound baseline for future analysis and decisions.

Abstract

Notifications of gonococcal infection are increasing in Australia and internationally. Alongside this, increasing rates of resistance to frontline treatments is causing widespread concern. This study provides an epidemiological description of gonococcal notifications in the ACT and analyses antimicrobial resistance data from 2009-2018.

Overall, the number of gonococcal notifications has risen 5-fold from a low of 14.9 per 100,000 population in 2010 to 77.9 per 100,000 population in 2018. The highest rates for males were 448.4 per 100,000 population for the 20-25-year age-group; for females the highest rate was 102.4 per 100,000 in the 20-25-year age-group.

Nearly half (49%) of all notifications were culture positive, of these 61 (8%) notifications reported either low-level resistance (LLR) to azithromycin (≥1.0 - <256mg/L) or decreased sensitivity to ceftriaxone (≥0.125 - <0.5mg/L). Only one case with decreased sensitivity to ceftriaxone has been reported since 2015. Of the 60 LLR azithromycin isolates, 57 (95%) were male and of these, 53 (88%) were male and reported same-sex exposure.

Canberra Sexual Health Centre (CSHC) diagnosed the majority of gonococcal infections overall (64%). The population that CSHC treat predominantly reports same-sex exposure (778/976, 80%) compared to General Practitioners (GPs) who generally see patients reporting heterosexual exposure (262/429, 61%). The majority of notifications diagnosed by CSHC were positive by culture (603/976, 62%), compared to GPs (106/429, 25%) indicating a gap in AMR surveillance in the ACT.

Targeted public health messaging for MSM and heterosexual females in their twenties is recommended as well as on-going engagement and education with GPs regarding appropriate laboratory testing and AMR for gonococcal infections.

Introduction

Gonorrhoea is a sexually transmitted disease, caused by *Neisseria gonorrhoeae,* most commonly via urogenital, anorectal or pharyngeal infection.

Males with urogenital infection are generally symptomatic with complications including epididymitis; whereas infections at other sites are often asymptomatic (3). Conversely infections at all sites in females are generally asymptomatic, yet complications following urogenital infection are most severe in this group and include: pelvic inflammatory disease, infertility, ectopic pregnancies; and vertical transmission to newborns (4). Asymptomatic gonococcal infections can still result in transmission of disease but infections are often self-limiting (5). It can persist for up to 12 months in anorectal and 12 weeks in pharyngeal infections if undetected and untreated (6).

Rates of infection differ across populations. Globally, rates amongst Indigenous people are significantly higher than other populations; this is seen in remote areas of Australia. Although population rates are lower in metropolitan areas, this is where the vast majority of gonococcal notifications occur in Australia. Men who have sex with men (MSM) account for the majority metropolitan notifications (7).

In Australia and globally, reported rates of gonococcal infection are rising rapidly, and antimicrobial resistant (AMR) infections in particular, are causing significant global concern (8,9). Agreement is emerging that incidence is increasing, particularly in the urban setting. However, uncertainty is still present as to how much the increase in reporting is accounted for by actual increasing infections and how much is artefactual due to increased testing. Testing practices changed around 2012 across Australia with the introduction of duplex nucleic acid amplification tests (NAAT) which identify *N. gonorrhoeae and Chlamydia trachomatis* from the same specimen (10). The increased sensitivity of NAAT for detecting *N. gonorrhoeae* (>90%) has resulted in an increase in incidental diagnoses overall, as well as identifying additional extra-genital infections (11). The increase in rates of gonorrhoea alongside increasing rates of antibiotic resistance may lead to multi-drug resistant (MDR) and extensively-drug resistant (XDR) cases of gonorrhoea. This has already been seen with two XDR cases in Australia in early 2018 (12).

Although pharyngeal gonorrhoea cases are usually asymptomatic and clear without treatment, there is increased interest in the role of pharyngeal gonococcal infections in transmission and antibiotic resistance (35,39). This is believed to be from a combination of a lack of testing due to asymptomatic infections resulting in persistent infection, difficulty in site penetration with the current antibiotic regimes; and potential horizontal transfer of genes conferring resistance (40–42).

Testing and diagnosis for gonococcal infection vary dependent on gender, sexual exposure and potential sites of infection. Diagnostic tests include nucleic acid amplification test (NAAT) and culture (13). The implication of these differences is that patients reporting high risk sexual practices, including MSM are more likely to be tested and at more anatomical sites.

Interpretation of AMR currently requires a positive culture, followed by antibiotic susceptibility testing (AST). Antibiotic resistance interpretations are produced by the laboratory by converting the numerical minimum inhibitory concentration (MIC) levels to a qualitative interpretation (resistant, decreased sensitivity or sensitive) using one of a number of validated methods. MIC levels are defined as the lowest concentration of an antibacterial agent required to inhibit visible growth of an organism (14). The qualitative interpretation is based on a defined MIC level called a MIC breakpoint. Antibiotic resistance interpretations can differ depending on the method the laboratory uses and may use different MIC breakpoints to determine interpretations (see chapter four – *surveillance of multi-drug resistant organisms*).

ACT is served by three pathology laboratories. ACT Pathology is the public health reference laboratory and provide most notifications. Laverty and Capital Pathology are both private laboratories who serve a large proportion of primary care.

AMR data has been received by the ACT Health Communicable Disease Control (CDC) for many years with limited on-going analysis and reporting. The epidemiology of gonococcal infections and gonococcal AST data in Australia are well described in isolation; however, there is limited published research presenting the epidemiology of gonococcal AMR in the ACT.

The primary aim of this study is to undertake a descriptive epidemiological analysis of gonococcal notifications in the ACT between 2009 and 2018. A description of the epidemiology of gonococcal AMR trends in the ACT during this time will also be presented. The study will inform ongoing AMR surveillance within the ACT, and clinical care and public health response, as well as identify priority groups for public health messaging.

Methods

Gonococcal infection is nationally notifiable and notifiable in every state and territory. Deidentified notifications are sent to the Australian Government Department of Health (DoH) National Notifiable Diseases Surveillance System (NNDSS). According to the national case definition, a confirmed case requires laboratory definitive evidence from either isolation of *N. gonorrhoeae* or detection of *N. gonorrhoeae* by nucleic acid testing (15). In the ACT every case is followed up by a public nurse and enhanced data is collected from the diagnosing clinician and provided to the DoH including: site of infection, sexual exposure, sex worker status and clinical facility type (16) (described fully in Chapter Five: *Gonorrhoea: Surveillance in the ACT*).

Epidemiological data collected included: age, sex, and Indigenous status. Individual risk data included: sexual exposure and sex worker status.

Full access to the ACT notifiable disease management system (NDMS) and original paper notifications was available to the authors. A small number of cases required referral to paper-based notifications to confirm missing or incorrect data prior to analysis. All gonococcal notifications from 1 January 2009 to 31 December 2018 were extracted from the NDMS; these data include a unique state identification number (ID). Onset of illness date was used for analysis.

Enhanced data variables are collected as separate Microsoft Excel files by year and include the state ID. Enhanced data were combined using Microsoft Excel and then linked deterministically with the NDMS data in Stata (version 15.1) using the state ID as the primary key.

AMR data for azithromycin and ceftriaxone were provided by ACT Pathology. These data included: surname; first name; date of birth; site tested; minimum inhibitory concentration (MIC) values for each antibiotic and site tested; and antimicrobial susceptibility interpretations. Neither AST interpretations nor MIC values were reliably provided. There was no unique identifier in the AMR data to link the NDMS data, however, the AMR data was still able to be combined using deterministic linkage with the NDMS data where an exact match for onset date, surname and first name were confirmed. AST data from laboratories other than ACT Pathology were entered manually from paper records and appended to the ACT Pathology AST data.

Comparison of antibiotic resistance results across laboratories who use different methods is possible using MIC levels rather than antibiotic resistance interpretations. Current MIC breakpoints were used for analysis as defined in the *Gonococcal Infection CDNA National Guidelines for Public Health Units* (Table). On occasion different MIC values were reported from the originating laboratory to the reference laboratory. In this instance the reference laboratory values were used for analysis. MIC scatterplots were produced using R and the ggplot2 package.

Table 1: Australian antimicrobial resistant gonococcal infection definitions (17)

Antibiotic	**MIC**	**Sensitivity**
Azithromycin	≥1.0 - <256mg/L	Low-level resistance
Azithromycin	≥256mg/L	High-level resistance
Ceftriaxone	≥0.125 - <0.5mg/L	Decreased susceptibility
Ceftriaxone	≥ 0.5mg/L	Resistant

The study population included all notifications meeting the national confirmed case definition for gonococcal infection for Australian Capital Territory (ACT) residents between 2009 and 2018. There is no national probable case definition for gonococcal infection.

Notifications for non-ACT residents were identified by postcode and excluded from analysis. Notifications for those less than 15 years were excluded from analysis due to very low numbers (<5) and to protect anonymity. Notifications with site of infection other than urogenital, anorectal and pharyngeal were excluded from analysis, focusing on sexually transmitted sites. Isolates from the same site within the infectious period (28 days) were treated as duplicates and excluded from analysis. AST data for penicillin and ciprofloxacin are not currently used clinically in the ACT and were not analysed.

Age and sex specific rates of illness per 100,000 population were calculated using mid-year residential population estimates from the Australian Bureau of Statistics (ABS) for the years 2009 to 2018. Comparison of sex and age specific rates of illness was made between 2011 and 2018 to avoid multiple zero cell counts in 2009/10. Increases in notification rates were calculated by dividing the greater notification rate by the smaller rate. Indigenous status is presented as Aboriginal and/or Torres Strait Islander according to ABS guidelines (18).

Descriptive analysis was undertaken aiming to describe variables by person, place and time.

Ethics approval was obtained from the Australian National University Human Research Ethics Committee [protocol 2018/455].

Results

Completeness of data from the NDMS was high with no data missing for age, sex and Indigenous status once data cleaning was completed. Of the 731 culture positive notifications, 637 (87%) included antibiotic resistance data. Culture positive notifications without antibiotic resistance results may not have had resistance testing or the data may not have been entered. Completeness of antibiotic resistance data (MIC and AST interpretations) supplied by ACT Pathology was unable to be tested but expected to be high with high quality database systems in the laboratory. All isolates reported as resistant to azithromycin were provided with MIC results to ACT Health CDC.

Notification rates

Between 1st January 2009 and 31st December 2018, 1478 gonococcal notifications were received by ACT Health communicable disease control (CDC). The annual crude notification rate per 100,000 population ranged from a low of 14.9 per 100,000 in 2010 to 77.9 per 100,000 in 2018; this represents a 4.2-times increase in notification rate for the whole population (Figure 1).

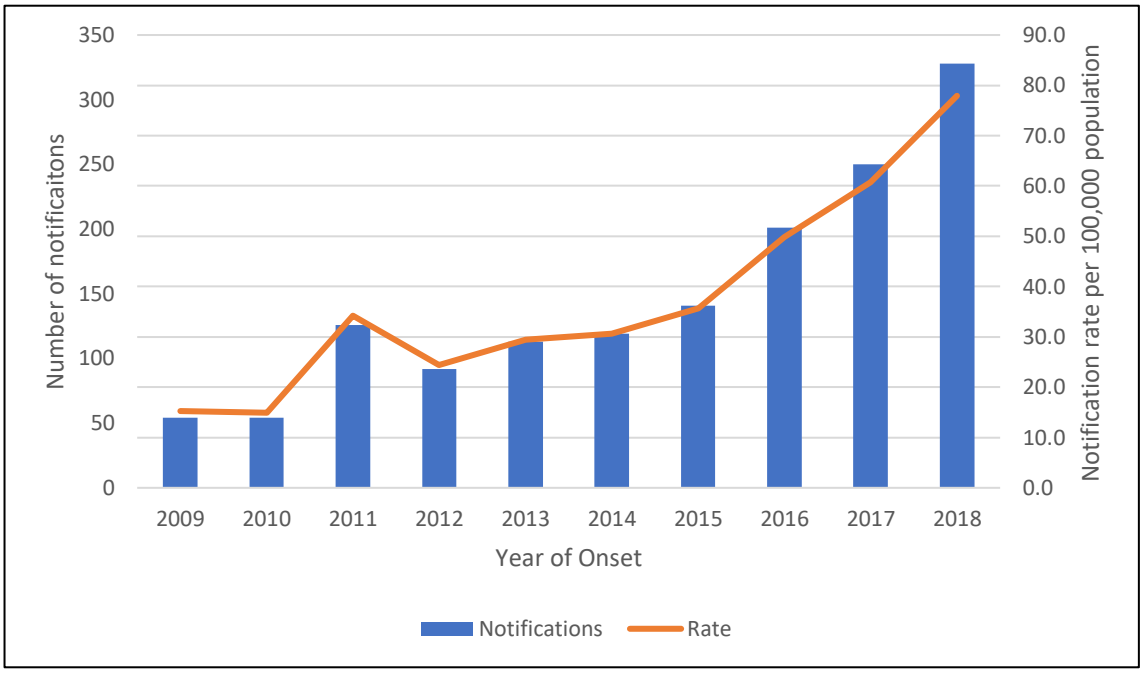

Figure 1: Number of gonococcal notifications and rate of notification per 100,000 population by year: ACT 2009-2018

Sex specific notification rates per 100,000 population showed an overall increase of 4.5 times in males (rate: 28.9 [51 cases] to 130.1 [271 cases]) and 15.2 in females (rate: 1.7 [3 cases] to 25.9 [55 cases]) from 2009 to 2018 (Figure 2).

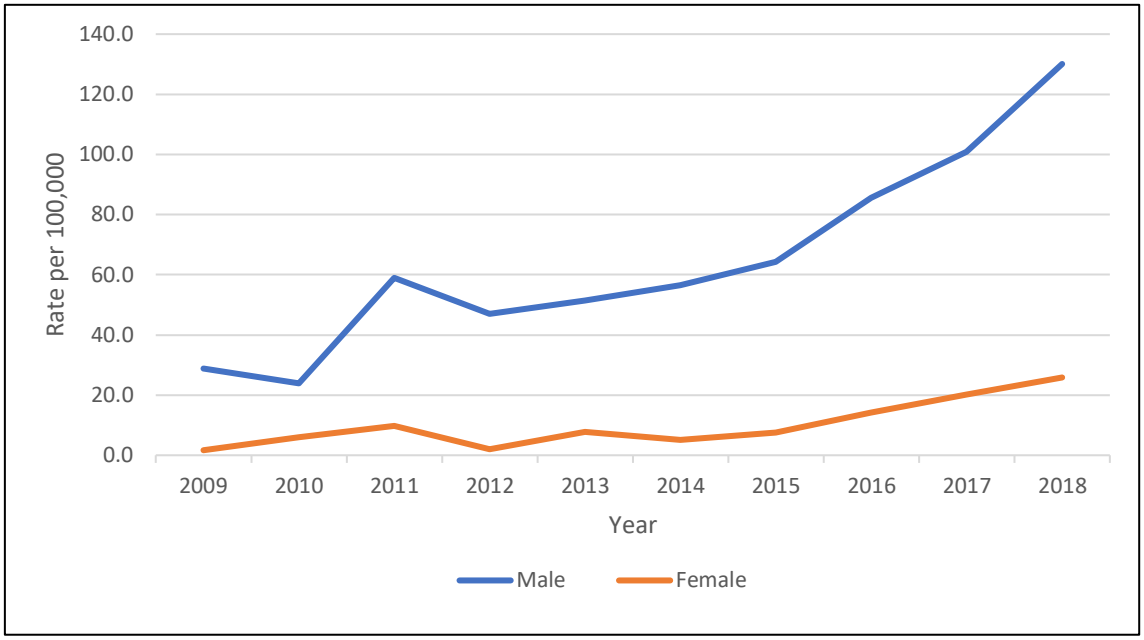

Figure 2: Gonococcal notification rate per 100,000 population by year and sex: ACT 2009-2018.

Age and sex specific notification rates per 100,000 population showed an overall increase of 2.2 times in males and 2.7 in females from 2011 to 2018. Males in the 35-39-year age group experienced the largest rise in notification rate from 36 per 100,000 in 2011 (5 cases) to 230 per

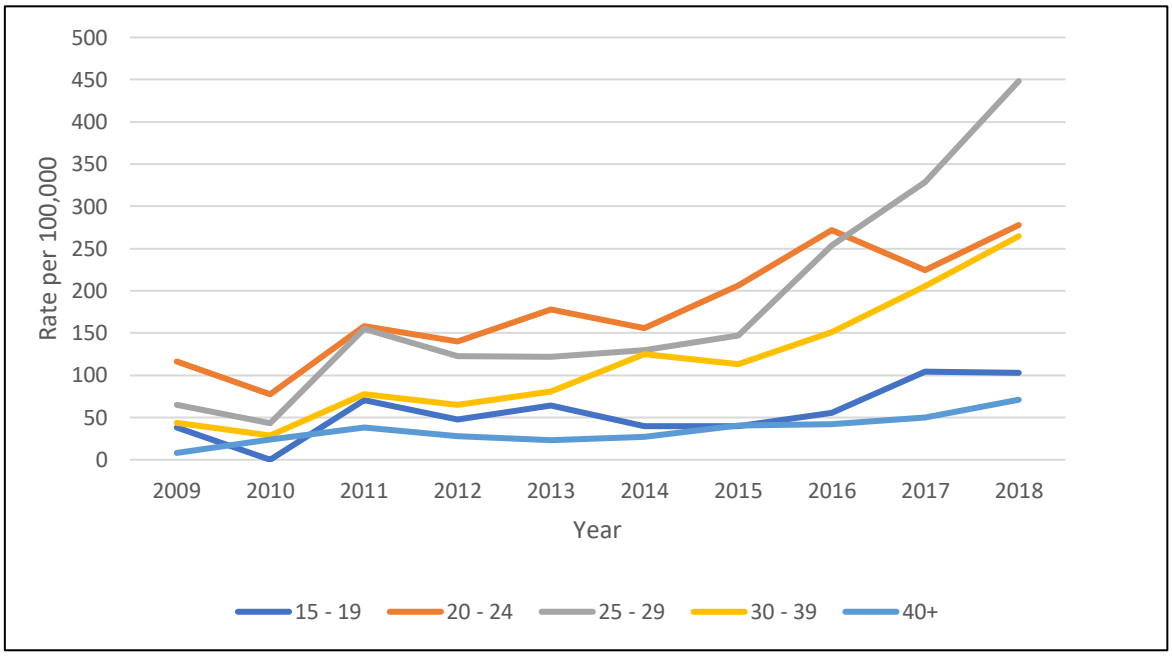

Figure 3: Age specific rates of male gonococcal notifications per 100,000 population: ACT 2009-2018.

100,000 (38 cases) in 2018, a 6.3 times rise (Figure 3). The next largest increase in notification rate was in females in the 20-24-year age group from 24 per 100,000 (4 cases) in 2011 to 102 per 100,000 (18 cases) in 2018, 4.2 times rise.

The rate of increase in females is similar to males in some age groups although the number of notifications is much lower in females. Most female age groups have multiple years with no cases notified. The rate of increase is the highest in the 25-29-year age group, increasing from 31 per 100,000 in 2011 to 91 per 100,000 in 2018; this increase was from 5 to 16 notifications (Figure 4). The 30-39-year age group increased from a rate of 14 per 100,000 in 2011 to 34 per 100,000 in 2018; this increase was from 4 to 11 notifications.

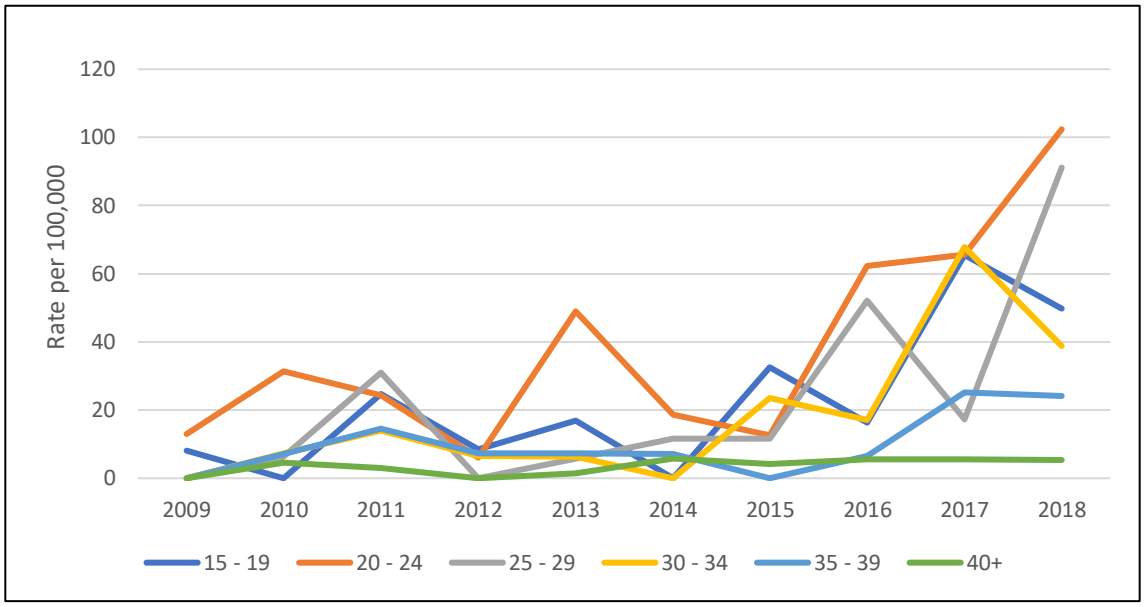

Figure 4: 5-year age group specific rates of female gonococcal notifications per 100,000 population: ACT 2009 - 2018

Sex and sexual exposure

Males account for the majority of notifications throughout the study period, ranging from a low of 80% of all notifications in 2010 to a high of 96% in 2012 (Table 1). Of the 1,271 male notifications during the study period, 935 (74%) reported same-sex exposure.

*Table 1: Gonococcal notifications by year and sex: ACT 2009-2018 **

Year of disease onset	Female		Male	
	n	%	n	%
2009	3	6	51	94
2010	11	20	43	80
2011	18	14	108	86
2012	4	4	88	96
2013	15	13	98	87
2014	10	8	109	92
2015	15	11	126	89
2016	29	14	171	85
2017	42	17	206	82
2018	55	17	271	83
Total	202	14	1,271	86

** Five notifications recorded as indeterminate sex not shown. These notifications were in 2016 (1), 2017 (2) and 2018 (2).*

The majority of notifications (64%) report same-sex exposure, of which 99.5% are male (Table 2). The proportion reporting same-sex exposure ranges from a low of 43% in 2010 to 79% in 2014 (Table 2). The proportion has remained relatively consistent since 2015.

*Table 2: Gonococcal notifications by year and sexual exposure: ACT 2009-2018**

	Sexual Exposure						
Year of onset	Opposite		Same sex		Both sexes		Total
	n	%	n	%	n	%	
2009	11	20	39	72	1	2	51
2010	30	56	23	43	1	2	54
2011	48	38	77	61	1	1	126
2012	24	26	66	72	1	1	91
2013	49	43	58	51	3	3	110
2014	21	18	94	79	2	2	117
2015	40	28	94	67	4	3	138
2016	61	30	125	62	12	6	198
2017	83	33	152	61	12	5	247
2018	100	30	211	64	15	5	326
Total	467	32	939	64	52	4	1458

** Sexual exposure reported as unknown (1 case) and other (19 cases) not shown. These data are self-reported via the clinician and the meaning of 'other' is unclear.*

Of those who reported sexual exposure with the opposite sex, the proportion of notifications by sex were more evenly dispersed (Figure 5). The proportion of female notifications who reported sexual exposure with the opposite sex has slowly increased in recent years representing more than half the notifications for this category in 2018. The number of notifications in heterosexuals increased by 4.8 times between 2014 and 2018. The largest increase in numbers and rates of female notifications was in the 20-29-year age group. Notifications reporting same sex exposure have increased by 2.2 times in the same time period.

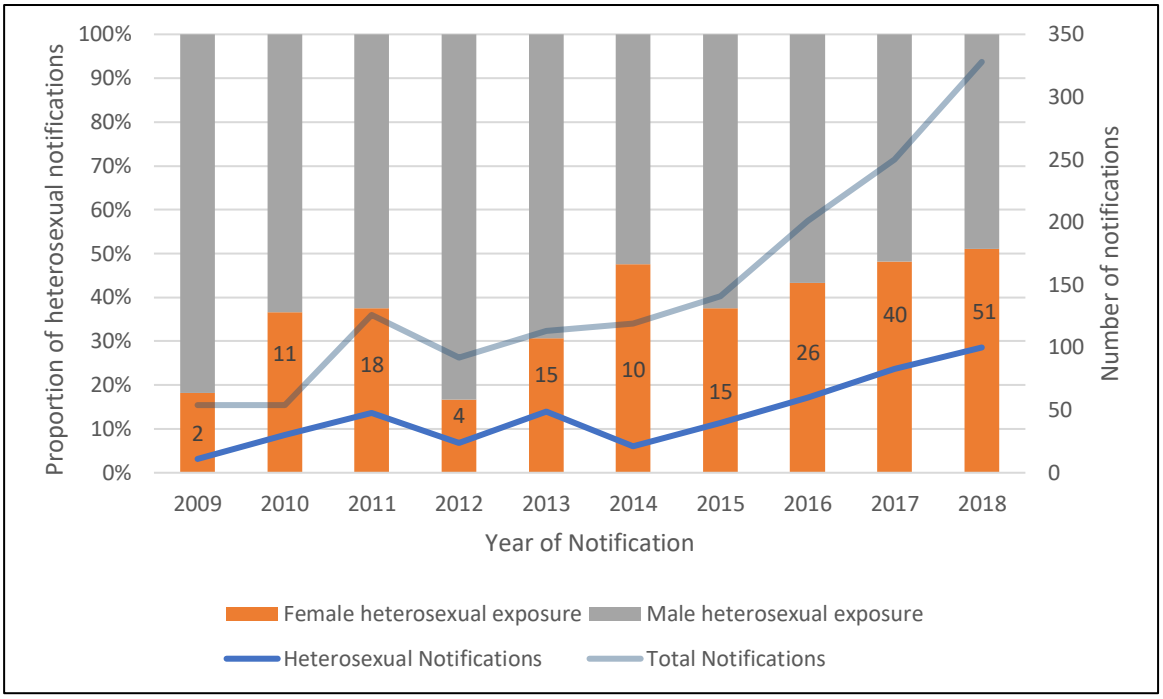

Figure 5: Heterosexual gonococcal notifications by gender proportion: ACT 2009-2018.

Number of female notifications reporting hetersexual exposure labeled by year
Secondary axis displays number of heterosexual and total notifications by year
** One case reporting indeterminate sex in 2016 not shown.*

Indigenous status of notifications

Although Aboriginal and/or Torres Strait Islanders represented 6% of gonococcal notifications in 2009, overall numbers were very low. Aboriginal and/or Torres Strait Islanders represented 1-2% of the annual gonococcal notifications from 2010 until 2016; in 2017 and 2018 the proportion increased to 4%. The number of Aboriginal and/or Torres Strait Islander gonococcal notifications was between 0 and 13 during the study period (Table 3).

Table 3: Gonococcal notifications by year and Indigenous status: ACT 2009-2018

Year of Onset	Aboriginal and/or Torres Strait Islander		Non-Indigenous	
	n	%	n	%
2009	<5	-	51	94
2010	0	-	54	100
2011	<5	-	123	98
2012	<5	-	91	99
2013	<5	-	111	98
2014	<5	-	118	99
2015	<5	-	139	99
2016	5	2	196	98
2017	11	4	239	96
2018	13	4	315	96
Total	41	3	1,437	97

Sex work as a risk factor

Few confirmed gonococcal cases in the ACT have reported working as a sex worker, however numbers have increased from 0-3 notifications per year in 2009-2016 to 8 cases (3%) in both 2017 and 2018 (Table 4). Of the 22 cases, 12 were female. Half of the notifications involved multiple sites of infection. The majority (20/22, 91%) of sex workers were seen at the CSHC. A culture positive result was received for 14/22 (64%) of these notifications. No isolates from sex workers were resistant to azithromycin or ceftriaxone during the study period.

Table 4: Gonococcal notifications by year & sex worker status: ACT 2009-2018

Year of Onset	Sex Worker		Not Sex Worker		Unknown	
	n	%	n	%	n	%
2009	0	-	44	81	10	19
2010	0	-	54	100	0	-
2011	0	-	126	100	0	-
2012	<5	-	91	99	0	-
2013	<5	-	111	98	0	-
2014	0	-	116	97	3	3
2015	0	-	138	98	3	2
2016	<5	-	191	95	7	3
2017	8	3	236	94	6	2
2018	8	2	315	96	5	2

Notification by Clinical Facility

Canberra Sexual Health Centre (CSHC) diagnosed the majority of gonococcal infections notified during most of the study period (Table 5). Of the 1,478 notifications during the study period, 1405 (95%) were diagnosed by either CSHC (976, 66%) or a General Practitioner (GP) (429, 29%). Other clinicians accounted for 73 (5%) of all notifications (Table 5).

Table 5: Gonococcal notification by clinical facility type: ACT 2009-2018

Year of Onset	CSHC		General Practice		Public Hospital		Other *		Total
	n	%	n	%	n	%	n	%	
2009	35	65	18	33	0	-	1	2	54
2010	22	41	27	50	5	9	0	-	54
2011	80	63	37	29	8	6	1	1	126
2012	69	75	20	22	2	2	1	1	92
2013	69	61	41	36	1	1	2	2	113
2014	88	74	30	25	0	-	1	1	119
2015	83	59	48	34	6	4	4	3	141
2016	134	67	60	30	3	1	4	2	201
2017	154	62	76	30	5	2	15	6	250
2018	242	74	72	22	5	2	9	3	328
Total	976	66	429	29	35	2	38	3	1,478

** Other includes private hospital (1), unknown (1) and Family planning centre (13)*

Of the 976 notifications diagnosed by CSHC, 778 (80%) reported same-sex exposure and 152 (16%) reported opposite sex exposure. Of the 429 notifications diagnosed by GP's, 147 (34%) reported same-sex exposure and 262 (61%) reported opposite sex exposure (Figure 6, Figure 7). Of all other clinicians notifying, 14 of 73 (19%) notifications reported same-sex exposure.

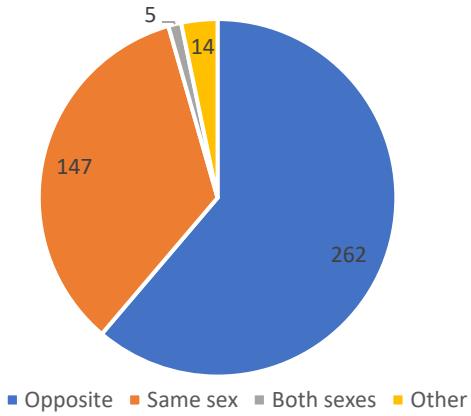

Figure 6: Gonococcal notifications from General Practitioners by sexual exposure: ACT 2009-2018

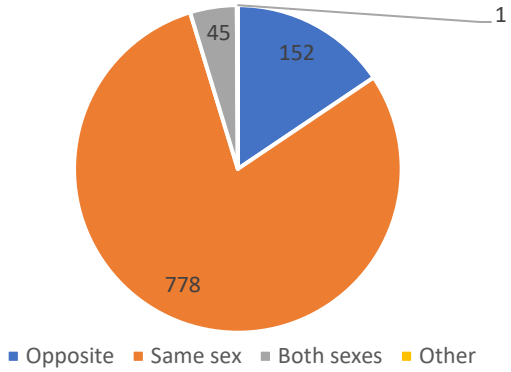

Figure 7: Gonococcal notifications from Canberra Sexual Health Centre by sexual exposure: ACT 2009 - 2018

Diagnostic testing

Of the 1,478 total notifications, 747 (51%) were notified following a positive-PCR test only, while 731 (49%) were also positive by culture (Table 6). Of the 976 notifications diagnosed by CSHC, 603 (62%) of these were culture positive, and 373 (38%) a PCR positive only. Of the 429 notifications that GP's diagnosed, 106 (25%) of these were positive on culture, and 323 (75%) positive by PCR only. Overall, the proportion of *N. gonorrhoeae* notified with a positive culture test has not changed remarkably since 2009 in the ACT. The proportion of those notified positive on culture ranged between 42% in 2013 to 59% in 2009.

Table 6: Gonococcal notifications by laboratory test and diagnosing clinician: ACT 2009-2018

	CSHC		**GP**		**Other**		**Total**
	n	%	n	%	n	%	
Positive-PCR only	373	38	323	75	51	70	747
Positive Culture	603	62	106	25	22	30	731
Total	976		429		73		1478

Of the 939 notifications who reported same-sex exposure, 519 (55%) were culture positive, compared to 178/467 (38%) of those reporting opposite sex exposure (Figure 8). Of those reporting opposite sex exposure, 109/274 (40%) of males and 68/193 (35%) of females were culture positive.

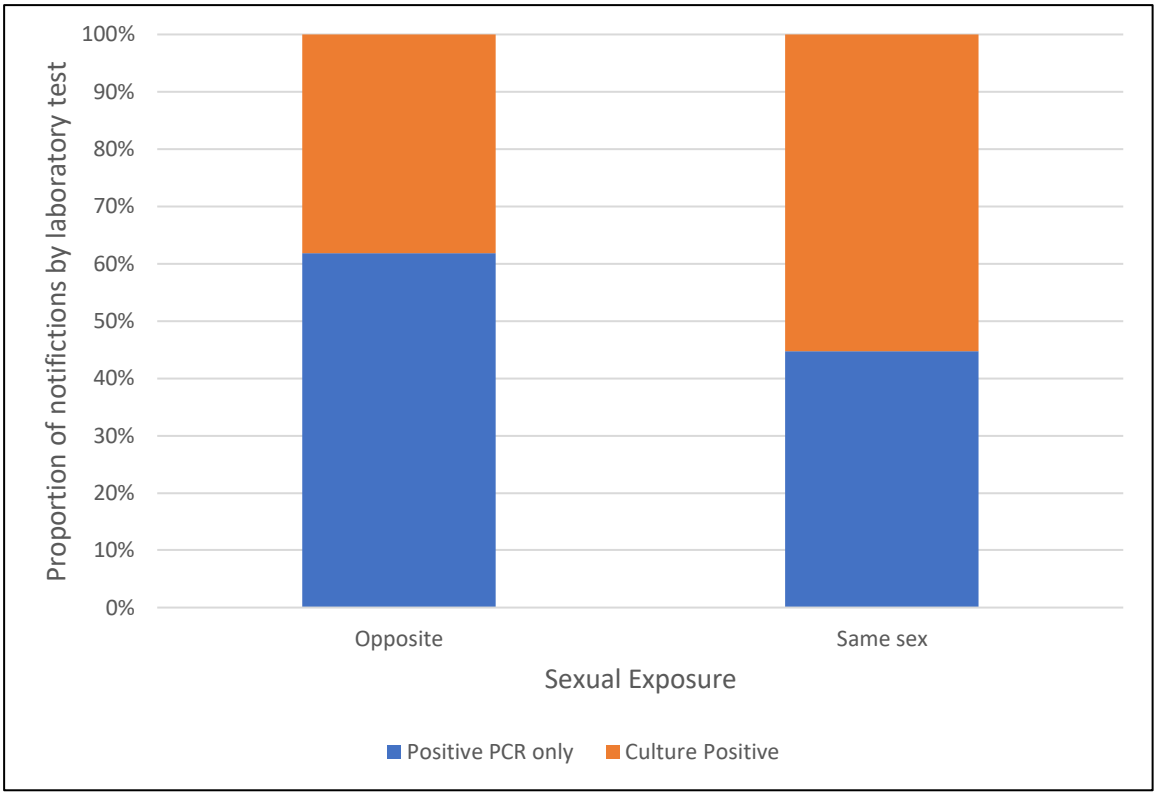

Figure 8: Gonococcal notifications by sexual exposure and laboratory test: ACT 2009-2018

Multiple sites of infection

The number of notifications with gonococcal infection at multiple sites was 1 (2%), 0, and 5 (4%) in 2009, 2010 and 2011, respectively. In 2012 this increased to 21 (23%) notifications and then rose from 17 (15%) in 2013 to a high of 76 (23%) in 2018 (Figure 9).

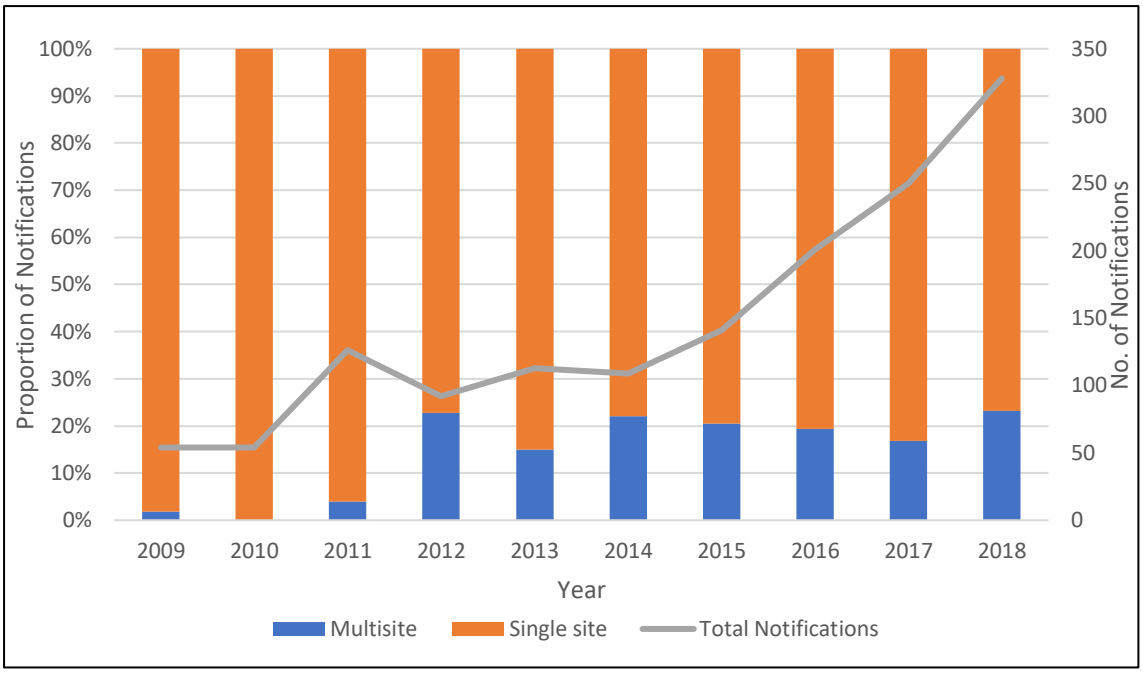

Figure 9: Notifications by multiple or single site gonococcal infections: ACT 2009-2018

Site of Infection

Although only three sites of infection are reported for this study, up to seven combinations of infection are described. These range from notifications with single site infections (1224, 83%), dual infections (220, 15%) or infections at three sites (34, 2.3%). For the 610 notifications reporting a single-site urogenital infection, the majority (410, 68%) reported heterosexual exposure; 42% in males and 26% in females.

Overall, females reporting heterosexual exposure accounted for 192 (13%) of all notifications. The proportion of heterosexual female notifications by site of infection was higher for urogenital infections (157, 26%) and in urogenital/pharyngeal infections (11, 26%). The proportion of heterosexual female notifications with multiple sites of infection has fluctuated since 2013 and increased to 5 (14%) in 2017 and 10 (20%) in 2018 (Figure 10).

For the 466 notifications reporting heterosexual exposure, single site urogenital infections accounted for 92% (253) of male and 82% (157) of female notifications over the study period. MSM was reported for most combinations of different sites of infection overall, ranging from 76 – 93%. By site of infection, the proportion of notifications reporting MSM was lower for single-site urogenital 176/610 (29%) and urogenital/pharyngeal 24/42 (57%) infections.

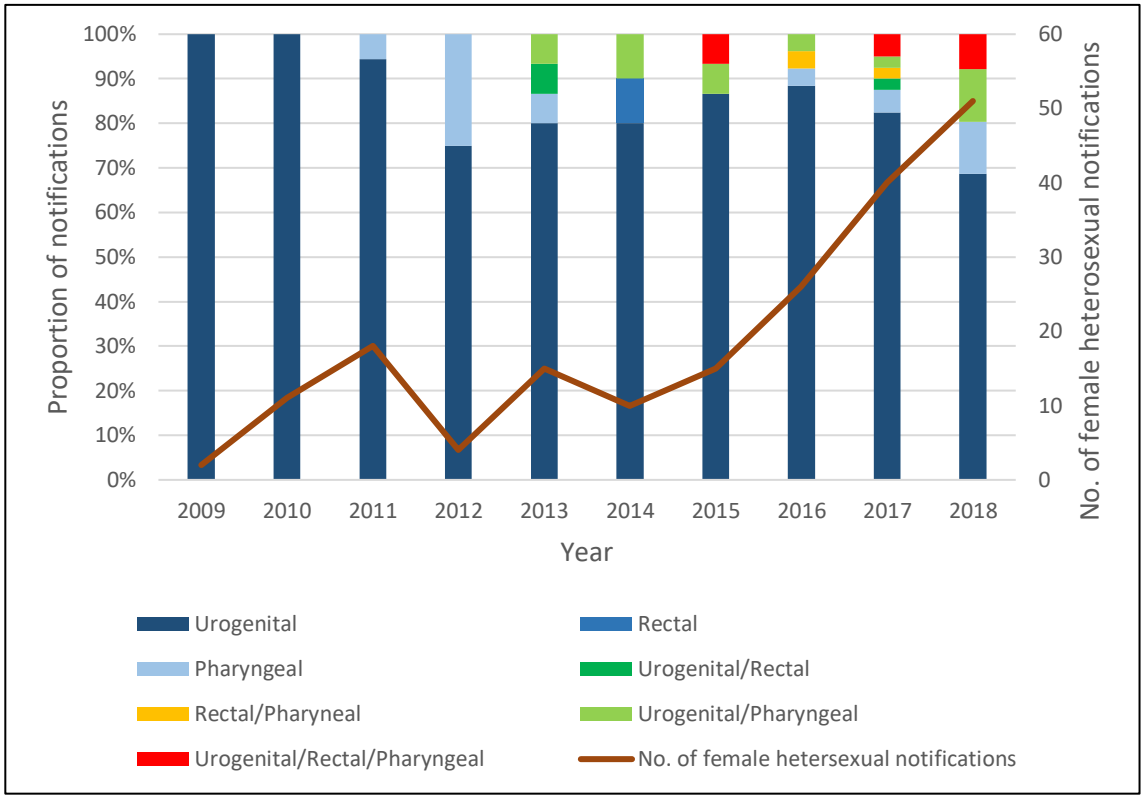

Figure 10: Heterosexual female gonococcal notifications by site of infection and year: ACT 2009-2018

Antibiotic Resistance

Over the study period 731 (49%) notifications were culture positive. Of these, 61 (8%) notifications were reported to have low-level resistance to azithromycin or display decreased sensitivity to ceftriaxone (Figure 11). This was consistent across 7/10 years analysed with more resistant cases reported in 2011, and less resistant cases reported in 2015 and 2017.

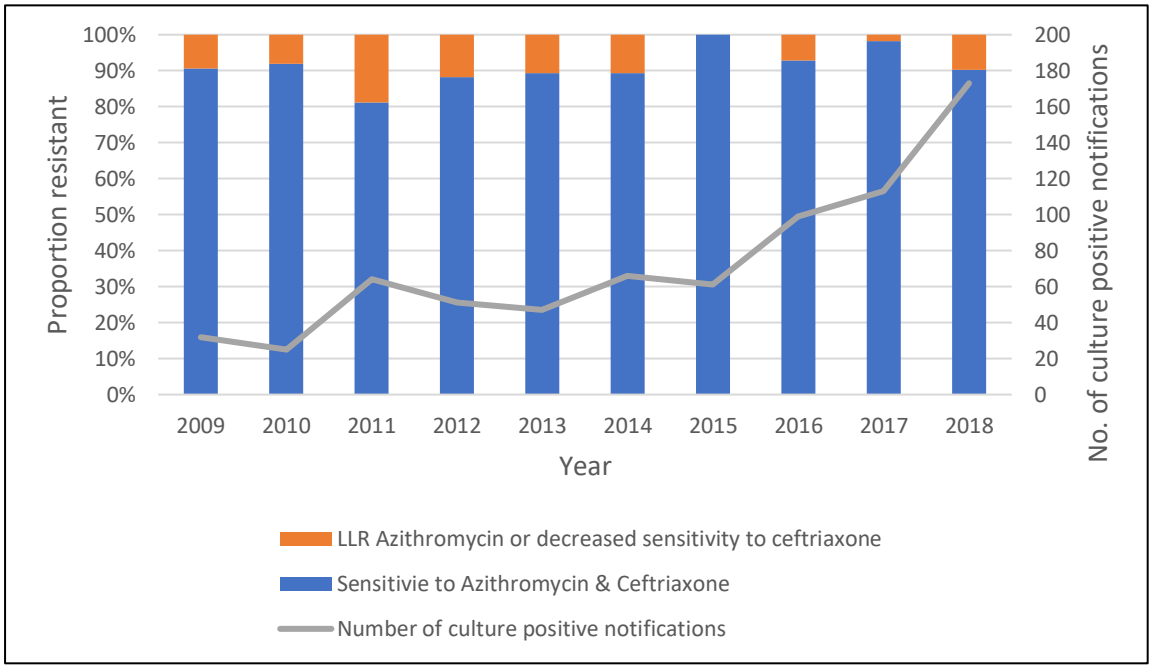

Figure 11: Proportion of culture positive gonococcal notifications resistant to azithromycin or ceftriaxone: ACT 2009-2018

Two cases were reported with decreased sensitivity to ceftriaxone and low-level resistance to azithromycin in the ACT, one in 2010 and the other in 2014. Both cases were male, reported same-sex exposure and had rectal infections.

Of the 731 notifications, MIC results were received for 637 (94%) notifications and 687 isolates; this difference is due to notifications with multisite infections. Ninety-five culture positive notifications were reported without MIC levels; all 95 included antimicrobial interpretations and were sensitive to azithromycin. No notifications reported as resistant to antibiotics were provided to CDC without MIC results.

Ceftriaxone Resistance

No gonococcal notifications with resistance to ceftriaxone were reported in the ACT during the study period. Decreased sensitivity to ceftriaxone is rarely reported in the ACT and has decreased in recent years. All eight notifications were male; all three cases with urogenital infection reported heterosexual exposure only; the remaining five cases reported same-sex exposure (Table 7).

*Table 7: Gonococcal notifications with decreased sensitivity to ceftriaxone (based on MIC) by site of infection: ACT 2009-2018 **

Site of Infection	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Urogenital	1	-	1	-	1	-	-	-	-	-	3
Rectal	1	1	-	-	-	1	-	-	-	1	4
Pharyngeal	1	-	-	-	-	-	-	-	-	-	1

** No cases with decreased sensitivity to ceftriaxone were reported without MIC*

Azithromycin Resistance

During the study period 55 notifications and 60 isolates were reported with low-level resistance (LLR) to azithromycin ((≥1.0 mg/l - <256 mg/L); 5 notifications reported two resistant isolates from different sites of infection. Of the 60 isolates, 57/60 (95%) were male and of these, 53/57 (93%) reported exclusive same-sex exposure (Figure 12).

No notifications with high-level azithromycin resistance (≥256mg/L) have been reported in the ACT. The number and MIC of resistant isolates is increasing, although the proportion of isolates resistant to azithromycin fluctuates and no clear trend over time was identified.

Of the 60 isolates with LLR to azithromycin, 20 were pharyngeal (2 female), 25 were rectal, and 15 were urogenital isolates (1 female) (Figure 13). Of the pharyngeal isolates with AST reported, the proportion of resistant isolates was similar between males and females (12% vs 14%) respectively (Table 8). The proportion of resistant urogenital isolates was higher in males (6%) compared to females (2%).

The CSHC diagnoses the majority of gonococcal infections in the ACT, including most antibiotic resistant cases. GP's see fewer cases, request less test of cultures and have treated two notified antibiotic resistant cases since 2014 (Figure 14).

Table 8: Proportion of isolates with AST reported as resistant to azithromycin by sex: ACT 2009-2018

	Male			**Female**		
	Antimicrobial susceptibility tested	LLR azithromycin		Antimicrobial susceptibility tested	LLR Azithromycin	
	n	n	%	n	n	%
Urogenital	220	14	6	45	1	2
Pharyngeal	149	18	12	14	2	14
Rectal	195	25	13	2	0	N/A

Azithromycin MIC by sex, year and sexual exposure

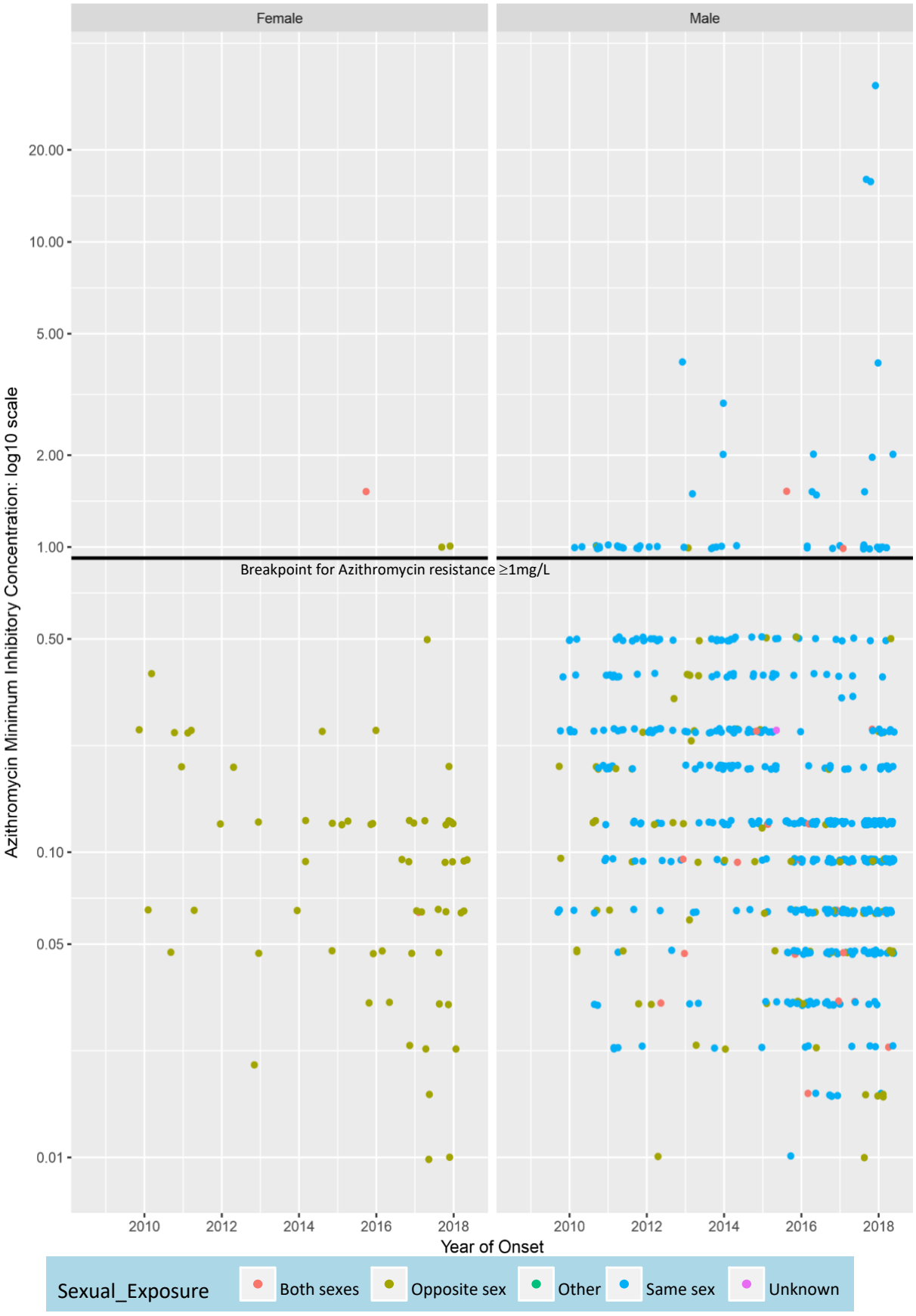

Figure 12: Culture positive gonococcal notifications reporting azithromycin resistance with MIC by year and sexual exposure and displayed by sex using log10 scale: ACT 2009 - 2018

Azithromycin MIC by site of infection, year and sex

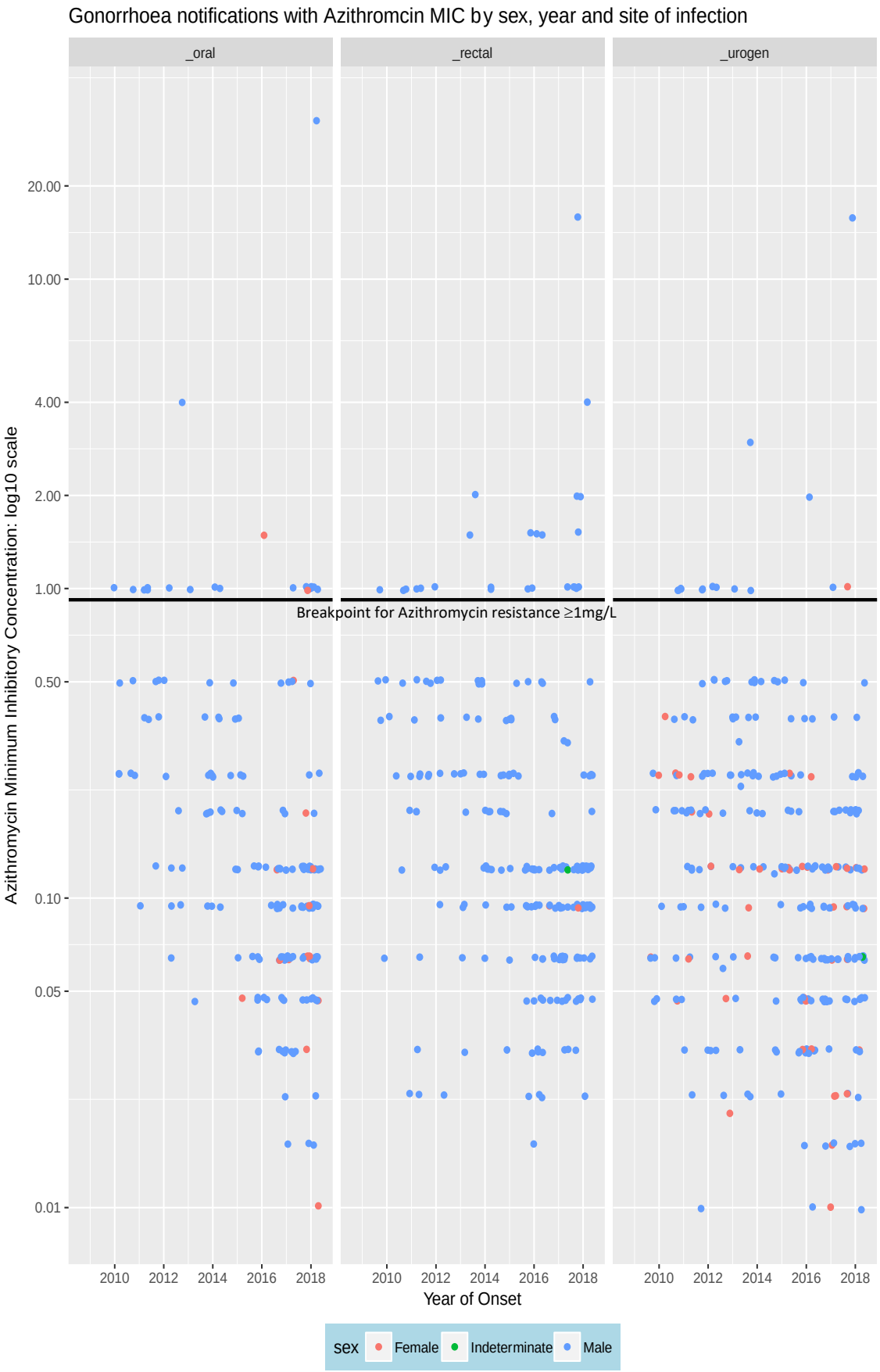

Figure 13: Gonococcal notifications reporting azithromycin resistance with MIC (687) by year, sex and split by site of infection using log10 scale: ACT 2009 - 2018

Azithromycin MIC by clinical facility, year and sex

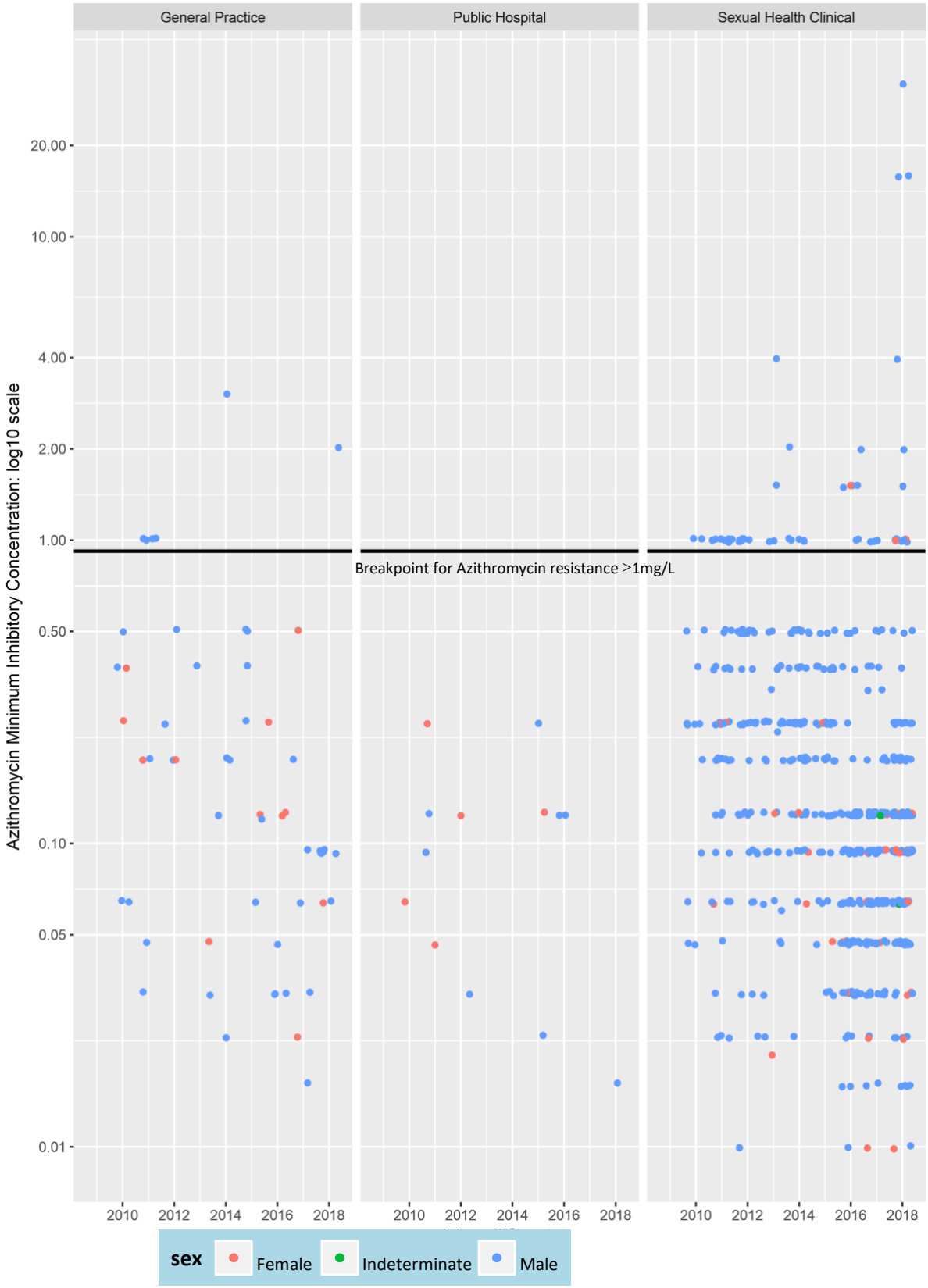

*Figure 14: Gonococcal notifications reporting azithromycin resistance with MIC (687) by year and sexual exposure and split by Clinical Facility type using log10 scale: ACT 2009 – 2018**

** A number of clinical facilities not displayed due to no resistant isolates and very few MIC reported. These facilities and number of isolates with MIC include: family planning clinic (2), other (6), private hospital (0) and unknown (0).*

Discussion

This study is the first-time epidemiological notification data, individual risk factors and antimicrobial isolate data have been combined and analysed for all gonococcal notifications in the ACT. Over the ten-year period (2009-2018) I found a dramatic increase in notification rates, predominantly in MSM, with overall low levels of azithromycin resistance, but increasing MIC levels in the last few years. Notifications in cases reporting heterosexual exposures were small in number but increasing faster than those for MSM.

Increase in rates of gonococcal infection

I identified a 4.2-fold increase in overall notification rates from 2010 to 2018. The sharp increase in notifications in 2011 in the ACT is consistent with other Australian jurisdictions, which all saw similar increases between 2009 and 2012 (19). The increase in rates is likely to be predominately as a result of increasing circulation of gonococcal infection, however a number of factors could also influence rates, including uptake of pre-exposure prophylaxis, the number of tests requested, and changes such as the introduction of duplex *N. gonorrhoeae* and *Chlamydia trachomatis* tests.

Pre-exposure prophylaxis (PrEP) aims to prevent HIV in high-risk sexually active populations and is purported to increase risky sexual practices, such as reduced condom use, and potentially increase rates of STI (20,21). PrEP requires sexually transmitted disease (STI) testing every 3 months and has been used since 2016 in clinical trials and subsidised through the Pharmaceutical Benefits Scheme (PBS) from April 2018 (22).

The number of *N. gonorrhoea* tests requested was not available for our study, therefore the proportion of tests positive cannot be reported. However, a recent study of the biggest laboratory in the ACT partially conducted over the same time period (2014-2018) showed a rise in positivity of NAATS performed. Proportion of tests positive increased from <3% in 2014 to >4% in 2018 for males, and from <0.5% in 2014 to >1.8% in 2018 for females (23). NSW also reported an increase in test to notification ratio from 0.70 per 100 *N. gonorrhoea* tests in 2014, to 1.13 in 2018 (24). Although the positivity rates are different due to methodology, the trend is similar. While increased testing would be expected to decrease the proportion of tests positive in a low-prevalence population, the proportion positive has increased. This further suggests incidence of gonococcal infection is increasing (23,25).

I recommend exploring the feasibility of routinely receiving denominator testing data to appropriately monitor true rates of disease incidence.

Antibiotic resistant gonococcal infection

Overall, the number of gonococcal infections with low-level resistance to azithromycin or decreased sensitivity to ceftriaxone were low and showed no increasing trend. However, the

number of isolates with LLR azithromycin increased in number in 2018, and with higher MIC in recent years, almost exclusively in MSM.

I found relatively consistent rates of low-level azithromycin resistance, averaging 8% over the study period although there was considerable variation in 2012 (18%) and 2015 (0%). In contrast, an increase in low-level azithromycin resistance has been reported in other jurisdictions and internationally (26). This difference may reflect the small numbers in the ACT making trends more difficult to identify or that there is less antibiotic resistant gonorrhoea present in the ACT.

Azithromycin resistance rates in the ACT were above the World Health Organization's (WHO) recommended 5% threshold for changing treatment recommendations in all years except 2015 and 2017 (27). Azithromycin was introduced to "ensure successful treatment of infection with reduced susceptibility to ceftriaxone" (28). However, in 2019 the United Kingdom withdrew azithromycin for uncomplicated infections (28).

MSM exposure is reported for nearly all (88%) antibiotic resistant cases in the ACT with few females (5%) or heterosexual cases identified (12%). This result should be interpreted with caution considering, the increase in female heterosexual notifications; the knowledge that females are more likely to be asymptomatic, and female isolates are much less likely than MSM to be cultured.

Compliance of health professionals with clinical and public health guidelines

STI guidelines clearly state that clinicians should always attempt culture prior to treating gonorrhoea (5). A recent unpublished study found the public ACT laboratory cultured 81% of NAAT positive specimens from 2014 – 2018 (23). This compares to our finding of 61% of notifications cultured from the same laboratory between 2009 - 2018. In other words, although only 61% of our gonorrhoea notifications were culture positive, 81% (between 2014 – 2018) were attempted to be cultured. I analysed the method of testing by clinician rather than laboratory and found 62% of notifications from CSHC were culture positive compared to 25% of notifications from a GP. Although I did not analyse testing data, more culture positive notifications from CSHC may be a result of sexual health specialists being more familiar with the diagnostic requirements, and subsequently requesting culture more frequently (13). Other explanations may include the disease burden being higher in the population they serve; 82% of notifications from CSHC reported being MSM compared with 34% of notifications from GPs.

I recommend ongoing education for general practitioners may improve their ability to request appropriate testing.

Infections among heterosexual population

Notifications of *N. gonorrhoeae* increased at more than twice the rate in people reporting heterosexual sex exposure since 2014 compared to those reporting same sex exposure. A steady

increase in the number and proportion of heterosexual females has been noted with a 5-fold increase in the number of *N. gonorrhoeae* notifications in females from 2014 to 2018. Only two isolates from heterosexual females resistant to azithromycin were identified during the study period; in 2016 and 2018. However, there is concern that an increase in notifications may lead to an increase in resistance.

Although most studies have found AMR *N. gonorrhoea* is more common in MSM (29), the three linked cases of extremely drug resistant gonorrhoea in 2018 (not in the ACT) all reported heterosexual exposure (30). These were most likely linked to overseas travel in South-East Asia (2). A study of gonorrhoea notifications in Victoria reported increased odds of multi drug resistant (MDR) *N. gonorrhoeae* for women compared to MSM (OR 1.96 95% CI 1.13-3.30) and was highest in women born in North-East Asia (26). Knowing that heterosexual gonococcal cases are more likely to be treated by a GP or other clinician and that these clinicians may be less likely to request culture; the rise in heterosexual notifications is concerning and further supports the case for continued support and education for these clinicians. I also recommend public health messaging should be targeted towards females in the 20-29-year age group.

Infection among Aboriginal or Torres Strait Islander population

The proportion of gonococcal notifications in Indigenous people in the ACT increased in 2017/18, representing 4% of all notifications. In 2016, the Indigenous population was estimated to be 3.3% of the total Australian population and 1.9% of the ACT population (31). This suggests the Indigenous population are over-represented in ACT gonococcal notifications; however the number of notifications are small (2017: 11, 2018: 13) and prone to fluctuations over time. Nevertheless, these results are consistent with international studies which report rates of infection among Indigenous populations between 4- to 10-fold higher compared with non-Indigenous populations (11). Australian Indigenous gonococcal notification rates were seven-fold higher compared to non-Indigenous people in 2017 (32). NSW reported Indigenous gonococcal notification rates 1.3 times higher than non-Indigenous in 2017 (33).

Infection among sex workers

Gonococcal notifications of current sex workers have noticeably increased in 2017/18; however, due to small numbers this increase should be interpreted with caution. Half of the notifications reporting to be sex workers had multiple sites of infection compared to an average of 17% and 23% across all gonococcal notifications in 2017, and 2018 respectively. This may reflect more screening of multiple sites due to a high-risk population or that the proportion of sex workers with multiple sites of gonococcal infection is higher than the general population. Although ACT numbers are small, 10/12 (83%) female sex workers (FSW) were diagnosed with oropharyngeal gonorrhoea, consistent with a recent Victorian study of FSW (34). Although culture positive

results were only received for 64% of notifications, these may have been tested and produced a negative result, particularly for extra-genital sites where culture is less sensitive.

Limitations

Analyses of this ACT dataset were limited in some instances owing to small numbers and may not be generalisable outside of the ACT.

Notification data may not be representative of the true disease burden due to ascertainment bias. Regular testing often takes place on high risk populations such as MSM, other high-risk population groups and those on PrEP compared to low-risk populations. Specialist sexual health centres serve a higher proportion of MSM patients compared to all other providers.

Data on whether testing is routine screening or symptomatic is not documented. This may affect the severity of disease and proportion of tests of culture requested. It should be noted however a test of culture is always recommended following a positive NAAT result requiring treatment (13).

Analysis of antibiotic resistant notifications included only culture positive results which reported the MIC. The majority of gonococcal notifications are not reported with MIC because; *N. gonorrhoeae* was not isolated during a culture test following a NAAT positive result, a culture test was not requested or antibiotic resistance interpretations were reported without MIC. Ninety-five antibiotic sensitive notifications were reported without MIC, therefore rates of resistance described are likely to be an overestimate.

Testing for gonococcal infection often occurs in the context of testing for other STI's and HIV during complex clinical consultations and may be an incidental diagnosis (35). This study reports a small part of the assessment and treatment process and I acknowledge the complexity of these interactions.

Conclusion

This study presents an ongoing, increasing rate of gonococcal notifications in the Australian Capital Territory, likely reflecting increasing transmission of gonococcal infection in the general population. The highest increase in notification rates since 2014 is in 20-29-year-old heterosexual females. Public health messaging is recommended for this population group.

Although stable rates of azithromycin resistance and decreasing ceftriaxone resistance are reported, azithromycin resistance is still consistently above the recommended WHO resistance rate of 5%. AMR is detected almost exclusively in the MSM population in the ACT. I recommend continued engagement with general practitioners to encourage adherence to clinical guidelines as well as public health messaging for the MSM population.

Requesting denominator data from laboratories could be considered to monitor true rates of disease incidence. I recommend investigating the feasibility of receiving laboratory testing data from ACT Pathology on an agreed routine basis.

Notifications following a positive test of culture were noticeably lower from GPs compared to specialist sexual health clinicians. I suggest this reflects less requests for a test of culture prior to treatment because of less familiarity with guidelines. I recommend on-going education for GPs regarding appropriate laboratory testing and AMR.

The number and proportion of notifications for Indigenous people and sex workers has risen noticeably in the past two years, although numbers are still small. I recommend continued monitoring of these groups and engagement with Indigenous health workers and sexual health specialists to ensure this does not continue.

References

1. Everett BG. Sexual Orientation Disparities in Sexually Transmitted Infections: Examining the Intersection Between Sexual Identity and Sexual Behavior. Arch Sex Behav [Internet]. 2013 [cited 2019 Jul 26];42(2):225–36. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3575167/pdf/nihms421943.pdf
2. European Centre for Disease Prevention and Control. Extensively drug-resistant(XDR) Neisseria gonorrhoeae in the United Kingdom and Australia. Heal Prot Rep Adv Access Rep [Internet]. 2018 [cited 2019 Jan 16];12(11):1–11. Available from: https://ecdc.europa.eu/sites/portal/files/documents/RRA-Gonorrhoea%2C Antimicrobial resistance-United Kingdom%2C Australia.pdf
3. Heymann D. Control of Communicable Disease manual. 20th ed. American Public Health Association; 2015.
4. Tapsall J, Frcpa BS. What is the economic burden imposed by antimicrobial resistance in Neisseria gonorrhoeae [Internet]. 2005 [cited 2018 Oct 30]. Available from: https://www.reactgroup.org/uploads/publications/react-publications/economic-burden-imposed-by-AR-in-neisseria-gonorrhoea.pdf
5. Australian Sexual Health Alliance. Gonorrhoea - Australian STI Management Guidelines [Internet]. 2018 [cited 2018 Oct 30]. Available from: http://sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea#clinical-presentation
6. Price, G. Bash M. Epidemiology and pathogenesis of Neisseria gonorrhoeae infection - UpToDate [Internet]. UpToDate. 2018 [cited 2018 Jun 21]. Available from: https://www.uptodate.com/contents/epidemiology-and-pathogenesis-of-neisseria-gonorrhoeae-infection#H853159200
7. Whittles, L. Didelot, X. Grad, Y. White P. Testing for gonorrhoea should routinely incude the pharynx. Lancet Infect Dis [Internet]. 2018 [cited 2019 Jul 5];18:716–7. Available from: https://www.gov.uk/
8. WHO. Ten threats to global health in 2019 [Internet]. 2019 [cited 2019 Jan 21]. Available from: https://www.who.int/emergencies/ten-threats-to-global-health-in-2019
9. CDC. Antibiotic resistance threats in the United States, 2013. Current [Internet]. 2013;114. Available from: http://www.cdc.gov/drugresistance/threat-report-2013/index.html
10. Donovan BA, Dimech W, Ali H, Guy R, Hellard M. Increased testing for Neisseria gonorrhoeae with duplex nucleic acid amplification tests in Australia: implications for surveillance. Sex Health [Internet]. 2015 [cited 2018 Aug 17];12:48–50. Available from: www.publish.csiro.au/journals/sh
11. Kirkcaldy RD, Weston E, Segurado AC, Hughes G. Epidemiology of gonorrhoea: a global perspective. Sex Health [Internet]. 2019;16(5):401. Available from: http://www.publish.csiro.au/?paper=SH19061
12. Jennison A V, Whiley D, Lahra MM, Graham RM, Cole MJ, Hughes G, et al. Genetic relatedness of ceftriaxone-resistant and high-level azithromycin resistant Neisseria gonorrhoeae cases, United Kingdom and Australia, February to April 2018. Eurosurveillance [Internet]. 2019 [cited 2019 Feb 22];24(8):1. Available from: www.eurosurveillance.org
13. Australasian Sexual Health Alliance. Gonorrhoea - Australian STI Management Guidelines [Internet]. 2019 [cited 2019 Aug 8]. Available from: http://www.sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea#diagnosis
14. Andrews J. Determination of minimum inhibitory concentration. J Antimicrob Chemother [Internet]. 2001 [cited 2019 Jun 27];48(suppl. S1, 5-16). Available from: https://academic.oup.com/jac/article/48/suppl_1/5/2473513

15. Australian Government Department of Health and Ageing. Communicable Diseases Network. Gonococcal infection case definition [Internet]. Australian Government Department of Health and Ageing; 2019 [cited 2019 Jul 5]. Available from: https://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_gono.htm

16. Communicable Disesases Network Australia. NNDSS STI Surveillance Dataset Field Specifications – Version 1 . 0. Canberra; 2005.

17. Communicable Diseases Network Australia. Gonococcal Infection CDNA National Guidelines for Public Health Units [Internet]. 2019 [cited 2019 Jul 26]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/063E816933017261CA2583F300074085/$File/Gonococcal-Infection.pdf

18. Australian Bureau of Statistics. Indigenous Status Standard Version 1.5 [Internet]. 2014 [cited 2019 Jul 5]. Available from: https://www.abs.gov.au/AUSSTATS/abs@.nsf/Latestproducts/1200.0.55.008Main Features92014, Version 1.5?opendocument&tabname=Summary&prodno=1200.0.55.008&issue=2014, Version 1.5&num=&view=

19. Roberts-Witteveen A, Pennington K, Higgins N, Lang C, Lahra M, Waddell R, et al. Epidemiology of gonorrhoea notifications in Australia, 2007–12. Sex Health [Internet]. 2014 [cited 2018 Aug 6];11(4):224–31. Available from: http://dx.doi.org/10.1071/SH13205

20. Lal, L, Audsley, J. Murphy, D. Fairley, C. Stoove, M. Roth, N. Moore, R. Tee, B. Puratmaja, N. Anderson, P. Leslie, D. Grant R. Medication adherence, condom use and sexually transmitted infections in Australian preexposure prophylaxis users. Aids. 2017;31(12):1709–14.

21. Grulich AE, Guy R, Amin J, Jin F, Selvey C, Holden J, et al. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. Lancet HIV. 2018 Nov 1;5(11):e629–37.

22. NPS MedicineWise. PrEP on the PBS: An opportunity in HIV prevention [Internet]. 2018 [cited 2019 Sep 17]. Available from: https://www.nps.org.au/news/pr-ep-on-the-pbs-an-opportunity-in-hiv-prevention#r15

23. Buttigieg, G. Kennedy, K. Martin S. Gonorrhoea epidemiology in the ACT. Canberra; 2019.

24. NSW Health. NSW Sexually Transmissible Infections Strategy 2016 - 2020 [Internet]. 2018 [cited 2019 Feb 1]. Available from: https://www.health.nsw.gov.au/Infectious/Reports/Publications/sti/nsw-sti-report-jan-june-2018.pdf

25. F Chow EP, Fehler G, H Read TR, Tabrizi SN, Hocking JS, Bradshaw MB BS CS, et al. Gonorrhoea notifications and nucleic acid amplification testing in a very low-prevalence Australian female population. MJA [Internet]. 2015 [cited 2019 Oct 9];202(6). Available from: www.mja.com.au.

26. Williamson DA, Fairley CK, Howden BP, Chen MY, Stevens K, De Petra V, et al. Trends and risk factors for antimicrobial-resistant Neisseria gonorrhoeae, Melbourne, Australia, 2007-2018. Antimicrob Agents Chemother [Internet]. 2019 [cited 2019 Sep 17]; Available from: http://aac.asm.org/

27. WHO. Global action plan to control the spread and impact of antimicrobial resistance in Neisseria gonorrhoeae [Internet]. 2012 [cited 2018 Nov 20]. Available from: http://apps.who.int/iris/bitstream/handle/10665/44863/9789241503501_eng.pdf;jsessionid=68192C1A160DAD11D3E802087B2149A5?sequence=1

28. Fifer H, Saunders J, Soni S, Sadiq ST, FitzGerald M. British Association for Sexual Health

and HIV national guideline for the management of infection with Neisseria gonorrhoeae (2019). Bashh [Internet]. 2019;1–25. Available from: https://www.bashhguidelines.org/media/1208/gc-2019.pdf

29. Abraha M, Egli-Gany D, Low N. Epidemiological, behavioural, and clinical factors associated with antimicrobial-resistant gonorrhoea: a review. F1000Research [Internet]. 2018 [cited 2019 Oct 23];7:400. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29636908

30. Public Health England. Update on investigation of UK case of Neisseria gonorrhoeae with high-level resistance to azithromycin and resistance to ceftriaxone acquired abroad. Heal Prot Rep. 2018;12(14).

31. Australian Bureau of Statistics. Estimates of Aboriginal and Torres Strait Islander Australians, June 2016 [Internet]. Australian Government Department; 2018 [cited 2019 Jul 8]. Available from: https://www.abs.gov.au/ausstats/abs@.nsf/mf/3238.0.55.001

32. Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report [Internet]. Sydney; 2018 [cited 2019 Jul 5]. Available from: https://kirby.unsw.edu.au/sites/default/files/kirby/report/KI_Annual-Surveillance-Report-2018.pdf

33. NSW Health. NSW Sexually Transmissible Infections [Internet]. 2019 [cited 2019 Sep 17]. Available from: https://www.health.nsw.gov.au/Infectious/Reports/Publications/sti/nsw-2018-sti-report.pdf

34. Chow EP, Williamson DA, Fortune R, Bradshaw CS, Chen MY, Fehler G, et al. Prevalence of genital and oropharyngeal chlamydia and gonorrhoea among female sex workers in Melbourne, Australia, 2015–2017: need for oropharyngeal testing. Sex Transm Infect [Internet]. 2019 May 21;sextrans-2018-053957. Available from: http://sti.bmj.com/lookup/doi/10.1136/sextrans-2018-053957

35. Ong JJ, Fethers K, Fairley CK, Chow EPF, Aung E, Chen MY, et al. Asymptomatic and symptomatic urethral gonorrhoea in men who have sex with men attending a sexual health service. Clin Microbiol Infect. 2017;

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Chapter Four: Determinants and uptake of antenatal vaccines in the ACT

Prologue

The Study

A cross-sectional survey of pregnant women who received antenatal care in the ACT and surrounds provides formal estimates of antenatal influenza and pertussis vaccine uptake. Self-reported rates of antenatal vaccination were found to be generally high, with some variability in update rates attributable to a set of other determinants that were considered.

Lessons learnt

The challenge of collecting primary data is significant, but the value of new data as well as the learning is worth it. Sending out a message to approximately one hundred different women 78 times over a 12-month period took a determined effort, but the result is that more than 1000 different women will have responded by the end of the study. This chapter presents and analyses the first six months of responses. The process of inviting participants highlighted the dogged nature of collecting raw data as well as the value of automation and simplifying processes as much as possible.

The ethics process was straight forward and proceeded smoothly through the first two ethics committees. The third application was not so simple, with ethics approval being declined by the Calvary hospital due to privacy concerns. Unfortunately, the time required to request reconsideration of this decision was impractical within the timeframe of the MAE. This meant I did not quite gather as broad a cross section women giving birth in the ACT as anticipated.

Ensuring the survey is working appropriately is essential as ideally a survey should not be altered once data is being collected. I did need to make two small changes. One included adding a page break on the last page to ensure most demographic questions were completed. The other was adding a response option of receiving influenza vaccine at work. This change was made prior to inviting cohort four (of 13 cohorts analysed). More than fifty respondents wrote this option in free-text as the location for receiving their influenza vaccine, therefore I added this option for subsequent cohorts. Although this is not ideal, I don't believe it altered the validity of the results; no differences in uptake were noted when analysed using multivariate logistic regression. Accounting for these differences could be done by weighting or during analysis; I chose the latter for practical reasons following discussion with a statistician. To avoid this change in the future I would conduct a formal pilot inviting one or two cohorts and conducting a detailed analysis of the responses before undertaking the full study.

During the writeup process I identified an administrative breach in ethics. I received ethics approval to invite only ACT resident women giving birth at The Canberra Hospital (TCH). The data I received included NSW residents, identifiable by postcode. They were to be excluded at the outset by postcode; however, some confusion resulted in 276 NSW resident women being

invited and 92 responding. Out of respect to the women who took the time to consent and provide a response I requested an amendment to our ethics approval to include their responses. Our proposed changes, along with an apology, were requested and granted by the ACT Health and ANU human research ethics committees. A more detailed analysis of the extract data prior to inviting participants may have identified the NSW postcode at an earlier stage.

It is important to have a mechanism for potential participants to decline. I provided two options, replying STOP to the text message or choosing NO during the consent process within the survey. Initially, if a participant chose NO within the survey, I had no way of identifying the participant to withdraw her from the study. Adding a response box to type their phone number in allowed us to do this.

Multi-answer questions should be avoided whenever possible for a large volume survey. Analysis of these questions, other than descriptive analysis is very difficult and significant data cleaning/manipulation was required to interpret findings from these questions.

In hindsight it would have been useful to identify if a woman had received both vaccines at the same time along with the exact dates of vaccine administration. This may not necessarily have been accurate, due to recall bias when recalling specific dates. The potential value in receiving both vaccines was an outcome of the research and identifies what could be documented or questioned in the future.

This study was presented at the New Zealand Immunisation Conference in Auckland in September 2019. A poster presentation is being prepared for the Communicable Disease Conference in Canberra in November 2019. An abstract is also being prepared for the Australian Immunisation Conference in 2020 as well as a journal publication, both based on the complete 12-months of data.

Public Health implications of this work

This is the first study looking at antenatal vaccination uptake in the ACT. This research demonstrates that the ACT are performing better than any other jurisdiction in Australia but also highlights some areas for improvement. While this study does use self-reported data, most studies in Australia rely on this. The key limitation is non-respondent bias, although verification with pertussis vaccine delivery data matched our results which gives us greater confidence in our results.

We know the value of antenatal vaccines, however we don't have a mechanism to routinely monitor whether women are receiving vaccines or not. Although this data is captured electronically to some extent in the ACT it is not completed at the time of administration or complete, and therefore not useful for our analysis. Other states also struggle with this problem.

Victoria does include this data in their registry, however, it is recorded following the birth and is still self-reported. Western Australia has explored the use of the midwives notification system to routinely monitor antenatal vaccination coverage; however, this was found to be unreliable with low sensitivity and specificity. A method to address this is recommended, ideally at a national level.

It is anticipated the results from this study will inform antenatal vaccination in the ACT in several ways. Providing these results to midwives may inform them of the value of antenatal vaccination, the important role they play in advising women to vaccinate as well as some of the barriers to vaccination. As a result of new recommendations for the timing of pertussis vaccination, a strategy to recommend vaccinating against influenza and pertussis at the same time may improve access to and uptake of antenatal vaccines.

This study also adds to the body of evidence supporting the importance of a healthcare provider's recommendation, and identifying drivers and barriers of antenatal vaccination. The insights obtained provide some new thoughts regarding the opportunity to vaccinate for pertussis and influenza at the same time.

Abstract

Background

Antenatal influenza and pertussis vaccination is recommended in Australia for every pregnancy, however uptake among pregnant women is not systematically documented. Estimates of uptake vary around Australia, ranging from 39-61% for influenza and 46-82% for pertussis. The aims of this study were to estimate antenatal pertussis and influenza vaccination uptake, and to describe key determinants of uptake, in the Australian Capital Territory (ACT).

Methods

All women with a live birth between 1 October 2018 and 30 September 2019 at The Canberra Hospital (TCH) were invited to participate in an online survey 4-6 weeks post-birth. Up to three invitation text messages were sent. Interim descriptive and univariate analysis of 6-months data are presented.

Results

During the six-month period, 3011 births occurred in the ACT and 1596 at TCH. A total of 1552 women were invited to participate, following exclusion. A total of 142 (9.1%) declined, 820 (52.8%) did not respond and 589 (38%) at least partially completed the survey.

Self-reported antenatal vaccination uptake among study participants was 95% (555/585; 95% CI 92.8-96.5) for pertussis and 74% (424/575; 95% CI 70.0-77.3) for influenza.

Univariate analysis of income and location of influenza vaccination detected a significant positive association between households who earn over $100,000 per year and vaccines received in the workplace (OR 7.7 95% CI 1.33-44.96 p=0.023).

Multivariate analysis identified those living in a household earning above $100,000 were significantly associated with women receiving antenatal influenza vaccine (aOR 1.98 95% CI 1.24-3.18 p=0.005).

Multivariate analysis identified mothers who received a healthcare provider recommendation to vaccinate reported significantly higher uptake of both pertussis (aOR 10.51 95% CI 3.68-30.00 p<0.001) and influenza (aOR 6.89 95% CI 4.15-11.44 p<0.001).

Conclusion

Self-reported antenatal vaccination uptake among respondents was high for pertussis and influenza, particularly when vaccination was recommended by a health professional. Expansion of the time-frame that pertussis vaccine can be given may allow a strategy to target receipt of both vaccines during the same visit.

Introduction

Influenza and pertussis are both highly communicable diseases that have an increased propensity to cause morbidity and mortality in pregnant women and very young infants.

Influenza has the potential to affect a significant proportion of society each year and novel strains can cause pandemics (such as A/H1N1 in 2009/10) (1). Public health management of influenza can be challenging with individuals needing annual vaccination due to both waning immunity and, as a result of gradual changes in circulating influenza strains (described as 'antigenic drift') (2). Population rates of laboratory confirmed influenza fluctuate significantly from year-to-year; in 2017, notification rates in the ACT were 4-fold higher than in 2018 (3).

The burden of disease differs between population groups; pregnant women are >4 times more likely to be admitted to hospital than the general population as well as increased rates of ICU admission and death. Influenza infection during pregnancy increases the risk of preterm birth and low birthweight. Infants aged <6 months also have the highest risk of hospitalisation and death from influenza (4,5).

Antenatal influenza immunisation has been recommended during pregnancy since 2000 and funded in Australia under the National Immunisation Program (NIP) since January 2010 (6). The Australian Immunisation Handbook currently advise antenatal influenza vaccination can be given at any time during pregnancy, however, they suggest timing should be considered in relation to the influenza season (7).

Pertussis is caused by *Bordetella pertussis*, a gram-negative bacterium that causes respiratory infection. It is highly infectious in susceptible people and vaccination does not provide lifelong protection. Pertussis in young children is often characterised by a prolonged paroxysmal cough and inspiratory 'whoop' (8).

The highest burden of severe disease for pertussis is in young infants, particularly those less than 6 months of age, where case fatality rates of 0.8% in unvaccinated individuals have been reported (9). Throughout the last decade of the 20th century and the first decade of the 21st century pertussis has occurred on a 3-4-year epidemic cycle. From 2009 to 2011 there were epidemic rates of disease in Australia, around the time of pertussis vaccine being recommended during pregnancy (10).

Pertussis vaccine was part of the original routine childhood immunisation schedule in 1975 and is currently funded under the National Immunisation Program (NIP), with doses given at 6 weeks, 4, 6 and 18 months, 4 years and approximately 12-13 years (9). A cocoon strategy of vaccinating parents and close family began in the ACT in 2009, aiming to protect unvaccinated babies. This ceased in 2011 due to growing Australian evidence of limited benefit/protection to young

infants. Antenatal pertussis vaccination was funded by the ACT government in April 2015. Since July 2018, antenatal pertussis vaccination has been funded under the Australian NIP (11). Recommended gestation of pertussis vaccination of pregnant women was expanded from 28-32 weeks to 20-32 weeks in April 2019 (7).

The safety of influenza and pertussis vaccines in pregnancy is well established internationally (12). A large prospective Australian study found no significant association between antenatal influenza or pertussis vaccination and adverse birth outcomes compared to unvaccinated pregnancies (13). A 2019 systematic review confirmed the safety of antenatal influenza and pertussis vaccination and also suggested a protective effect against preterm birth and low birth weight (14). A large observational study of antenatal vaccinations in the United Kingdom general practitioner database found no increased risk of any pregnancy adverse events following antenatal influenza vaccination, including stillbirth (14).

The effectiveness of antenatal vaccination is well established internationally for both pertussis and influenza vaccination (15–18). Research has consistently reported effectiveness of antenatal pertussis vaccination to prevent illness during the first 2-6 months of life to be >90% compared to infants born to unvaccinated mothers (15,16,19).

In Australia, midwives are involved in most models of maternity care (20). Four models account for the majority of maternity care in the ACT. Two are medically led by either GPs or obstetricians, two are midwife led and both are based in-hospital. All high-risk pregnancies are cared for by obstetricians, which includes public and private care. GP led care is shared with a consistent midwife throughout the pregnancy. The Canberra Midwifery Program (CMP) and Continuity at The Canberra Hospital (CaTCH) are both midwife led programs where the same midwife provides consistent care for an individual. CMP provides a low-intervention model for low-risk women. CaTCH leads care for medium-risk women but can refer to specialists when required (21). Hospital based antenatal care is midwife led, in the hospital, but can provide care in the community; a duty midwife provides care on the day.

Although Australian research investigating what influences antenatal vaccination uptake has identified recurring themes (22–24), this is the first study conducted in the ACT. The main identified driver for antenatal vaccination uptake is receiving a recommendation from a health professional (range 13 - 33 times more likely to receive an antenatal vaccine) (25–27). Other drivers that have been identified include: model of antenatal care, perceived risk of illness, demographic differences, first child, and confidence in the schedule (28,29).

The only estimates of antenatal vaccine uptake in the ACT come from a pertussis antenatal vaccine program evaluation in 2016. Vaccine uptake estimates ranged from 74% based on

vaccine delivery data to 29% based on hospital administration data, although the data sources were not considered to be reliable due to low compliance with data entry (30). Our study recruited women from The Canberra Hospital (TCH). This is one of two public hospitals in the ACT and provides the highest of six levels of maternity care. Half of all births in the ACT occur at TCH. The other public hospital provides care at the fifth level of maternity care, while the surrounding areas provide care for routine pregnancies with no planned pre-term deliveries (31). TCH also receives NSW resident women from the surrounding region. NSW residents birthing at TCH have a higher proportion of Indigenous women and pre-term births compared to ACT resident women (32).

The primary aim of this study was to estimate antenatal pertussis and influenza vaccination (APIV) uptake in the ACT. The secondary aim was to identify key determinants of antenatal vaccine uptake in the ACT.

Methods

Study Design and Population

This was a cross-sectional survey inviting all women who received antenatal care and delivered a live baby at TCH between 1 October 2018 and 30 September 2019. This chapter reports the first 6 months of data collected for births between 1 October 2018 to 31 March 2019. A non-probability sample was used inviting women from one hospital, TCH. The source population included both ACT and NSW residents. Women with no cell phone number or those who experienced a stillbirth, or neonatal death, were excluded from the study prior to an export of eligible women.

Study enrolment

Eligible women were identified by accessing an export of an administrative hospital dataset which records all birth encounters that occurred at TCH. These data were extracted on a fortnightly basis and included all births within the preceding fortnight to create 13 groups (referred to as birth periods) over the 6-month study period. Variables for all eligible women included: date of birth for mother and child, first and last name of the mother, postcode, Indigenous status, mother's country of birth and all available phone numbers. A study database was created in Excel and the participant's phone number was used as a unique study ID.

Study invitation

Participants were then invited to participate in the study by text message. An Australian based online text message service, (SMSbroadcast) was used to send and track text messages. The message provided a link to a smart-phone friendly online survey, using SurveyMonkey (33). If a text message failed to send, a secondary number was used if available.

Participants were able to decline by replying directly to the text message with the message 'STOP'. This message was automatically forwarded to a study email address. The participant was manually identified in the study database, withdrawn from the study and coded as declined. If the participant clicked on the survey a consent page followed the study information page. If the participant declined to provide consent and also provided their phone number their details were manually identified in the study database and coded as declined. If no response was received, two further text message reminders were sent approximately one week after the previous message. If a participant declined or completed the survey, a further reminder was not sent.

Survey questions

The online survey asked up to 31 questions, some of which were repressed for respondents based on previous answers using skip logic. Question topics included model of care, pre-pregnancy knowledge about antenatal vaccines, the participant's views on who should be responsible for advising and administering antenatal vaccines, and whether they had enough information to make an informed decision. After being asked whether they were vaccinated for each vaccine, they were asked when, why and where they received their vaccine or why they were not vaccinated. The survey concluded with demographic questions including: age, Indigenous status, first language spoken, number of children, education, and income. Survey question design was modelled off a similar survey conducted in Western Australia (24) and a study in Victoria using registry data to answer a similar question (34). The survey was piloted amongst ACT health staff assessing framing of questions and survey flow on mobile phones.

Some respondents reported receiving an influenza vaccine prior to pregnancy within a free-text answer. If they specified the month received and it was during the same influenza season, this was categorised as an appropriate antenatal influenza vaccine. If they stated it was received 'just prior' or 'immediately before' becoming pregnant and deemed likely to be within the same influenza season according to the birth date, this was categorised as an appropriate antenatal influenza vaccine. If it was unclear when the vaccine was received, the response was categorised as vaccine not received.

Verification of vaccination

Vaccination status was self-reported, therefore we asked participants who reported being vaccinated to verify their vaccination status by taking a photo of their antenatal personal health record and uploading this in response to one of the survey questions. This personal health record documents all antenatal and post-natal related health information in a booklet, which most women are known to carry on them up until 6-8 weeks post-birth. As the survey link was sent via text message, it was anticipated most participants would complete the survey on an internet enabled camera phone. The reason for requesting verification was respondents were not

identifiable once the survey was completed, and we did not seek consent to verify responses via patients records.

Another method of verification compared self-reported pertussis vaccine uptake for all women who reported receiving their vaccine from hospital-based staff (midwives and obstetricians) with the number of pertussis vaccines delivered to TCH. All pertussis vaccines delivered to TCH are used for antenatal vaccination.

Statistical Methods

A t-test was conducted to identify differences in age between respondents and non-respondents. A χ^2 test was conducted to identify differences in country of birth, Indigenous status and multiple births between respondents and non-respondents. Birth gestation was collapsed into two categories, pre-term (<38 weeks) and term (≥38 weeks).

Factors potentially associated with vaccination were analysed using univariate logistic regression. Univariate analysis was used to identify variables associated with either pertussis or influenza vaccine uptake. Variables significant at α=0.05 were included in the relevant hierarchical multivariate logistic regression models to control for potential confounding. A backward stepwise method was used to remove variables with a non-significant result. Reference categories used were defined by STATA. Age and country of birth were initially included in the logistic regression models to account for differences in population of those that responded compared to non-respondents. Income was collapsed into two categories (above and below $100,000) when there was a linear relationship to simplify the model. A linktest was used to check for specification error. A Hosmer-Lemeshow goodness of fit test was conducted for each model using the lfit command. Analyses were performed in STATA 15.0 (35).

Ethics was approved by ACT Health Human Research Ethics Committee (HREC) 2018/LRE/00147 and The Australian National University Human Research Ethics Committee 2018/586.

Results

A total of 3011 births occurred in the ACT during the 6-month recruitment period, of these, 1596 gave birth at TCH. Forty-four women were excluded according to our exclusion criteria of stillbirth or peri-natal death. Of the 1552 who were invited, 142 (9%) declined to participate, 820 (53%) did not respond and 589 (38%) at least partially completed the survey. The primary outcome of antenatal vaccination uptake was provided by 98% (575/589) of respondents for influenza and 99% (585/589) for pertussis. Participants replied following one text message (267/589, 45%), two text messages (199/589, 34%), or three text messages (97/589, 16%). Twenty-six participants (4%) completed the survey but were unable to be matched by phone number, subsequently I could not determine after how many messages they responded.

A total of 3978 text messages were sent; 52 (1%) failed to send. Most of these messages (42/52, 78%) failed during the first invitation but were subsequently successfully sent using a secondary phone number. In total, eighteen (1%) participants were excluded due to either an invalid phone number or no mobile number being provided.

Verification of antenatal vaccination was provided by 74/555 (13%) and 50/395 (13%) of those who reported receiving pertussis and influenza vaccine respectively.

Source population

Of the 1552 women invited to participate, 589 (38%) responded (Table 1). Of those who responded, the youngest age group (16-24 years) were under represented (6 vs 12 %) compared to non-respondents (Table 1). A one-year difference in mean age was found between respondents (30.7) and non-respondents (31.9); this was statistically significant (t-test $p<0.001$). Four hundred and seventy-one (84%) respondents were ACT residents and 92 (16%) respondents were residents of NSW. A significant difference in country of birth was also present between respondents and non-respondents (χ^2 p = 0.003). No significant difference in Indigenous status was present between respondents and non-respondents (χ^2 p = 0.095). There was no difference in the proportion of twin births among respondents and non-respondents (17/587 [3%] vs 28/963 [3%]), respectively.

*Table 1: Characteristics of respondents and non-respondents to survey **

	Responded		No-response		2017 ACT births † §	
	n	%	n	%	%	P value
Age Category						
16-24 years	36	6	114	12	9	
25-29 years	133	23	269	28	24	
30-34 years	251	43	351	36	39	
35-39 years	137	23	189	20	22	
40+ years	29	5	40	4	5	
Total	586	38	963	62		
$\bar{X}$ = 31.5 (95% CI 30.7-32.2)			$\bar{X}$ = 31.0 (95% CI 30.4-31.9)			p <0.001 § ±
Indigenous Status**†						
Indigenous	14	2	33	3		
Non-Indigenous	538	96	904	94		
Not stated	11	2	26	3		
Total	563		963			p = 0.095 ††
Country of Birth						
Australia	395	67	573	60		
Overseas	194	33	390	41		
Total	589		963			p = 0.003 ††

** Denominators differ according to whether respondent answered or not*

† Proportion of all births in the ACT (including NSW residents) by age-group in 2017 from 'Australia's mothers and babies 2017' report (32)*.*

§ t-test performed using numerical age

*** 26 participants unable to be matched between extracted data and respondent data due to incorrectly entered phone numbers in the online survey.*

†† χ^2 test

More than 50% of respondents reported living in a household earning more than $100,000 per year and >60% reported university level education (**Error! Not a valid bookmark self-reference.**). The vast majority reported a full-term birth (87%) of 38 weeks or more. The total proportion of babies born at a gestation >37 weeks in the ACT in 2017 was 88% (32).

*Table 2: Characteristics of respondents to survey **

Household Income	**n**	**%**
<$50,000	49	9
$50,000 - $100,000	120	23
>$100,000 - $150,000	132	25
>$150,000	167	31
Rather not say	63	12
Total	531	
Education		
Primary school	6	1
High school	81	15
TAFE, trade, vocational	120	23
Undergraduate	167	32
Postgraduate	156	29
Total	530	
Birth gestation		
≥38 weeks	467	87
34 – 37 weeks	52	10
28 – 33 weeks	14	3
<28 weeks	2	0.4
Total	535	

** Denominators differ according to whether respondent answered or not*

Antenatal Influenza uptake

The overall self-reported uptake of influenza vaccine among study participants was 74% (424/575; 95% CI 70.0-77.3) (Figure 1). There was seasonal variation in uptake which ranged from a low of 32% for the birth period 18 March – 31 March 2019 to a high of 95% for the birth period 15 October – 28 October 2018.

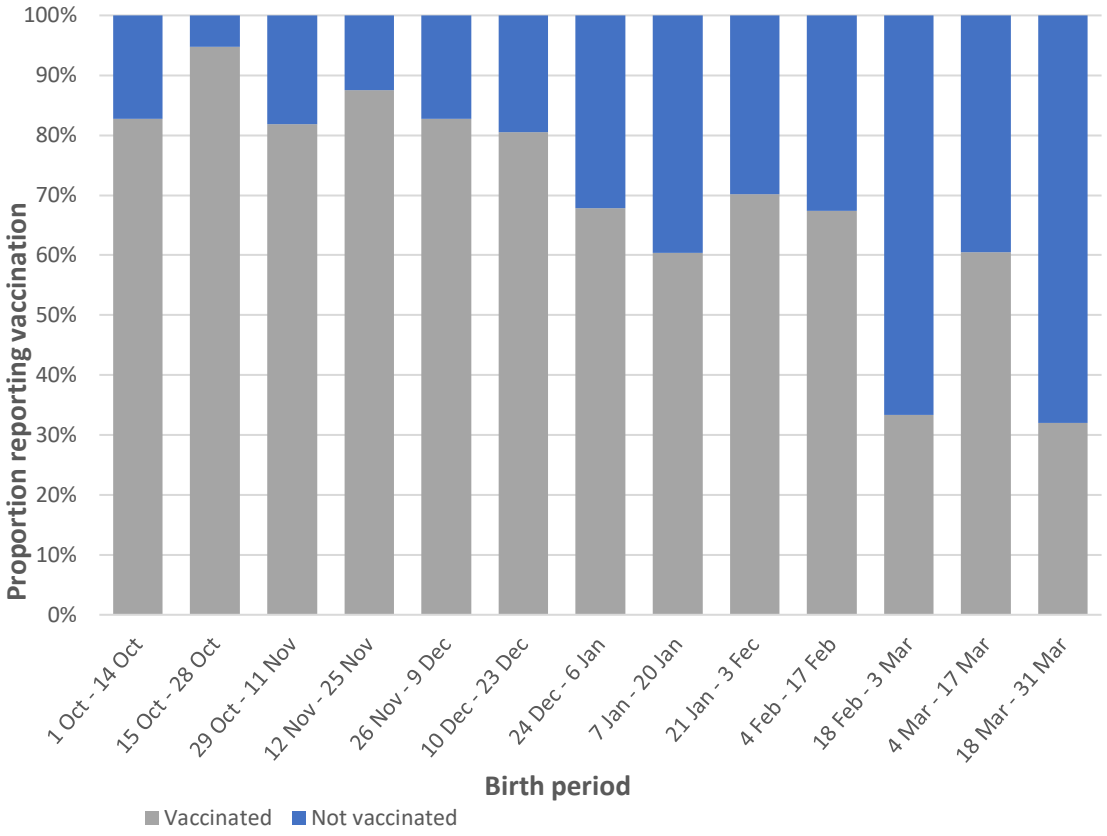


Figure 1: Influenza antenatal vaccination uptake by birth period for women who gave birth at The Canberra Hospital: 1 October 2018 – 31 March 2019

Antenatal Pertussis uptake

The overall self-reported uptake of antenatal pertussis vaccine among study participants was 95% (555/585; 95% CI 92.8 - 96.5) (Figure 2). Uptake ranged from 90% for those who gave birth from 1 October to 14 October 2018 to 100% for those who gave birth from 24 December 2018 to 6 January 2019.

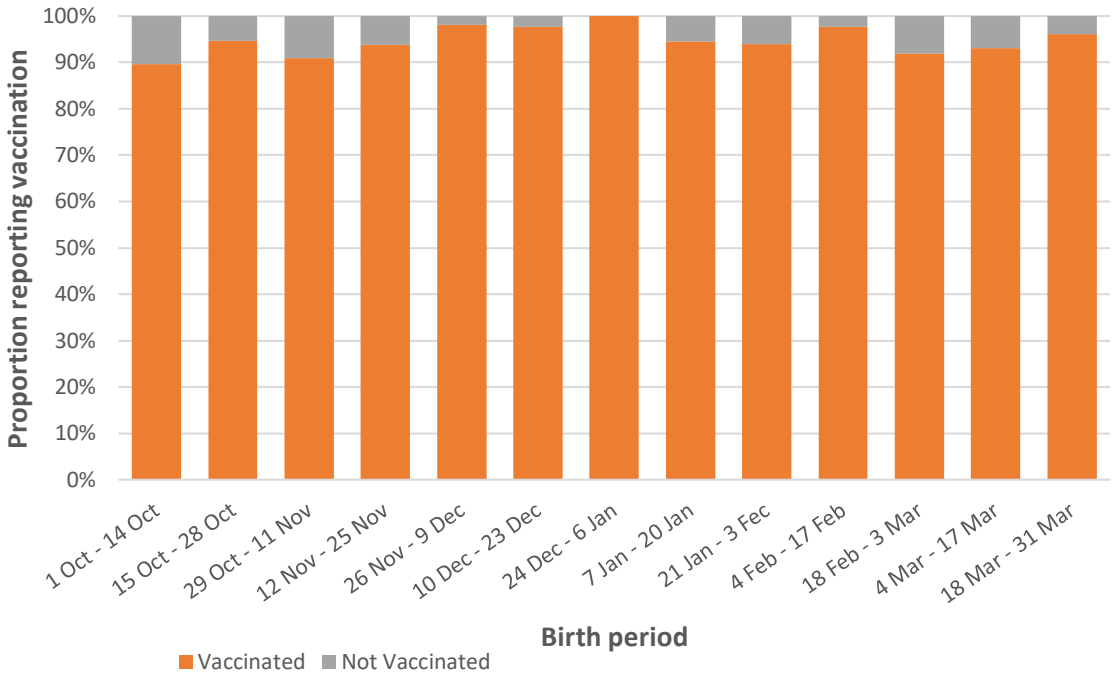


Figure 2: Pertussis antenatal vaccine uptake by birth period for women who gave birth at The Canberra Hospital: 1 October 2018 – 31 March 2019

Characteristics of those vaccinated

A total of 586 respondents reported their antenatal vaccination status for at least one vaccine. One respondent did not report their pertussis vaccination status but did report their influenza status; 11 reported their pertussis vaccination status but not their influenza status.

Of those who received at least one antenatal vaccine, 417/574 (73%) reported receiving both vaccines. Of those who received both vaccines, 50/417 (12%) received their vaccine at the same location during the same trimester of pregnancy; 367/417 (88%) received their vaccines during different trimesters and at different locations (Figure 3). Of those that recalled the point in gestation at which they received an influenza vaccine, 203/424 (48%) received it either during the first trimester of pregnancy or immediately prior to being pregnant; 156 (37%) received it in the second trimester (Figure 3). The majority of those who received pertussis vaccine (381/552, 69%) did so in the third trimester of pregnancy (28-34 weeks). A smaller proportion (101/552, 18%) received their pertussis vaccine in the second trimester of pregnancy.

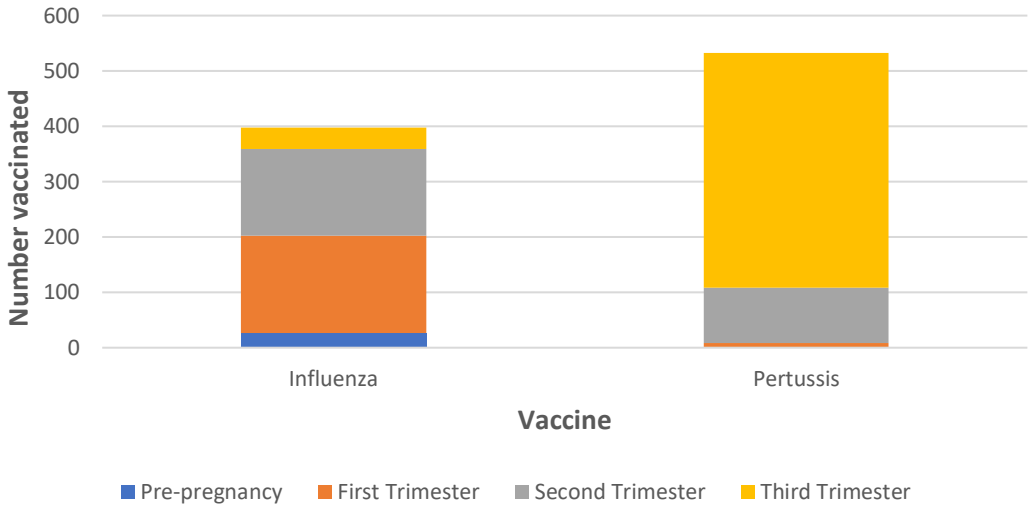


Figure 3: Number of antenatal vaccinations by type of vaccine and gestation vaccine received for births at The Canberra Hospital: 1 October 2018 – 31 March 2019.

Most influenza vaccinations were received at a General Practice (GP) (180/393, 46%) or in a workplace setting (132/393, 34%). Most pertussis vaccines were given by a midwife at the hospital antenatal unit (336/549, 61%), or in a GP setting (137/549, 25%) (Table 3).

Table 3: Location of antenatal vaccination: Oct 2018 – Mar 2019

Location of antenatal vaccination administration	Influenza		Pertussis	
	n	%	n	%
Obstetrician/other specialist: private setting	3	1	6	1
Obstetrician/other specialist: public setting	14	4	36	7
General Practice	180	46	137	25
Midwife at community antenatal unit	9	2	33	6
Midwife at hospital antenatal unit	47	12	336	61
Workplace	132	34	N/A	NA
Other	8	2	1	-
Total	393		549	

The most commonly reported reason for receiving antenatal influenza vaccine was for the mother to protect herself (297/395, 75%), followed by protecting their baby (237/395, 60%). Many chose multiple reasons for receiving the flu vaccine including: protecting both mother and child (212/395, 54%); and as a result of either a GP/midwife recommendation along with protecting mother and child (169/395, 43%) (Table 4).

The most common single reason by new mothers for receiving antenatal pertussis vaccine was to protect their baby (470/552, 85%) (Table 4). Other reasons included a midwife recommendation (306/552, 55%) and to protect themselves (292/552, 53%). Many respondents reported multiple reasons for receiving antenatal pertussis vaccine, the most common combination included a GP or midwife recommendation along with protecting their child (377/552, 68%).

Table 4: Reasons for receiving antenatal vaccination: Oct 2018 - Mar 2019

Reasons for receiving vaccine *	Influenza (n=552)		Pertussis (n=424)	
	n	%	n	%
GP recommended	167	42	165	30
Midwife recommended	104	26	306	55
Obstetrician/another specialist recommended	30	8	56	10
To protect myself	297	75	292	53
To protect my baby	237	60	470	85
Partner/family/friends encouraged it	36	9	60	11
I always get it	19	5	n/a	n/a

** Respondents could provide multiple answers to this question. The percentage represents the number of people who chose this answer compared to all who received that vaccine and answered that question.*

New South Wales (NSW) residents represented 92/589 (16%) of all respondents. Of the 92 NSW resident women who reported gestation at birth, 27 (30%) experienced a pre-term birth compared to 39/421 (9%) of ACT residents; this was statistically significant (p<0.001).

All seventeen participants who gave birth to twins reported receiving antenatal pertussis vaccine. A total of 10/16 (63%) reported receiving antenatal influenza vaccine.

All respondents (589) reported their model of care during pregnancy (Figure 4). The majority received their antenatal care from: shared care (243, 41%), CMP/CaTCH (222, 38%) or the hospital antenatal clinic (70, 12%).

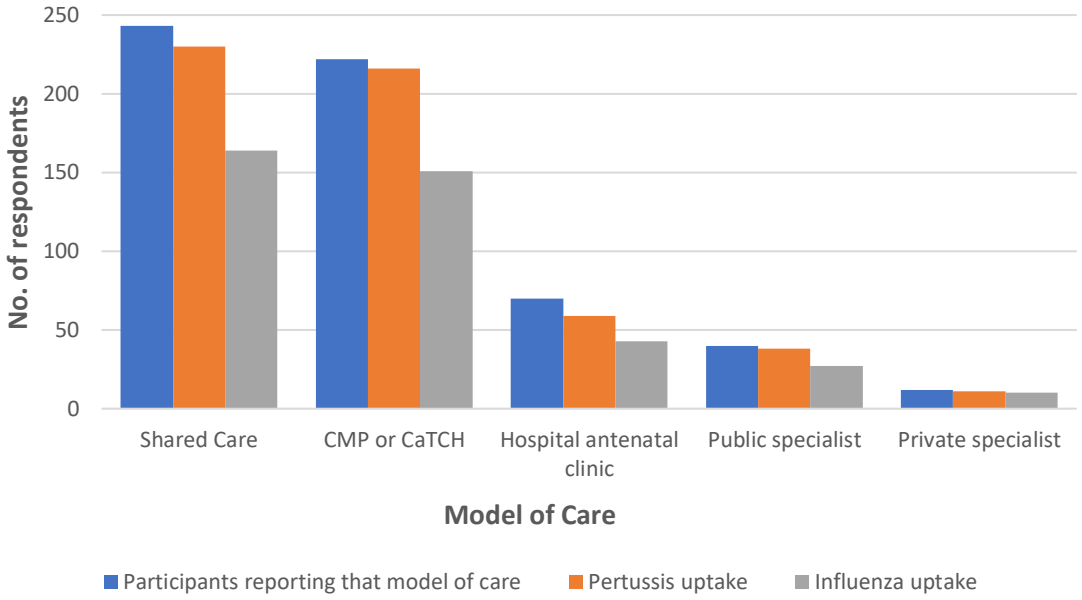


Figure 4: Self-reported model of care during pregnancy and antenatal vaccine uptake for women who gave birth at The Canberra Hospital: 1 October 2018 – 31 March 2019

Predictors of vaccination – Influenza

Univariate analysis of income and location of influenza vaccination detected a significant positive association between households who earn over $100,000 per year and vaccines received in the workplace (OR 7.7 95% CI 1.33-44.96 *p*=0.023).

Multivariate analysis identified those living in a household earning above $100,000 (*p* =0.005) and having their first child (*p* =0.011) were both significantly associated with women receiving antenatal influenza vaccine (Table 5).

There was a significant association between healthcare providers recommending receiving flu vaccine and receipt of both vaccines (aOR 6.9, 95% CI 4.15 – 11.44 *p* <0.001). Of those that were recommended to receive an influenza vaccine, 83% received both vaccines; compared to 41% of those who were not recommended to receive an influenza vaccine.

No specification error was detected in the multivariate model. The model was found to fit well (Hosmer-Lemeshow goodness of fit test [GOf] $x^2 = 1.37$, p = 0.987). The model has a moderately strong ability to discriminate between uptake and no-uptake (area under the receiver operator curve [AUROC] 0.75).

Table 5: Multivariate logistic regression model for antenatal influenza vaccination including those vaccinated prior to pregnancy for women who gave birth at The Canberra Hospital: 1 October 2018 – 31 March 2019.

	Influenza					
	Vaccinated		**Non-vaccinated**		**Adjusted odds ratio* (95% CI)**	*p*
	n	%	n	%		
Influenza Recommendation						
No	48	41	69	59	1	
Yes	369	83	77	17	6.89 (4.15-11.44)	<0.001
	417	74	146	26		
Household income						
<$100,000	110	67	54	33	1	
>$100,000	234	79	63	21	1.98 (1.24-3.18)	0.005
	344	75	117	25		
First child						
No	190	69	87	31	1	
Yes	200	80	50	20	1.85 (1.15-2.98)	0.011
	390	74	137	26		

** Adjusted odds ratios are adjusted for all other factors in the table. Missing data were excluded from odds ratio calculations.*

Predictors of vaccination- Pertussis

Univariate analysis showed a highly significant association between pertussis vaccination and both CMP/CaTCH (p <0.001) and shared care (*p*=0.002), compared to the hospital antenatal clinic.

Multivariate analysis identified that recommendation of a healthcare provider to receive antenatal pertussis vaccination was significantly associated with the uptake of antenatal pertussis vaccine (*p* <0.001 [Table 6]). Being cared for by a hospital midwife under the CaTCH or CMP team (*p* =0.005), shared care (*p* =0.011) or a public specialist (*p* =0.024) were all significantly associated with receiving pertussis vaccine compared to receiving care at the hospital antenatal clinic. One household income category ($100,000 - $150,000) was significantly associated with receiving pertussis vaccine compared to households earning $50,000 -$100,000 (*p*=0.039). When analysed as households earning above or below $100,000 per year, there was a significant association (aOR 2.36 95% CI 1.08-5.17) with those reporting higher household incomes more likely to receive a pertussis vaccine.

There was a significant negative association between births <38 weeks gestation and receiving pertussis vaccine (*p* = 0.028). Two respondents reported births <28 weeks and 14 reported births between 28 and 33 weeks.

No specification error was detected in the multivariate model. The model was found to fit well (GOF $x^2 = 4.40$, *p* = 0.820). The model has a moderately strong ability to discriminate between uptake and no-uptake (AUROC 0.81). There was no association between a healthcare provider's recommendation to receive pertussis vaccine and receiving both vaccines (*p*=0.886).

Table 6: Final multivariate logistic regression model for antenatal pertussis vaccination

	Vaccinated		Non-vaccinated		Adjusted odds ratio* (95% CI)	*p*
	n	%	n	%		
Pertussis Recommendation						
No	24	73	9	27	1	
Yes	530	96	21	4	10.51(3.68-30.00)	<0.001
	554	6	30	94		
Clinical Care						
Hospital Antenatal Clinic	59	84	11	16	1	
Public Specialist Care	38	95	2	5	8.65(1.33-56.47)	0.024
Hospital Midwife (CMP or CaTCH)	216	98	5	2	5.23(1.65-16.60)	0.005
Shared Care	230	96	10	4	3.62(1.35-9.71)	0.011
Private Specialist Care	11	92	1	8	1.60(0.17-9.71)	0.678
	555	95	30	5		
Income Category						
<$50 000	44	94	3	6	2.87(0.67-12.31)	0.155
$50 000 - $100 000	108	90	12	10	1	
$100 000 - $150 000	127	96	5	4	3.54(1.07-11.74)	0.039
>$150 000	160	96	7	4	2.97(0.99-8.88)	0.052
Rather not say	59	95	3	5	3.02(0.74-12.34)	0.124
	498	94	30	6		
Birth gestation						
<38 weeks	59	87	9	13	0.35(0.14-0.90)	0.028
≥38 weeks	443	95	21	5	1	
	502	94	30	6		

** Adjusted odds ratios are adjusted for all other factors in the table. Missing data were excluded from odds ratio calculations.*

Advice and administration of vaccine

Nearly all respondents (568/578, 98%) reported that midwives should be responsible for advising pregnant women to receive antenatal vaccination. The majority (490/578, 85%) also considered GPs to be responsible for this advice, as well as obstetricians (295/578, 51%). Most considered any or all clinicians (midwife, GP, obstetrician) to be responsible (292/578, 51%) for this advice.

Responsibility for provision of antenatal vaccines was predominantly perceived to be midwives (493/564, 87%) and GPs (466/564, 83%). Many considered provision of vaccines to be a joint responsibility with 396/564 (70%) selecting both midwives and GPs as responsible, while 201/564 (36%) selected midwives, GPs, and obstetricians.

Most respondents (pertussis: [536/585, 91%], influenza: [501/585, 85%]) reported having enough information from healthcare providers to make an informed decision regarding antenatal vaccination

Reasons against vaccination

The main reasons reported for not receiving pertussis vaccine were concerns about the risks of the vaccine to the mother or baby (8/27, 30%) or self-reported history of allergy to the vaccine (6/27, 20% [Table 7]). Overall, seven (26%) respondents reported not being recommended or offered a pertussis vaccine.

The main reason for not receiving influenza vaccine was not being convinced of the benefits of the vaccine (51/175, 29%). Forty-eight (28%) respondents reported not being recommended influenza vaccination by a health professional. Nineteen mothers (11%) reported being concerned about the risk to them or their baby. Nine women (5%) reported being advised not to receive the influenza vaccine.

Table 7: Reasons why antenatal vaccination did not occur for one or both vaccines.

Why did you NOT get one of the antenatal vaccines during pregnancy? *	Influenza ††		Pertussis §	
	n	%	n	%
Vaccine not recommended by health professional	48	28	7	26
I wasn't convinced of the benefits of the vaccine	51	29	2	7
I was concerned about the risk to me or my baby	19	11	8	30
A healthcare provider advised against getting a vaccine	9	5	2	7
Deemed not required by respondent or provider due to season	19	11	-	-
Recently had it prior to being pregnant	29	17	-	-
History of allergy to vaccine	-	-	6	20
I gave birth earlier than 28 weeks	-	-	2	7

** Both of these were multiple answer questions; there may be more responses than respondents.*

§ Thirty respondents reported not receiving pertussis vaccine during pregnancy; 27 provided a reason.

†† 151 respondents reported not receiving influenza vaccine during or prior to pregnancy; 175 valid responses are reported.

Discussion with family and friends

Participants were asked whether they discussed vaccination with family or friends. Univariate analysis found a significant negative association between those who discussed antenatal vaccination and influenza vaccine uptake (OR 0.58 95% CI 0.39-0.85 p=0.005).

A group of twenty-nine respondents reported receiving influenza vaccine prior to pregnancy; all 29 also reported receiving pertussis vaccine. Of this group, who all received both vaccines, 20/29 (69%) reported not discussing antenatal vaccination with family or friends.

Verification of vaccine administration

Seventy-four respondents (13%) reported receiving pertussis vaccination and all provided appropriate verification evidence. Of these, a further 28 (7%) also reported receiving influenza vaccine and provided appropriate verification evidence.

Of the 549 who responded to the survey and reported the location of their pertussis vaccination, 411 (75%) reported receiving their vaccine in the hospital. It was therefore estimated that approximately 1,145/1,526 (75%) women may have received their antenatal pertussis vaccine at the hospital. Based on delivery data, 1130 vaccines were delivered to the hospital during the study period. Estimating wastage to be 1% and stock levels at approximately 50 vials, I calculated approximately 1068 antenatal vaccines may have been given within the hospital system. Therefore, delivery data suggests 1068/1145 (93%) of those who may have received antenatal vaccine in the hospital did so. The remaining quarter of antenatal vaccinations were provided by GPs (n=138).

Discussion

Main Findings

This cross-sectional survey provides the first formal estimates of antenatal influenza and pertussis vaccine uptake in the ACT and surrounds. Our main finding was, that of women who responded, most received the recommended vaccines during pregnancy. We also found that a healthcare provider's recommendation is the most important predictor of antenatal vaccination.

High vaccine uptake

Self-reported antenatal vaccine uptake of 74% for influenza and 95% for pertussis demonstrates very high uptake. This is the highest uptake currently reported in Australia (13,23–27,34,36–38). No pertussis notifications have been received in unvaccinated children less than one year of age since 2016 in the ACT supporting the view of high antenatal vaccine coverage (39). Although self-reported pertussis vaccine uptake may be reaching a high-point, there is still room to increase the uptake of influenza vaccination.

Differences in uptake between pertussis and influenza vaccines are well documented and were not unexpected (34,38). Pertussis is perceived as a serious illness for babies; supported by the vast majority (85%) of respondents reporting that protecting their baby was the primary reason for receiving the pertussis vaccine. In contrast influenza is perceived as a relatively mild illness and more likely to affect the mother. The main reason respondents reported for receiving influenza vaccine (75%) was to protect themselves.

Healthcare provider recommendation

Results from this survey support the strong evidence that a healthcare provider's recommendation is highly influential for the receipt of antenatal vaccination (22,40–46). The significant association detected between receiving a recommendation to be vaccinated against influenza and receipt of both vaccines is likely to be as a result of already extremely high uptake of pertussis vaccines. Because a healthcare provider's recommendation is so influential, and influenza uptake was significantly lower, the recommendation to receive influenza vaccine became a more predictive factor of whether both vaccines were given.

Income and influenza vaccination

A significant positive association was found between women who reported living in a household with income above $100,000 per year and both influenza vaccination uptake (p=0.005) and influenza vaccine received in the workplace (p = 0.023*)*. I believe these results highlight an issue of access and affordability. Influenza is part of the National Immunisation Program (NIP) (47). As such it is fully-funded for pregnant women and cost should not be a determinant. Our results are similar to a highly powered population level registry study in Victoria which reported a significant linear trend; as socio-economic status increased, influenza vaccination rates

increased (38). Conversely, an annual, random sampled survey in Western Australia found no association between influenza vaccine uptake and socio-economic status (34). It is possible that income is a confounding problem and the key driver is those earning higher incomes may have easier access to free influenza vaccines through their workplace. They may also have fewer financial barriers to receiving influenza vaccine through their GP where out-of-pocket costs are normally present. ACT, in particular has less bulkbilled GP services than other states (48). These results are consistent with Thomson (32) who presents access and affordability as a root cause of under vaccination.

Advice against vaccination

A small number of healthcare providers were reported to be advising against antenatal vaccines (9/175 5% influenza, 2/27 7% pertussis); this is consistent with a 2018 Western Australia study (7% influenza, 8% pertussis) (34). Research suggests a spectrum of views are still present amongst midwives regarding vaccination, and suggests ongoing education of healthcare providers is necessary (20). Attwell (20) also suggested that midwives may be more inclined to inform women about recommendations of antenatal vaccination without opinion or guidance. This is compared to physicians who are more likely to advise and recommend, a subtle but potentially important difference. I recommend on-going education amongst midwives may be beneficial to maintain current levels of antenatal vaccination.

Gestation and pertussis uptake

Antenatal pertussis vaccination has been recommended to be given between 20 – 32 weeks gestation since 29th March 2019 (7). A significant negative association was found between those giving birth between >27 - <38 weeks gestation and pertussis vaccine uptake (p=0.028). While this is not a surprising result for those giving birth around 28 weeks, six of the nine gave birth after 34 weeks and according to gestation at birth did have the opportunity to receive pertussis vaccine. This suggests reasons other than a pre-term birth influenced them not receiving pertussis vaccine. The remaining three pre-term births who didn't receive pertussis vaccine may have had a greater opportunity to receive the vaccine with the expanded recommendations.

Discussion of influenza vaccine with family and friends

A negative association between discussing vaccination with family or friends and influenza vaccination uptake was unexpected. It is not clear whether those who discuss vaccination are more or less inclined to vaccinate; no evidence in the literature has reported this negative association. The negative association included 29 respondents who received influenza vaccine prior to pregnancy; all 29 also received antenatal pertussis vaccine and are clearly in favour of vaccination. When a sensitivity analysis was conducted without this group, the negative association was not present. This group were slightly older, reported higher income and a higher proportion were having their first child compared to other respondents. I believe this finding

along with the highly significant association with healthcare providers recommendation suggests that family and friends may not play a significant a role in whether to vaccinate or not. A small survey-based evaluation of antenatal influenza vaccination in NSW, reported GPs, midwives, brochures and the internet were of higher importance to women who vaccinated (49). Another Australian study reported that the primary source of information for pregnant women is healthcare providers, followed by family and friends (49). Similarly, Mak (34) reported 52% of respondents received antenatal influenza vaccine because of family and friends, lower than all healthcare providers.

Comparison of findings with literature

Differences between states and territories

This study suggests a large increase in antenatal uptake compared to the only other previous ACT estimate (30). It provides a more robust estimate for pertussis and the first estimates for antenatal influenza vaccine uptake in the ACT. Very recent estimates of uptake are: 82% for pertussis and 39% for influenza in Victoria (registry study) (38), and 71% for pertussis and 61% for influenza in Western Australia (cross sectional random sample) (34). A randomised study of >8,000 women conducted across six Australian states in 2012-2015 found antenatal vaccine uptake of 46% and 45% for pertussis and influenza, respectively (13). A 2016 multi-state Australian study reported antenatal pertussis and influenza vaccination uptake of: 82% and 46% in Victoria; 74% and 46% in South Australia; and 86% and 40% in Western Australia, respectively (43).

Socio-economic status may account for some of the differences between states and territories. In 2017, 94% of all women who gave birth in the ACT were categorised as quintile four or five (least disadvantaged) and 1% in quintile one or two (most disadvantaged). This compares to NSW where 46% of babies were born to mothers in quintile one or two. Rowe et al also found a significant association between Indigenous, overseas born and low-socioeconomic women, and lower vaccination rates (38).

Dual vaccination

Provision of both antenatal vaccinations during the same visit has not been widely discussed due to the previous short window available for the administration of pertussis vaccine (28-32 weeks). However, by increasing this timeframe to 20-32 weeks, the potential to recommend and administer both vaccines together has increased. We reported that 79% of influenza vaccinations were administered in the first or second trimester and 77% of pertussis vaccinations administered in the third trimester (Figure 3). This contrasts with a Western Australian survey conducted in 2015 which reported that 70% of women who vaccinated against

both influenza and pertussis received them on the same day (34). A strategy suggesting dual vaccination is presented below.

First pregnancy

Women who were pregnant for the first time were more likely to receive antenatal influenza vaccine than women in subsequent pregnancies. This is consistent with a large study in Victoria which found a significant association between first-time mothers and both influenza and pertussis vaccine uptake. In contrast, a study of South Australian, Victoria and Western Australian pregnant women, found first time mothers were more vaccine hesitant; however, these views did not appear to effect antenatal vaccine uptake (46).

Strengths and limitations

Self-selection bias

The key limitation of this study is self-selection bias. Some differences in those who responded compared to those who did not respond were noted. Attempts were made to account for non-respondent bias by including country of birth and age category in each multivariate logistic regression model. Neither produced significant associations nor affected the models produced. It is possible however that differences between respondents and non-respondents may be unknown characteristics which have contributed to non-respondent bias (50).

Self-reported vaccination status

Vaccination status was self-reported, which studies suggest may lead to an overestimation of vaccination coverage (22,51). Disease prevalence studies suggest that odds ratios are overestimated for respondents vs non-respondents. It is possible that vaccinators may be more inclined to participate as they recognise the importance of antenatal vaccination, which may overestimate vaccination uptake. To account for this, verification of vaccination was requested. Although the participants that provided verification for pertussis were correctly self-reported it is difficult to have the same level of confidence for those reporting influenza vaccination and those not providing verification. Only 23 (46%) of the 50 who reported receiving both vaccines and provided verification had documentation of this for influenza. This suggests that vaccination was carried out in a different setting, prior to pregnancy, documented elsewhere, not documented, or not completed at all.

Participant representativeness

A statistically significant difference in mean age (1 year) was found between respondents and non-respondents. However, this difference is not considered meaningful for a number of reasons. A large sample were invited to participate which included all mothers who gave birth at TCH, the main referral hospital in the ACT. No significant associations were found between age and vaccine uptake during statistical analysis. Study respondents also appeared to be

representative of all births in the ACT in 2017 by age category (32). Nonetheless, overall results may not be generalisable to all women in the ACT or in other states and territories.

State of residence

There is no reason other than geography that women would attend TCH or Calvary public hospital except for high-risk and pre-term births. A significant difference was found in the proportion of pre-term births between ACT and NSW residents birthing at TCH (p<0.001). This is not unexpected and supports previous literature (32). All surrounding NSW hospitals are level 3 or 4 which cater for: births at >37 or >34 weeks; and pregnancies with routine or moderately complex needs, respectively (31). Therefore, high-risk pregnancies and pre-term births are likely to be transferred to TCH.

Implications for practice/research

Consistent and timely antenatal vaccination data is not routinely available in the ACT or in most jurisdictions in Australia. Currently, most estimates originate from research and publications, which is both expensive and untimely. A method for antenatal vaccination to be electronically documented at the time of administration by the provider could allow evaluation of current strategies and guide future public health approaches in a timely manner. A national solution is recommended; creating an antenatal or pregnancy field within the Australian Immunisation Register (AIR) would allow documentation at the time of administration, as well as allow routine, national reporting.

A change in recommendation for the timing of antenatal pertussis vaccination has made it feasible for a new strategy encouraging dual antenatal vaccination of pertussis and influenza during the same antenatal visit. Promoting dual vaccination could be an effective strategy for women who have an expected delivery date between mid-May and early-November (gestation of 20-32 weeks between 1 April and 31 July). Although influenza vaccine is recommended to be given at any time in pregnancy, the increased risk during pregnancy means the timing of vaccination is important. Ensuring vaccine coverage throughout the influenza season whilst promoting dual vaccination is feasible. If influenza vaccine has not been received from August onwards, dual vaccination could still be promoted as a catch-up for influenza, up until the time that the vaccine is no longer available in February. Seasonal influenza vaccines are often not available between February and March primarily due to previous year's stock expiring, and also not being an appropriate strain match for the upcoming influenza season. Therefore, a dual vaccination strategy could be strongly promoted on arrival of the new influenza vaccine and then employed as a back-up strategy from August onwards to ensure influenza vaccine has been received, even if late in the influenza season.

Considering healthcare provider recommendation is a key determinant of antenatal vaccination, a targeted communications campaign towards maternal care clinicians prior to and during the key influenza vaccination period may encourage increased influenza uptake during the most at-risk months. This could lead to higher uptake overall of influenza vaccine, provide more equitable access and reduce affordability as a barrier.

Ongoing education to healthcare providers, including midwives is recommended considering a small number of midwives were reported to be recommending women against antenatal vaccination. This could be undertaken in the form of continuing education emphasising the benefits and safety of vaccination to mothers and babies.

Conclusion

The study shows that the ACT has the highest self-reported rates of antenatal vaccination for influenza and pertussis in Australia. Self-reported uptake was very high and consistent for pertussis, and high but seasonally variable for influenza. ACT has been successful in achieving appropriate levels of antenatal pertussis vaccination.

Our findings support the strong evidence that healthcare providers recommendations influence antenatal vaccine uptake for both influenza and pertussis vaccines. This suggests influenza vaccine uptake rates could approach those of pertussis at certain periods during the year if a strategy to encourage dual vaccination was adopted. This could reduce barriers of access and affordability. A recent change in recommendation increasing the period during pregnancy that pertussis can be safely given would allow this strategy to be adopted.

An electronic method of documenting antenatal vaccines at the time of administration could be pursued to monitor, maintain and increase antenatal vaccination uptake in the future.

References

1. Girard MP, Tam JS, Assossou OM, Kieny MP. The 2009 A (H1N1) influenza virus pandemic: A review. Vaccine [Internet]. 2010 Jul 12 [cited 2018 Apr 16];28(31):4895–902. Available from: https://www.sciencedirect.com/science/article/pii/S0264410X1000719X#section0010

2. Carrat F, Flahault A. Influenza vaccine: The challenge of antigenic drift. Vaccine. 2007;25:6852–62.

3. ACT Government: ACT Health. ACT Government: HealthStats, Influenza. Notification Rates, Influenza. 2018.

4. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol [Internet]. 2012 Sep 1 [cited 2018 Jul 11];207(3):S3–8. Available from: https://www.sciencedirect.com/science/article/pii/S0002937812007223

5. Yudin MH. Risk management of seasonal influenza during pregnancy: current perspectives. 2014 [cited 2019 Aug 28]; Available from: http://dx.doi.org/10.2147/IJWH.S47235

6. National Centre for Immunisation Research & Surveillance. Significant events in diptheria, tetanus and pertussis vaccination practice in Australia. 2018.

7. Australian Government Department of Health. Vaccination for women who are planning pregnancy, pregnant or breastfeeding [Internet]. Australian Immunisation Handbook. 2019 [cited 2019 Aug 15]. Available from: https://immunisationhandbook.health.gov.au/vaccination-for-special-risk-groups/vaccination-for-women-who-are-planning-pregnancy-pregnant-or

8. Heymann D. Control of Communicable Disease manual. 20th ed. American Public Health Association; 2015.

9. Centers for Disease Control and Prevention. Pertussis - United States, 2001-2003. Morb Mortal Wkly Rep. 2005;54(50):1283–6.

10. Campbell P, McIntyre P, Quinn H, Hueston L, Gilbert GL, McVernon J. Increased population prevalence of low pertussis toxin antibody levels in young children preceding a record pertussis epidemic in Australia. PLoS One. 2012;7(4).

11. ATAGI. Changes to the recommended use of pertussis vaccines in pregnant women [Internet]. 2019 [cited 2019 Jan 17]. Available from: https://consultations.health.gov.au/ohp-immunisation-branch/maternal-pertussis-vaccination/supporting_documents/Final public changes to the recommended use of pertussis vaccines in pregnant women.pdf

12. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: Observational study. BMJ. 2014;349.

13. Mchugh L, Marshall HS, Perrett KP, Nolan T, Wood N, Lambert SB, et al. The Safety of Influenza and Pertussis Vaccination in Pregnancy in a Cohort of Australian Mother-Infant Pairs, 2012-2015: The FluMum Study. Clin Infect Dis [Internet]. 2019 [cited 2018 Dec 3];68(3):402–8. Available from: https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciy517/5202330

14. Giles ML, Krishnaswamy S, Macartney K, Cheng A. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. Hum Vaccin Immunother [Internet]. 2019 [cited 2019 Sep 2];15. Available from:

https://doi.org/10.1080/21645515.2018.1540807

15. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet [Internet]. 2014 [cited 2018 Jun 7];384:1521–8. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)60686-3/fulltext

16. Amirthalingam G, Campbell H, Ribeiro S, Fry NK, Ramsay M, Miller E, et al. Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction. Clin Infect Dis. 2016;63(Suppl 4):8.

17. Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis. Pediatrics [Internet]. 2017 May 3 [cited 2018 Jun 7];139(5):e20164091. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28557752

18. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of Maternal Influenza Immunization in Mothers and Infants. N Engl J Med. 2008;

19. Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis. Pediatrics [Internet]. 2017 [cited 2019 Sep 2];139(5). Available from: https://pediatrics.aappublications.org/content/139/5/e20164091

20. Attwell K, Wiley KE, Waddington C, Leask J, Snelling T. Midwives' attitudes, beliefs and concerns about childhood vaccination: A review of the global literature. 2018 [cited 2018 Oct 19]; Available from: https://doi.org/10.1016/j.vaccine.2018.02.028

21. Goodman, R. Buehler, J. Koplan J. Defining Field Epidemiology. Am J Epidemiol [Internet]. 1990;132:91–6. Available from: https://www.cdc.gov/eis/field-epi-manual/chapters/Defining-Field-Epi.html

22. Mak DB, Regan AK, Joyce S, Gibbs R, Effler P V. Antenatal care provider's advice is the key determinant of influenza vaccination uptake in pregnant women. Aust New Zeal J Obstet Gynaecol [Internet]. 2015 Apr 1 [cited 2018 Mar 20];55(2):131–7. Available from: http://doi.wiley.com/10.1111/ajo.12292

23. Regan, A. The uptake, safety and effectiveness of seasonal influenza vaccination during pregnancy: an evaluation of the maternal influenza immunisation program in Western Australia safety and effectiveness of seasonal influenza vaccination during pregnancy: an eval [Internet]. 2016 [cited 2018 Mar 29]. Available from: http://research-repository.uwa.edu.au/files/10032032/THESIS_DOCTOR_OF_PHILOSOPHY_REGAN_Annette_Karena_2016.pdf

24. Regan AK, Mak DB, Hauck YL, Gibbs R, Tracey L, Effler P V, et al. Trends in seasonal influenza vaccine uptake during pregnancy in Western Australia: Implications for midwives. Women and Birth [Internet]. 2016 [cited 2018 Apr 5];29:423–9. Available from: https://www.sciencedirect.com/science/article/pii/S1871519216000330?via%3Dihub

25. Wiley KE, Massey PD, Cooper SC, Wood NJ, Ho J, Quinn HE, et al. Uptake of influenza vaccine by pregnant women: A cross-sectional survey. Med J Aust. 2013;

26. Maher L, Hope K, Torvaldsen S, Lawrence G, Dawson A, Wiley K, et al. Influenza vaccination during pregnancy: Coverage rates and influencing factors in two urban districts in Sydney. Vaccine [Internet]. 2013;31(47):5557–5564. Available from: https://www.sciencedirect.com/science/article/pii/S0264410X13011936

27. Lotter K, Regan AK, Thomas T, Effler P V., Mak DB. Antenatal influenza and pertussis vaccine uptake among Aboriginal mothers in Western Australia. Aust New Zeal J Obstet

Gynaecol [Internet]. 2017 Nov 14 [cited 2018 Mar 20]; Available from: http://doi.wiley.com/10.1111/ajo.12739

28. Krishnaswamy S, Wallace EM, Buttery J, Giles ML. A study comparing the practice of Australian maternity care providers in relation to maternal immunisation. Aust New Zeal J Obstet Gynaecol. 2019 Jun 1;59(3):408–15.

29. Mohammed H, Clarke M, Koehler A, Watson M, Marshall H. Factors associated with uptake of influenza and pertussis vaccines among pregnant women in South Australia. PLoS One [Internet]. 2018 [cited 2019 Oct 23];13(6). Available from: https://doi.org/10.1371/journal.pone.0197867

30. ACT Health. Antenatal Pertussis Vaccination Program Evaluation Report. 2016.

31. Standing Council on Health and Community Disability Services. National Maternity Services Capability Framework Standing Council on Health and Community Disability Services [Internet]. 2013 [cited 2019 Aug 28]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/FC3A10DCCCE8CC0BCA257D2A0016CD0E/$File/capab.pdf

32. Australian Institute of Health and Welfare. Australia's mothers and babies 2017 - in brief [Internet]. Canberra; 2019 [cited 2019 Sep 24]. Available from: www.aihw.gov.au/

33. SurveyMonkey. SurveyMonkey Inc. [Internet]. San Mateo, California, USA; 2019. Available from: www.surveymonkey.com

34. Mak DB, Regan AK, Vo DT, Effler P V. Antenatal influenza and pertussis vaccination in Western Australia: a cross-sectional survey of vaccine uptake and influencing factors. BMC Pregnancy Childbirth [Internet]. 2018;18:416-. Available from: https://doi.org/10.1186/s12884-018-2051-3

35. StataCorp. Stata Statistical Software: Release 15 [Internet]. College Station; 2017. Available from: https://www.stata.com/support/faqs/resources/citing-software-documentation-faqs/

36. Overton K, Webby R, Markey P, Krause V. Influenza and pertussis vaccination coverage in pregnant women in the Northern Territory in 2015—new recommendations to be assessed. North Territ Dis Control Bull [Internet]. 2016 [cited 2018 Mar 21];23(4). Available from: http://digitallibrary.health.nt.gov.au/prodjspui/bitstream/10137/506/553/Vol. 23 no 4 December 2016.pdf

37. Wong C, Thomas N, Clarke M, Boros C, Tuckerman J, Marshall H. Maternal uptake of pertussis cocooning strategy and other pregnancy related recommended immunizations. Hum Vaccin Immunother [Internet]. 2015;11(5):1165–1172. Available from: http://www.tandfonline.com/doi/full/10.1080/21645515.2015.1019188

38. Rowe SL, Perrett KP, Morey R, Stephens N, Cowie BC, Nolan TM, et al. Influenza and pertussis vaccination of women during pregnancy in Victoria, 2015–2017. Med J Aust. 2019;210(10):454–62.

39. Commonwealth Department of Health: Communicable Disease Branch. National Notifiable Diseases Surveillance System [Internet]. Australia. Commonwealth Department of Health; 2018 [cited 2019 Jan 9]. Available from: http://www9.health.gov.au/cda/source/rpt_4.cfm

40. Yuen CYS, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women – A systematic review. Vaccine [Internet]. 2014;32(36):4602–4613. Available from: https://www.sciencedirect.com/science/article/pii/S0264410X14008688

41. Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: A literature review. Vaccine [Internet]. 2015 [cited 2018 Apr 10];33:6420–9. Available from: https://www.sciencedirect.com/science/article/pii/S0264410X15011731?via%3Dihub

42. Wiley KE, Cooper SC, Wood N, Leask J. Understanding pregnant women's attitudes and behavior toward influenza and pertussis vaccination. Qual Health Res. 2015;

43. Danchin MH, Costa-Pinto J, Atwell K, Willaby H, Wiley K, Hoq M, et al. Vaccine decision-making begins in pregnancy: Correlation between vaccine concerns, intentions and maternal vaccination with subsequent childhood vaccine uptake. Vaccine [Internet]. 2018 [cited 2018 Jun 8];36(44). Available from: https://www.sciencedirect.com/science/article/pii/S0264410X17310691

44. Wolstenholme A, Duffy C, Smith C. Community Attitude Research on Influenza Vaccination. 2017;(September).

45. Smith C, Duffy C, Kirszner M. Research to identify immunisation information needs. 2016;

46. Danchin MH, Costa-Pinto J, Attwell K, Willaby H, Wiley K, Hoq M, et al. Vaccine decision-making begins in pregnancy: Correlation between vaccine concerns, intentions and maternal vaccination with subsequent childhood vaccine uptake. 2017 [cited 2018 Oct 19]; Available from: http://dx.doi.org/10.1016/j.vaccine.2017.08.003

47. Australian Government Department of Health. National Immunisation Program Schedule [Internet]. 2019 [cited 2019 Oct 29]. Available from: https://www.health.gov.au/health-topics/immunisation/immunisation-throughout-life/national-immunisation-program-schedule

48. Australian Department of Health. Annual Medicare Statistics. Medicare Statistics. 2019.

49. Carlson SJ, Scanlan C, Marshall HS, Blyth CC, Macartney K, Leask J. Attitudes about and access to influenza vaccination experienced by parents of children hospitalised for influenza in Australia. Vaccine. 2019;

50. Groves RM. Nonresponse rates and nonresponse bias in household surveys. Public Opin Q. 2006;70(5):646–75.

51. Jiménez-García R, Hernandez-Barrera V, Rodríguez-Rieiro C, Carrasco Garrido P, López de Andres A, Jimenez-Trujillo I, et al. Comparison of self-report influenza vaccination coverage with data from a population based computerized vaccination registry and factors associated with discordance. Vaccine. 2014;

Appendix One: Questionnaire

Please note logic will be used in the online version which is not displayed here. This is an example of the questions only.

1. How were you mainly cared for during your pregnancy? (please do not include the care you had during the birth)

- ○ Shared Care (GP & midwife/antenatal clinic)
- ○ Public Specialist Care only (Obstetrician)
- ○ Hospital Midwife only (continuity model CMP or CaTCH)
- ○ Private Specialist Care only (Obstetrician)
- ○ Hospital Antenatal Clinic
- ○ Other - please specify: _____

2. Before this pregnancy, did you know that whooping cough and flu vaccines were recommended for pregnant women (i.e. that women should get these vaccines during their pregnancy)?

- ○ I only knew about the whooping cough vaccine
- ○ I only knew about the flu vaccine
- ○ I knew both were recommended
- ○ I didn't know either vaccine was recommended

3. Who do you feel should be responsible for telling you that whooping cough and flu vaccinations were recommended for you during pregnancy? (Please select all that apply)

○ Midwife

○ GP

○ Obstetrician

○ Other specialist

○ Other – please specify: _____

4. Who do you feel should be responsible for actually giving you the whooping cough and flu vaccinations during your pregnancy? (Please select all that apply)

○ Midwife

○ GP

○ Obstetrician

○ Other specialist

○ Other – please specify: _____

5. During your pregnancy how many health professionals provided care for you? (In-depth or consultative care rather than just a pregnancy scan or incidental contact)

○ One person most of the time eg. just one midwife, one GP or one obstetrician/specialist

○ Two consistent people most of the time eg. one GP & one midwife

○ Three consistent people most of the time

○ Lots of different people

6. Did you receive a whooping cough vaccine during your most recent pregnancy?

- ○ Yes
- ○ No
- ○ Don't Know

7. At what stage in your pregnancy did you receive your whooping cough vaccine?

- ○ First Trimester (up to 12 weeks)
- ○ Second Trimester (12 - 27 weeks)
- ○ Third Trimester (28 - 34 weeks)
- ○ Third Trimester (35 weeks or later)
- ○ Don't Know

8. Did you receive flu vaccination during your most recent pregnancy?

- ○ Yes
- ○ No
- ○ Don't Know

9. At what stage in your pregnancy did you receive your flu vaccination?

- ○ First Trimester (up to 12 weeks)
- ○ Second Trimester (>12 - 27 weeks)
- ○ Third Trimester (28 – 34 weeks)
- ○ Third Trimester (35 weeks or later)
- ○ Don't Know

10. Was your partner (or any close family/friend) involved in your decision on whether or not to get the whooping cough and/or the flu vaccine during pregnancy?

- ○ Yes
- ○ No
- ○ Rather not say

11. Did a healthcare provider tell you that it is recommended for pregnant women to have a whooping cough and/or flu vaccine during pregnancy?

- ○ Told me about the whooping cough vaccine only
- ○ Told me about the flu vaccine only
- ○ Told me about both whooping cough and flu vaccines
- ○ Did not tell me about either vaccine
- ○ Don't know

12. Did a healthcare provider inform/educate you (i.e. talk to you about in more detail) about benefits of whooping cough and/or flu vaccination during pregnancy by a healthcare provider?

- ○ Informed about whooping cough vaccine benefits only
- ○ Informed about flu vaccine benefits only
- ○ Informed about both whooping cough and flu vaccine benefits
- ○ Not informed about benefits of either vaccine
- ○ Don't know

13. Do you feel you had enough information/education to make an informed decision whether to get the whooping cough vaccine during pregnancy?

- ○ Yes
- ○ No
- ○ Don't Know

14. Do you feel you had enough information/education to make an informed decision whether to get the flu vaccine during pregnancy?

- ○ Yes
- ○ No
- ○ Don't know

15. Did a health professional recommend or encourage you to have a whooping cough vaccine during pregnancy?

- ○ Yes
- ○ No
- ○ Don't know

16. Did a health professional recommend or encourage you to have a flu vaccine during pregnancy?

- ○ Yes
- ○ No
- ○ Don't know

17. Why did you decide to get the whooping cough vaccine? Please select all that apply

- ○ My GP recommended/encouraged it
- ○ My midwife recommended/encouraged it
- ○ My obstetrician/other specialist recommended/encouraged it
- ○ I wanted to protect myself from getting whooping cough
- ○ I wanted to protect my baby against whooping cough
- ○ My partner/family/friends encouraged it
- ○ Other_____

18. Where did you get your whooping cough vaccine?

- ○ From my GP
- ○ From a midwife at an antenatal clinic
- ○ From my obstetrician/other specialist in a public setting
- ○ From my obstetrician/other specialist in a private setting
- ○ Other – please specify: _____
- ○ Don't remember

19. Why did you decide to get the flu vaccine? Please select all that apply

- ○ My GP recommended/encouraged it
- ○ My midwife recommended/encouraged it
- ○ My obstetrician/other specialist recommended/encouraged it
- ○ I wanted to protect myself from getting flu
- ○ I wanted to protect my baby against flu
- ○ My partner/family/friends encouraged it
- ○ Other_____

20. Where did you get your flu vaccine?

- ○ From my GP
- ○ From a midwife at an antenatal clinic

○ From a midwife at a hospital-based antenatal appointment

○ From my obstetrician/other specialist in a public setting

○ From my obstetrician/other specialist in a private setting

○ Other – please specify: _____

○ Don't remember

21. Were there any things that influenced you NOT to get the whooping cough vaccine? (Please select all that apply)

○ I knew about it but none of my healthcare providers recommended or offered it to me during my pregnancy

○ I did not know about it and none of my healthcare providers recommended or offered it to me during my pregnancy

○ I wasn't convinced of the benefits of the vaccine

○ I didn't think I needed it - please specify why: _____

○ A healthcare provider advised against getting this vaccine

○ I gave birth earlier than 28 weeks so was too early to receive it

○ Other – please specify:

22. Were there any things that influenced you NOT to get the flu vaccine? (Please select all that apply)

○ I knew about it but none of my healthcare providers recommended or offered it to me during my pregnancy

○ I did not know about it and none of my healthcare providers recommended or offered it to me during my pregnancy

○ I wasn't convinced of the benefits of the vaccine

○ I was concerned about the safety/risk of this vaccine to my baby or myself

○ I didn't think I needed it – please specify why: _____

○ A healthcare provider advised against getting a flu vaccine

○ Other: please specify why _____

23. Approximately how many weeks pregnant were you when you gave birth?

- ○ 38 weeks or more
- ○ Between 34 and 37 weeks
- ○ Between 28 and33 weeks
- ○ Less than 28 weeks

24. Were you born in Australia?

- ○ Yes
- ○ No – please specify your country of birth: _____

25. Are you of Aboriginal and/or Torres Strait Islander Origin?

- ○ Yes - Aboriginal
- ○ Yes – Torres Strait Islander
- ○ Yes – Both Aboriginal and Torres Strait Islander
- ○ No
- ○ Prefer not to say

26. Was English your first language?

- ○ Yes
- ○ No

27. How many children have you now given birth to?

- ○ One
- ○ Two or more

28. How old are you?

- ○ Younger than 20 years
- ○ 20 to24 years
- ○ 25 to 29 years
- ○ 30 to 34 years
- ○ 35 to 39 years
- ○ 40 and over
- ○ Rather not say

29. What is your highest level of education you have completed?

- ○ Primary school
- ○ High school
- ○ TAFE, trade, technical or other vocational training
- ○ University undergraduate
- ○ University postgraduate

30. What is your estimated total **Household** income for the past year?

- ○ < $50,000 per year
- ○ $50,000 - $100,000 per year
- ○ > $100,000 - $150,000 per year
- ○ > $150,000 per year
- ○ Rather not say

31. If you were vaccinated for whooping cough and/or flu and this was completed in your maternity record, please upload a photo of that page of your maternity record showing the vaccination details (page 21). To do this, click on the link and take a photo of that page. When taking the photo, please make sure none of your personal details (e.g name, address or date of birth) are visible in the photo.

Appendix Two: Information Sheet

Pertussis and influenza vaccine uptake in pregnancy in the ACT

Thanks for taking the time to follow the link and your willingness to participate.

Before you decide whether or not you wish to participate in this survey, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully.

1. What is the purpose of this study? The purpose is to find out how many women had pertussis or flu (influenza) vaccine during their pregnancy. We also want to find out what is important to pregnant women when they are deciding to receive a vaccine.

2. Why have I been invited to participate in this study? You have been asked to participate in this study because you have recently been pregnant and were a patient at one of the public hospitals in the ACT.

3. What if I don't want to take part in this study or if I want to withdraw later? Participation in this study is voluntary. It is completely up to you whether or not you participate. If you do not want to participate now, do not complete the survey. If you participate (complete the survey) but change your mind later, you can still withdraw from the study at any time. Just contact the study team on 6205 2155 if you wish to withdraw your survey responses from the study (we will delete all your survey responses and they will not be used).

4. What does this study involve? This study involves a short (15min) online survey. No further contact is required.

5. How is this study being paid for? The study is being run by ACT Health. Participation in this study will not cost you anything. Participants will not be paid for their involvement.

6. Are there risks to me in taking part in this study? There is no physical risk from taking part in this study. Although participation in this study is unlikely to cause emotional distress,

if you do experience emotional distress during or following completion of this survey, please click on this link for assistance: www.healthyfamilies.beyondblue.org.au/pregnancy-and-new-parents ph 1300 22 4636

7. Who is organising and funding the research? This study is being conducted by and funded by ACT Health. The study lead (primary investigator), Callum Thirkell, is a Masters student enrolled at the Australian National University (ANU) but on placement at ACT Health. All work on this study is being supervised by staff members at ACT Health and the ANU. Staff members involved in this study will not receive any personal financial benefit from your involvement in

this study or by conducting the study. The study investigators declare no conflicts of interest relevant to undertaking this study.

8. How will my confidentiality be protected? The survey itself does not ask you for your name or any other identifiable details. We will ask you for the last five digits of your mobile phone number so we can tell if you have completed the survey (so we don't send you any more reminders). All information that is collected about you in connection with this study (i.e. your survey responses) will remain confidential and will not be disclosed. Only the researchers named above will have access to your survey answers, which will be held securely at ACT Health on password protected computers.

9. What happens with the surveys and results? When the survey responses are analysed, responses from all participants will be grouped together (i.e. we will not be looking at any individual's responses alone). Results from the analysis will be presented to ACT Health staff and published in a peer reviewed journal in a grouped (aggregated and non-identifiable) way. If you would like the results provided to you when the study is complete, please contact the investigators.

10. What should I do if I want to discuss this study further before I complete the survey? If you have any questions about this study, please contact Callum Thirkell. You are also able to think about this information and discuss it with your family, friends or any other person you choose, before completing the survey. If you would like to know more at any stage, please do not hesitate to contact Callum Thirkell on:

Phone: 62052155 Email: callum.thirkell@act.gov.au

11. Who should I contact if I have concerns about the conduct of this study? This study has been approved by the ACT Health Human Research Ethics Committee (HREC) and the ANU Human Research Ethics Committee. If you have any concerns or complaints about the study or conduct of the study team, and do not feel comfortable discussing this with the study team, you can contact the ACT Health HREC secretariat on 6174 7968 or email ethics@act.gov.au.

Appendix Three: Text messages

Text messages for recruitment

First Message

Hi [name],

ACT Health would like to invite you to participate in a survey of recently pregnant women which asks about whooping cough and flu vaccination in pregnancy. We would like you to participate even if you did not get vaccinated during your recent pregnancy. To find out more and complete the survey, please follow this link:… The survey will take about 10 minutes and can be done on your phone anytime that suits you in the next 3 weeks (we will send you a couple of reminders). Participation is completely voluntary. If you do not want to participate or hear from us again, please reply STOP.

Thanks,

Callum, ACT Health

Second Message

Hi [name],

Last week we sent you a message inviting you to participate in our survey about whooping cough and flu vaccination in pregnancy. We would still like you to participate! It will only take about 10 minutes. To find out more and complete the survey, please follow this link:…

Participation is completely voluntary. If you do not want to participate or hear from us again, please reply STOP.

Thanks,

Callum, ACT Health

Third Message

Hi [name],

There is only one week left to participate in our survey about whooping cough and flu vaccination in pregnancy. To find out more and complete the survey, please follow this link:… Participation is still completely voluntary. This is the last time we will contact you about the survey.

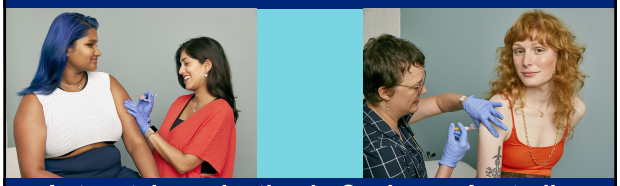
Thanks,

Callum, ACT Health

Appendix Four: Conference presentation

ACT Government | ACT Health

Australian National University



Antenatal vaccination in Canberra, Australia

Have we reached a ceiling?

Master of Applied Epidemiology Scholar (MAE)
Australian FETP training program
Australian National University
Communicable Disease Control, ACT Health

Callum Thirkell

Picture credit: Heather Hazzan, *SELF Magazine*

1

Outline

- Antenatal vaccines in the Australian context
- Methods
- Results
- Implications for public health

2

Introduction - Influenza

Vaccines in Australia
Commonwealth
State
Private

Picture credit: Heather Hazzan, *SELF Magazine*

- Influenza
- Effectiveness
- Safety

3

Introduction - Pertussis

- Pertussis
- Effectiveness
- Safety

Recommended gestation of administration

28 – 32 weeks

↓

20 – 32 weeks

4

Aims

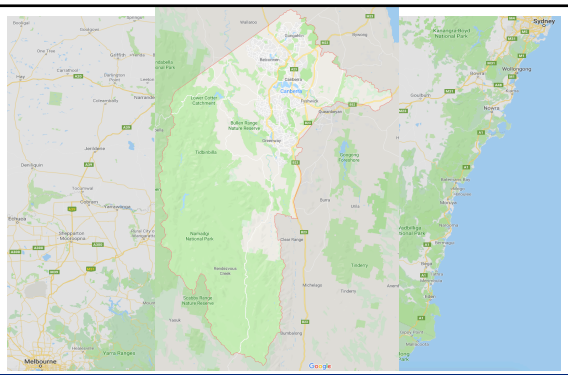
Primary Aim

Estimate antenatal vaccine uptake in the ACT

Secondary Aim

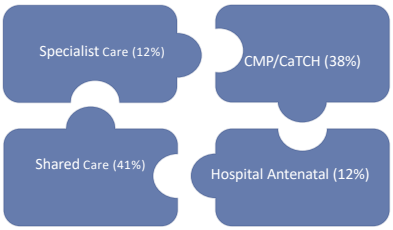
Identify key determinants of antenatal vaccine uptake in the ACT

5



6

Models of Antenatal Care



7

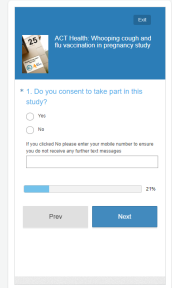
Methods

Design: Cross sectional survey
Ethics: ACT Health (2018/LRE/00147) ANU (2018/586)
Analysis: Descriptive & Multivariate logistic regression model

Inclusion criteria
- All women who gave birth at The Canberra Hospital (TCH) between 1 October 2018 – 31 March 2019

Exclusion criteria
- Women who had a stillbirth and uncontactable

Study Invitation
- Women grouped by fortnight of birth
- Invited by text message, 4 weeks after birth



8

Results

Daily Birth Register
- 22 women who had stillbirth excluded
- 18 inactive phone numbers excluded

1552 Women invited

143 (9.2%) Declined

820 (52%) No response

589 (38%) Valid Responses
- 575 (98%) provided flu vaccine status
- 585 (99%) provided pertussis vaccine status

9

Source Population

		Responder		Non-responder		
		n	%	n	%	*p*
Age Category	16-24 years	34	6	114	12	
	25-29 years	128	22	269	28	
	30-34 years	243	41	351	36	
	35-39 years	131	22	189	20	
	40+ years	53	9	40	4	
	Total	589		963		$p < 0.001$
Indigenous Status	Indigenous	14	2	33	3	
	non-Indigenous	538	96	904	94	
	not stated	11	2	26	3	
	Total	563		963		$p = 0.095$
Country of Birth	Australia	395	67	573	60	
	non-Australia	194	33	390	41	
	Total	589		963		$p = 0.003$

10

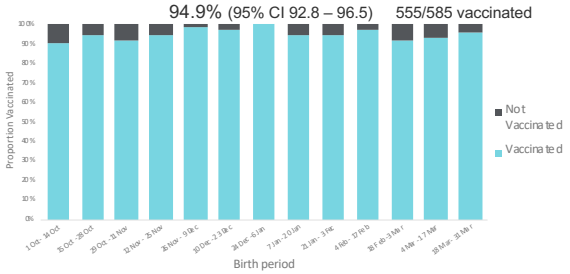
Responders

		n	%
Household Income	<$50,000	49	9
	$50,000 - $100,000	120	23
	>$100,000 - $150,000	132	25
	>$150,000	167	31
	Rather not say	63	12
Education	Primary school	6	1
	High school	81	15
	TAFE, trade, vocational	120	23
	Undergraduate	167	32
	Postgraduate	156	29
Birth gestation	≥38 weeks	467	87
	34 – 37 weeks	52	10
	38 – 33 weeks	14	3
	<28 weeks	2	0.4

11

Antenatal vaccine uptake - Pertussis

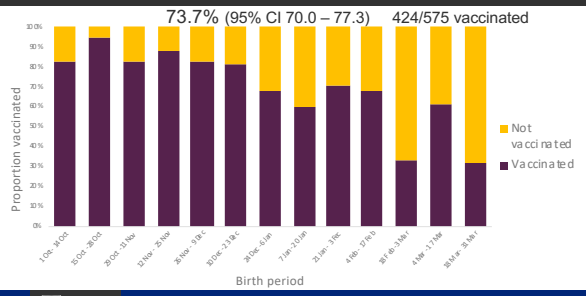
94.9% (95% CI 92.8 – 96.5) 555/585 vaccinated



12

Antenatal vaccine uptake - Influenza

73.7% (95% CI 70.0 – 77.3) 424/575 vaccinated



13

Association between: Healthcare provider recommendation and vaccine uptake

Pertussis	Vaccine Uptake
Recommended	96%
Not recommended	73%
aOR 10.5; 95% CI 3.7 – 30.0 p < 0.001	

Influenza	Vaccine Uptake
Recommended	79%
Not recommended	33%
aOR 7.9; 95% CI 4.9 – 12.7 p < 0.001	

14

Other points of note

Timing of Vaccination

88% of those receiving both vaccines received them in different trimesters from different providers.

Access & Affordability

Higher income associated with increased influenza vaccination

OR 1.6 95% CI 1.07-2.41 *p=0.023*

Higher income associated with workplace influenza vaccinations

OR 7.7 95% CI 1.33-44.96 *p*=0.023

15

Other points of note

Timing of Vaccination

Association between first child and influenza vaccine uptake

aOR 1.85 (1.15-2.98) *p* = 0.011

16

Limitations

- Self-selection bias
- Self-reporting bias

17

Implications for practice

1. Supports existing evidence regarding importance of healthcare recommendation
2. Appropriate, timely method of routine documentation at time of administration
3. Strategies to encourage dual vaccination

18

Take home points

- Very high self-reports of antenatal pertussis vaccine uptake
- Encourage recommendation and administration of flu vaccine at the same time as pertussis vaccine.

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20

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Chapter Five: A surveillance and response plan to control and manage the threat of antimicrobial resistance of *Neisseria gonorrhoeae* and *Shigella* in the ACT

Contents

Abbreviations

ACT	Australian Capital Territory
AMR	Antimicrobial resistance
AST	Antimicrobial susceptibility test
AURA	Antimicrobial Use and Resistance in Australia Surveillance System
CARAlert	National Alert System for Critical Antimicrobial Resistances
CDC	Communicable Disease Control (ACT Health)
CDNA	Communicable Disease Network Australia
CLSI	Clinical and Laboratory Standards Institute
CPE	Carbapenemase-producing Enterobacterales
CSHC	Canberra Sexual Health Centre
DALY	Disability-Adjusted Life Year
ECDC	European Centre for Disease Prevention and Control
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GLASS	Global Antimicrobial Resistance Surveillance System
HAI	Healthcare-associated infections
MDR	Multiple drug resistance
MIC	Minimum inhibitory concentration
MRO	Multi-drug resistant organisms
MSM	Men who have sex with men
NAAT	Nucleic acid amplification test
NATA	National Association of Testing Authorities
NDMS	Notifiable Disease Management System (ACT Health)
NNDSS	National Notifiable Diseases Surveillance System
NNN	National Neisseria Network
PCR	Polymerase chain reaction
PrEP	Pre-exposure prophylaxis
REDCap	Research Electronic Data Capture
SEALS	South Eastern Area Laboratory Services (WHO *N. gonorrhoeae* reference laboratory)
USA CDC	USA Centers for Disease Control and Prevention
WGS	Whole genome sequencing
WHO	World Health Organization

Prologue

Antimicrobial resistance is a significant topic of interest at the moment, therefore at the request of the Public Health Physician I was asked to investigate the possibility of an AMR surveillance system for the ACT. Initially, we planned to investigate *N. gonorrhoea, Shigella* and Carbapenemase-producing Enterobacterales (CPE). As the project progressed, it became clear that including CPE would present additional challenges as CPE are not notifiable. Therefore, another process would be required before including them in a public health surveillance system.

Lessons learnt

This was the most challenging chapter to develop, conceptually. Elements of evaluation were required as some surveillance is already carried out for AMR gonorrhoea, however, this was not an evaluation. Elements of establishing a surveillance system were also required, as everything recommended for *Shigella* was new, however, the project was not intended to be fully implemented at this stage. In the end we agreed this should be a surveillance plan articulating the rationale and feasibility of AMR surveillance, while also proposing how this plan might work.

Upon reflection, particularly following a number of MDR *Shigella* cases further stakeholder engagement could have taken place regarding response and control. Significant discussion took place, particularly around the question of asymptomatic cases and what response was required. I did not anticipate the extent of a multi-disciplinary response involving public health, sexual health, infectious disease, and microbiology clinicians. A clearer approach for this situation, with prior multi-disciplinary agreement may have provided more guidance at the time.

Public Health Implications

The relevance and importance of this work was highlighted late in my thesis writing when a cluster of MDR *Shigella* cases were identified. Appropriate public health response to asymptomatic cases in particular caused significant discussion. The need for national public health guidelines for *Shigella* and enhanced surveillance for AMR was clear when trying to make decisions about treatment of asymptomatic cases, test of cure, and the need for contact tracing. A national working group is in the process of developing National Guidelines for *Shigella*. This group were contacted to seek advice regarding asymptomatic cases specifically, which had not been discussed, nor was it in the draft guidelines developed to-date. It highlighted that the evidence is sparse regarding transmission, and time of carriage of *Shigella*, particularly for asymptomatic cases. An outcome of these cases and this surveillance plan is that the national working group will specifically consider this question.

The use of REDCap for AMR enhanced surveillance will be implemented in 2020. This is a positive step following the development of this surveillance plan. It is anticipated the development of this AMR surveillance system will progress throughout 2020.

Abstract

Antimicrobial resistance (AMR) is an emerging problem, globally and within Australia. There is currently limited public health surveillance of AMR in the ACT. This surveillance plan articulates the rationale and provides recommendations, with the aim to initiate an AMR surveillance system in the ACT; commencing with drug-resistant shigellosis and gonorrhoea.

A literature review was undertaken to establish the rationale, ACT notifiable data was analysed to understand the current burden, and a number of stakeholders were consulted including public health staff, clinicians and laboratory staff. The surveillance plan was then developed using the WHO *Communicable disease surveillance and response systems* as the framework. The primary focus was the feasibility of establishing a surveillance system, and also to consider the structure, its core functions and support functions. Key definitions are consistent with the Antimicrobial Use and Resistance in Australia (AURA) surveillance system; the national system for critical AMR.

Increased AMR may lead to increased morbidity and mortality along with an increase in the cost of healthcare. An Australian national strategy has been developed with two of the seven objectives focused on surveillance and governance at the jurisdictional level. While some surveillance is occurring within hospital, the ACT currently has no jurisdiction-wide surveillance or a documented strategy for talking AMR. Gonococcal and shigellosis notifications and AMR continue to increase in specific populations across Australia and in the ACT. As such there is a need to initiate AMR surveillance as well as an appropriate public health response.

The objectives of this surveillance plan are; timely detection of drug resistant cases; prompt identification of drug-resistant strains; and to monitor the epidemiology drug-resistant *N. gonorrhoeae* and *Shigella.* All of these are to facilitate prompt investigation an implementation of interventions, urgent case management, contact tracing, and to evaluate public health strategies.

A surveillance structure is recommended, considering the legislation which allows the documentation of these data, and integrating within the existing respective surveillance systems. Proposed core functions are based on national definitions or guidelines when available (eg. AURA and Series of National Guidelines [SoNG]), best available evidence, or expert opinion where required. Twelve recommendations were made; the first being the development and implementation of a surveillance system built on the REDCap platform (a secure web application for managing data). Other recommendations included: case detection and registration, data analysis, interpretation and reporting, a response and control process, training, and evaluation.

Introduction

Antimicrobial Resistance: a growing concern at global, national and local levels

Antibiotic resistance: a global perspective

Antibiotics are one of modern medicine's greatest successes. A major threat to their effectiveness is emerging however in the form of resistance to antibiotics used to treat common infection. The World Health Organization (WHO) has deemed antimicrobial resistance (AMR) one of the top ten global health threats in 2019. Antibiotic resistance could potentially lead to the loss of modern medicine as we know it, with a return to the pre-antibiotic era if this threat is not addressed (1).

This chapter makes the case for an AMR surveillance plan, and provides evidence of the need to provide a public health response. The CDC define public health surveillance as the ongoing collection, analysis, interpretation, and dissemination of data to provide "actionable public health knowledge" (2). Antimicrobial resistance includes bacteria, viruses, fungi and parasites; this surveillance plan primarily addresses antibiotic resistance, that is, drugs used for treating bacterial infections (3).

Pathogens can develop antibiotic resistance as a result of genetic mutations, gene transfer or natural selection. Since the discovery of antibiotics, the incidence of antibiotic resistance has slowly increased. A significant driver of this is the misuse of antibiotics in both humans and animals (Figure 1) (4), which leads to sensitive bacteria being killed, while resistant strains

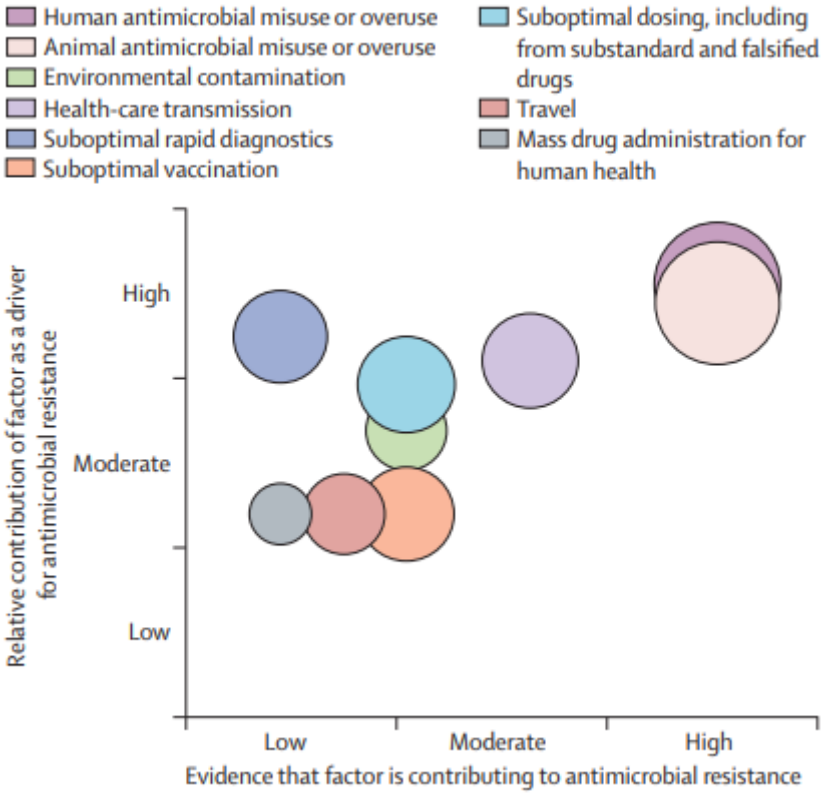


FIGURE 1: ROLE OF MODIFIABLE DRIVERS FOR ANTIMICROBIAL RESISTANCE

survive and multiply. A concern is that a number of organisms are now resistant to commonly prescribed antibiotics, in addition to developing resistance to last line antibiotics (5).

AMR could change the way healthcare is provided. As a result of reduced efficacy of antimicrobials, surgery and chemotherapy may involve an increased risk of infection, and common infections such as gonorrhoea and shigellosis may require treatment in hospital instead of in primary care. It is possible that AMR could cause certain infections to become untreatable with existing antimicrobials. Consequently, AMR is expected to lead to increased morbidity and mortality along with an increase in the cost of healthcare (4).

Antibiotic resistance was attributed to an estimated 23,000 deaths in the USA in 2013 (6), an estimated 33,000 deaths amongst European Centre for Disease Prevention and Control (ECDC) countries in 2018 (7), and 700,000 deaths globally in 2018 (1). This is predicted to increase to 10 million deaths globally and cost $US100 trillion by 2050 if no action is taken to address this emerging threat (Figure 2) (8). The number of healthy years of life lost, (described as disability adjusted life years [DALYS]) as a result of antibiotic resistance has been estimated at 170 per 100,000 population in the European Union (EU), close to the combined burden of influenza, tuberculosis and HIV (183 per 100,000 pop) (7).

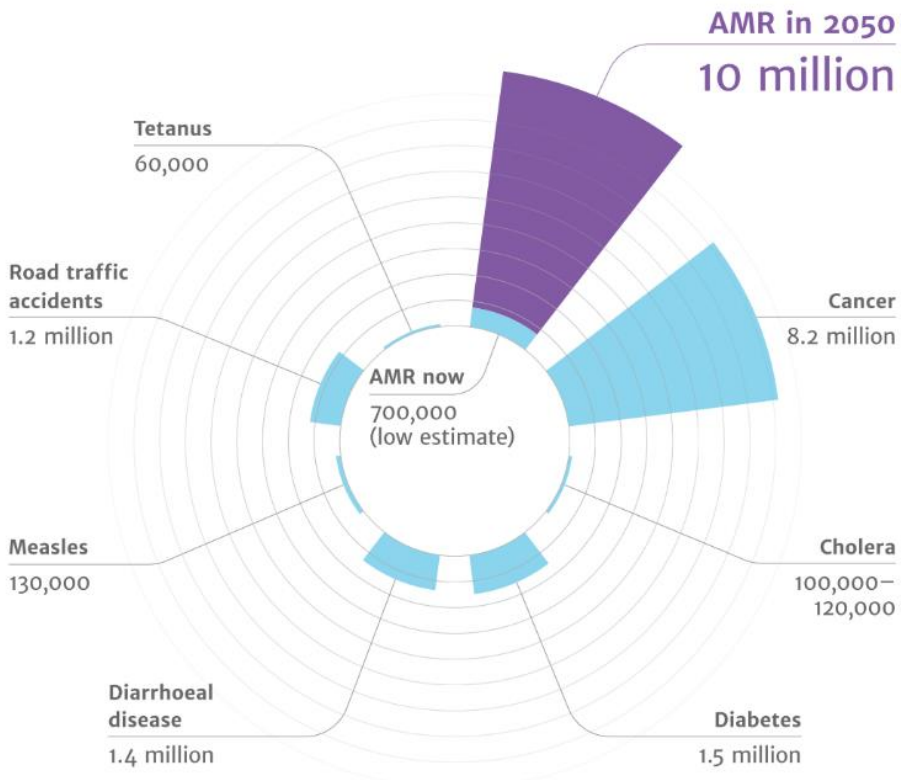


FIGURE 2: PROJECTED GLOBAL DEATHS ATTRIBUTABLE TO AMR

The use of antibiotics within the community and healthcare facilities rose 40% in humans between 2000 and 2010 (Figure 2) (9). Together with decades of uncontrolled antibiotic use, such as the use of non-prescription penicillin in the USA throughout the 1950's, this has contributed to the persistence of resistance mechanisms (4). Within healthcare facilities, the spread of resistant pathogens between patients and the transmission of resistance mechanisms between organisms also contributes to the propagation of AMR (4). Due to the increasing availability and frequency of human and animal migration, along with imported and exported food products, pathogens are readily able to cross international boundaries, further aiding the spread of AMR (10). Antibiotics are also used in animals to prevent disease, reduce stock losses and increase growth. This has contributed to increasing levels of AMR through a number of pathways. To adequately address interactions of AMR at the animal, human and ecosystem interface, an interdisciplinary One Health approach is required (8).

Antibiotic resistance: Global response

In May 2015 the World Health Assembly adopted the Global Action Plan on Antimicrobial Resistance (11). Although global AMR surveillance has existed for many years for *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae,* this has been expanded with the development of the Global Antimicrobial Resistance Surveillance System (GLASS) (12). The aim of GLASS is to support global AMR surveillance and research, a key objective of the Action Plan (13). This is done through a standardised approach to data collection and analysis to strengthen the evidence base on AMR. Disparities in the capacity to establish and maintain AMR surveillance amongst low and middle-income countries still hinder the ability to monitor global AMR trends.

In recent years, high income countries have also developed detailed strategies to combat AMR, consistent with the Global Action Plan. In 2013, the UK launched an AMR strategy, which was updated in 2019 (14). They have taken a genuine One Health approach and routinely report on human and livestock antibiotic consumption as well as AMR in humans, food and livestock (14). They have seen significant reductions in the use of antibiotics for farmed animals (40%), a reduction in the amount human and animal antibiotics consumed (7.3%), and slight reductions in AMR for some bacteria. The UK has invested nearly £500 million globally to support laboratory, surveillance and response capacity (14). Similarly, in 2018 the USA Centers for Disease Control (USA CDC) invested US $350 million domestically and US$11 million globally towards combating AMR (15). Three of the key aspects of their strategy focus on: detection of AMR cases; building epidemiological capacity for public health response; and prevention through surveillance (16).

Surveillance and response to multi-drug resistant organisms in Australia

Australia's response to addressing AMR is guided by Australia's First National Antimicrobial Resistance Strategy 2015-2019 (the 'First Strategy') (17). The strategy supports a One Health approach by providing seven common objectives which span human health, animal health and agricultural sectors. Together these objectives support the overarching goal of minimising the development and spread of AMR and ensuring the continued availability of effective antimicrobials.

Objective three of the Strategy aims to monitor AMR through nationally coordinated One Health surveillance. A key action of this objective was the development of the Antimicrobial Use and Resistance in Australia Surveillance System (AURA) which is the mainstay of national AMR surveillance in Australia (18). This system collates AMR data from a number of different sources including: the National Notifiable Disease Surveillance System (NNDSS) (19); the National Neisseria Network (NNN) (20); Australian passive AMR surveillance (APAS) and a National Alert System for Critical Antimicrobial Resistances (CARAlert) (21). Multiple and sometimes disparate sources of information means the flow of information into AURA is often delayed and a barrier to meaningful and timely use of the data for public health action. This further highlights the need for data at the patient level to be collected by public health units and actionable at the time of case follow-up.

AMR surveillance in Australia is complicated by three different susceptibility testing systems used across public and private microbiology laboratories (22), this is a potential barrier to conducting cohesive AMR surveillance. These systems include: the USA based Clinical and Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial susceptibility testing (EUCAST), and the Australian developed Calibrated Dichotomous system (CDS) (22). Antimicrobial susceptibility test (AST) results generated using different testing methods are difficult to compare. Furthermore, laboratories may use CLSI or EUCAST guidelines to interpret minimum inhibitory concentration (MIC) levels, whereby isolates are deemed to be sensitive, of decreased sensitivity, resistant or highly resistant to the antibiotic being tested. MIC levels are defined as the lowest concentration of an antibacterial agent required to inhibit visible growth of an organism (23).

The CARAlert system was established in March 2016 to identify organisms with critical resistance to last-line antimicrobial agents (24). The focus of CARAlert is to identify drug resistant organisms that are rare or have not been detected in Australia, with the aim of preventing multi-resistant organisms (MROs) from becoming endemic (25). If an isolate is identified as meeting the criteria set by CARAlert the testing laboratory sends the isolate to the relevant reference laboratory who perform confirmatory testing.

The system is intended to monitor trends of AMR in Australia and to help identify clusters or outbreaks. CARAlert provide a weekly email with each confirmed CARAlert to identified jurisdictional authorities, including public health. However, no identifiable information is provided. Additionally, these alerts can sometimes arrive a number of weeks following the initial notification and are therefore not always timely enough to facilitate a public health response. Community and aged care facilities are also likely to be under-represented in CARAlert notifications because private laboratories, which undertake a significant proportion of testing of community isolates, are currently under-represented in CARAlert, which relies on laboratories voluntarily opting into the system.

Antimicrobial susceptibility testing (AST) data are also collected routinely for invasive pneumococcal disease (IPD) and *M. Tuberculosis* (TB) at a national level. AST data are collected in addition to the National Notifiable Disease Surveillance System (NNDSS) core dataset. As part of the NNDSS, AST data on first-line antibiotics for IPD are collected for every state and territory. A full panel of susceptibility testing is only carried out by Queensland and Northern Territory (26).

Surveillance of multi-drug resistant organisms in the ACT

ACT is served by three laboratories. ACT Pathology is the public health reference laboratory and provides the majority of notifications to the CDC surveillance team. ACT Pathology services all public hospitals in Canberra, some private hospitals and some general practices. Laverty Pathology is a private laboratory in NSW and ACT with a reference laboratory located in Sydney. Capital Pathology is a Canberra based private laboratory who refer testing out-of-state when required. These private laboratories service a large proportion of primary care and aged care facilities.

In the ACT, surveillance of MROs has traditionally been conducted in hospitals as part of routine surveillance of healthcare-associated infections (HAIs). That is, AMR has been managed principally as a patient safety and quality of healthcare issue in siloed Territory hospitals. The two public hospitals are served by the same laboratory. As a result of recent outbreaks in other jurisdictions and a recognition of the increasing prevalence and risk of AMR in the community, nationally there is an impetus to treat AMR as a public health issue and move towards a more cohesive, multi-disciplinary approach.

While some surveillance is occurring within hospitals, the ACT currently has no jurisdiction-wide surveillance or a documented strategy in place for tackling AMR. There are currently no guidelines for surveillance and response to MRO's outside of a hospital setting. A number of national reports are produced reporting on the epidemiology and trends of AMR and MROs

which include ACT data. These are not produced in a timely manner with public health response in mind; rather many are published on an annualised basis or even less frequently.

As noted above, for two notifiable diseases; Invasive Pneumococcal Disease (IPD) and TB, AMR data is routinely captured nationally as part of the NNDSS. In the ACT, IPD and TB AST data are collected manually in Microsoft Excel spreadsheets and sent to the Commonwealth on a quarterly basis (27).

Epidemiology of MROs in Australia and in the ACT

In 2018, the most commonly reported CARAlerts in Australia were Carbapenemase-producing Enterobacterales (CPE [44%]) and azithromycin-nonsusceptible (LLR) *N. gonorrhoeae* (37%), which together accounted for >80% of all 2,979 alerts (28). Nearly 79% of these alerts were detected in hospitalised patients or hospital outpatients, which may reflect testing practices as well as participating laboratories. The majority of CARAlerts from people aged 15–50-years were community acquired LLR *N. gonorrhoeae*. The majority over 50 years were CPE, detected in hospital, and a very small number of alerts were for CPE in young children. Provision of data is voluntary and the level of involvement changes yearly which may affect comparisons across years. Data from aged care and community are still limited compared to data collected in hospital.

ACT had 31 CARAlerts in 2017 and 27 in 2018; the vast majority were CPE (87% and 59% respectively) and seven LLR *N. gonorrhoeae* were reported in 2018. ACT Pathology is currently the only laboratory contributing to AURA in the ACT.

Enterobacterales are a complex family of bacteria that can produce different enzymes capable of destroying carbapenem based antibiotics that are used to treat infections; bacteria carrying this carbapenemase enzyme are known as Carbapenemase-producing Enterobacterales (CPE). *Escherichia coli* and *Klebsiella pneumoniae* are the most common and important enterobacterales. They are a cause of hospital and community associated infections. Resistance rates are higher in the aged care setting for *E. coli* compared to the hospital setting, and vice versa for *K. pneumoniae*.

Enterococcus species are a family of bacteria that are naturally resistant to a number of antimicrobials and opportunistically cause illness in compromised patients following surgery or through invasive devices (28). Although national rates of vancomycin resistant *enterococci* (VRE) infections have levelled off recently, our rates remain some of the highest in the world.

A number of community acquired organisms are showing increasing antimicrobial resistance nationally: *Shigella* species; ceftriaxone-nonsusceptible Salmonella species; LLR azithromycin and ceftriaxone-nonsusceptible *N. gonorrhoeae*. None of these organisms are unique to

Australia and as noted earlier, are causing significant international concern. Other organisms generally imported with limited local transmission to date are showing increasing resistance including *Salmonella Typhi*, *S*. Paratyphi, and *Mycobacterium tuberculosis* (28).

Aged care is an area of focus for AMR for several reasons including: a vulnerable population; high rates of inappropriate prescribing; and the high frequency of residents being transferred in and out of hospital: a known risk for contracting or colonising multi-drug resistant (MDR) organisms. Although not notifiable, rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and *E. coli* in aged care continue to be high (28).

Candida auris is an emerging MDR yeast that has recently been reported in Australia and has caused hospital associated infections overseas. The high mortality rate and difficulty in identification has led to *C. auris* being included as a CARAlert in 2019.

In summary, a national strategy for the response to multi-drug resistant organisms in Australia has been published in the Strategy. As part of this, AURA provides national surveillance of critical antimicrobial resistance. Jurisdictions provide differing levels of surveillance and response to AMR. The need for public health surveillance and a co-ordinated response to MRO's has been presented.

Scope and aims

This plan articulates the rationale and provides recommendations for an AMR surveillance system in the Australian Capital Territory (ACT). Guidance is also provided regarding the public health response to drug resistant *Shigella* and *N. gonorrhoeae.*

The aim of this chapter is to provide recommendations to initiate AMR surveillance in the ACT, so as to improve public health outcomes through more efficient and effective AMR surveillance and response. The scope of the plan is restricted to antibiotic resistant *Shigella* and *N. gonorrhoeae* within the ACT.

The primary purposes of an AMR surveillance system are to collect data on AMR prevalence, analyse and detect emergence of AMR, and ultimately to facilitate a public health response (13,29). This plan provides the framework of an AMR surveillance system to meet these purposes. Additional outcomes of a surveillance system include: guiding patient treatment; identifying populations at risk; informing policy development; hypothesis formation and assessing the impact of interventions.

In 2015, Australia's First National Antimicrobial Resistance Strategy ('the Strategy') recommended seven broad objectives to combat antimicrobial resistance (17). This surveillance plan addresses objectives three (focusing on 3.5, Improving human health surveillance) and objective seven.

> **Objective Three**: Develop nationally coordinated One Health surveillance of antimicrobial resistance and antimicrobial usage.
>
> **Objective Seven**: Establish and support clear governance arrangements at the local, jurisdictional, national and international levels to ensure leadership, engagement and accountability for actions to combat antimicrobial resistance (17).

A comprehensive response to AMR requires a 'One Health' approach as noted in the Strategy. This includes "coordination, collaboration and multi-disciplinary participation across human health, animal health and agricultural sectors" (30). Fully implementing a One Health surveillance system, which would incorporate animal data, is beyond the scope of this project and not specifically addressed.

Methods

A literature search using Scopus, PubMed and google scholar was performed utilising multiple search terms including: AMR, MDR, *Shigella*, shigellosis, gonorrhoea, gonococcal and surveillance, reviewing international and Australian evidence.

A search of Australian grey literature on AMR were also performed. Major reports were reviewed including annual AURA reports and Neisseria Network reports. Several unpublished reports were used including internal documents from Communicable Disease Network Australia (CDNA) and jurisdictional reports.

Notifiable Disease Management System (NDMS) data were used to report on the current numbers of gonococcal and shigellosis infections in the ACT, along with diagnostic methods.

Consultation with experts and colleagues outside of ACT Health was conducted in July 2019. Informal open-ended interviews were conducted with the three main laboratories serving ACT to confirm the flow of isolates, as well as what tests are conducted where for *Shigella* and *N. gonorrhoea*. Specialist sexual health clinical advice was provided by Professor David Lewis (Director, Western Sydney Sexual Health Centre) regarding the practicalities and acceptability of testing, particularly for MSM cases. Informal open-ended interviews also took place with Keira Glasgow (NSW Health Enterics Manager) and Professor Vitali Sintchenko (Director, Centre for Infectious Diseases and Microbiology) regarding *Shigella* testing in NSW. ACT Health public health nurses and epidemiologists were regularly consulted to determine current processes, opportunities and barriers to data collection, entry and analysis.

The public health importance and the existing surveillance for the two conditions was described. The surveillance plan was then developed using the *Communicable disease surveillance and response systems - a guide to planning* as the framework (31). The primary focus was the feasibility of establishing a surveillance system, including consideration of its structure and core functions, with a secondary focus on support functions (Figure 3) (31). Surveillance quality is reflective of system outputs following implementation and therefore not a primary focus of this plan. Assessment of the quality of this surveillance system will be addressed when key outcome measures are defined, and during evaluation of the system.

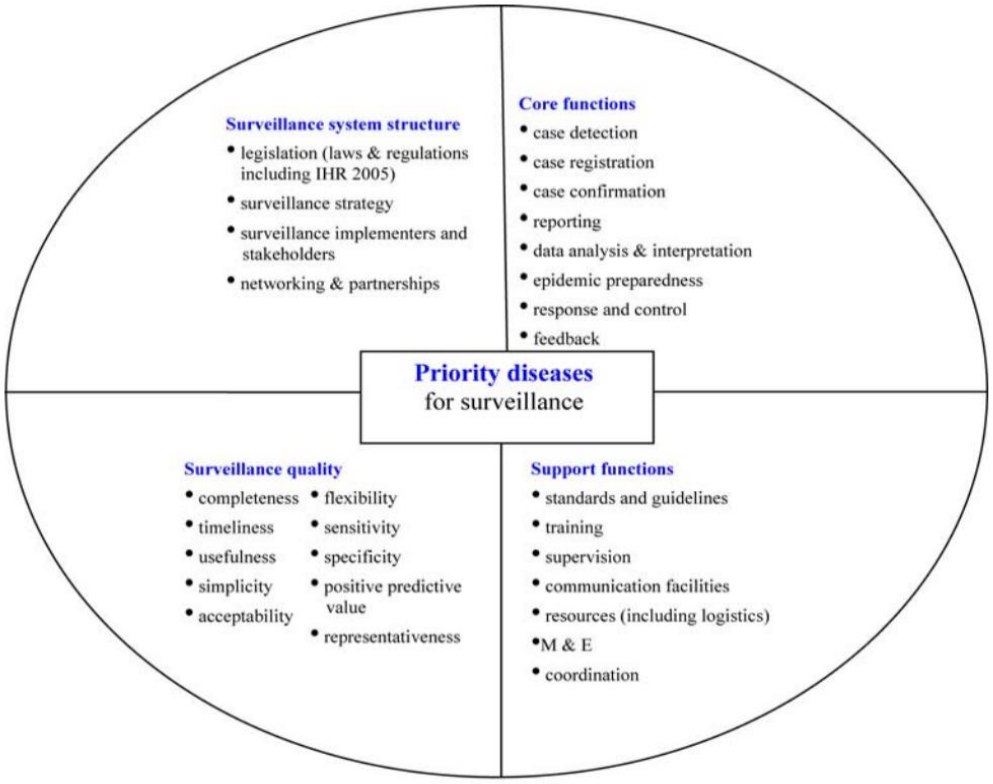


FIGURE 3: COMPONENTS OF SURVEILLANCE AND RESPONSE SYSTEMS

Results

Gonorrhoea

Public Health Importance

An estimated 78 million cases of gonorrhoea are reported globally every year, 35 million of these in the Western Pacific region (32). In 2013, the USA CDC declared multi-drug resistant gonorrhoea one of three diseases to be considered an "immediate public health threat requiring urgent and aggressive action" (6).

Nationally, annual notification rates of gonorrhoea have risen threefold since 2009 and at a similar rate in the ACT (33). The greatest rise nationally, both proportionally and in number of notifications has been amongst adult males in metropolitan areas, although the number of notifications for adult females has also risen. Notification rates differ amongst populations and jurisdictions; however, research shows that Indigenous people living in remote areas and men who have sex with men (MSM) living in metropolitan areas have the highest notification rates. In 2018, MSM accounted for the majority of notifications (64%) in the ACT (34).

Antimicrobial treatment of gonorrhoea has changed significantly as a result of AMR over the past 70 years. Some antibiotics have long been superseded (tetracyclines among others) and some are used infrequently depending on location and resistance patterns (penicillins, fluoroquinolones). Extended-spectrum cephalosporins (ESCP) such as ceftriaxone, are last-line treatment options for drug resistant *N. gonorrhoeae*. In an attempt to delay the further spread of resistance, many countries, including Australia (in 2011) have introduced dual antimicrobial therapy consisting of an extended-spectrum cephalosporin plus azithromycin as first-line treatment (35–37).

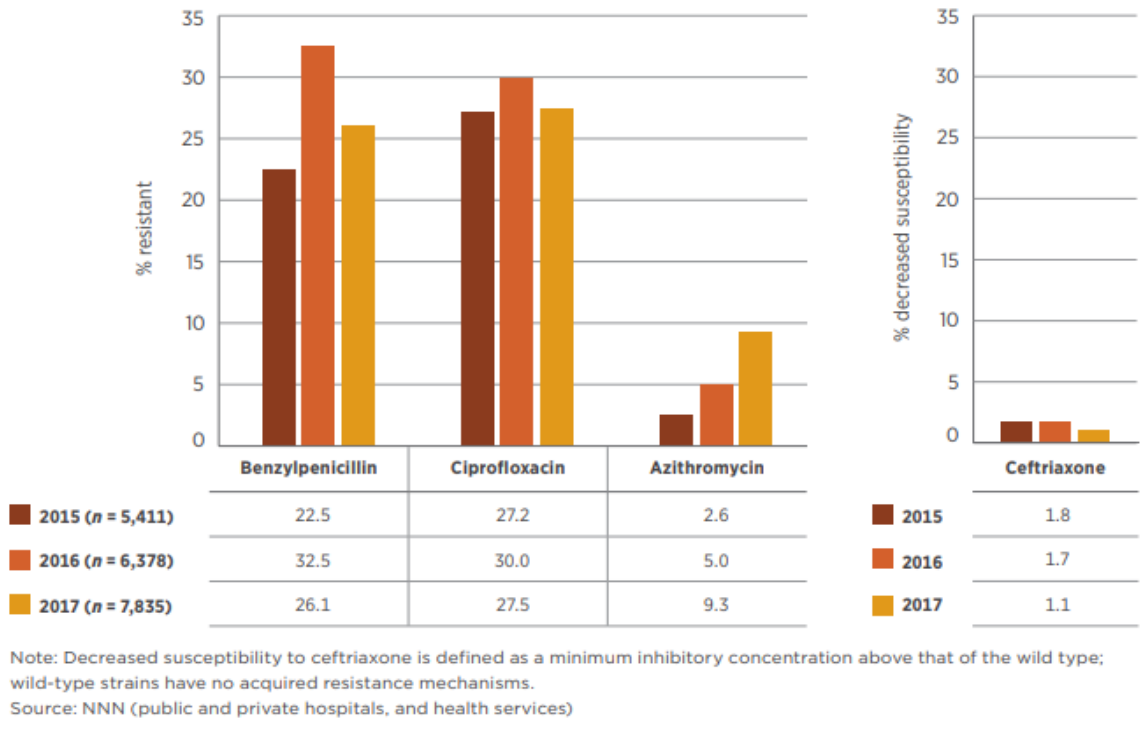
It was anticipated that azithromycin would help delay resistance of *N. gonorrhoeae* to ceftriaxone. This has been successful in part, although at the expense of increased low-level resistance to azithromycin (38). This increase is seen globally including the UK, who have seen azithromycin MIC levels drift towards resistance for those isolates still sensitive, as well as an increase in low-level resistance (39). Three cases of extremely drug resistant *N. gonorrhoea* (XDR-NG) were reported in early 2018: one in the UK and two in Australia. The UK and one of the Australian cases acquired the infection from South-East Asia where very little AMR surveillance data is publicly available. The isolates displayed high level resistance to azithromycin (MIC ≥256 mg/L) and resistance to ceftriaxone (40).

The problem of increasing disease incidence is compounded by the increase in AMR. Treatment failures as a result of AMR impact at both an individual and population health level. Reduced ability to treat compromises the control of gonococcal disease while increasing the associated complications of untreated gonorrhoea (41). These complications are most severe in females and include: pelvic inflammatory disease, infertility, ectopic pregnancies; and vertical transmission to newborns (42). Up to 80% of women and 10-15% of men with urogenital gonorrhoea have no genital symptoms, although asymptomatic infections can still lead to the already mentioned complications. Infections at other sites, including throat and rectum, are also often asymptomatic (43). This highlights the need to undertake regular screening for high risk patients (including MSM, sex workers, Aboriginal and Torres Strait Islander populations) as well as taking specimens from the appropriate sites (44).

Although pharyngeal gonorrhoea cases are usually asymptomatic and clear without treatment, there is increased interest in the role of pharyngeal gonococcal infections in transmission and antibiotic resistance (39,45). The reason for this is suggested to be a combination of a lack of testing due to asymptomatic infections resulting in persistent infection, difficulty in site penetration with the current antibiotic regimes, and potential horizontal transfer of genes conferring resistance (46–48).

The rationale for a public health response to cases with reduced susceptibility is based on evidence that suggests high-level azithromycin resistance can emerge from susceptible strains or strains with low-level resistance in a short amount of time (49). Additionally, it is suspected that even low-level azithromycin resistance may cause treatment failures and potential transmission should an infecting strain harbour ceftriaxone non-susceptibility. The point at which low-level azithromycin resistance my cause treatment failure is unknown, therefore, vigilant contact tracing and test-of-cure are important public health actions.

N. gonorrhoeae (NG) resistance levels remain high for penicillin and ciprofloxacin, and neither are used for treatment in the majority of Australia (Figure 4) (25,28). A small number of remote areas in Western Australia recommend penicillin routinely due to low AMR (50). Resistance trends differ by sex, sexual exposure, site of infection, Indigenous status and jurisdiction (51). In 2016, 6,378 isolates were tested by the NNN; 5,078 (80%) were male of which 3,050 (60%) were urogenital and 1,240 (24%) were rectal. Most culture positive isolates from females were from urogenital sites (85%) followed by pharyngeal (9%). One isolate displaying decreased



Note: Decreased susceptibility to ceftriaxone is defined as a minimum inhibitory concentration above that of the wild type; wild-type strains have no acquired resistance mechanisms.
Source: NNN (public and private hospitals, and health services)

FIGURE 4: NEISSERIA GONORRHOEAE RESISTANCE IN AUSTRALIA, 2015-2017 (28)

susceptibility to ceftriaxone was reported in the ACT in 2016. Eight (7.1%) isolates resistant to Azithromycin (MIC ≥1.0 mg/L) were reported in the ACT in 2016, 3 (2.5%) in 2017 and 19 (11.5%) in 2018.

Antimicrobial susceptibility testing (AST) currently requires a swab to be taken from the affected site and cultured. Nucleic acid amplification testing (NAATs) does not allow for AST. The widespread move to NAATs in 2012 has therefore reduced the proportion of isolates receiving AST nationally (52). ACT has maintained the highest national number of *N. gonorrhoeae* isolates tested as a proportion of all notifications with 56% (112/201) cultured in 2016 (51). A key contributor to this high proportion of isolates receiving AST is the major sexual health clinic in the ACT who diagnose 66% of all gonococcal notifications and request culture for 62% of their *N. gonorrhoeae* isolates (53).

In summary, gonococcal notifications continue to increase across Australia and in ACT; as such antimicrobial resistance is of significant public health concern. This could result in more complex, expensive treatment and treatment failures amongst an increased burden of disease.

Surveillance in the ACT

All laboratory confirmed gonococcal infections are notified to CDC as required by the *Public Health Act 1997* (the Act) according to the national surveillance gonococcal case definition (54,55). Notifications are manually entered into the ACT Notifiable Disease Management System (NDMS). The majority of cases are diagnosed by polymerase chain reaction (PCR); approximately half undergo culture as well as AST.

All three laboratories in the ACT notify CDC upon identification of gonococcal species and then send isolates to the South Eastern Area Laboratory Services in Sydney (SEALS) (Figure 5). SEALS are the official reference laboratory for all laboratories in the ACT, as well as the *Neisseria* reference laboratory for Australia. The primary laboratories have a range of capabilities to conduct AST (Figure 5). For all antibiotic resistant cases in 2017-2018, the time from notification to receipt of AST results ranged from 4-11 days with a median of 5 days. Some AST results have been quite delayed from SEALS as a result of inconsistencies in how results arrive; these include via fax, email or post.

Public health nurses follow-up the treating clinician for every gonococcal case to collect enhanced data which is reported to the Commonwealth quarterly. Antibiotic resistance data has also been collected since mid-2017 within an enhanced data spreadsheet. This includes a qualitative interpretation (such as resistant or sensitive) and the numerical minimum inhibitory concentration (MIC) levels. MIC levels are always provided for resistant cases, but not consistently for antibiotic sensitive cases.

Enhanced data is captured within an Excel spreadsheet, which precludes version control and validation of data captured. Enhanced data is also documented in a free-text field within the NDMS system. The follow-up process is a manual, paper-based system. No automated reminder system is possible, and the case remains open until 'signed off' within the NDMS system.

Currently, AMR data collection is complex with multiple steps of duplication, leaving the process open to unidentified errors and reducing data quality requiring manual checking. The AST results are entered in a complicated manner in one field with no data validation. A number of variables from the enhanced data are duplicated in the NDMS free text field which seems to be a historical practice and reduces simplicity. Because of the many manual processes there is a reduced capacity to scale up in the event of a continued increase in notifications.

Public health nurse follow-up differs by diagnosing clinician. The majority (66%) of gonococcal infections are notified by sexual health specialists who provide enhanced data via an email template. General practitioners are often less familiar with the testing and treatment guidelines for gonorrhoea cases; therefore, direct contact is made with these clinicians to ensure completeness of testing and treatment. Case management relies on paper reminders and human recall which is again prone to human error and memory.

The resource requirements of an improved AMR surveillance system may actually decrease with a more refined system if information flows are more automated and reliable, data entry points are reduced and validated, and case management flows are automated.

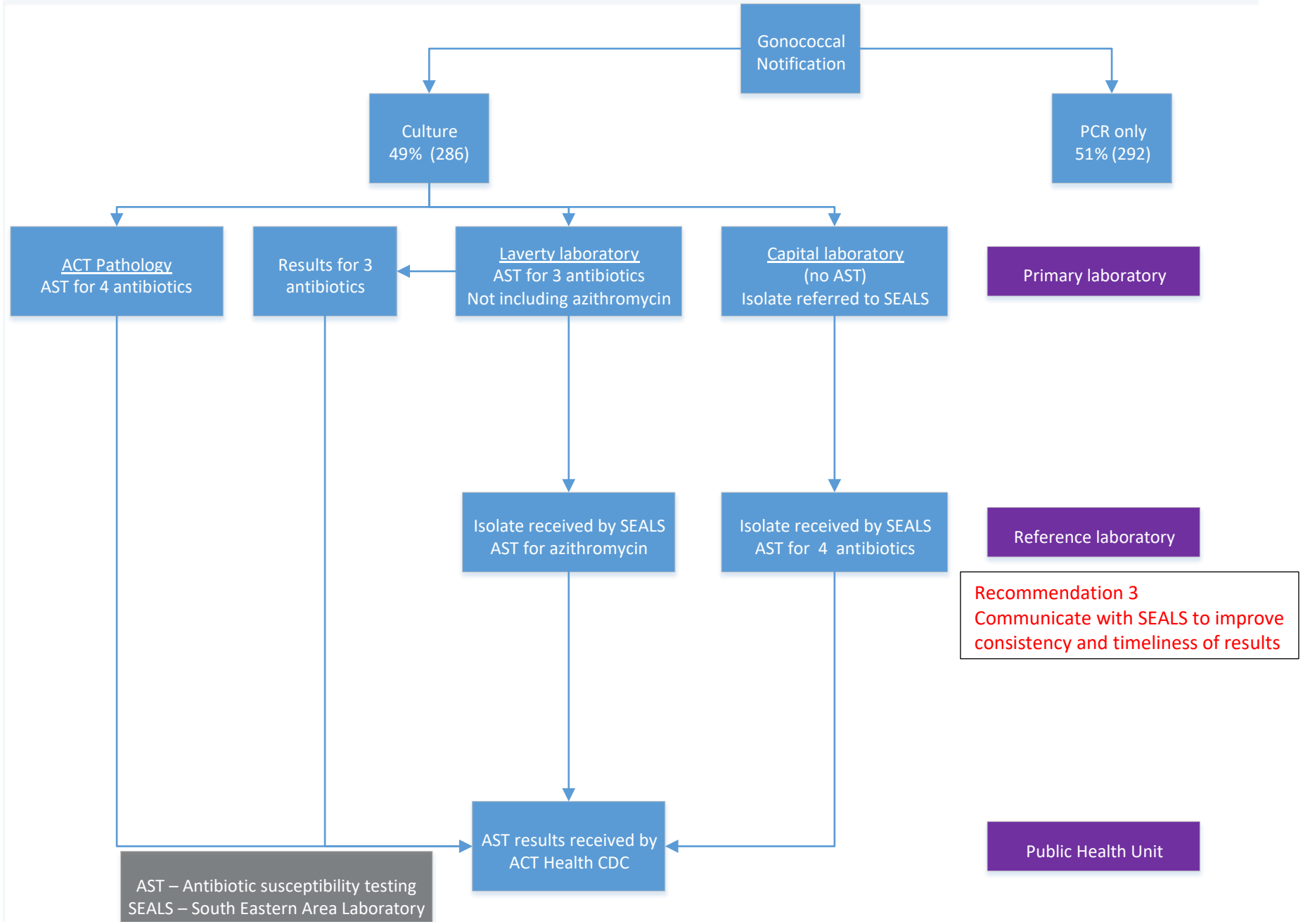


FIGURE 5: LABORATORY TESTING PROCESS FOR ACT GONOCOCCAL NOTIFICATIONS: 1 JANUARY 2017 - 31 DECEMBER 2018

Shigella

Public Health Importance

Shigella is a gram negative, facultatively anaerobic bacteria spread person-to-person via the faecal-oral route. *Shigella* is a leading cause of diarrhoeal deaths for children <5 years overseas, in the setting of poor hygiene and sanitation. (56). In high-income countries, shigellosis occurs predominantly in overseas travellers or MSM (57). Antibiotic resistance amongst these groups is causing global concern. Shigellosis infection is increasingly being treated as a sexually transmitted disease in these countries, including Australia.

The *Shigella* genus can be divided into four species; *S*. *dysenteriae, S*. *flexneri, S. boydii* and *S. sonnei,* which can then be further sub-typed and bio-typed. The predominant species in Australia is *S. sonnei,* although there was a large *S. flexneri* outbreak in the Northern Territory in 2017 (57).

Shigellosis can manifest as mild or severe disease dependent on species. *S. flexneri* and *S. sonnei* generally present with mild to moderate illness. *S. dysenteriae* causes the most severe complications, including haemolytic uraemic syndrome(HUS) primarily due to the production of Shiga toxin type 1; this is very rare in Australia and exclusively travel related (58,59).

Shigella is highly transmissible and the infective dose is known to be low (10 -100 organisms). Prevention methods generally consist of promoting basic hygiene practices by washing hands with soap and water, avoiding food preparation, and avoiding sexual contact while symptomatic. There is currently no effective vaccine available for the prevention of shigellosis (60).

In 2017, there were 1,770 shigellosis notifications in Australia (7.2 per 100,000 population), a three-fold increase from 2013 when there were 537 notifications (2.3 per 100,000 population) (33). This rise represents a combination of an increase in NAAT testing (61), a change in the national case definition (62) and an actual increase in numbers of infections. An outbreak in central Australia ongoing since 2017 has also increased overall notifications (60). The number of culture confirmed *Shigella* notifications in the ACT, annually, ranged between 5 and 11 from 2009 to 2018 (33).

Antibiotic treatment for shigellosis infection is recommended for some patients to reduce duration of illness and asymptomatic bacterial shedding. These cases include those with severe symptoms who are immunocompromised and in some instances, those who present a high risk of transmission, such as children in care or food handlers (63,64). Resistance to antibiotics is well documented in Australia and globally (65–67). The World Health Organization (WHO) and the USA CDC have both stated that drug-resistant *Shigella* is a serious global concern, particularly in the context of rising numbers of notifications (6,68). Drug resistance is emerging as an issue in Australia, as well. An outbreak of multi-drug resistant *Shigella* amongst MSM in Sydney in 2018

resulted in 2-5 related cases in the ACT (58). This resulted in a public health alert being issued to clinicians in the region and some cases requiring IV antibiotic treatment in hospital (69). ACT Health was alerted to these cases by NSW Health. A review of paper records in the ACT was required to identify potential cases.

A recent study (1 January 2016 – 31 March 2018) of Victorian *Shigella* isolates (545 of 1269 shigellosis notifications) utilising whole genome sequencing highlighted very high rates (93% in *S. sonnei)* of azithromycin resistance in MSM-associated *Shigella.* In comparison, high rates of ciprofloxacin resistance were found to be associated with travel to South East-Central Asian countries (70). A NSW study of all *Shigella* notifications referred to the reference laboratory between 1 May 2013 and 30 April 2014 showed 45% involved international travel. Of those with local acquisition, 74% were male, of whom 95% reported MSM (71).

The incidence of *Shigella* is rising in specific populations in Australia; alongside increasing antimicrobial resistance, there is significant public health concern. This could result in increasing numbers of outbreaks, more severe illness and more costly treatment.

Surveillance in the ACT

All *Shigella* notifications are received automatically from the laboratory and manually entered into NDMS. PCR-positive only cases, previously recorded as not meeting public health criteria became nationally notifiable in June 2018 and are now recorded as probable cases. Culture positive cases are confirmed cases. AST is routinely received for culture positive cases but not otherwise documented for surveillance or public health purposes.

ACT Pathology culture all requests for *Shigella* testing and do not perform NAAT tests for *Shigella.* All isolates are referred to the Microbiological Diagnostic Unit Public Health laboratory (MDU), the reference laboratory, for further testing (Figure 7). Whole genome sequencing (WGS) is performed by MDU on all isolates but not analysed or reported to CDC. The use of different laboratories for WGS analysis prevents consistent analysis of all ACT cases together.

Capital and Laverty Pathology both conduct *Shigella* testing, predominantly in Sydney. Following a positive PCR-result, reflex culture tests are not always done (Figure 6). The majority of PCR-positive results between 2014 – 2018 have had a culture test, but in 2018/19, confirmation of a negative culture result has only been received for 30/55 cases ([Table 1] [Figure 6]). It may be that culture tests have been completed on all PCR-positive results; however, this is unclear.

TABLE 1: *SHIGELLA* NOTIFICATIONS IN THE ACT BY LABORATORY AND METHOD OF TESTING: 2014 - JUNE 2019

ACT Pathology *Shigella* Notifications ¥							
	2014	**2015**	**2016**	**2017**	**2018**	**2019**	**Total**
Culture positive	3	4	1	4	5	2	19
Capital Pathology *Shigella* Notifications							
PCR-positive-Culture negative ≠	4 (80%)	8 (89%)	7 (78%)	11 (92%)	15 (83%)	2 (25%)	47 (78%)
PCR-positive no culture result *	1	1	2	1	3	6	13
Total PCR positive	**5**	**9**	**9**	**12**	**18**	**8**	**60**
Culture positive	2	0	1	0	0	0	3
Laverty Pathology *Shigella* Notifications							
PCR-positive-Culture negative ≠	10 (71%)	15 (100%)	17 (85%)	17 (100%)	8 (38%)	5 (63%)	72 (76%)
PCR-positive no culture result *	4	0	3	0	13	3	23
Total PCR positive	**14**	**15**	**20**	**17**	**21**	**8**	**95**
Culture positive	1	2	3	2	1	1	10

¥ ACT Pathology do not conduct PCR *Shigella* testing.
≠ PCR-positive were recorded as not meeting public health criteria prior to June 2018, now recorded as probable cases.
*This means a culture test may not have been requested or culture result was negative but not reported or followed up by ACT

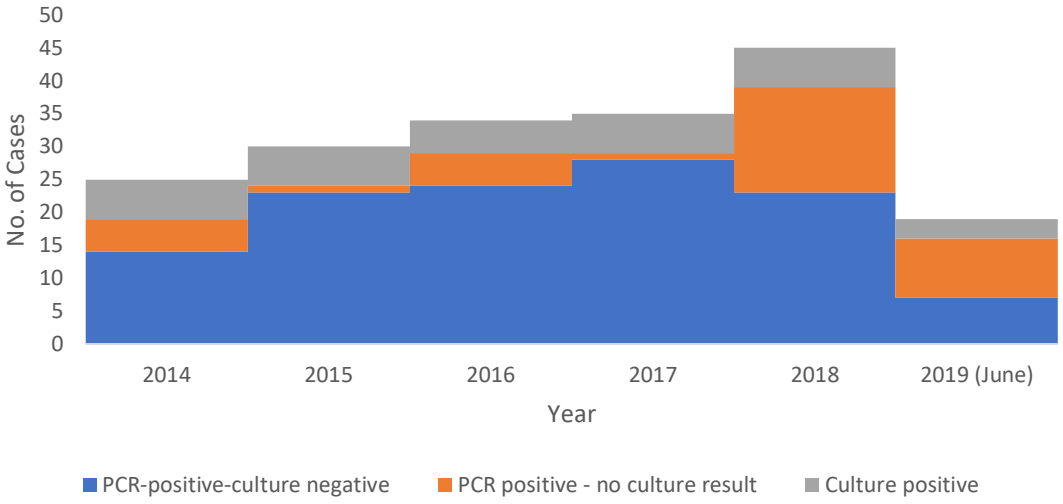


FIGURE 6: *SHIGELLA* NOTIFICATIONS IN THE ACT BY METHOD OF TESTING: 2014 - JUNE 2019

Since early 2018, all notifications have been sent a text message asking if they have travelled overseas during the incubation period. If they have travelled, they are recorded as overseas acquired and not interviewed. If the infection was potentially locally acquired, the GP is contacted for further information and permission to contact the case, who is then interviewed. Information is entered into a free-text field in the NDMS.

A culture test, following a positive-PCR test is important as culture positive cases are known to result in illness of longer duration and greater severity; this is also required to test antibiotic sensitivities (72). MSM are more likely than other population groups to present with culture positive isolates. Laboratories are not required to report negative results; therefore, a surveillance officer has historically followed up to check a culture has been requested. This process is not documented and since the change in case definition along with text-message follow-up, this has not been routinely completed.

Development of a national guideline for the public health management of *Shigella* is currently underway with the guidance of a CDNA working group. National guidance, along with refinement of data collection may decrease resource requirements, as suggested for gonorrhoea.

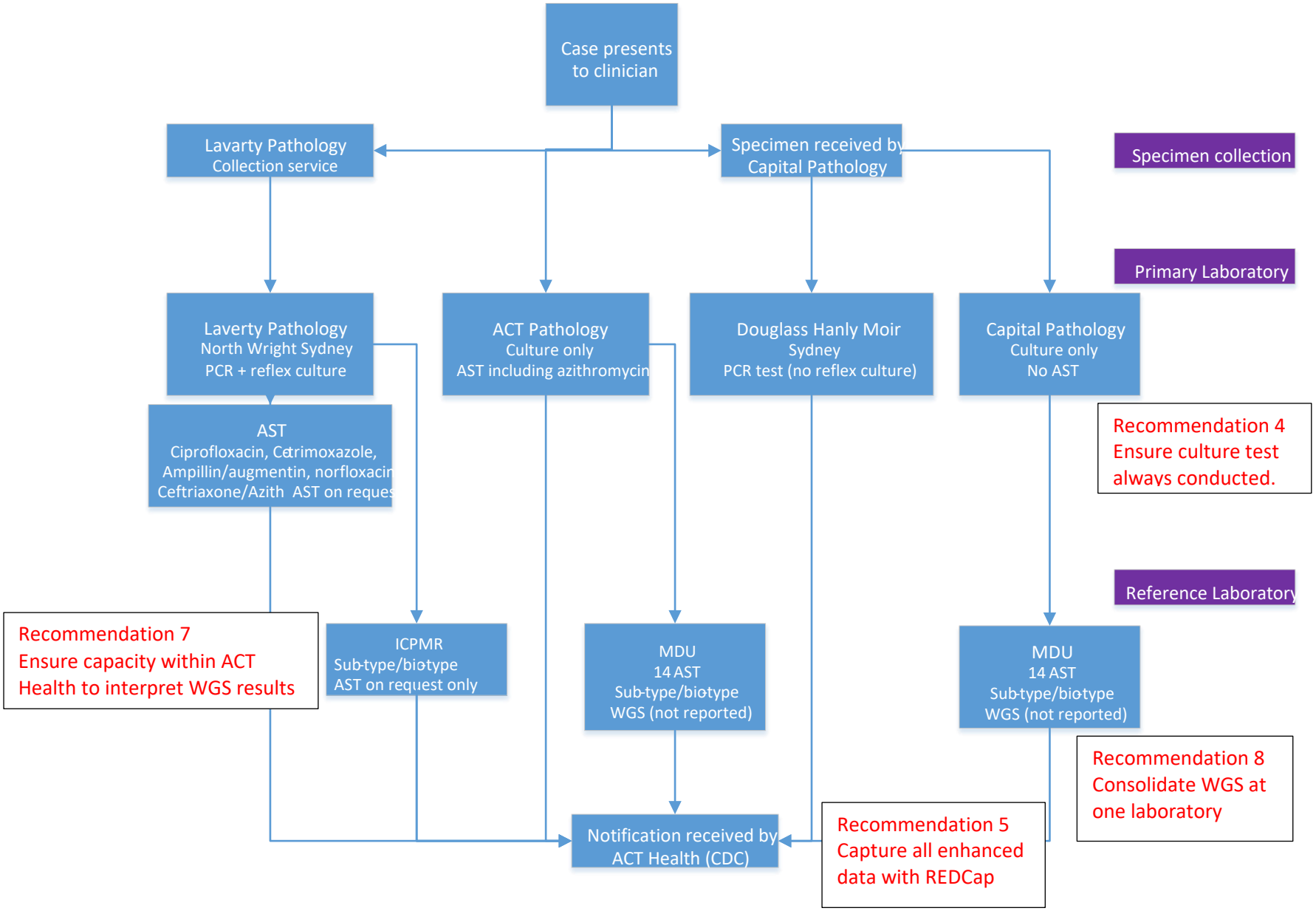


FIGURE 7: LABORATORY TESTING PROCESS FOR ACT SHIGELLA NOTIFICATIONS: 1 JANUARY 2014 - JUNE 2019

A surveillance system for antimicrobial resistant *N. gonorrhoeae* and *Shigella*

This section proposes objectives for, and components of a surveillance system for AMR *N. gonorrhoeae* and *Shigella.* These components take into account relevant legislation and legal regulations, and integrate with existing surveillance systems which are well set up for early warning and rapid response. The proposed plan places particular weight upon good case detection and registration, ability to analyse trends, effective reporting, and a well configured response system.

The objectives of a systematic surveillance system for antimicrobial resistance in *N. gonorrhoeae* and *Shigella* are:

1. To ensure timely detection of clusters and outbreaks of drug resistant cases to facilitate prompt investigation and implementation of interventions to control transmission
2. To promptly identify extensively and drug-resistant strains to facilitate urgent case management and contact tracing
3. To monitor epidemiology of drug-resistant *N. gonorrhoeae* and *Shigella* in order to inform and evaluate public health strategies

Surveillance System structure

Legislation

A number of national and ACT Acts are relevant when capturing information for notifications of gonococcal infection and shigellosis, these include:

- *National Health Security Act 2007* (Cth) div 5 s11 that maintains the national notifiable disease list.
- *Public Health Act 1997* (ACT) that provides territory level legislation to collect notifiable disease information.
- *International Health Regulations 2005,* Annex 1A (WHO) which describes the “core capacity requirements for surveillance and response” (73).

There is clearly scope in the *Public Health Act 1997* to utilise information acquired as a result of a notification "for the prevention and control of notifiable conditions” (ref (Part 6, Division 6.1 109 [1a]). This includes the collection of antimicrobial resistance data in the interests of controlling the public health impact of gonorrhoea and shigellosis. Further legal guidance would be required to assess whether we can mandate the provision of these data from laboratory providers.

Surveillance strategy

This AMR surveillance plan for drug-resistant *Shigella* and *N. gonorrhoeae* will be integrated within the existing respective surveillance systems. It is important for two reasons, these being, early warning and routine monitoring. It is critical that CDC can identify clusters and outbreaks of drug-resistant infections (as well as identifying extensively drug-resistant gonococcal strains and multi-drug resistant shigellosis) to facilitate a rapid public health response. Monitoring trends in resistance over time is important for identifying risk groups, monitoring outcomes of interventions, informing treatment guidelines and evaluating overall control interventions.

Organisation of surveillance system

The current flow of surveillance data for *N. gonorrhoeae* and *Shigella* is documented in Figure 5 and Figure 7, respectively. A key stakeholder group for both diseases is clinicians who play a central role throughout the care of the patient. Clinical decisions, supported by public health staff where required, include: whether to test in the first instance, the site and type of test (PCR, culture and AST); treatment, including the need for and type of antibiotic; and, test of cure.

Laboratories are responsible for providing consistently reliable testing techniques and of notifying the CDC of cases of gonorrhoea and shigellosis, as legislated under the *Public Health Act 1997*. Appropriate quality of testing techniques is required and monitored via an accreditation process by the National Association of Testing Authorities (NATA). Notification of antimicrobial susceptibility data by laboratories is not a legislated requirement and currently relies on their cooperation. Additional AST is often performed by a reference laboratory which for the ACT are: SEALS for all gonococcal isolates, and either ICPMR or MDU for *Shigella*, depending on the primary laboratory (Figure 5, Figure 7).

Antimicrobial resistance data is received for all confirmed shigellosis notifications however this data is not currently systematically documented by CDC (Figure 5, Figure 7). The ability of laboratories to test all clinically relevant antibiotics is variable. When contacted, reference laboratories were willing to undertake additional testing for public health surveillance on request with no attached costs.

For gonorrhoea, the public health nurse is responsible for ensuring accurate data collection as well as ensuring clinicians test and treat appropriately. This includes collecting all enhanced data via a standardised investigation form as well as checking the Australian STI management guidelines are appropriately followed (43). Surveillance of AMR *N. gonorrhoeae* would benefit from a simplified, consistent system of receiving AST results to the CDC from SEALS to allow a timely public health response to MRO cases.

The epidemiologist will oversee implementation of the AMR surveillance system, assisted by the public health nurses (for gonorrhoea) and public health officers. The epidemiologist will be

responsible for quality assurance and reporting of AMR data, as well as overseeing evaluation of the system as required.

Core functions

All shigellosis and gonococcal cases are currently notified as per the Australian national notifiable diseases case definition (55); drug resistant shigellosis and gonococcal cases will be documented within this surveillance system. The focus for this plan is on the core functions of antimicrobial resistance surveillance of *N. gonorrhoeae* and *Shigella*. The proposed core functions are based on national definitions or guidelines when available (eg. AURA and Series of National Guidelines [SoNG]), best available evidence following literature review, or expert opinion where required.

Case Detection for antibiotic resistant *N. gonorrhoeae*

The majority of gonococcal infection notifications are initially received by the public health unit following a positive PCR test. Positive culture results normally follow a number of days later, depending on the laboratory.

Detection of antimicrobial resistance currently requires isolation *of N. gonorrhoeae* by culture and AST. The implication of this is that a public health response is likely to have been initiated at the time of notification, prior to the receipt of AST results. Nevertheless, further public health action may be necessary at the time of receiving AST results, depending on the level of resistance detected.

AMR cases definition is consistent with the AURA definitions and will be defined according to the results of AST (74):

1. **Critical antimicrobial resistant gonococcal infection**
    - Resistance to ceftriaxone (MIC > 0.5mg/L) OR
    - High level resistance to azithromycin (MIC ≥256mg/L) OR
    - Both of the above (including extensively drug resistant (XDR) isolates)

2. **Gonococcal infection with reduced susceptibility to first-line treatment** (49)
    - Decreased susceptibility to ceftriaxone (MIC ≥0.125mg/L - <0.5mg/L) OR
    - Low level resistance to azithromycin (MIC ≥1mg/L - <256mg/L) OR
    - Both of the above

Case Detection for MDR *Shigella*

Laboratory confirmed shigellosis cases are most often notified by ACT Pathology, as they do not do PCR testing. Positive culture results, when available, often follow several days after a PCR-positive result from Capital and Laverty laboratories.

Detection of antimicrobial resistance currently requires isolation of *Shigella* species by culture and AST. Due to differences in laboratory requests from clinicians and laboratory testing

protocols, CDC needs to continue to engage with clinicians to encourage best practice investigation of suspected cases of shigellosis.

In 2018, the ACT Chief Health Officer wrote to all general practitioners, sexual health and infectious diseases physicians reminding them to request stool culture and full sensitivities, including azithromycin, from their diagnostic laboratory (acknowledging that not all laboratories test routinely for azithromycin sensitivity). There will likely continue to be under-ascertainment of drug-resistant cases because stool culture is not routinely requested or undertaken by some clinicians and laboratories currently. It is likely that CDC will at times need to liaise with laboratories to request further antibiotic testing in the event of a drug-resistant case or a cluster of high-risk cases.

For ongoing multi-jurisdictional investigations, and to place ACT shigellosis cases in a national/international context, WGS is critical to establish relatedness of isolates to one-another (75). However, for routine surveillance with the purpose to provide immediate public health action, descriptive epidemiology along with differentiation by serotype, biotype and AST is likely to be sufficient. Currently, ACT Health does not have the bioinformatics skillset to interpret WGS data, nor does it receive these data. All isolates undergo WGS at two different laboratories (MDU and ICPMR). It would be beneficial to consolidate these data at one facility. This, along with development of bioinformatic analysis skills would allow ongoing surveillance using WGS data.

The case definition of multi-drug resistant *Shigella* is taken from the most recent CARALert Laboratory Handbook (74).

MDR *Shigella* **case definition**:

Resistance to three or more of the following agents: ampicillin/amoxicillin, ciprofloxacin/norfloxacin, co-trimoxazole, third generation cephalosporins (ceftriaxone/cefotaxime/ceftazidime) or azithromycin.

Case registration

Enhanced data are currently collected using Excel for all gonococcal infection notifications, including AST results.

Questionnaire data for *Shigella* are currently captured as free text within the NDMS system. These data include: clinical symptoms, treatment, risk categorisation, likely source of infection and if the source is unknown a 3-day food history. AST results for *Shigella* are often received and sometimes captured as free text within the NDMS system.

A new database called Research Electronic Data Capture (REDCap) is likely to be introduced during 2019 in CDC for the purposes of collecting enhanced data (76). REDCap is a secure web application for managing survey data and databases. This database would decrease the double entry currently required, while improving the timeliness, acceptability and accuracy of data

collection. A data dictionary for existing and suggested new variables are presented in Appendices 1 and 2.

Case confirmation

Nearly 90% of all culture positive gonococcal notifications are received by ACT pathology, reliably accompanied by AST results. SEALS is the reference laboratory for all laboratories in the ACT. On occasion AST MIC results differ between the primary laboratory and SEALS. If this occurs, SEALS results are used as the confirmed result which helps to provide validity and reliability of AST test results.

All confirmed *Shigella* cases, by definition, undergo culture and all receive AST either from the primary laboratory (ACT Pathology, Laverty Pathology) or the reference laboratory (MDU for Capital pathology [primary laboratory], ICPMR for Laverty pathology [primary laboratory]. The process to identify and confirm a notification with a drug resistant infection is routinely available. The *Shigella* subtype/biotype is provided by the reference laboratories only.

Data analysis, interpretation and Reporting

It is recommended that routine reporting of AMR data be produced internally by CDC surveillance on a quarterly basis. It is also recommended for a public summary of AMR data to be produced annually along with notification data. In addition, any cases (including critical AMR gonococcal cases) resulting in an incident management team being stood up in CDC will be reported according to the normal process. There are currently no standard operating procedures (SOP) in place for the public health response to *Shigella* or gonococcal notifications. A CDC Public Health Manual, which outlines the key elements of surveillance and response requirements for all notifiable diseases in the ACT is near completion. Surveillance and response to multi-drug resistant *Shigella* and drug resistant gonococcal cases will be incorporated in the manual. It is recommended a semi-automated data extraction and analysis process be developed (using STATA or similar format) to ensure regular reporting is feasible and timely. This could be completed using a macro in excel which automatically completes simple routine tasks or using a do file in STATA which can automatically clean data and produce descriptive numerical data.

To provide more context, testing data for *N. gonorrhoeae* may be collected in collaboration with the main provider of AST results, ACT Pathology. Receiving epidemiological data in conjunction with negative testing results would allow more detailed and informative analysis. This could be completed on an on-going or intermittent basis depending on feasibility of data extraction and analysis.

A routine report summarising the epidemiology and trends of drug-resistant *Shigella* and *N. gonorrhoeae* will be provided to inform policy development and current trends for clinicians. Data to be reported are included in Appendix 3. Gonococcal reports will be provided to a newly

developed Sexually Transmitted Infections and Blood Borne Virus Health Advisory Committee (HAC). This committee represent the main sexual health stakeholders in the ACT and provide advice to the ACT Health directorate Executive on sexual health policy and programs.

Response and control: Drug resistant *N. gonorrhoeae*

The public health response to AMR cases will depend on the case definition being met and follows the gonococcal infection Series of National Guidelines (SoNG). Responsibility of follow-up with cases and contacts rests with the treating clinician and is supported by public health staff.

1. **Critical antimicrobial resistant gonococcal infection response should include:**
    - Contact the treating clinician within one working day of notification to discuss case and contact management, following the risk assessment and response process in the gonococcal infection SoNG, including:
        i. Informing the clinician of the AST findings
        ii. Discuss and agree actions regarding case and contacts
        iii. Gather information from the clinician using the investigation form
        iv. Recommend specialist service by a sexual health physician
        v. Ensure swabs are requested from all relevant sites (including pharyngeal) (77)
    - Ensure a test of cure is performed and any clinical treatment failure is identified.
    - Form an acute response team
        i. Consider involving: sexual health physician, laboratory physician, public health nurse, epidemiologist, ACT Health media, reference laboratory representative
    - Undertake active case finding.
    - Consider the need for a public health alert to relevant clinicians, based on risk of ongoing transmission.
    - Consider the benefits of a media statement (in the context of an outbreak).
    - Request all laboratory testing be conducted at ACT Pathology to enable a swift public health response.
    - Request isolates be referred to the appropriate reference public health laboratory for whole genome sequencing of isolates.
2. **Gonococcal infection with reduced susceptibility to first-line treatment response should ensure enhanced surveillance is collected (appendix one) and include:**
    - Contact the treating clinician within three working days to ensure:
        i. The case has received appropriate treatment
        ii. Contact tracing has been initiated and offer of further assistance with contact tracing if needed to ensure contacts are treated and tested
        iii. Communication about the risk of transmission has been provided to the case
        iv. Ensure test of cure for all cases
        v. Referral to specialist is warranted if treatment failure is suspected
        vi. Provide diagnosing clinician and case with information materials about gonorrhoea, if required.

Response and control: MDR *Shigella*

Public health management of MDR shigellosis infections focuses on identifying potential cases that need investigation and preventing onward transmission of infection. Public health response depends on a risk assessment which categorises cases into a risk group. When AST data is received, some responses may already have been initiated (i.e. clinician contacted, provision of hygiene advice etc.). There are currently no national guidelines for the surveillance and response to *Shigella*. There is also a varied approach between jurisdictions, and limited evidence regarding the most appropriate response and control measures. This proposed response and control section is based on evidence where available, and current accepted practices based on expert opinion.

High Risk groups (57,70,78–80)

- Occupation (paid or volunteer) involving childcare, healthcare, aged care or homecare;
- Child attending: day-care, pre-school or school;
- Food handler (paid or volunteer);
- Person unable to perform adequate personal hygiene (aged care or disability related care); and
- Men who have sex with men (MSM).

The risk of transmission for *Shigella* among MSM is primarily through sexual practices, as well as traditional enteric illness transmission pathways such as toileting, handwashing and food preparation. From a legislative perspective, ACT Health is unable to exclude MSM cases from further sexual exposure, therefore different approaches are required. The focus is on ensuring appropriate treatment (if required and following AST) along with public health advice. Advice includes encouraging either abstinence from sex (while symptomatic and until 7 days after), avoidance of particularly risky sexual practices (rimming or anal receptive sex) or alternative protections such as condoms (81).

MDR shigellosis case response should include:

- Contact clinician within one working day.
- Consider requirement of additional AST by the laboratory if all relevant antibiotics not tested (some laboratories do not routinely test ceftriaxone or azithromycin).
- Provide hygiene advice to case and establish risk group.
- Ensure exclusion from work depending on risk group.
- Complete questionnaire.
- Establish list of contacts (78)

i. Immediate family, household members and sexual partners, including those who stayed and used the same bathroom as the case.
ii. Persons who consumed food prepared by the case and not subjected to further cooking.

- Once symptom free for at least 24 hours (82):
  i. If documented appropriate antibiotic treatment, no test of cure required.
  ii. If no/inappropriate antibiotic treatment, one negative PCR test of cure required.
- Contact laboratory to confirm sub-type/bio-type being tested.

If case is high risk:

- Additional list of contacts:
  i. If case is a food handler; other food handler colleagues.
  ii. If case is in nappies; those who changed cases nappies.
  iii. If case attends childcare/preschool; other people (children & carers) in the same classroom.
- Consider specialist medical input for antibiotic treatment.
- Consider whether whole genome sequencing analysis would be beneficial.
- Consider contacting other jurisdictions if an outbreak is suspected.

If case is MSM:

- Educate on hygiene and recommend abstinence from sex until at least 7 days following symptom resolution (81)
  - Including handwashing, avoidance of rimming, use of condoms
- If antibiotics prescribed, ensure treatment consistent with AST results.
- Encourage importance of contact tracing partners if possible.
- Consider encouraging referral to STI specialists for follow-up STI screening

Contact response should include:

- Hygiene advice should be provided to all contacts
- If contact is symptomatic:
  i. Arrange for stool specimen collection and PCR/culture.
    - Ensure exclusion from work or swimming while awaiting results or resolution of symptoms.
  ii. Complete questionnaire.

- Consider screening contacts with one PCR test on a case-by-case basis considering factors such as, if the case is under 5 years (83), extent of drug resistance, risk of prior/ongoing transmission).

Support functions

Standards and guidelines

This surveillance and response plan will inform the drug resistant *N. gonorrhoeae* and MDR *Shigella* sections in the ACT Public Health Manual. This will highlight the rationale for collecting AST data and summarise: the case definition, data capture guidance and public health response.

Training

Training for public health nurses and officers will be required to ensure the process of enhanced surveillance is conducted consistently. Training will need to include understanding of the enhanced dataset and data dictionary, case questionnaire, understanding of AST data sought and the public health response to an MDR case. Gonorrhoea and shigellosis cases are likely to require follow up a number of times through contacting the clinician, laboratory staff and cases. Strategies will need to be agreed to ensure a timely response and follow-up of all MDR cases. A table-top exercise may be beneficial to engage stakeholders and ensure suggested processes are appropriate.

If REDcap is utilised, training will be required for public health nurses and officers to implement the AMR surveillance system.

Resources

Implementation of REDCap will require on-going institutional IT support although the program itself is cost neutral.

Additional time will be required for the epidemiologist to:

- Implement the surveillance system;
- Development of a new investigation form using REDCap;
- Monitor the quality of the surveillance in conjunction with the public health nurses and public health officers;
- Provide on-going analysis and reporting of the data; and
- Assist in a public health response to a critically-resistant gonococcal infection or MDR shigellosis infection, when required.

A costing analysis is beyond the scope of this project; however this should be undertaken prior to initiation.

Evaluation

Evaluation of the AMR surveillance system is recommended 12 months following implementation. The CDC guidelines for evaluation of public health surveillance systems should be used as the framework (84). Evidence used to evaluate the AMR surveillance system should include:

- Usefulness of data collected: whether the data collected is meaningful for analysis, reporting, and informing public health action; particularly considering the additional burden collecting these data places on clinicians and public health staff. Assess if objective 3 of the surveillance system is being met (i.e. providing useful information that inform public health strategies).
- Timeliness of AST data: timeliness of antimicrobial data is of most importance, especially if a highly-resistant isolate is identified. Assess if objective 1 of the surveillance system is being met, including timely detection, prompt investigation, and implementation of interventions.
- Simplicity of data collection, and ability to analyse and report: laboratory data for gonorrhoea is complex in that multiple infections may be notified for one case and AST may be reported for all sites. The feasibility of collecting enhanced data for every case will need to be evaluated especially if the number of cases continues to rise.
- Acceptability of requirements to staff: Collecting additional enhanced data may place additional pressure on time-poor clinicians, public health staff and potentially laboratory staff. Feedback will need to be sought from all relevant stakeholders to identify whether the system is acceptable and realistic.
- Stability of the system, particularly if REDCap is introduced: the ability to provide a stable database without dedicated IT support should be evaluated and also consider security of the system.
- Data quality, following internal audit: all of the above factors influence the quality of the data which impacts the ability to provide an informed public health response.

Summary of Recommendations

This surveillance plan recommends the following:

1. **Surveillance strategy:** Surveillance of drug resistant *N. gonorrhoea* and MDR *Shigella* proceed through the development and implementation of a surveillance system built on the REDCap platform (partially completed).
2. **Organisation of surveillance system:** Investigate feasibility of receiving laboratory testing data from ACT Pathology for the purpose of monitoring incidence of gonococcal disease.
3. **Case Detection:** Communicate with SEALS laboratory to improve the consistency and timeliness of *N. gonorrhoeae* AST results (completed).
4. **Case Detection:** Develop and implement a process to ensure a culture test is conducted for every PCR-positive shigellosis case (ideal recommendation - relies on private pathology to implement).
5. **Case registration:** Develop an electronic *Shigella* and *N. gonorrhoeae* enhanced data form on REDCap utilising validation of all responses and logic where appropriate (see Appendix 1 and 2) (completed).
6. **Data analysis, interpretation and reporting:** Implement routine reporting of *N. gonorrhoeae* and *Shigella* AMR trends on an agreed time basis (partially completed).
7. **Data analysis, interpretation and reporting:** Ensure ACT Health has personnel with the capability to interpret WGS analysis received from the laboratory, acknowledging this may only be possible in the medium term (one staff member possess this capability).
8. **Data analysis, interpretation and reporting:** Negotiate consolidation of *Shigella* WGS results currently held at MDU and ICPMR (ideal recommendation – relies on private pathology to implement).
9. **Response and control:** Adopt response and control process for drug resistant *N. gonorrhoeae* and MDR *Shigella* cases, as described in this report.
10. **Standards and guidelines:** Document surveillance, response and control processes in the ACT public health manual (partially completed).
11. **Training:** Test response and control process for drug resistant *N. gonorrhoeae* and MDR *Shigella* cases.
12. **Evaluation:** Evaluate AMR surveillance system after 12 months, particularly noting resource requirements prior to expanding AMR surveillance further.

Conclusion

The threat of antimicrobial resistance is rapidly emerging both globally and in Australia and may rapidly spread without effective public health surveillance and response. This surveillance plan provides the rationale for AMR surveillance, along with the need to provide a public health response. Current surveillance in the ACT is described highlighting the gaps in AMR *N. gonorrhoeae,* and lack of MDR *Shigella* surveillance. A surveillance system structure within the current surveillance approach is recommended, as well as the core and support functions. Twelve recommendations are suggested and include: adopting REDCap, an online database to collect AMR data, and documenting a response and control process in the event of multi-drug resistant *Shigella* and *N. gonorrhoeae* cases. It is recommended these are documented within the CDC Public Health manual.

References

1. Williams P. Antimicrobial resistance Eleventh Report of Session 2017-19 Report, together with formal minutes relating to the report [Internet]. 2018 [cited 2019 Jan 15]. Available from: www.parliament.uk/hsccom

2. Hall, I. Correa, A. Yoon, P. Braden C. Lexicon, Definitions, and Conceptual Framework for Public Health Surveillance. MMWR Morb Mortal Wkly Rep. 2012;61(July 27):10–4.

3. Australian Commission on Safety and Quality in Healthcare. Antimicrobial resistance in key bacteria in the community [Internet]. 2019 [cited 2019 Oct 1]. Available from: www.safetyandquality.gov.au/antimicrobial-use-and-resistance-in-australia/

4. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet [Internet]. 2016 [cited 2019 Jan 21];387:176–87. Available from: http://dx.doi.org/10.1016/

5. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence [Internet]. 2017 [cited 2018 Oct 22];8(4):460–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27593176

6. CDC. Antibiotic resistance threats in the United States, 2013. Current [Internet]. 2013;114. Available from: http://www.cdc.gov/drugresistance/threat-report-2013/index.html

7. Cassini A, Diaz Högberg L, Plachouras D, Quattrocchi A, Hoxha A, Skov Simonsen G. Articles Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. 2018 [cited 2018 Nov 19]; Available from: www.thelancet.com/infection

8. O'Neill J. TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS THE REVIEW ON ANTIMICROBIAL RESISTANCE CHAIRED BY JIM O'NEILL [Internet]. 2016 [cited 2018 Nov 19]. Available from: https://amr-review.org/sites/default/files/160525_Final paper_with cover.pdf

9. O'Neill J. Tackling Drug resistant infection globally: Final report and recommendations The review on antimicrobial resistance [Internet]. 2016 [cited 2019 Oct 21]. Available from: https://amr-review.org/sites/default/files/160518_Final paper_with cover.pdf

10. Antimicrobial Resistance-Implications for New Zealanders [Internet]. 2017 [cited 2019 Jan 18]. Available from: https://royalsociety.org.nz/assets/documents/Antimicrobial-resistance-factsheet-May-2017.pdf

11. WHO. Global Action Plan on Antimicrobial Resistance [Internet]. 2015 [cited 2018 Oct 29]. Available from: http://www.wpro.who.int/entity/drug_resistance/resources/global_action_plan_eng.pdf

12. WHO. Global Antimicrobial Resistance Surveillance System Manual for Early Implementation ISBN 978 92 4 154940 0 [Internet]. 2015 [cited 2018 Nov 1]. Available from: http://www.who.int/drugresistance/en/

13. WHO. SURVEILLANCE AND MONITORING FOR ANTIMICROBIAL USE AND RESISTANCE Surveillance and monitoring for antimicrobial use and resistance. 2018;2015(March):1–14.

14. Department of Health. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018 [Internet]. 2013 [cited 2019 Feb 4]. Available from: www.nationalarchives.gov.uk/doc/open-government-licence/

15. CDC. Antibiotic Resistance Investments in the USA [Internet]. 2018 [cited 2019 Feb 4]. Available from: https://wwwn.cdc.gov/arinvestments

16. CDC. CDC's Antibiotic Resistance (AR) Solutions Initiative [Internet]. 2018 [cited 2019 Jan 21]. Available from: https://www.cdc.gov/drugresistance/pdf/ARSI-Overview.pdf

17. Australian Government Department of Health and Australian Government Department of Agriculture and Water Resources. Australia ' s First National Antimicrobial Resistance Strategy 2015 - 2019. 2019;(November 2017). Available from: http://www.agriculture.gov.au/animal/health/amr/antimicrobial-resistance-strategy

18. Commission on Safety A, in Health Care Q. AURA 2017: Second Australian report on antimicrobial use and resistance in human health [Internet]. 2017 [cited 2018 Jul 25]. Available from: http://www.safetyandquality.gov.au/antimicrobial-use-and-

19. Health TD of. Introduction to the National Notifiable Diseases Surveillance System [Internet]. Introduction to the National Notifiable Diseases Surveillance System. 2015 [cited 2018 Oct 29]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-nndssintro.htm

20. Division CD of H and ACPH. The National Neisseria Network 1979 - 200? [cited 2018 Jun 21]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/content/cda-pubs-cdi-2000-cdi2407-cdi2407b.htm

21. CARAlert: Summary report 1 October 2017 - 31 March 2018. 2018.

22. Turnidge J. The AURA Project Antimicrobial Use and Resistance in Australia [Internet]. [cited 2018 Oct 29]. Available from: http://www.cec.health.nsw.gov.au/__data/assets/pdf_file/0005/284135/AMS-Forum-Antimicrobial-Usage-and-Resistance-in-Australia-JTurnidge.pdf

23. Andrews J. Determination of minimum inhibitory concentration. J Antimicrob Chemother [Internet]. 2001 [cited 2019 Jun 27];48(suppl. S1, 5-16). Available from: https://academic.oup.com/jac/article/48/suppl_1/5/2473513

24. National Alert System for Critical Antimicrobial Resistances: CARAlert | Safety and Quality [Internet]. [cited 2018 Sep 26]. Available from: https://www.safetyandquality.gov.au/antimicrobial-use-and-resistance-in-australia/what-is-aura/national-alert-system-for-critical-antimicrobial-resistances-caralert/

25. Commission on Safety A. Review of CARs reported to CARAlert – 2018 : Survey results , commentary and proposed amendments. 2019.

26. Marmor AM, Harley D. Evaluation of Australia's Enhanced Invasive Pneumococcal Disease (IPD) Surveillance Program. Commun Dis Intell [Internet]. 2018 [cited 2019 Jan 9];42. Available from: http://www.health.gov.au/cdna

27. National Tuberculosis Advisory committee. Tuberculosis guidelines Guidelines for Australian Mycobacteriology Laboratories National Tuberculosis Advisory Committee. Commun Dis Intell [Internet]. 2006 [cited 2019 Mar 25];30(1). Available from: http://www.moh.govt.

28. Australian Commission on Safety and Quality in Healthcare (ACSQHC). AURA 2019: Third Australian report on antimicrobial use and resistance in human health [Internet]. Sydney; 2019 [cited 2019 Jul 4]. Available from: https://www.safetyandquality.gov.au/sites/default/files/2019-06/AURA-2019-Report.pdf

29. Groseclose SL, Buckeridge DL. Public Health Surveillance Systems: Recent Advances in Their Use and Evaluation. 2016 [cited 2018 Nov 1]; Available from: https://doi.org/10.1146/annurev-publhealth-

30. Turnidge JD, Medical Advisor Kathy Meleady ST. Antimicrobial Use and Resistance in Australia (AURA) surveillance system: coordinating national data on antimicrobial use and resistance for Australia. Aust Heal Rev [Internet]. 2018 [cited 2018 Jul 24];42:272–6. Available from: www.publish.csiro.au/journals/ahrhttp://dx.doi.org/10.1071/AH16238

31. WHO. Communicable disease surveillance and response systems A guide to planning [Internet]. 2006 [cited 2018 Nov 16]. Available from: http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_LYO_2006_1.pdf

32. Wi T, Lahra MM, Ndowa F, Bala M, Dillon J-AR, Ramon-Pardo P, et al. Antimicrobial resistance in Neisseria gonorrhoeae: Global surveillance and a call for international collaborative action. PLOS Med [Internet]. 2017 Jul 7 [cited 2018 Nov 20];14(7):e1002344. Available from: https://dx.plos.org/10.1371/journal.pmed.1002344

33. Commonwealth Department of Health: Communicable Disease Branch. National Notifiable Diseases Surveillance System [Internet]. Australia. Commonwealth Department of Health; 2018 [cited 2019 Jan 9]. Available from: http://www9.health.gov.au/cda/source/rpt_4.cfm

34. Roberts-Witteveen A, Pennington K, Higgins N, Lang C, Lahra M, Waddell R, et al. Epidemiology of gonorrhoea notifications in Australia, 2007–12. Sex Health [Internet]. 2014 [cited 2018 Aug 6];11(4):224–31. Available from: http://dx.doi.org/10.1071/SH13205

35. Australasian Sexual Health Alliance. Gonorrhoea - Australian STI Management Guidelines [Internet]. 2019 [cited 2019 Aug 8]. Available from: http://www.sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea#diagnosis

36. Chesson, H. Kirkcaldy, R. Gift, T. Owusu-Edusei, K. Weinstock H. An illustration of the potential health and economic benefits of combating antibiotic-resistant gonorrhea. Sex Transm Dis [Internet]. 2018;45(4):250–3. Available from: https://www-scopus-com.virtual.anu.edu.au/record/display.uri?eid=2-s2.0-85044196776&origin=resultslist&sort=plf-f&src=s&st1=gonorrhoea+costs&st2=&sid=ad5daacd9d05c8dab6856c243188559c&sot=b&sdt=b&sl=31&s=TITLE-ABS-KEY%28gonorrhoea+costs%29&relpos=18&citeCn

37. Petousis-Harris, H. Paynter, J. Morgan, J. Saxton, P. McArdle, B. Goodyear-Smith, F. Black S. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. Lancet [Internet]. 2017 [cited 2018 Oct 30];390:1603–10. Available from: https://ac-els-cdn-com.virtual.anu.edu.au/S0140673617314496/1-s2.0-S0140673617314496-main.pdf?_tid=f78c43f9-c09a-4320-8006-3a1ebf25732d&acdnat=1540865463_46250eb1054c905cc93c095393b752c7

38. Group W, Chen M, Lahra M, Lewis D, Marshall L, Paterson D, et al. RECOMMENDATIONS FOR TREATMENT OF GONOCOCCAL INFECTIONS IN THE ERA OF MDR / XDR GONORRHOEA (Document for Sexual Health and Infectious Disease Specialists) Summary Document of Discussions held by a Working Group established to report to the Communicable D. 2019.

39. Whittles L, White P, Paul J, Didelot X. Epidemiological Trends of Antibiotic Resistant Gonorrhoea in the United Kingdom. Antibiotics [Internet]. 2018;7(3):60. Available from: http://www.mdpi.com/2079-6382/7/3/60

40. European Centre for Disease Prevention and Control. Extensively drug-resistant(XDR) Neisseria gonorrhoeae in the United Kingdom and Australia. Heal Prot Rep Adv Access Rep [Internet]. 2018 [cited 2019 Jan 16];12(11):1–11. Available from: https://ecdc.europa.eu/sites/portal/files/documents/RRA-Gonorrhoea%2C Antimicrobial resistance-United Kingdom%2C Australia.pdf

41. Tapsall JW, Ndowa F, Lewis DA, Unemo M. Meeting the public health challenge of multidrug-and extensively drug-resistant Neisseria gonorrhoeae. Expert Rev Anti Infect Ther [Internet]. 2009 [cited 2019 Jan 17];7(7):821–34. Available from: www.expert-reviews.com

42. Tapsall J, Frcpa BS. What is the economic burden imposed by antimicrobial resistance in Neisseria gonorrhoeae [Internet]. 2005 [cited 2018 Oct 30]. Available from: https://www.reactgroup.org/uploads/publications/react-publications/economic-burden-imposed-by-AR-in-neisseria-gonorrhoea.pdf

43. Australian Sexual Health Alliance. Gonorrhoea - Australian STI Management Guidelines [Internet]. 2018 [cited 2018 Oct 30]. Available from: http://sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea#clinical-presentation

44. Communicable Diseases Network Australia. Gonococcal Infection CDNA National Guidelines for Public Health Units [Internet]. 2019 [cited 2019 Jul 26]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/063E816933017261CA2583F300074085/$File/Gonococcal-Infection.pdf

45. Bignell C, Frcp B, Fitzgerald M, Fsrh F. UK national guideline for the management of gonorrhoea in adults, 2011. [cited 2019 Jan 23]; Available from: http://bashh.org/

46. Lewis DA. Will targeting oropharyngeal gonorrhoea delay the further emergence of drug-resistant Neisseria gonorrhoeae strains? Sex Transm Dis [Internet]. 2015 [cited 2019 Mar 25];0. Available from: http://sti.bmj.com/

47. Whittles, L. Didelot, X. Grad Y, White P. Testing for gonorrhoea should routinely include the pharynx. Lancet Infect Dis [Internet]. 2018 [cited 2019 Mar 25];18(July):716. Available from: https://www.thelancet.com/journals/laninf/issue/vol18no7/PIIS1473-3099(18)X0007-3

48. Barbee LA, Kerani RP, Dombrowski JC, Soge OO, Golden MR. A retrospective comparative study of 2-drug oral and intramuscular cephalosporin treatment regimens for pharyngeal gonorrhea. Clin Infect Dis [Internet]. 2013 Jun [cited 2019 Mar 25];56(11):1539–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23408680

49. Fifer H, Cole M, Hughes G, Padfield S, Smolarchuk C, Woodford N, et al. Sustained transmission of high-level azithromycin-resistant Neisseria gonorrhoeae in England: an observational study. Lancet Infect Dis [Internet]. 2018 May 1 [cited 2019 Feb 4];18(5):573–81. Available from: https://www.sciencedirect.com/science/article/pii/S1473309918301221?via%3Dihub

50. Western Australia Department of Health. Gonorrhoea [Internet]. Notifiable Infections. 2018 [cited 2019 Feb 19]. Available from: https://ww2.health.wa.gov.au/Silver-book/Notifiable-infections/Gonorrhoea

51. Monica M Lahra RPE. Australian Gonococcal Surveillance Programme annual report , 2016. Aust Gonococcal Surveill Program. 2018;39(1):137–45.

52. Donovan BA, Dimech W, Ali H, Guy R, Hellard M. Increased testing for Neisseria gonorrhoeae with duplex nucleic acid amplification tests in Australia: implications for surveillance. Sex Health [Internet]. 2015 [cited 2018 Aug 17];12:48–50. Available from: www.publish.csiro.au/journals/sh

53. ACT Health. Notification rates - Gonorrhoea. Health Stats ACT. 2019.

54. ACT Government. Public Health Act. 1997;(1).

55. Australia AGD of H and ACDN. Gonococcal infection case definition [Internet]. Australian Government Department of Health and Ageing; [cited 2018 Dec 4]. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_gono.htm

56. GBD Diarrhoeal Diseases Collaborators C, Forouzanfar M, Rao PC, Khalil I, Brown A, Reiner RC, et al. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis [Internet]. 2017 Sep 1 [cited 2019 Jun 27];17(9):909–48. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28579426

57. Lane CR, Sutton B, Valcanis M, Kirk M, Walker C, Lalor K, et al. Travel Destinations and Sexual Behavior as Indicators of Antibiotic Resistant *Shigella* Strains—Victoria, Australia. Clin Infect Dis [Internet]. 2016 Mar 15 [cited 2018 Oct 23];62(6):722–9. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/civ1018

58. Wood N, Nolan T, Marshall H, Richmond P, Gibbs E, Perrett K, et al. Immunogenicity and Safety of Monovalent Acellular Pertussis Vaccine at Birth: A Randomized Clinical Trial. JAMA Pediatr. 2018;172(11):1045–52.

59. Heymann D. Control of Communicable Disease manual. 20th ed. American Public Health Association; 2015.

60. Draper, A. Markey P. Shigella flexneri 2b in the Northern Territory in 2017. North Territ Dis Control Bull [Internet]. 2017 [cited 2018 Nov 12];24(4). Available from: http://www.nt.gov.au/health/cdc/cdc.shtml

61. May FJ, Stafford RJ, Carroll H, Robson JM, Vohra R, Nimmo GR, et al. The effects of culture independent diagnostic testing on the diagnosis and reporting of enteric bacterial pathogens in Queensland. Orig Artic [Internet]. 2017 [cited 2019 Aug 25];41(3). Available from: https://lifescience.roche.

62. Australia AGD of H and ACDN. Shigellosis Surveillance Case Definition [Internet]. Australian Government Department of Health and Ageing; 2018 [cited 2019 Aug 25]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_shigel.htm

63. Agha, R. Goldberg M. Shigella infection: Treatment and prevention in adults [Internet]. 2019. Available from: https://www.uptodate.com/contents/shigella-infection-treatment-and-prevention-in-adults?search=shigella&source=search_result&selectedTitle=2~143&usage_type=default&display_rank=2#H2

64. Therapeutic Guidelines. Acute infectious diarrhoea: Shigella enteritis [Internet]. 2019. Available from: https://tgldcdp.tg.org.au/viewTopic?topicfile=acute-gastroenteritis&guidelineName=Antibiotic#toc_d1e1168

65. Brown JD, Willcox SJ, Franklin N, Hazelton B, Howard P, Reinten T, et al. Shigella species epidemiology and antimicrobial susceptibility: the implications of emerging azithromycin resistance for guiding treatment, guidelines and breakpoints. [cited 2018 Oct 23]; Available from: https://academic.oup.com/jac/article-abstract/72/11/3181/4080234

66. Lane CR, Sutton B, Valcanis M, Kirk M, Walker C, Lalor K, et al. Clinical Infectious Diseases Travel Destinations and Sexual Behavior as Indicators of Antibiotic Resistant Shigella Strains-Victoria, Australia. 2015 [cited 2019 Jan 24]; Available from: https://academic.oup.com/cid/article-abstract/62/6/722/2462740

67. Yeoh H-L, Hall V, Williamson DA, Gardiner BJ. Locally acquired extended-spectrum β-lactamase Shigella infection. Med J Aust [Internet]. 2019 Jun 17; Available from: http://doi.wiley.com/10.5694/mja2.50245

68. WHO. Ten threats to global health in 2019 [Internet]. 2019 [cited 2019 Jan 21]. Available from: https://www.who.int/emergencies/ten-threats-to-global-health-in-2019

69. ACT Health. Multi-drug-resistant (MDR) shigellosis. 2018.

70. Ingle DJ, Easton M, Valcanis M, Seemann T, Kwong JC, Stephens N, et al. Co-circulation of multidrug-resistant Shigella among men who have sex with men, Australia. Clin Infect Dis [Internet]. 2019 [cited 2019 Jan 24]; Available from: https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciz005/5274662

71. Brown JD, Willcox SJ, Franklin N, Hazelton B, Howard P, Reinten T, et al. Shigella species epidemiology and antimicrobial susceptibility: the implications of emerging azithromycin resistance for guiding treatment, guidelines and breakpoints. [cited 2018 Oct 25]; Available from: https://academic.oup.com/jac/article-abstract/72/11/3181/4080234

72. Quinn E, Najjar Z, Huhtinen E, Jegasothy E, Gupta L. Culture-positive shigellosis cases are epidemiologically different to culture-negative/PCR-positive cases. Aust N Z J Public Health. 2019 Feb 1;43(1):41–5.

73. WHO. International Health Regulations [Internet]. 3rd ed. World Health Organization. Geneva; 2005 [cited 2019 Aug 25]. Available from: https://apps.who.int/iris/bitstream/handle/10665/246107/9789241580496-eng.pdf;jsessionid=325C9D1C92EFA759D1A8AB3304AC11BF?sequence=1

74. Australian Commission on Safety and Quality in Health Care. Handbook - CARAlert Laboratories. Sydney; 2019.

75. Williamson DA, Kirk MD, Sintchenko V, Howden BP. The importance of public health genomics to ensure health security for Australia. Med J Aust [Internet]. 2019 Mar 19 [cited 2019 Mar 25];mja2.50063. Available from: https://onlinelibrary.wiley.com/doi/abs/10.5694/mja2.50063

76. PA Harris, R Taylor, R Thielke, J Payne, N Gonzalez JC. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support,. Jounral Biomed Inf. 2009;42(2):377–81.

77. Eyre DW, Sanderson ND, Lord E, Regisford-Reimmer N, Chau K, Barker L, et al.

Gonorrhoea treatment failure caused by a Neisseria gonorrhoeae strain with combined ceftriaxone and high-level azithromycin resistance, England, February 2018. Euro Surveill [Internet]. 2018 Jul [cited 2019 Feb 20];23(27). Available from: http://www.ncbi.nlm.nih.gov/pubmed/29991383

78. NSW Health. Shigellosis Control Guidelines [Internet]. Control Guidelines. 2018. Available from: https://www.health.nsw.gov.au/Infectious/controlguideline/Pages/shigellosis.aspx

79. Brown JD, Willcox SJ, Franklin N, Hazelton B, Howard P, Reinten T, et al. Shigella species epidemiology and antimicrobial susceptibility: the implications of emerging azithromycin resistance for guiding treatment, guidelines and breakpoints. [cited 2018 Nov 7]; Available from: https://academic.oup.com/jac/article-abstract/72/11/3181/4080234

80. Tai AYC, Easton M, Encena J, Rotty J, Valcanis M, Howden BP, et al. A review of the public health management of shigellosis in Australia in the era of culture-independent diagnostic testing. Aust N Z J Public Health. 2016;40(6):588–91.

81. Clutterbuck D, Asboe D, Barber T, Emerson C, Field N, Gibson S, et al. 2016 United Kingdom national guideline on the sexual health care of men who have sex with men. Int J STD AIDS [Internet]. 2018;095646241774689. Available from: http://journals.sagepub.com/doi/10.1177/0956462417746897

82. Carias C, Undurraga EA, Hurd J, Kahn EB, Meltzer MI, Bowen A. Evaluation of the impact of shigellosis exclusion policies in childcare settings upon detection of a shigellosis outbreak. BMC Infect Dis. 2019;19(1):1–7.

83. Boveé L, Whelan J, Sonder GJ, Van Dam AP, Van Den Hoek A. Risk factors for secondary transmission of Shigella infection within households: implications for current prevention policy [Internet]. BMC Infectious Diseases. 2012 [cited 2019 Jul 4]. Available from: http://www.biomedcentral.com/1471-2334/12/347

84. Centers for Disease Control and Prevention. Updated guidelines for evaluating public health surveillance systems: recommendations from the guidelines working group. MMWR Morb Mortal Wkly Rep [Internet]. 2001;50. Available from: https://stacks.cdc.gov/view/cdc/13376

Appendices

Appendix One: Gonococcal AMR Data dictionary

Variable	New / Existing	Rationale	Data fields
Reason for test	New	This informs our understanding of why clinicians are testing.	Symptomatic, STI screening, PreP screening, dual Chlamydia test, other
MIC level per antibiotic & source	New	To monitor for MIC 'drift'. This is an increase in the MIC within sensitive isolates or an increase in low-level azithromycin resistance MIC. Although crude numbers are small there has been a noticeable increase in the MIC of low-level azithromycin resistant cases over the past two years.	1,2,4,8,16,32,64,128, >256
Laboratory number	New	To allow merging of laboratory data, avoid duplicated cases and identify multiple isolates tested per notification.	M######
HIV status	New	This is a known risk factor for contracting gonococcal infection as well as undiagnosed gonorrhoea being a risk factor for contracting HIV.	HIV positive, HIV negative, unknown
Diagnostic test(s)	New	The current database doesn't easily allow the proportion of notifications that receive only NAAT or NAAT and culture.	NAAT only, NAAT & culture
Date first AST results received	New	To monitor the time taken from notification to receiving AST results to ensure a timely response to resistant cases.	Date AST results received to CDC
Laboratory name for first AST result received	New	Different tests (PCR and culture) may be received from different laboratories for the same notification. This allows surveillance staff to accurately assess timeliness for each conducted.	Laboratory name
Source of isolate	Existing	To monitor site of infection	Urogenital, pharyngeal, rectal
Qualitative interpretation of antibiotic susceptibility by site and antibiotic	Existing	To monitor AMR trends	Sensitive, resistant
Sexual exposure	Existing	To monitor a known risk factor	Same sex, both sexes, opposite sex
Source of referral	Existing	To understand which clinicians are seeing and treating gonococcal infections.	
Sex worker status	Existing	To monitor a vulnerable population.	Yes, No, unknown
Recent travel	Existing	To identify potential overseas/interstate imported infections.	Yes, No, unknown
PreP status	Existing	This group receive regular STI screening and represent a noticeable proportion of gonococcal notifications (approximately 30% in 2019)	Yes, No, Unknown
Reference laboratory data	New	We have little understanding of when subsequent information arrives beyond the initial notification	Date of entry, laboratory name

Appendix Two: Shigella AMR Data dictionary

Variable	New / Existing / Amended	Rationale	Data fields
High risk case	Amended	MSM dominate notifications of drug-resistant shigellosis in ACT and NSW and may be considered high risk (consistent with NSW). Child in childcare common cause of institutional outbreaks overseas. Unable to perform personal hygiene (e.g. Aged care, disability care)	Yes / No Risk specified as sub-field if Yes: Food-handler, healthcare workers, childcare worker, child in childcare, Men who have sex with men (MSM)
Overseas travel during incubation period	Existing	A known risk factor for AMR	Yes / No Country specified as sub-field if Yes
NAAT test	New	To monitor proportion of notifications receiving NAAT testing	Yes / No
NAAT test laboratory	New	To identify the origin of laboratory results	Laboratory name
Date NAAT test result received	New	To monitor timeliness of data	Date received
Culture test	New	To monitor proportion of notifications receiving culture testing	Yes / No
Culture test laboratory (if culture performed)	New	To identify the origin of laboratory results	Laboratory name
Culture result	New	To monitor proportion of notifications that are culture negative	Positive / Negative
Date first Culture test result received	New	To monitor timeliness of data	Date received
Antibiotic sensitivity test: qualitative results	New	To monitor trends of antimicrobial resistance	Amp/Amoxicillin, Cefazolin, Ciprofloxacin, Cotrimoxazole, Ceftriaxone, Azithromycin, Norfloxacin, Tetracycline. Recorded as Resistant or Sensitive
Serotype result	New	To monitor the epidemiology of Shigella notifications	*S. dysenteriae serotype 2-15, S. flexneri, S. boydii, S. sonnei*
Serotype test laboratory	New	To identify the origin of laboratory results	Laboratory name
Shigella biotype	New	Likely to be required to identify outbreaks	Free text field initially

Appendix Three: Shigella and gonorrhoea reporting data

Reportable Data	Regularity
Shigella: Number/proportion of MDR *Shigella* isolates, presented by reporting period, year to date and 5-year summary.	Annual
Shigella: Tabulation of antibiotic resistance interpretation by risk factors: international travel, MSM and other, by reporting period, year to date and 5-year summary.	Annual
Shigella: Tabulation of antibiotics resistance among *Shigella isolates* by species, presented by reporting period, year to date and 5-year summary.	Annual
Gonorrhoea: Proportion of isolates resistant to ceftriaxone, azithromycin, penicillin and ciprofloxacin: by reporting period, year to date and 5-year summary.	Quarterly, Annual
Gonorrhoea: Tabulation of isolate sensitivity (ceftriaxone, azithromycin) interpretation by sex and sexual exposure: by reporting period, year to date and 5-year summary	Quarterly, Annual
Gonorrhoea: Test positivity percentage (ACT Pathology isolates). Presented by reporting period, year to date and 5-year summary (or as far as feasible).	6-month, Annual
Gonorrhoea; Tabulation of isolate sensitivity by site of infection and sexual exposure (ceftriaxone, azithromycin).	Quarterly

Appendix Four: Shigella childcare exclusion criteria evidence

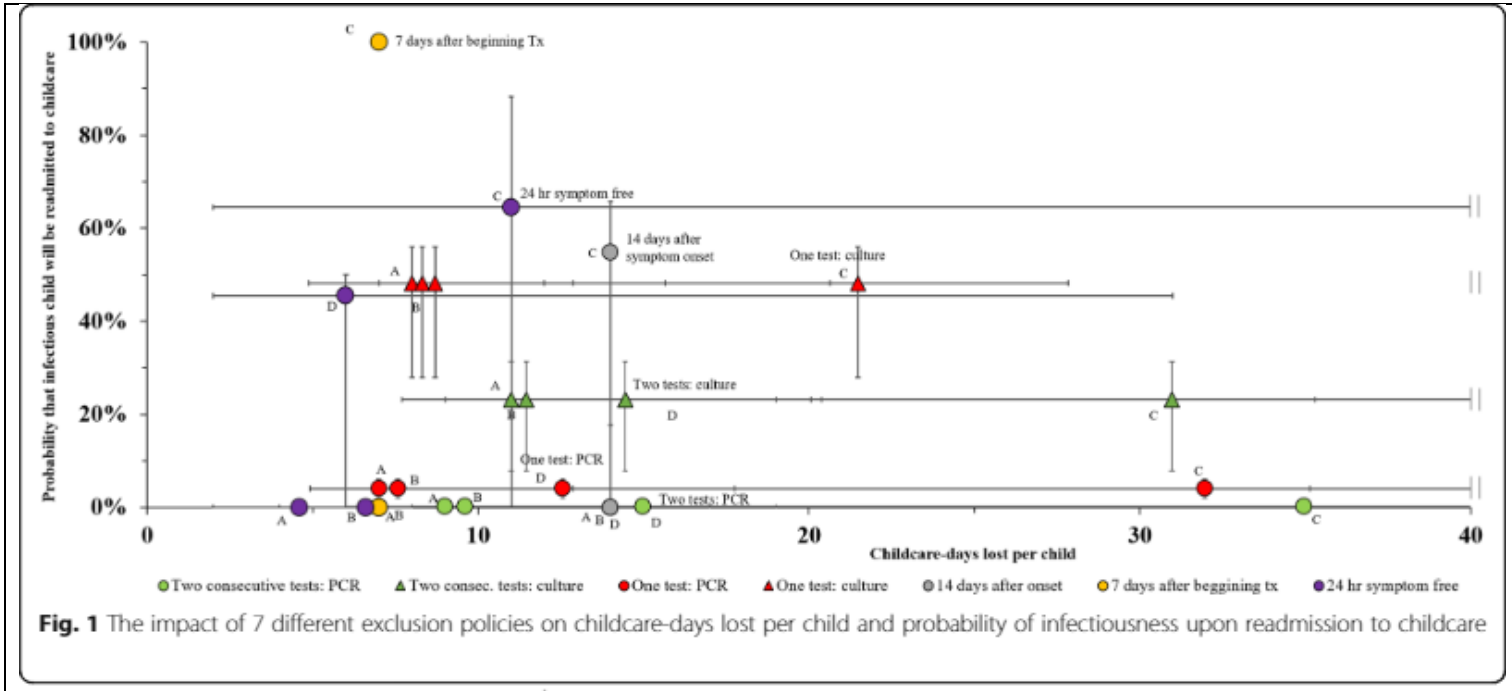


Fig. 1 The impact of 7 different exclusion policies on childcare-days lost per child and probability of infectiousness upon readmission to childcare

II. Treatment scenarios for each exclusion policy[d]

A. Immediate, effective treatment	Child visits healthcare provider and starts effective antimicrobial treatment without requiring any further diagnosis or test on the second day of illness
B. Effective treatment after diagnosis	Child visits healthcare provider on the second day of illness, gets a stool culture with antimicrobial susceptibility testing, and starts effective treatment after results are available[e]
C. Ineffective treatment	Child visits healthcare provider and starts ineffective antimicrobial treatment on second to fourth day of illness
D. No treatment	Child receives no antimicrobial treatment[f]

This study evaluated the impact of different childcare (<5years) exclusion policies including either test of cure or days symptom free policies (82). They investigated the number of days lost and the likelihood of a child returning while still infectious for five different exclusion policies.

- Rationale for criteria is 1 PCR TOC (red A or B) shows a risk of approximately 4% even if not all children are being treated and a number have presumptive treatment.
- Regardless of treatment or non-treatment if cases receive 2 PCR TOC, they suggest a 0% chance of missing an infectious person.
- If appropriate treatment provided there is 0% chance of being infectious 24hrs symptom free (purple B)

ACT Government | ACT Health

Dear **MAE examiner,**

As the surveillance manager of the Communicable Disease Control team at ACT Health I can confirm that some of the recommendations presented in this chapter have been completed, some are in progress and some have not yet been implemented. Except for two of the recommendations which rely on private laboratory providers to implement, all other recommendations are feasible when time and resources allow.

Following the pandemic response to COVID-19 we plan to focus again on AMR surveillance and implement the remaining recommendations.

Sincerely,

Rebecca Hundy

22 June 2020