The epidemiology of sexually transmitted infections and neglected tropical diseases in Oceania

A thesis submitted for the degree of Master of Philosophy

(Applied Epidemiology) of the Australian National University

Sophie Louise Phelan

February 2019

The Kirby Institute, University of New South Wales, Sydney

Funded by: The Kirby Institute

Field supervisors: John Kaldor and Rebecca Guy

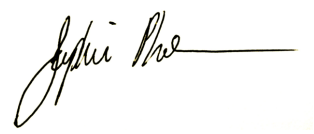
ANU Research School of Population Health supervisor: Kathryn Glass

Australian National University

I declare that:

- this thesis is my own work, except where otherwise indicated;
- when reporting another author's point of view, I have used my own words and correctly acknowledged the sources of the material;
- I have read and understood the rules and regulations regarding plagiarism;
- no part of this work has been copied from another person's work (either published or not); and
- no part of this work has been written by any other person.

Signed



Date: 19th February 2019

Acknowledgements

My Master of Applied Epidemiology (MAE) would not have been possible without the meaningful contributions of many people, all of whom are acknowledged in relevant chapters. Here, I want to take the opportunity to recognise those who have been a constant source of guidance and support throughout the whole experience.

Firstly, thanks must go to my field supervisors at the Kirby Institute, John Kaldor and Rebecca Guy, and to my academic supervisor at the National Centre for Epidemiology and Population Health (NCEPH) at the Australian National University (ANU), Kathryn Glass. John and Bec, thank you for sharing your experience, expertise and advice. Katie, thank you for being a huge support, and a constant source of calm. I have learnt a lot from you. I must also thank Ross Andrews from NCEPH, for helping me to steer a path through the MAE to completion. Katrina Roper, you set a high standard for us during our 2017 course blocks, yet simultaneously instilled in us the drive to reach beyond it. Thank you for your energy and mentorship, 2017 course block and beyond.

To the staff of the Kirby Institute: special thanks must go to Jane Costello, Morgan Stewart and Liza Doyle. You instantly made me feel comfortable, and part of the Kirby community. Kate Whitford, Elaine Lee, Rata Oka Joseph, Estelle Jones, Luci Bamford, Adam Craig, Shawn Clackett and Pratiksha Bhatt: thank you for extending your friendship to me. Skye McGregor and Lucia Romani, you both continue to be marvelous role models.

Thank you to Tove Lysa-Fitzgerald, Christine Selvey, Vicky Sheppeard, Jeremy McAnulty and the rest of the team at Communicable Diseases Branch, New South Wales Health, for the warm welcome and inclusion in your team. I appreciated the opportunity to learn more about communicable disease surveillance and control in New South Wales. Additionally, as Jeremy was the first person to encourage me to apply for the MAE, it was great to come full circle and work on an MAE project together. On the topic of those who encouraged me to apply for the MAE, thanks must also go to Martyn Kirk and Bev Paterson.

The challenges of the MAE were made lighter through sharing the experience with such a talented and warm cohort. To the two MAE's also based at the Kirby Institute, Jana Sisnowski and Aurysia Hii: thank you for everything! You are both incredible field epidemiologists, and people. I can't wait to see what you do next. Patiyan Andersson, Kaitlyn Vette, Bobby Maher, Gabriella Willis, Roxanne Jones, Brigitta Osterberger, Belinda Jones, Charlee Law, Kelley Meder, Julia Maguire, Ximena Tolosa, Cushla Coffey, Bernadette Kenny, Natalie Strobel, Kim Greaves: I

have learnt something from each one of you. Thanks also to the 2017 cohort, for sharing your experiences with us during overlapping course blocks.

Thank you to my parents, sister and Nana for your constant faith in me, and for always checking in, no matter the geographical distance between us. Granma and Opa: I could not have finished this thesis without your love, hot dinners, or the soul restoring sea breeze of Austinmer. Cameron Walker: thank you for your big picture perspectives.

Lastly, yet most importantly: Random Dudley. I couldn't have achieved this MAE without your love, level headedness, patience, encouragement, postcards and maple syrup. I can only hope that one day I can follow in your footsteps and support you in the same way.

Abstract

From February 2017-February 2019 I undertook a field placement at the Kirby Institute, University of New South Wales (UNSW), as part of my Master of Philosophy in Applied Epidemiology (MAE). An MAE graduate is required to be competent in four skills that are essential for an applied epidemiologist. These competencies are demonstrated through four chapters within this MAE: 1) Design and conduct an epidemiological study, 2) Analyse a public health dataset, 3) Investigate an acute public health problem, and 4) Conduct a surveillance evaluation. An additional chapter detailing teaching experience follows the main competency chapters.

To meet the epidemiological study component, I conducted the first prevalence study of scabies and impetigo in a primary school in Gizo, the main town on a small island in The Solomon Islands. The prevalence of scabies and impetigo were found to be 56.7% and 43.9% respectively - a significant burden. I also set up two other international epidemiological studies in Fiji and the Solomon Islands, however the implementation of these studies proved to be beyond the timeframe of the 2-year MAE program.

For the data analysis component, I investigated the association between the prevalence of clean faces and the prevalence of trachoma in Australian communities endemic for trachoma between 2007-2017 using a binomial logistic regression model. A significant association was found, however a number of caveats need to be considered in the interpretation of this association.

My investigation of the increase in gonorrhea notifications in New South Wales (NSW) women in 2018 demonstrated the third competency: investigation of an acute public health problem. Through a case series study, I found that the outbreak appeared to be related to local, heterosexual, condomless sex. As this study was of a sensitive nature, careful methodologies were required. Their success meant that these study methods can serve as a template for future sexually transmitted disease outbreak investigations in Australian women.

For the evaluation of a surveillance system competency, I conducted a systematic review of the access and utility of testing (or denominator) data for chlamydia and influenza in Australia. This study found that the most common source of denominator data for these diseases was sentinel surveillance data; and the most common uses were to describe testing practices (chlamydia) and to estimate disease burden (influenza).

The final chapter in my bound volume demonstrates my completion of the teaching requirements for the MAE: a Lesson from the Field (LFF) and a group teaching session with MAE

peers. My LFF summarized key issues I encountered when setting up the Fiji epidemiology project, and was titled “Ethical, Cultural and Practical Study Design Challenges in the Pacific”. My group teaching session was titled “Communicating as a Field Epidemiologist during Public Health Emergencies” and flagged a number of considerations for communicating in the field for first year MAEs.

The projects within this bound volume reflect the Kirby Institute’s area of work within marginalized and at-risk populations, and demonstrate my completion of the MAE competencies. The diseases in focus include the sexually transmitted infections (STIs): chlamydia and gonorrhea; and the neglected tropical diseases (NTDs): scabies and trachoma. The research I completed was based in three countries: Australia, Fiji and the Solomon Islands; all within Oceania region. Findings from these projects will contribute to the ever-growing body of public health knowledge on sexually transmitted infections and neglected tropical diseases in Oceania, and thus provide important information to guide public health policy and stimulate future research, both within and beyond the region.

Contents

Chapter 1: MAE Experience

Field placement and summary of core activities

Contents

1.1 Introduction

My main motivation for applying to the Master of Applied Epidemiology (MAE) program was to gain practical training in field epidemiology. Field epidemiology is a broad area, evidenced by Porta's paragraph-long definition, summarised here as:

> "*The practice of epidemiology in the field—in the community—commonly in a public health service. Field epidemiology is how epidemics and outbreaks are investigated, and it is a tool for implementing measures to protect and improve the health of the public. Field epidemiologists must deal with unexpected, sometimes urgent problems that demand immediate solution*."[1]

Understanding issues in field epidemiology requires the researcher to investigate the issue through at least two lenses: one of health and disease, and one of socio-ecologic systems. The synthesis of these two areas, with the goal of solving issues of public health importance, particularly appealed to me because of my background in immunology, biological anthropology and international public health. When I was accepted into the MAE, I looked forward to gaining practical training in field epidemiology, and specifically using it in application to the research and elimination of neglected tropical diseases.

Each of my MAE projects taught me specific lessons, which are discussed further in the prologue of each chapter. There are three lessons that stand out particularly as my take home messages of the MAE. Firstly, the lesson of McMichael's "prisoner of the proximate"[2]. As a result of the words of Mohammad Patel at the start of our MAE course block, I applied McMichael's "prisoner of the proximate"[2] principle to my MAE experiences and learnt to think outside the box when solving epidemiological issues. Secondly, I learnt to understand the benefit of "Occam's razor", the problem solving principle which states that simpler solutions are more likely to be correct than complex ones. Initially, I eagerly anticipated learning advanced analytical skills in biostatistics, and the conduct of highly technical epidemiological studies through my MAE. However, through the practical and ethical challenges of field epidemiology I encountered in my MAE, I learnt to never overlook a simplistic approach. The final, and most important lesson I learnt through the "deep end" challenges of the MAE was to have confidence and faith in myself. I started my MAE journey with the unassuming belief that when my ideas were questioned by someone of greater authority, my ideas were automatically wrong. Now I have the faith in myself to put my opinions forward more confidently in the first instance; and when challenged; to pursue further respectful, open discussion instead of immediately acquiescing.

1.2 About the Kirby Institute

Mission statement

The mission statement of the Kirby Institute is to lead the research effort against blood-borne viruses and related infections in Australia and in our region[3]. This research draws from many disciplines to develop outcomes that bolster prevention efforts, provide improved treatments and build regional capacity against infections that occur in every community, with a focus on marginalized and at-risk populations.

Background

The Kirby Institute was formed on the 25th anniversary of the National Centre in HIV Epidemiology and Clinical Research (NCHECR) in April 2011[3]. NCHECR was established back in 1986 in response to the then-emerging and little understood HIV pandemic. As NCHECR began to use the skills, techniques and expertise developed through the study of HIV in application to other infectious diseases, it was renamed as the Kirby Institute to encompass this broader scope of research. Named after former High Court judge the Hon Michael Kirby AC CMG, this also reflects Mr Kirby's lifetime interest in health, human rights, and the diverse and often disadvantaged communities affected by the diseases researched here.

The Kirby Institute is now primarily responsible for the epidemiology and surveillance of HIV/AIDS, viral hepatitis and sexually transmissible infections (STIs) in Australia and the Pacific region. Other programs of the Kirby Institute are responsible for the training of health professionals, and the development and implementation of health policy and programs. The Kirby Institute are directly affiliated with the Faculty of Medicine at the University of New South Wales, and the majority of their funding comes from the Australian Government Department of Health and Ageing. The Kirby Institute also works with an extensive range of collaborators including other national HIV research centres, State and Territory health departments, public and private clinical units, national and international organisations, and the corporate sector. The late Scientia Professor David A. Cooper AO FAA was the initial director of the Kirby Institute, and was previously the inaugural director of NCHECR. His long association with HIV research spanned nearly three decades. The new director, Professor Anthony Kelleher, was announced in January 2019.

Organisational structure

The Kirby Institute consists of twelve research programs; however, the organisational structure will be revised in 2019. Currently, all twelve programs report to the Director's Unit. I worked within two programs during my placement at the Kirby Institute: the Public Health Interventions

Research Group (PHIRG) led by John Kaldor, and the Surveillance Evaluation and Research Programme (SERP) led by Rebecca Guy.

PHIRG staff undertake a diverse range of projects that focus on the evaluation of strategies to prevent infectious disease and benefit the health of disadvantaged populations in Australia and the Asia-Pacific Region. Current projects concentrate on the control of HIV, STIs, viral hepatitis, tuberculosis and neglected tropical diseases. SERP staff focus on two main areas: (i) monitoring the pattern of transmission of HIV, viral hepatitis, and specific STIs in Australia, and (ii) conduct research and evaluation of public health interventions.

I really enjoyed working alongside the diverse, warm and intelligent staff of the Kirby Institute. As a new staff member, I was instantly embraced into a wonderful community. It was fantastic to have the opportunity to be involved in many of the activities that were organised outside of work by the Kirby community, including participating in the annual Sydney Mardi Gras Parade, and celebrating the results of the Australian Marriage Law Postal Survey on the 15th November, 2017, and the passing of the marriage equality law in Australian Parliament on the 9th December 2017, pictured below.

1.3 Summary of MAE requirements

Note: a tabulated summary of the sections below can be found in Table 1.

Field Projects

Chapter 2: Design and conduct an epidemiological study:

- Evaluation of the impact of azithromycin mass drug administration for trachoma on the prevalence of sexually transmitted infections in Fiji
- Regimens of Ivermectin for Scabies Elimination (RISE)
- Prevalence of scabies in Gizo Primary School, Western Province, Solomon Islands

Chapter 3: Analyse a public health dataset: Association between clean faces and trachoma in remote Australian communities prior to implementation of community-wide control strategies

Chapter 4: Investigate an acute public health problem: Characteristics of females with gonorrhoea in NSW, 2018 – a case series investigation

Chapter 5: Evaluate a surveillance system or other health information system: In search of a denominator: a systematic review of the source and public health utility of data on numbers tested for chlamydia and influenza

Teaching requirements

Chapter 6: Lesson from the Field: Ethical, Cultural and Practical Study Design Challenges in the Pacific

Peer to Peer Teaching Session: Communicating as a Field Epidemiologist during Public Health Emergencies

Additional MAE competencies:

Advanced draft peer reviewed publication

Chapter 5:	In search of a denominator: a systematic review of the source and public health utility of data on numbers tested for chlamydia and influenza

Communication for a non-scientific audience

Chapter 1:	Annex 1A: Aboriginal and Torres Strait Islander Community Report Reflection
Chapter 2:	Annex 2A: Participant Information and Consent Forms (PICFs), Fiji study (Annex 5 and 6 within Annex 2A)
	Annex 2D: PICF, RISE study
Chapter 4:	Annex 4A: Gonorrhoea in NSW women case series investigation brief to chief health officer

Oral presentation at an international scientific conference

Chapter 4:	Oral presentation at International Union against Sexually Transmitted Infections (IUSTI) Asia Pacific Congress, New Zealand 2nd November 2018. Annex 4E: Oral presentation slides.

Literature Review

Chapter 2:	Annex 2A: Evaluation of the impact of azithromycin mass drug administration for trachoma on the prevalence of sexually transmitted infections in Fiji – study protocol (Section 1.1)
Chapter 4:	Systematic review: In search of a denominator: a systematic review of the source and public health utility of data on numbers tested for chlamydia and influenza

Table 1: Summary of Core Competencies

	Chapter					
MAE Competency	1	2	3	4	5	6
Investigation of an acute public health problem				✓		
Evaluate a surveillance system or other health information system					✓	
Analyse a public health dataset such as surveillance data			✓			
Design and conduct an epidemiological study		✓				
Preparation of an advanced draft of a paper for publication in a national or international peer-reviewed journal					✓	
A literature review that demonstrates skills in conducting a targeted literature search and synthesis		✓			✓	
An abstract and oral presentation of the project at national or international scientific conference				✓		
A relevant report on the project to a non-scientific audience.	✓	✓		✓		
Prepare and deliver a lesson from the field (LFF)						✓
Prepare and conduct a teaching session for first year MAEs						✓

Summary of course work

I attended all three course block sessions at ANU and completed all five course subjects listed below.

Course subjects:

POPH8317	Public Health Surveillance - Semester 1, 2017
POPH8916	Outbreak Investigation - Semester 1, 2017
POPH8915	Research Design and Methods - Semester 2, 2017
POPH8913	Analysis of Public Health Datasets - Semester 2, 2017
POPH8914	Issues in Applied Epidemiology- Semester 1, 2018

1.4 References

1. Porta M. 2014. A Dictionary of Epidemiology. Sixth Edition. *Oxford University Press*, New York, United States of America.
2. McMichael A. 1999. Prisoners of the proximate: loosening the constraints on epidemiology in an age of change. *American Journal of Epidemiology* 15;149(10):887-97.
3. The Kirby Institute. 2019. About the Kirby Institute. Accessed on 29th January 2019, from https://kirby.unsw.edu.au/about-kirby-institute

Annex 1A: Communication to a non-scientific audience: Aboriginal and Torres Strait Islander Community Report Reflection

I acknowledge the traditional owners of the lands that provided the data for this Community Report. I acknowledge their continuing connection to land, sea and community. I pay my respects to them, their cultures and their elders, past, present and emerging.

Project outline: Annually the Kirby Institute collates national data on HIV, sexually transmitted diseases and blood borne viruses. The data is analysed by the Kirby Institute, and findings are collated into the Annual Surveillance Report (ASR) which is publicly available online. In response to feedback from Aboriginal Community Controlled Health Services (ACCHSs) to the Kirby Institute in 2016, the aim of this project was to summarise the key findings of the ASR with regard to Aboriginal and Torres Strait Islander people for stakeholders in Aboriginal Health. Our primary audience was staff and management of ACCHSs and state-based affiliates. Our secondary audience was other service providers working with Aboriginal and Torres Strait Islander people. Based on feedback from stakeholders from ACCHSs in 2016, we presented this information in a short three-page report, or "Annual Surveillance Report (ASR) Community Report", created in close collaboration with the Aboriginal health sector. The goal was to release the ASR Community Report alongside the launch of the annual ASR Report at the Australian Society for HIV, Viral Hepatitis and Sexual Health Medicine Australia (ASHM) Conference in Canberra in early November 2017. The final version of the ASR Community Report follows this reflection.

My role: An internal Kirby Institute working group was assembled to create this report in April 2017. This team included two sexual health epidemiologists (Praveena Gunaratnaram and myself), communications manager (Luci Bamford), digital communications officer (Elaine Lee), and two Aboriginal Health researchers (Robert Monaghan and Marlene Kong). Robert is a descendant of the Bundjalung Nation; his family and extended family are from the North Coast alongside the Clarence River at Baryulgil. Marlene is a descendant of the Worimi Nation; which envelops the Port Stephens area, extends from the Hunter River in the south to Forster in the north and as far west as the Barrington Tops and Maitland.

Praveena provided general oversight for this project, while I was in charge of developing the physical report in terms of content, wording, and stakeholder feedback. Praveena and Kate Whitford, a sexual health researcher at the Kirby Institute, provided invaluable assistance in terms of wording. I worked closely with Robert Monaghan to arrange the distribution of the report to 14 key stakeholders in Aboriginal health across Australia, the majority from NSW, and

some from Congress and the Victorian Aboriginal Health Service (VAHS). We also obtained feedback on the report from the UNSW Centre for Social Research in Health Community Reference Panel. Elaine Lee was responsible for the design and presentation of the report.

Why this project did not go ahead: This project did not go ahead – at least not in the planned format of a Community Report. The day before the November launch, an editor noticed that we had not appropriately acknowledged the artist (Jasmine Sarin, an Aboriginal artist from Kamileroi and Jeringa country of New South Wales) who provided the graphic on the top of the Community Report. Due to the last-minute nature of this finding, the Community Report could not be launched alongside the ASR in November 2017. The final version of the Community Report without the graphic can be found at the end of this reflection. Following this, a meeting of the internal Kirby Institute steering group was held. The major action item was to change the document format from the report originally requested by stakeholders to a poster format. This required the project to start again from the beginning. Due to my MAE project timelines, I was unable to assist with the next phase of this project.

Lessons Learned: Although the Community Report was never published, I still learnt many valuable lessons through the challenges I encountered as a member of the internal steering group. These included interpreting statistical evidence for a non-scientific audience, the need to be flexible regarding the time required to engage with stakeholders to ensure their perspectives were included, and the back and forth nature of the negotiation process between Kirby and stakeholders regarding what content to include, and how. I also learnt about the dynamics of working in a team to publish a report like this, and the different roles and skills that are required. While reviewing statistics to include in this report, I became aware of the level of incompleteness of reporting of Aboriginal and Torres Strait Islander status, and the difficulties this places on the interpretation of data. This is something that all jurisdictions could work on improving.

Public health implications: This report was strengthened by internal and external consultations. Drawing on the insights and expertise of our internal Aboriginal colleagues, Robert and Marlene helped to guide the report in the right direction initially. Then, the extent of engagement with the external Aboriginal health sector as primary stakeholders assisted in contextualising the statistical evidence, and the impact that these findings would have had for Aboriginal communities. This report would have responded directly to the needs of key stakeholders in Aboriginal Health in Australia and made key statistics in Aboriginal Health accessible and interpretable for them. It would have been an important resource for informing end users of

relevant and up to date statistics, which would have contributed to informing health promotion activities and policy development.

Acknowledgements: I would like to acknowledge Praveena Gunaratnaram, Elaine Lee, Robert Monaghan, Luci Bamford, Rebecca Guy, Marlene Kong, Kate Whitford, and John Kaldor from The Kirby Institute UNSW, the UNSW Community Reference Panel, and Katie Glass from the Australian National University for their assistance in putting the ASR Community Report together. I would like to thank the following stakeholders in Aboriginal Health for their feedback: Sandra Gregson, from the Victorian Aboriginal Health Service; Leon Bradfield, an Aboriginal Sexual Health Program Manager from NSW STI Programs Unit; Sallie Cairnduff, from the Aboriginal Health and Medical Research Council of NSW; and Ronald May, an Aboriginal Health Promotion Officer from the Aids Council of NSW (ACON).

Bloodborne viral and sexually transmissible infections in Aboriginal and Torres Strait Islander People: Community Health Service Summary 2017

For 21 years, the Kirby Institute has collected and analysed data relating to HIV, viral hepatitis and sexually transmissible infections in Australia. Monitoring and analysing disease data provides vital information to inform public health responses, and helps to show what is working well, and what needs to be improved. This document is a summary of the "Bloodborne viral and sexually transmissible infections in Aboriginal and Torres Strait Islander People: Annual Surveillance Report 2017" compiled by the Kirby Institute. The aim of this Community Health Service Summary is to provide a snapshot of relevant statistics from the full report to people working in Aboriginal and Torres Strait Islander community health services. Unless stated otherwise, all data in this report are national figures current to the end of 2016.

Completeness: It is important to note that the numbers of diagnoses for many diseases (particularly chlamydia, hepatitis C and B) are likely to be underrepresented for Aboriginal and Torres Strait Islander people because of the under reporting of Aboriginal and Torres Strait Islander status. More information about completeness can be found in the full report.

HIV infection

In Australia, HIV is mostly transmitted sexually, but also through injecting risk behaviour. A total of 1,013 notifications of newly diagnosed HIV infection were reported in 2016, including 46 notifications (5%) in Aboriginal and Torres Strait Islander people. The notification rates of newly diagnosed HIV infection in Aboriginal and Torres Strait Islander people may reflect localised occurrences rather than national patterns.

x2

In the past five years, the notification rate of HIV diagnoses in Aboriginal and Torres Strait Islander people almost doubled, with increases in urban, regional and remote areas. In 2016, the notification rate was 2 times higher in Aboriginal and Torres Strait Islander people than in non-Indigenous people, compared to a much smaller difference in 2012.

Of the Aboriginal and Torres Strait Islander people who were diagnosed with HIV in the last five years, about half were reported to have acquired the infection from male-to-male sex, and 12% from male-to-male sex or injecting drug use. A further 20% were from heterosexual sex and 14% from injecting drug use only, which is higher than for non-Indigenous people (15% and 3%). This means HIV prevention programs need to be comprehensive.

Immune function tests suggest that just over a quarter of Aboriginal and Torres Strait Islander people were diagnosed late with HIV in 2016, meaning that they had been living with the infection for four years or more. People diagnosed late with HIV can have poorer health outcomes, and may pass on HIV to someone else without knowing, so regular testing is important.

Sexually transmitted infections

6,925

A total of 71,751 chlamydia notifications were reported in 2016; including 6,925 (10%) from Aboriginal people. Aboriginal and Torres Strait Islander status was not reported for 50% of chlamydia notifications.

3,779

A total of 23,887 gonorrhoea notifications were reported in 2016; including 3,779 (16%) from Aboriginal people. Aboriginal and Torres Strait Islander status was not reported for 35% of gonorrhoea notifications.

530

A total of 3,367 infectious syphilis notifications were reported in 2016; including 530 (16%) from Aboriginal people. Aboriginal and Torres Strait Islander status was not reported for 10% of infectious syphilis notifications.

In 2016, Aboriginal and Torres Strait Islander people were:

3 times more likely to be diagnosed with chlamydia;
7 times more likely to be diagnosed with gonorrhoea; and
5 times more likely to be diagnosed with infectious syphilis,

compared to non-Indigenous people.

Aboriginal and Torres Strait Islander people living in remote locations were more likely to be diagnosed with chlamydia (5 times more likely), gonorrhoea (30 times more likely) and infectious syphilis (50 times more likely), than non-Indigenous people in these areas.

Most diagnoses of sexually transmitted infections both in Aboriginal and Torres Strait Islander people and in non-Indigenous people are in young people aged between 15 and 29 years.

As most sexually transmitted infections don't have symptoms, all sexually active young people should be tested.

Globally, there is a goal to eliminate congenital syphilis. Of the 16 congenital syphilis cases reported over the period 2012–2016, 10 cases were Aboriginal and Torres Strait Islander.

Some good news. In 2007, a vaccination program was introduced in schools to protect people from getting cervical cancer and genital warts. As a result, among Aboriginal and Torres Strait Islander people aged 21 years or younger, there has been an 88% decrease in genital warts among men and a 100% decrease among women.

Hepatitis C

In Australia, hepatitis C transmission is strongly associated with injecting risk behaviour. A total of 11,949 notifications of newly diagnosed hepatitis C infection were reported in Australia in 2016, including 1,122 (9%) which were identified as Aboriginal and Torres Strait Islander. Aboriginal and Torres Strait Islander status was not reported for 54% of hepatitis C notifications.

x4

In the past five years, the notification rate of hepatitis C diagnoses in Aboriginal and Torres Strait Islander people increased by 25%, with increases in urban, regional and remote areas. The notification rate of hepatitis C diagnoses in the non-Indigenous population remained stable over the same time. In 2016, the notification rate of hepatitis C was 4 times higher in Aboriginal and Torres Strait Islander people than in non-Indigenous people.

An annual survey of people attending needle and syringe programs has shown that needle and syringe sharing among Aboriginal and Torres Strait Islander people who inject drugs is increasing. Needle sharing is the most important risk factor for getting hepatitis C.

Some good news. New treatments for hepatitis C became available in 2016, and about 2 in 10 Aboriginal and Torres Strait Islander people who have hepatitis C received treatment in the last year.

Hepatitis B

Hepatitis B in adolescents and adults is transmitted through a variety of pathways, including both injecting drug use and sexual transmission. However, most Australians living with chronic hepatitis B acquired it at birth or in early childhood. A total of 6,555 notifications of newly diagnosed hepatitis B infection were reported in 2016, including 176 (3%) which were identified as Aboriginal and Torres Strait Islander. Aboriginal and Torres Strait Islander status was not reported for 56% of hepatitis B notifications.

In 2016, 92% of Aboriginal and Torres Strait Islander babies received a hepatitis B vaccination by 12 months of age, which is excellent coverage. However, this was lower than the 94% coverage for non-Indigenous babies.

Almost 4 out of every 100 Aboriginal and Torres Strait Islander people had chronic hepatitis B in 2016.

Some good news. From 2012 to 2016, notifications of hepatitis B have halved in Aboriginal and Torres Strait Islander people. This was probably due to the neonatal vaccination program, which started as early as 1990 in some parts of Australia, and was universal by 2000.

Prepared by Sophie Phelan and Robert Monaghan; with assistance from Kirby Institute staff. We are grateful to a number of community health services for their input.

Chapter 2: Design and conduct an epidemiological study

Chapter 2a: Design an epidemiological study

Part 1: Evaluation of the impact of azithromycin mass drug administration for trachoma on the prevalence of sexually transmitted infections in Fiji

Part 2: Regimens of Ivermectin for Scabies Elimination (RISE) – Baseline survey

Chapter 2b: Conduct an epidemiological study

Prevalence of scabies in Gizo Primary School, Western Province, Solomon Islands

Preface

The most interesting and demanding part of my MAE was the Epidemiology Project requirement. For me, this involved fully setting up two international field epidemiology projects, and completing a school-based prevalence survey of scabies in the Solomon Islands. The two international field epidemiology projects could not be completed in the time frame of my MAE. This chapter will consist of a short project summary and reflection on the work that I did on the two international field epidemiology projects, followed by a formal chapter on my final epidemiology project (see the contents section on the following page).

Prior to the MAE, I had developed an interest in neglected tropical diseases and their control – in particular, trachoma. I had worked as an intern at the WHO Department of Neglected Tropical Diseases in the trachoma section in 2016. As a result of my experience and interest, it was suggested I could become involved in a study on the evaluation of the impact of azithromycin mass drug administration (MDA) for trachoma on the prevalence of sexually transmitted infections (STIs) in Fiji (Chapter 2a, Part 1), for my epidemiology project. I undertook a preparatory field-trip, developed a protocol and submitted the project for ethics review, but the project was ultimately placed on hold for reasons beyond my control (see Part 1, Reflection, for more details).

However, another opportunity presented to work on a study on regimens of ivermectin MDA for scabies elimination in the Solomon Islands (Chapter 2a, Part 2). I was very interested to take on this project because of my passion for neglected tropical diseases and their control. I undertook a field trip, and developed the protocol for ethics approvals. Due to a delay in the time frame of implementation I decided, in consultation with my supervisors, not to continue to work on this project (see Part 2, Reflection, for more details). However, I was able to assist the scabies study team with a side project linked to the larger study, and to include this as the main epidemiology project for my MAE BV (Chapter 2b).

Despite the setbacks above, I learnt many valuable lessons through these projects. I am delighted to share these experiences in the following chapter.

Contents

Appendices

Chapter 2a, Part 1: Evaluation of the impact of azithromycin mass drug administration for trachoma on the prevalence of sexually transmitted infections in Fiji

Project summary

Title	Evaluation of the impact of azithromycin mass drug administration for trachoma on the prevalence of sexually transmitted infections in Fiji.
Objectives	i. To conduct a baseline survey of the prevalence of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoea* (NG) among women aged 18-29 years attending ANCs in Fiji. ii. Estimate the change in prevalence of CT and NG one month and one year after MDA for trachoma in Fiji.
Design	The study design was repeat cross-sectional, with three identical prevalence surveys conducted from 2017 to 2018 in pregnant women attending selected clinical services in Fiji. The study aimed to recruit women attending each of the participating clinics over three points in time as follows: 1) Prior to the implementation of the trachoma MDA; 2) Immediately following completion of the trachoma MDA and 3) Twelve months after the completion of the trachoma MDA.
Outcomes	The prevalence of CT and NG at baseline, one-month post trachoma MDA, and 12 months post MDA.
Study Duration	2 years.
Interventions	The intervention we planned to assess was the government administered Mass Drug Administration of trachoma, estimated to begin in Fiji in September/October 2017.
Number of subjects	3000 women (1000 women at each of the three study survey periods).
Population	Participants were to be pregnant women aged 18-29 years attending their Booking Visit in Fiji.
Ethics approvals	Fiji National Health Research and Ethics Review Committee (FNHRERC): Protocol number: 2017.88.NW, approval date: 21/03/2018 UNSW HREC: Protocol number: HC17651, approval date: 22/09/2017 ANU HREC: this could only be given once approval had been granted by FNHRERC and the UNSW HREC. By the time these institutions had granted approval, the trachoma MDA intervention had been cancelled so the project did not go ahead, and therefore ANU ethics was not required.

Reflection

My role: I was the study coordinator for this project, which was a primary focus during the first 6 months of my Master of Applied Epidemiology (MAE). I provided major input into study design, completed sample size calculations, wrote the study protocol, designed the study forms including consent form and participant information sheets (see Annex 2A), obtained Australian and Fijian ethical approval (see Project Summary – Ethics Approvals), created a detailed project budget, and made presentations within the Kirby Institute (to the PHIRG, SHP and SERP programmes – see Annex 2C for slides). Additionally, the participant information and consent forms I designed for this study meet the MAE competency of a communication to a non-scientific audience (Annexes 5 and 6 within Annex 2A).

The role of study coordinator also involved a field trip. I spent two weeks in Fiji liaising with stakeholders from the Ministry of Health and Medical Services, Fiji Centre for Disease Control (CDC), and clinic staff at the six proposed study sites in order to develop a culturally and clinically appropriate study protocol. I visited four out of six proposed study sites across Fiji to meet with their antenatal clinic (ANC) staff and discuss the project. During these meetings I also visited the available laboratory facilities to determine if it would be feasible to test the study samples at each site (see Annex 2B: Laboratory and Site visit report). In the capital, Suva, I also liaised with staff at Fiji CDC so I could organize the study logistics including personnel, sample transport, budget, equipment and laboratory testing and study SOPs.

Why this project was not feasible as an MAE project: The main reason that this project was not feasible as an MAE project was because in-country ethical approval from Fiji National Health Research and Ethics Review Committee (FNHRERC) took 9 months (submitted 8th June 2017, approved 21st March 2018), so it was not possible for us to conduct the baseline sexually transmitted infection (STI) prevalence survey in the remaining timeframe of my MAE. Even though the completion of this project was not feasible within my MAE, I learnt many epidemiological skills and was also able to use it as an example for my "Lesson from the Field".

Public health impact: This would have been only the second study in the world to assess the effect of using trachoma mass drug administration (MDA) as a control strategy for sexually transmitted infections (STIs). The findings would have provided important information on the role of trachoma MDA for STI control, both for Fiji and internationally. All women who were found to have an STI in the prevalence surveys would have received treatment free of charge.

This study also would have provided a population prevalence estimate of STIs. This is very important as even though STIs are frequently asymptomatic, lack of resources in Fiji mean that they are only notified through syndromic surveillance. A population polymerase chain reaction

(PCR) prevalence estimate would provide accurate data to base other interventions on, and to ensure more resources are allocated to this issue by the Fijian government. This is especially important as the last PCR prevalence survey of STIs in Fiji was in 2008[1].

Lessons learned: This project allowed me to apply my skills in project management, epidemiology and biostatistics. In doing so, I significantly extended my project management skills, particularly in terms of documenting project progress, delegating and keeping on top of upcoming tasks. However, the most important lesson I learnt was in regard to informed consent of participants in low- and middle-income countries, and the concept of "gratuitous concurrence" which is a phenomenon where a person appears to assent to every proposition put to them, even when they do not agree.

During my first few meetings in Suva I noticed how helpful local staff appeared to be. Nothing was a problem, and they would say "yes" to anything I asked or requested. Did they have a GeneExpert machine available for this study at Mataika House CDC? Yes. Did they have a GeneExpert machine available for this study at Twomey Hospital? Yes. I followed up these initial "yes-es" to confirm. The laboratory assistant at Mataika House CDC showed me a different laboratory machine – while I could see the GeneExpert in the corner. And as for the GeneExpert machine at Twomey Hospital – it was actually in continuous use analyzing tuberculosis samples, a much higher priority than our study.

I began to notice a similar "yes" pattern during my clinic visits. After discussing the project with the sister in charge, I would ask if she (always a she) had any questions. She never would. Then I asked if it would be OK for us to collect samples from her clinic. She would always say yes. However, often after the official end of the meeting on the way out, I would receive a flood of very simple and basic questions. This made three things apparent to me: 1) I had not explained the project in a way that was easy for the sisters to understand; 2) I had not created a comfortable environment for them to ask me questions during the meeting; and 3) they were saying "yes" without knowing what they were saying yes to.

This worried me and I couldn't help feeling uncomfortable about what was happening. I recalled similar experiences from pre-MAE work in Tanzania and Uganda. I knew that local staff were not meaning to mislead me when they were saying that the GeneExpert machines were available. My experience in Fiji worried me especially as it was clear from the ANC nurses' questions that came after agreeing to the project, that they did not really understand what was involved in our study. This prompted me to consider how often a "yes" in Fiji was really an "I'm not sure, but I'm too embarrassed to ask" or a "No, but I will say yes to make you happy".

A few weeks after my Fiji field trip, I heard an interesting talk at the Kirby Institute by Dr Sarah Bernays, a lecturer from USYD School of Public Health. Dr Bernays spoke about the process of gaining informed consent for sexual health interventions in developing countries. Her final sentence really resonated with my Fiji experience - "It is important to consider: is there anything your participants wouldn't say yes to?". This made me very concerned. I couldn't stop thinking about how easily this had happened to me. I had gone in to this project with the best intentions. I discussed this issue with some of the MAEs who have had experience working on STI projects in Indigenous communities in Australia. They had seen this happen time and time again – and they told me the name of this phenomenon: "gratuitous concurrence".

Essentially, gratuitous concurrence is when a person appears to assent to every proposition put to them, even when they do not agree[2]. This reaction has been observed in many Indigenous peoples for a long time[3, 4]. However, gratuitous concurrence is widely recognized in people in a position of powerlessness when confronted by alien institutions and authority figures. The people may feel powerless because they are disadvantaged due to a language barrier, and just adopt the strategy of agreement or assent with the person in authority regardless of the truth of their feelings. Learning more about gratuitous concurrence made me think - in how many other studies in developing countries has this happened – and on a more worrisome note, in how many other studies has this been taken advantage of?

In a way, I am glad that I became mindful that my approach was generating gratuitous concurrence before this study was able to start, and that I have now learnt a serious lesson. In future work in developing countries, or in any situation when I am asking something of someone in a situation where there is a power imbalance, I will ensure that a local study team member looks after local negotiations, and if there is no option but for me to do it, I will properly research culturally appropriate forms of going about my request.

Culturally appropriate forms of communication could be things like avoiding direct yes/no questions e.g. "Do you have any questions?", "Would it be OK for us to collect samples from your clinic?", and enabling a more open discussion with opportunity for people to describe things in their own words. Also, being patient and giving time for silence and pause to allow people to put thoughts together, instead of rushing through a list of questions, may help to facilitate a more comfortable, safe and open environment. I'll also make sure to research the use of body language in the culture I'm working in. For example, for Aboriginal Australian people, direct eye contact may be seen as a sign of aggression, rudeness or disrespect, and lowered eyes and talking in a quiet manner are seen as much more respectful.

I believe that the concept of gratuitous concurrence is something that should be highlighted with MAE students at their first course block. I also believe it should be a significant central theme for the studies of all international public health students in Australia, with a focus on the key cultures Australian researchers work with: Aboriginal Australians and our neighbors in the Pacific Islands. This way, the best intentions of the students can be channeled in a more culturally appropriate and timely way.

While this project was unable to go ahead, I still learnt some invaluable lessons that will stay with me, and guide my research and work in field epidemiology in the future. I am incredibly grateful to my field supervisor, John Kaldor, for giving me the opportunity to work on this project, and to Lucia Romani for sharing her knowledge and experience of working in the Pacific.

Acknowledgements: I would like to thank my field placement supervisors John Kaldor and Rebecca Guy for providing the opportunity for me to work on this project, and for their technical support with this project. I would like to acknowledge Lucia Romani from the Kirby Institute for sharing with me her knowledge of working in the Pacific, and for introducing me to her colleagues in Fiji. I would like to acknowledge Stephen Badman from the Kirby Institute for his assistance in planning study logistics. Thank you to Katie Glass, my academic supervisor who was also a great support for this project. And of course, I must acknowledge our Fijian co-investigators from the Fiji Centre for Communicable Disease Control: Aminiasi Koroi, Mike Kama, and Daniel Faktaufon, and from the Fiji Ministry of Health and Medical Services: Torika Tamani, Dashika Balak, Merelesita Rainima-Qaniuci, and Luisa Cikamatana, and from the Fred Hollows Foundation Fiji: Anaseini Cama. I would also like to acknowledge our final investigator, Andrew Steer, from the Murdoch Childrens Research Institute, Australia.

References

1. Cliffe S, Tabrizi S, Sullivan E. 2008. Chlamydia in the Pacific: The Silent Epidemic. *Sexually Transmitted Diseases* 35(9):801-6.
2. Legal Services Commission of South Australia, 2018. Gratuitous Concurrence. Accessed on 11th December 2018, from https://lsc.sa.gov.au/dsh/ch03s04.php
3. Liberman K. 1980. Ambiguity and Gratuitous Concurrence in Inter-cultural Communication. *Human Studies* 3(1):65-85.
4. Manez S. 2007. The road to reconciliation: Should the legal system, Aboriginal customs and the government play a role to reinstall some pride and sense of empowerment to Aboriginal people of Australia? Journal of eLaw 14(54).

Photos from the field

Into the field

Meeting with the ANC staff, Sister Luisa and Sister Vena at Lautoka ANC.

Nadi Hospital

Beautiful Leleuvia Island

Chapter 2a, Part 2: Regimens of Ivermectin for Scabies Elimination (RISE) – Baseline Survey

Project summary

Note: below is a summary of the entire RISE project for context. See the last section on "My Role" which describes how part of the RISE project fitted in with my MAE.

Title	**A Cluster Randomised Non-Inferiority Trial of One Versus Two Doses of Ivermectin for the Control of Scabies Using a Mass Drug Administration Strategy**
Objectives	**Primary Objective:** 1. To determine if mass drug administration (MDA) with one dose of ivermectin is as effective as MDA with two doses in reducing the prevalence of scabies at 12 months after the intervention. **Secondary Objectives:** 1. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing the prevalence of scabies at 24 months; 2. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing the prevalence of impetigo at 12 and 24 months; 3. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing presentations to health clinics with scabies and impetigo; and 4. To determine the safety of one compared to two doses of ivermectin for ivermectin-based MDA.
Design	Prospective comparison of the efficacy and safety of two different treatment regimens for scabies in 20 villages in the Western Province of the Solomon Islands. One treatment arm involves a single dose of oral ivermectin delivered through MDA, and the other treatment arm involves two doses of oral ivermectin (one week apart). The prevalence of scabies and impetigo will be measured before treatment at baseline (my MAE epi project), then at 12 and 24 months post treatment (post MAE).
Outcomes	The primary outcome measure is the prevalence of scabies at 12 months. Secondary outcome measures are:

	- the prevalence of scabies at 24 months; - the prevalence of impetigo at 12 and 24 months; - the number of presentations with scabies and impetigo to primary health care clinics by age group in the 24 months after MDA; and the number of adverse events measured by active surveillance immediately after MDA and by passive surveillance in the 24 months after MDA.
Study Duration	3 years.
Interventions	Each of the 20 villages will be randomised equally to one of the following two treatment arms (10 in each arm): *Group 1 - Oral ivermectin-based MDA (single dose)*: Participants will be offered 1 dose of oral ivermectin at 200 ug/kg unless contra-indicated. Individuals with a contra-indication will be offered topical permethrin. *Group 2 - Oral ivermectin-based MDA (two-doses)*: Participants will be offered the first dose of MDA treatment as in the single dose group, and then a second dose 7 to 14 days later, identical to the first.
Number of subjects	Approximately 5000.
Population	All individuals living in the selected study sites, agreeing to participate.
Ethics approvals	Royal Children's Hospital Melbourne HREC: HREC reference number is HREC/18/RCHM/178 and RCH HREC Reference Number 38099A, approval date: 13/07/18 Solomon Islands Research and Ethics Review Board: HREC reference number is HRE005/18, approval date 31/07/2018 ANU HREC approval: this could only be given once approval had been granted by RCH HREC and the Solomon Islands HREC. By the time these institutions had granted approval, the project timelines had been stretched to point of infeasibility for this project to be included in my MAE.
MY ROLE WITHIN RISE	My MAE Epidemiology project was to set up the baseline scabies survey, and to administer the ivermectin intervention.

Reflection

My role: I was the study coordinator for this project, which took up much of my time during the first half of the second year of the MAE. While the overall RISE project was extensive, it was planned that I would complete the baseline survey as my MAE Epidemiology project, and continue working on the rest of the project post MAE. This said, setting up the baseline survey also essentially meant setting up the whole RISE project. I provided input into study design, sample size calculations, wrote the study protocol (see Annex 2D), designed the study forms including consent form and participant information sheets (see Annex 2E), obtained Australian and Solomon Islands ethical approval (see Project Summary – Ethics Approvals), and also went on an initial scoping trip (see Annex 2F – Scoping Trip Report).

On the scoping trip, I met with local study members, Solomon Islands Ministry of Health staff, and hospital staff. We refined the protocol together, and discussed the most appropriate villages in the Western Province to survey (see the map in Annex 2 of Annex 2E for final villages and their locations). I was mindful of my experiences in Fiji with gratuitous concurrence as mentioned in Chapter 2a Part 1, and used a more open and quiet manner in my interactions with local staff. I felt that I was able to earn their respect, and my impression was that they felt that they could answer me truthfully, even if that meant saying no. We worked together to design a study census (see Annex 3 of Annex 2F for the census data collection form we designed together) as there was no population data from the villages in Western Province within the past 10 years. We needed this data to plan logistics for the baseline scabies survey, and it was also essential data for the Solomon Islands Ministry of Health.

Public health impact: The pre-baseline survey census would have provided the Solomon Islands Ministry of Health with much needed data on age and sex distribution within the Western Province, along with an estimate of the number of people living in each household. The baseline scabies survey will provide much needed data on the scabies burden in the Western Province of the Solomon Islands. The entire RISE study will be the first study to provide evidence on the efficacy of one versus two doses of ivermectin in the treatment of scabies. If a single dose proves as effective as two doses, this will halve program costs and will therefore have major implications for countries where scabies is endemic.

Why this project was not feasible as an MAE project: There were two key reasons why this project was not feasible as an MAE project. Firstly, it was initially anticipated that my other MAE projects would be completed before the baseline survey. This was essential as the baseline survey was going to require 100% of my time. However, the timelines of my other MAE projects were delayed – particularly my gonorrhea outbreak investigation which required unexpected

months of protocol revisions before it was accepted under the NSW Public Health Act. Secondly, it was incredibly difficult for me to manage the study coordinator position of this international project when I was based in Sydney, particularly before I had been connected with the local counterparts of the project. This meant further delays in communication and in-country study set up.

Lessons learned: I learnt a lot from my involvement in the RISE project, and am still reflecting on it. But the three major things I learnt were to recognize my own limits; the importance of taking the time to invest in local relationships; and to prioritise a work life balance for myself in the future.

I now know that this project was too big for me to take on during the MAE, especially as I was not based in the Solomon Islands, and was finishing off three other MAE projects. For this project to be successful, I think that it would have been best if I was based in Gizo, with the support of a local study co-ordinator and a study logistician. I also think that a minimum 6 months of in-country preparation time is necessary for a study coordinator leading a study such as this. Before this experience I did not know my own limits. Now I can better identify challenges that I can achieve (and their potential timelines), and challenges that I can best achieve with support from others.

I also learnt that the key to success of international projects is building respectful and strong relationships with local counterparts – which is not something that can be instantly achieved. If you are really passionate about your work, taking the time to get to know people and conveying this genuine interest will greatly help. While I feel this is something I enjoy and prioritise when working internationally, the three days that I originally spent in Gizo were not enough time to develop the relationships that were essential for this project. I spoke to a few DFAT volunteers while in Gizo and they mentioned that for the first few months of their program, they were instructed to focus on getting to know people, attend local gatherings, and genuinely build a network for themselves within the community. I think this is an essential part of any international collaboration, particularly when there are large cultural and economic divides between the countries of the various stakeholders involved.

The final lesson I learnt was about looking after myself. I will now ensure that I prioritise a healthy work life balance in the future. This was a huge project, and while it was unfortunate that I couldn't continue leading it, I still learnt a lot. I am grateful to my supervisor, John Kaldor, for his faith in me to take on this project, and to my close-knit family for supporting me in everything I take on.

Acknowledgements: I would like to thank my field supervisor, John Kaldor, Lucia Romani from the Kirby Institute, and Andrew Steer and Daniel Engelman from the Murdoch Childrens Research Institute for their supervision and technical advice regarding this project. I would like to thank Michael Marks from the London School of Hygiene and Tropical Medicine for his assistance with the ethics applications, protocol and sharing his in country knowledge. Matthew Parnaby, Millicent Osti, Myra Harding and Li Jun Thean, from the Murdoch Childrens Research Institute, thank you for your moral support and technical advice. Thank you to our collaborators from Gizo Hospital, Western Province, Solomon Islands for your warm welcomes and support, particularly Tina Galona, Oliver Sokana and Dickson Boara. For helping to keep me on a path to MAE completion, I would like to thank Ross Andrews and my academic supervisor Katie Glass from the Australian National University, and my field supervisor Rebecca Guy.

Photos from the field

Flying over Guadalcanal

Cloud forming over the dormant volcano Kolombungara

Gizo Hospital

Arriving at Gizo harbor by boat

Chapter 2b:

Conduct an epidemiological study

Prevalence of scabies in Gizo Primary School, Ghizo Island, Western Province, Solomon Islands

2.1 List of abbreviations

DALYs	Disability-Adjusted Life-Years
GBD	Global Disease Burden
HDI	Human Development Index
MAE	Master of Applied Epidemiology
MCRI	Murdoch Children's Research Institute
YLD	Years Lived with Disability
RISE	Regimens of Ivermectin for Scabies Elimination
WHO	World Health Organization

2.2 Prologue

My role: Although the baseline scabies survey within the Regimens of Ivermectin for Scabies Elimination (RISE) study that I set up (see Chapter 2a, Part 2) was not feasible within my Master of Applied Epidemiology (MAE), I was able to assist the scabies team with a scabies diagnostic accuracy study as a side project to RISE for my official MAE epidemiology project. My work in setting up RISE also contributed to the set-up of the scabies diagnostic study. The scabies diagnostic study was covered by the RISE ethics approvals that I obtained, and I also assisted in identifying Gizo Primary School as the study base for the scabies diagnostic study on my scoping trip for RISE. As the scabies diagnostic study was being led by another student, Millicent Osti (MO), my new role was primarily to assist her. This included helping with study set-up and administration in the field, creating a secure database using REDCap with online and offline data entry options, and data entry. The write up and analyses of this project for my MAE chapter was conducted independently of MO, and includes the prevalence study component only.

Lessons learned and reflections: Special considerations are required when working in overseas community settings. Community engagement and investment in building relationships based on trust and respect are important when engaging and collaborating at the community level. On reflection, more time could have been spent on these considerations. For example, the concerned parents at the parent teacher night demonstrated that the community awareness component could have been more substantial. Another oversight became evident when we arrived to a week of torrential rain. Because the rain makes the unsealed roads on Ghizo Island difficult to use, most students don't come to school because they have no way of getting there. In addition, we had assumed that the school day in Gizo ran from approximately 9-5pm, however on arrival a week before the study, we found out that it ran from 8-1pm. As the study period had been planned around the number of children that could have been screened by examiners in a 9-5 day, it meant that we had to rethink this process in the field.

Another lesson that I learnt was that it never hurts to over-communicate, especially in a cross-cultural study team. An example of this was in relation to our study recruitment method. Approximately a week before the study, we handed the information sheets and permission slips to the principal of Gizo Primary School, and asked her to pass them on to the teachers to then pass on to the students. After a few days we returned to see how things were going and were relieved that we did, as we discovered that the message had been confused, and the principal had asked the teachers to only hand the permission slips to children that they thought already had scabies.

Finally, I learnt that no matter how positive or ethically sound your intervention or study may be, it is important to consider the potential negative consequences ahead of time so that mitigation strategies can be put in place. Some of these negative consequences may be common in all settings, and some may be particular to the culture you are working in. In this study, after a few days we discovered that children who had been found to have scabies were being treated differently, and we became concerned with the potential of stigma arising. Some of the teachers had commented to the local study team that they did not want children with scabies in their classes, and some had been teased by other children. Luckily members of the local study team brought this to our attention, and they went and spoke to the teachers.

Public health impact: This was the first scabies prevalence study conducted in Gizo, and the first scabies prevalence study conducted in a primary school setting in the Solomon Islands. The high prevalence of scabies and impetigo found in Gizo Primary School indicates that this setting would benefit from community-wide scabies treatment.

Acknowledgements: I would like to thank Millicent Osti, and her supervisor Daniel Engelman (both from Murdoch Children's Research Institute [MCRI]) for allowing me to assist them with their study and to complete the prevalence assessment component. I would also like to acknowledge my field supervisor John Kaldor and Andrew Steer from MCRI for making this opportunity a possibility for me. Thank you to Ross Andrews from the Australian National University and to my academic supervisor Katie Glass for assisting with ethics applications, data analysis plans and timelines. Thank you to Matthew Parnaby from MCRI for your logistical support. I would also like to acknowledge the rest of the study team: Margot Whitfeld (St Vincents Hospital Sydney, Department of Dermatology); Michael Marks (The London School of Hygiene and Tropical Medicine); Deanne Seppy (MCRI); Tina Galona, Una Gagahe, Ender Malasa (Gizo Hospital, Western Province Solomon Islands); and of course the Western Province Community Nurses: Sana Bisili, Stephen Tiazi, Arthur Keremama and Winter Sino.

2.3 Abstract

Introduction: Scabies and impetigo are associated skin conditions commonly found in resource-limited settings. Globally, the highest prevalence of these conditions is in children in the Pacific, however limited prevalence data exist. We conducted a prevalence survey of scabies and impetigo in Gizo Primary School, Western Province, Solomon Islands.

Methods: Consenting students from Gizo Primary School were clinically examined for scabies and impetigo by a paediatrician and a dermatologist over the period of 1 week during August, 2018.

Results: 171 participants were examined out of 693 eligible students. Scabies was observed in 97 participants (56.7%) of the population surveyed, a prevalence which increased to 63.7% (95% CI 55.6-71.1%) when standardised to the age and sex structure of the total school population. Impetigo was observed in 75 participants (43.9%) of the population surveyed. When this was standardised to the age and sex distribution of the total population of Gizo Primary School, a lower impetigo prevalence of 41.9% (95% CI 44.0-50.3%) was estimated. Almost half (48%) of children with scabies also had impetigo, however the presence of scabies was not significantly associated with impetigo (relative risk 1.3, 95% CI 0.9-1.8).

Conclusions and Public Health Implications: A higher than expected prevalence of scabies and impetigo was found in Gizo Primary School. School based and community wide treatment strategies are a consideration for this setting.

2.4 Photos from the Field

Gizo Primary School

Study set up in Gizo Primary School library

Rainy weather all week meant the roads were often impassable by traffic

Field study team: Sophie Phelan, Deanne Seppy and Millie Osti

2.5 Introduction

Scabies is a parasitic disease caused by infestation with a microscopic mite (*Sarcoptes scabiei* var *homini*) that burrows under the skin of hosts causing extreme itching[1]. Intense scratching as a consequence of the itching can tear the surface of the skin and result in complications due to bacterial infection of the skin. The most common of these is known as impetigo, which is predominantly caused by *Staphylococcus aureus* and *Streptococcus pyogenes*[2]. Other infections that scabies can lead to range from skin abscesses, cellulitis, and necrotising fasciitis, through to septicaemia, renal disease, and potentially rheumatic heart disease[3, 4]. Scabies is highly contagious, and transmission commonly occurs through prolonged direct contact with infested skin and also during sexual contact[1]. Transfer of mites can also occur through clothes and bedding.

Scabies particularly affects people in resource poor areas, particularly young children and people who live in conditions where close body and skin contact is common[1, 4]. In developed countries, prevalence is generally low but outbreaks amongst populations in institutionalised care (for example nursing homes, child care centres, extended-care facilities and prisons) are well described[1,5]. Historical epidemics were attributed to poverty, poor sanitation or crowding associated with war, mass movement of people or economic crises[1]. Impetigo is also common in overcrowded and resource poor settings, but is particularly exacerbated by hot and humid conditions and limited access to water[6].

There are several effective options for the treatment of both scabies and impetigo at the individual level. Standard approaches to scabies control in these situations usually focus on treating the infested individual and their household contacts. The topical cream (permethrin or benzoyl benzoate) is applied to the whole body and a follow up review conducted 2 weeks later. However, treatment at the community level in endemic populations is challenging because of the high chance of reinfestation[7]. Attention has recently shifted to the role that mass drug administration (MDA) of antiparasitic medication can play in these settings[8].

When it comes to health programmes and research, scabies has frequently been accorded low priority despite regular reports of its high prevalence[7]. It has been suggested that this is because the disease complications of scabies are spread across a broad range of disciplines including dermatology, infectious diseases and paediatrics[7]. Another issue is that scabies and impetigo are diseases of tropical developing countries where resources for new health initiatives are scarce. While scabies has been recognised as a neglected disease for a long time[3, 9-10], it was only added to the WHO portfolio of neglected tropical diseases in 2017, under “scabies and

other ectoparasites"[11]. Neglected tropical diseases are a diverse group of communicable diseases that prevail under conditions of poverty in tropical and subtropical climates.

Social and economic consequences of scabies are rare in developed countries, while its impact is much greater in resource poor and overcrowded settings[12]. This is largely through its contribution to serious bacterial infection. Scabies has a direct impact on quality of life due to the intense itching it causes, causing sleep disturbances in up to 70% of cases, leading to substantial delays in development and learning in the young children it predominantly infests[13]. Treatment of scabies can inflict a considerable economic cost on individuals, families and health services[14]. Because of this, scabies often goes untreated as people living in resource poor settings need to prioritise treating other diseases of greater morbidity and mortality.

Scabies is a substantial contributor to global morbidity and mortality, and the World Health Organization (WHO) estimates that over 100 million people worldwide have scabies every year. Global Disease Burden (GBD) provides a way to measure morbidity and mortality in terms of health loss from disease and injury across age, sex, location and time using the disability-adjusted life-years (DALYs) metric. DALYs combines mortality (estimated using years of life lost [YLL]) and morbidity (estimated using years lived with disability [YLD]) components. In 2017 a study[15] investigated the GBD of scabies and found that the world regions of east Asia (age-standardised DALYs 136·32), southeast Asia (134·57), Oceania (120·34), tropical Latin America (99·94), and south Asia (69·41) had the greatest burden of DALYs from scabies. A recent systematic review on the global prevalence of scabies[7], found that overall scabies prevalence was highest in the Pacific and Latin American regions, consistently being higher in children than in adolescents and adults. This study also found that impetigo was common in children, with the highest global prevalence in Australian Aboriginal communities (49.0%)[7].

The previously mentioned systematic review found that some countries within the Pacific have a scabies prevalence in children approaching 50%[7]. Unfortunately, epidemiological data on scabies and impetigo are scarce in Pacific countries. Fiji and The Solomon Islands have however conducted fairly recent prevalence surveys. A recent prevalence study of scabies in Fiji[16] reported a scabies prevalence of 23.6%, which reduced to 18.5% nationally when adjusted for age and location structure in census data. The prevalence was highest in children aged five to nine years (43.7%), followed by children aged less than five (36.5%). The prevalence of impetigo was 19.6%, with a peak in children aged five to nine years (34.2%). Scabies was very strongly associated with impetigo, with an estimated 93% population attributable risk. In a recent study conducted in 10 villages in the Western Province of the Solomon Islands, an all-ages scabies prevalence of 19.2% was estimated[17]. The highest prevalence was found in infants <1 year of age (34.1%) and children aged 1-4 years (25.7%). The total unweighted prevalence of active

impetigo was 32.7%, with the highest prevalence in children aged 1–4 years (42.6%). Scabies infestation was associated with active impetigo infection (AOR 2.0, 95%CI 1.6–2.6); with 41.1% of active impetigo cases also having scabies.

The aim of this study was to determine the prevalence of scabies and impetigo by age and sex in Gizo Primary School, one of two main primary schools in the town of Gizo on Ghizo Island in the Western Province of the Solomon Islands. All children found to have scabies were provided with treatment for themselves and their families, and any with impetigo were referred to Gizo Hospital for further examination. These data will be provided to the school and the Solomon Islands Ministry of Health, who have collaborated closely in the development of this study. The data from this study will also contribute to knowledge of the burden of scabies and impetigo in the Solomon Islands and inform further public health interventions.

2.6 Methods

Complete methods for the broader scabies diagnostic accuracy study will be written up by Millicent Osti (MO) for her Master of Philosophy. Below are the methods relating to the prevalence study component.

Study type

A cross sectional prevalence survey was conducted at Gizo Primary school from Monday 20th – Friday 24th August 2018.

Setting

Gizo Primary School is one of two primary schools on Ghizo Island in the Western Province of the Solomon Islands, an area home to approximately 76,649 individuals according to the 2009 census[18]. The Solomon Islands is a country in the South Pacific comprised of an archipelago of 992 islands, low-lying coral atolls and volcanic calderas. The Solomon Islands were ranked 152nd on the Human Development Index (HDI) in 2018[19], and the country has considerably poorer health outcomes compared to South Pacific regional averages[20].

Study Population

Any child enrolled in Gizo Primary School, Western Province, Solomon Islands with a permission slip returned by a parent or guardian was eligible for this study. The age range was 4-14 years of age.

Recruitment

Teachers sent a paper-based information sheet and permission slip home with the students approximately one week before the planned first day of the study. Students took these forms home to their parents or guardians who provided written consent on behalf of their child. Failure to bring back a form was regarded as non-consent.

Sample size

At the time of this study, there were 693 children enrolled in the school. A participation rate of 62% (430 students) was expected based on the participation rate of a school-based scabies prevalence survey in Fiji in 2006[2]. Separate sample size calculations were conducted to meet the requirements of the scabies diagnostic accuracy study.

Testing procedures

The study was conducted in the library at Gizo Primary School. There were six examiners in total: two expert examiners and four local nurses trained by the study team in scabies diagnosis. A station was set up for each of the six examiners, and study team members were positioned at enrolment and tracking stations to ensure participants visited all stations, and that consensus diagnosis was reached by the two expert examiners. A separate room was available for children who wished to be examined in private. Local study team members were called upon as needed to act as translators for some of the smaller children who could not speak English, and communicated with them in Solomon Island Pijin or their local dialect.

Scabies and impetigo diagnosis was based on a set of consensus clinical criteria that was developed using a Delphi process with input from a large number of scabies experts. Further explanation of these methods are described by MO for the scabies diagnostic accuracy study. Four local nurses were trained in the application of the clinical criteria and assisted with the examinations. While definitive scabies diagnosis requires visualization of the mite products using magnification imaging, the facilities and time needed for these techniques were not readily available at the study setting. Expert clinical consensus was deemed an appropriate substitution method in this case, as clinical diagnosis is the mainstay of diagnostic techniques in low resource settings.

We therefore sought out two experts who obtained a consensus diagnosis, therefore increasing the likelihood of a true positive diagnosis. These expert examiners were a paediatrician with extensive experience in scabies endemic areas and a dermatologist who has been involved in multiple large scabies trials. All examinations and diagnoses between the six examiners were blinded to each other. When the two expert examiners disagreed, this was flagged by a study team member after the second examination. After a discussion between the two experts, a consensus diagnosis was obtained.

For the scabies diagnostic accuracy study, a minimum sample size of 100 participants comprising at least 40 with scabies and at least 40 without scabies was needed. Once this number was reached, the four local nurses completed the remainder of the scabies screening as the two experts were only available for a short period of time. The primary outcome measure of the scabies diagnostic accuracy study was the sensitivity and specificity of the nurses' diagnosis compared to the expert consensus. Unfortunately the sensitivity and specificity of the nurses diagnoses was found to be low, so we only included participants examined by the two experts for this prevalence analysis.

Treatment

Any child found to have scabies was provided with 5% topical Permethrin cream free of charge. Any child found to have impetigo or another health condition was referred to Gizo Hospital.

Information Collected

A number of variables were extracted from the scabies diagnostic accuracy study database for the prevalence study component. Demographic details extracted included: study ID, age, sex and grade. The grade variable was excluded from this analyses (this analysis, or these analyses?) because it was highly correlated with age (Pearson's correlation coefficient = 0.92). The diagnosis variables of scabies, impetigo – mild, and impetigo – moderate or severe were used as the outcome variables of this study. Examiner identification and consensus variables were also extracted and any data from participants not examined by the two expert examiners were not used in this analysis.

Data analysis

Data analysis was completed using Microsoft Excel 2018 version 16.9 (Microsoft Corporation, Washington, USA) and Stata version 15.1 (StataCorp, Texas, USA). Crude prevalence of scabies and impetigo was calculated with their 95% confidence intervals. Directly standardised prevalence for scabies and impetigo was calculated using Gizo Primary School 2018 population data (age was standardised by year – not age group). An adjusted odds ratio for scabies was calculated using a logistic regression model that incorporated the demographic factors of gender and age group. Age was grouped for the logistic regression model as there were very low numbers for some ages. The association between scabies and impetigo was explored in a table calculating the prevalence of scabies in children with impetigo (by severity of impetigo), and the relative risk of scabies causing impetigo was calculated. The attributable fraction and population attributable fraction were not calculated because the relative risk was not significant.

Data collection

Paper based forms were used for data collection by examiners. At the end of each day, data were entered electronically into a REDCap database that I helped to design (Annex 2G). We made sure to design the database in two different ways depending on internet availability. If there was strong internet signal, data could be manually entered directly to the online REDCap database. If the internet signal was weak or not existent, data could be entered into a preformatted excel spreadsheet on a password protected computer. This spreadsheet was uploaded to the online database as soon as the internet was available.

Data storage

Data was encrypted and stored on a high security database (REDCap). Data downloaded for analysis did not include study participants' names. Data collected about the participants was coded and de-identified and held in strict confidence. No data identifying individuals or households will be available in any publication produced as a result of the work.

The REDCap database was accessible by investigators only using a password protected log-in that was only known to the investigators. The REDCap database files were downloaded onto a separate password-protected computer for analysis. A password protected copy of the full database was provided to the Solomon Islands Ministry of Health.

Stakeholder engagement

We travelled to Gizo prior to the study to meet with staff from Gizo Hospital and the Solomon Islands Ministry of Health to discuss this study. Both stakeholders strongly support scabies research in the region, have worked with the study team previously, and see scabies as a priority health area. A member of the study team (SP) discussed potentially appropriate schools with Gizo Hospital staff on her field visit, and met with the Gizo Primary School Principal, Nester Nadi.

Community engagement

The Gizo Primary School Principal, Nester Nadi, ensured that teachers and parents were aware of the planned scabies screening ahead of time. She also suggested that some study team members attend one of their regular parent-teacher nights so that the study team could explain the study to the parents and answer any questions, so two study team members (SP and DS) attended the next parent-teacher night. One form of community engagement that was overlooked by the study team was the Gizo Facebook Forum, however news of the school prevalence study found its way onto this platform through local channels anyway.

Ethics approvals

- Royal Children's Hospital HREC approved this project (13/07/18) and the HREC reference number is HREC/18/RCHM/178 with the RCH HREC Reference Number 38099A.
- Solomon Islands Research and Ethics Review Board also approved this project (31/07/2018) and the HREC reference number is HRE005/18.
- ANU HREC also approved this project (17/08/2018) and the HREC reference number is 2018/551

2.7 Results

The total number of students attending Gizo Primary School in August 2018 was 693. In our August 2018 survey, all students from Gizo Primary School who returned permission slips were screened for scabies. However, among the 328 students who returned permission slips (47%), only 171 (25%) students were screened using the gold standard examiners – the rest were screened by the nurses. As the sensitivity and specificity of the nurses' diagnoses were found to be extremely low in MO's data analyses, the analysis in this chapter only reports prevalence results from the 171 students screened using the gold standard examiners.

A total of 171 children with an age range of 4 to 14 years were included in this analysis; 82 (48.0%) were males and 89 (52.0%) were females (Table 1). The largest proportion of children were aged 8-10 years (42.7%). The mean age of males (9.1 years) was slightly older than that of females (8.4 years), however this difference was not significant (P=0.0594) in a two-sample t test.

Table 1: Age and sex distribution of study participants

Age group (years)	Females	%	Males	%	Total	% of total
4-7	33	54.1	28	45.9	61	35.7
8-10	40	54.8	33	45.2	73	42.7
11-14	16	43.2	21	56.8	37	21.6
Total	89	52.0	82	48.0	171	100.0

Compared to the population of Gizo Primary School, in our sample there was an under representation of males and an over representation of females, and an over representation of children aged 4-7 years (Table 2).

Table 2. Demographics of study sample compared to Gizo Primary School

	Study Sample (N=171) n (%)	Gizo Primary School (N=693) n (%)
Gender		
Male	82 (48.0)	371 (53.5)
Female	89 (52.0)	322 (46.5)
Age (years)		
4-7	61 (35.7)	134 (19.3)
8-10	73 (42.7)	331 (47.8)
11-14	37 (21.6)	226 (32.6)
15	0	2 (0.3)

Scabies was observed in 97 participants (56.7%) of the population surveyed (Table 3). When this was standardised to the age and sex distribution of the total population of Gizo Primary School, a higher scabies prevalence of 63.7% (95% CI 55.6-71.1%) was estimated. Scabies prevalence was highest in males, who had 1.9 times the odds of females of having scabies (95% CI 1.0-3.7). The prevalence of scabies increased with age, with the highest prevalence of scabies (70.2%) among children aged 11-14 years, who had 4.4 times the odds of having scabies (95% CI 1.8-10.6) compared to children aged 4-7 years. Almost half (48.5%) of children with scabies also had impetigo (Table 4), however the presence of scabies was not significantly associated with impetigo (relative risk 1.3, 95% CI 0.9-1.8).

Table 3. Prevalence of scabies in Gizo Primary School, Western Province Solomon Islands

		Sample	Participants with scabies			
Factor		N	n	%	95% CI	Adjusted OR (95% CI)
Total	Crude prevalence	171	97	56.7	49.1-64.0	-
	Age and sex standardised prevalence	691	-	63.7	55.6-71.1	-
Sex	Male	82	53	64.6	53.6-74.3	1.9 (1.0-3.7)
	Female	89	44	49.4	39.1-59.8	1
Age (yrs)	4-7	61	21	32.4	23.6-47.2	1
	8-10	73	50	68.5	56.9-78.1	4.3 (2.1-9.0)
	11-14	37	26	70.2	53.7-82.8	4.4 (1.8-10.6)

*OR adjusted for age and sex

Table 4. Association between scabies and impetigo

		Total (n=171)		Participants with scabies (n=97)		Participants without scabies (n=74)	
		n	%	n	%	n	%
Impetigo		75	43.9	47	48.5	28	37.8
Severity	Mild	63	84.0	41	87.2	22	78.6
	Moderate or severe	12	16.0	6	12.8	6	21.4

Impetigo was observed in 75 participants (43.9%) of the population surveyed (Table 5). When this was standardised to the age and sex distribution of the total population of Gizo Primary School, a lower impetigo prevalence of 41.9% was estimated. Impetigo prevalence was higher in males, who had two times the odds of females of having impetigo (95% CI 1.1-3.6). Children aged 4-7 years old had the highest prevalence of impetigo (49.2%), however no significant association between age and impetigo was found. Most participants who had impetigo had mild impetigo (84%) (Table 4).

Table 5. Prevalence of impetigo in Gizo Primary School, Western Province Solomon Islands

Factor		Sample N	Participants with impetigo			
			n	%	95% CI	OR* (95% CI)
Total	Crude prevalence	171	75	43.9	36.5-51.5	-
	Age and sex standardised prevalence	691	-	41.9	44.0-50.3	-
Sex	Male	82	43	52.4	41.5-63.1	1.86 (0.99-3.48)
	Female	89	32	36.0	26.6-46.5	1
Age (yrs)	4-7	61	30	49.2	36.9-61.6	1
	8-10	73	29	39.7	29.1-51.4	0.56 (0.26-1.18)
	11-14	37	16	43.2	28.4-59.5	0.60 (0.25-1.44)
Scabies	No	74	28	37.8	27.5-49.4	1
	Yes	97	47	48.5	38.6-58.4	1.71 (0.87-3.39)

**OR adjusted for age, sex and scabies*

2.8 Discussion

In this cross sectional prevalence survey we report a high burden of scabies and impetigo in Gizo Primary School, Western Province, Solomon Islands. The age and gender adjusted prevalences of scabies (63.7%) and impetigo (41.9%) were substantially higher than the reported prevalences from other school based cross sectional prevalence surveys in the Pacific Region; 18.5% and 25.6% respectively in Central Division, Fiji[2], and 5.2% and 8.2% in Dili, Timor Leste in 2016[21].

In our study, the prevalence of scabies and impetigo was highest in males, which was also found in the school based studies in Fiji[2] and Timor Leste[21]. The odds of having scabies increased with age in our study, however the inverse of this trend was found in the Fiji study[2]. Age was not a significant predictor of scabies in the Timor Leste study[21]. In Gizo Primary School, we did not find a significant trend between impetigo and age, and neither did the Timor Leste study[21]. However, the Fiji study[2] found a significant association between younger age and impetigo. This could be due to sample size – the Fiji study contained the pooled results of 21 schools which included approximately 3,500 students, while both the Timor Leste study and our study had substantially less, at 502 and 171 students respectively.

While the odds ratio of scabies for causing impetigo in our study was 1.7, this was not significant (0.87-3.39). The lower limit of this confidence interval is close to 1, which along with the fact that scabies is a well-known risk factor for impetigo[22-24] suggests that if we had a larger sample size we may have had enough power to detect a significant relative risk. A post-hoc sample size calculation indicates that if we enrolled 768 students we could have detected a significant relative risk (based on an alpha value of 0.05, beta value of 0.2, and 80% power).

Our study had a number of limitations. The first of these was the low recruitment rate of 47% (328/693) of total students screened for scabies by any of our study examiners. We had expected a recruitment rate of 62% based on a previous study[2]. Further to the low recruitment rate, the number of results that could be included in these analyses was even lower (25%, 171/693). We did not expect the sensitivity and specificity of the nurses to be so low. The data in our prevalence study sample under-represented males, over-represented females, and over-represented represented children aged 4-7 years. While we can provide an age and sex standardized estimate for our prevalence estimate, we cannot be certain of the influence of only collecting data from a non-randomly selected quarter of the population. Children were selected for this study by class group, depending on a time their teachers communicated was appropriate for the screening. It is possible that there were differences between children who came to school during the rain and those who did not, which is likely to introduce other biases.

It should also be noted that our results are only generalisable to children attending Gizo Primary School, and therefore that our prevalence estimates are not representative of all school aged children in Gizo.

Another study limitation was the lack of private examination facilities available. While we had access to a small room next to the library to conduct private examinations, we were unable to examine all participants here as this would have caused a significant bottleneck to the flow of participants through the examination stations. This may have resulted in non-differential measurement bias due to the potential underdiagnoses of scabies and impetigo we missed because they were distributed on private body regions.

While ultimately the aim of the scabies diagnostics study was to assess the accuracy of a new method of scabies diagnosis based on skin examination and clinical history alone, it was a limitation that we did not compare the sensitivity and specificity of our two expert examiners to the gold standard of scabies diagnosis. The gold standard method of scabies diagnosis involves obtaining skin scrapings off a patient for direct microscopy and magnification with dermoscopy, and these facilities were not available in our setting – which highlights the need for the scabies diagnostics study as scabies frequently affects people in under resourced settings and more practical methods of diagnosis are required. As experts were required to reach consensus, any deviations from the gold standard would have thus resulted in a non-differential measurement bias. In addition, the fact that our two expert examiners were foreigners could have meant that children acted differently around them when their clinical histories were being taken, and perhaps important information could have been lost in translation.

In the Western Province of the Solomon Islands, limited options for the treatment of scabies and impetigo are available. First line treatment for scabies is typically with topical agents, such as Permethrin. However, Permethrin is expensive and not widely available in the Western Province. A more frequently used topical agent for scabies in the Western Province and other low resource settings are sulfur containing preparations and benzyl benzoate 10-25%[25], while oral antibiotics are used to treat skin infections. However, regular supply of treatment options for scabies and impetigo is unreliable. While it was a strength that the study team brought a supply of Permethrin to give free of charge to children with scabies, it was an oversight that they did not do the same for treatment for impetigo. While oral antibiotics for bacterial skin infections are available at Gizo Hospital and local clinics in the Western Province, their supply is unreliable and was found to be minimal at the time of our study.

2.9 Conclusion and Public Health Implications

Despite these limitations, there are important public health implications from our study. Our study provided important data on the high prevalence of scabies and impetigo in Gizo Primary School, which is most likely an indicator of the prevalence on Ghizo Island. These data will provide evidence on the prevalence of these skin diseases in the Western Province. We found that the resources available to treat these infections are disproportionately low compared to the burden they place on individuals and the community. While scabies was not a significant risk factor for impetigo in our study, this was most likely due to small sample size, and the opportunity to reduce the burden of impetigo by treating scabies should be explored further in this setting.

Topical scabicides and oral ivermectin have been recently trialed successfully for mass drug administration in settings with a high prevalence of scabies and limited resources including the Solomon Islands[26] and Fiji[8]. Given the extremely high prevalence of scabies in this sample and limited treatment available, consideration for mass drug administration is urgently needed. It has been found that MDA is effective in island settings with a high baseline prevalence of scabies such as Pacific countries[27], as limited population movement can occur between villages.

It is also of upmost importance to address the environmental and socioeconomic factors known to perpetuate skin disease in parallel to MDA. This could be done through community education and water, sanitation and hygiene programs. Economically sustainable and pragmatic treatment and prevention options should not be overlooked. While scabies and impetigo are often considered trivial in developed countries, ongoing efforts to address the great burden in Oceania including the Solomon Islands, Aboriginal communities of northern Australia, and the Pacific is extremely important.

2.10 References

1. Deming M, Martin D. 2015. Scabies. Control of Communicable Diseases Manual. Heymann D. Washington DC, *Alpha Press*: 550-552.
2. Steer A, Jenney A, Kado J et al. 2009. High burden of impetigo and scabies in a tropical country. *PLoS Neglected Tropical Diseases* 3(6): e467.
3. Engelman D, Kiang K, Chosidow O et al. 2013. Toward the global control of human scabies: introducing the International Alliance for the Control of Scabies. *PLoS Neglected Tropical Diseases* 7(8): e2167.
4. Heukelbach J, Feldmeier H. 2006. Scabies. *Lancet* 367(9524): 1767-1774.
5. Currie B, McCarthy J. 2010. Permethrin and ivermectin for scabies. *New England Journal of Medicine* 362(8): 717-725.
6. Mahe A, Hay R. 2005. Epidemiology and management of common skin diseases in children in developing countries. Geneva, World Health Organisation. Accessed on 11th November 2018, from https://apps.who.int/iris/bitstream/handle/10665/69229/WHO_FCH_CAH_05.12_eng.pdf;jsessionid=00296131F4AF379656134485DF4AA6FA?sequence=1
7. Romani L, Steer A, Whitfeld M et al. 2015. Prevalence of scabies and impetigo worldwide: a systematic review. *Lancet Infectious Diseases* 15(8): 960-967.
8. Romani L, Whitfeld M, Koroivueta J et al. 2015. Mass Drug Administration for Scabies Control in a Population with Endemic Disease. *New England Journal of Medicine* 373(24): 2305-2313.
9. Chosidow O. 2006. Clinical practices. Scabies. *New England Journal of Medicine* 354(16): 1718-1727.
10. Walton S, Currie B. 2007. Problems in diagnosing scabies, a global disease in human and animal populations. *Clinical Microbiology Reviews* 20(2): 268-279.
11. World Health Organization. 2018. Neglected Tropical Diseases. Accessed on 19th November 2018 from http://www.who.int/neglected_diseases/diseases/en/.
12. Yeoh D. Bowen A and Carapetis J. 2016. Impetigo and scabies - Disease burden and modern treatment strategies. *Journal of Infection* 72 Suppl: S61-67.
13. Jackson A, Heukelbach J, Filho A et al. 2007. Clinical features and associated morbidity of scabies in a rural community in Alagoas, Brazil. *Tropical Medicine and International Health* 12(4): 493-502.
14. Hay R, Castanon R, Hernandez H et al. 1994. Wastage of family income on skin disease in Mexico. *British Medical Journal* 309(6958): 848.

15. Karimkhani C, Colombara D, Drucker A et al. 2017. The global burden of scabies: a cross-sectional analysis from the Global Burden of Disease Study 2015. *Lancet Infectious Diseases* 17(12): 1247-1254.
16. Romani L, Whitfeld M, Koroivueta J et al. 2017. The Epidemiology of Scabies and Impetigo in Relation to Demographic and Residential Characteristics: Baseline Findings from the Skin Health Intervention Fiji Trial. *American Journal of Tropical Medicine and Hygiene* 97(3): 845-850.
17. Mason D, Marks M, Sokana O et al. 2016. The Prevalence of Scabies and Impetigo in the Solomon Islands: A Population-Based Survey. *PLoS Neglected Tropical Diseases* 10(6): e0004803.
18. Solomon Islands Government. 2009. Provincial profile of the 2009 population and housing census, Western Province. Accessed on the 5th December 2018 from http://www.mof.gov.sb/Libraries/Statistics/2011_06__Report_on_2009_Population_Housing_Census.sflb.ashx
19. United Nations Development Program. 2018. Human Development Index 2018. Accessed on the 5th December 2018 from http://hdr.undp.org/en/countries
20. World Health Organization. 2015. Solomon Islands: WHO Statistical Profile 2012. Accessed on the 5th December 2018 from http://www.who.int/gho/countries/slb.pdf?ua=1
21. Korte M, Bowen A, Draper A, et al. 2018. Scabies and impetigo in Timor-Leste: A school screening study in two districts. *PLoS Neglected Tropical Diseases* 12(5): e0006400.
22. Gear R, Carter J, Carapetis J et al. 2015. Changes in the clinical and epidemiological features of group A streptococcal bacteraemia in Australia's Northern Territory. *Tropical Medicine and International Health* 20: 40-47. doi:10.1111/tmi.12405
23. Skull S, Krause V, Coombs G et al. 1999. Investigation of a cluster of Staphylococcus aureus invasive infection in the Top End of the Northern Territory. *Australian and New Zealand Journal of Medicine* 29: 66-72. doi:10.1111/j.1445-5994.1999.tb01590.x
24. Currie B, Carapetis J. 2000. Skin infections and infestations in Aboriginal communities in northern Australia. *Australasian Journal of Dermatology*, 41: 139-143. doi:10.1046/j.1440-0960.2000.00417.x
25. Hay R, Steer A, Engelman D et al. 2012. Scabies in the developing world--its prevalence, complications, and management. *Clinical Microbiology and Infection* 18(4): 313-323.

26. Lawrence G, Leafasia J, Sheridan J et al. 2005. Control of scabies, skin sores and haematuria in children in the Solomon Islands: another role for ivermectin. *Bulletin of the World Health Organization* 83(1): 34-42.
27. Engelman D, Steer A. 2018. Control Strategies for Scabies. *Tropical Medicine and Infectious Diseases* 5;3(3) pii e98.

Annex 2A: Evaluation of the impact of azithromycin mass drug administration for trachoma on the prevalence of sexually transmitted infections in Fiji: FNHMREC and UNSW HREC approved protocol

Principal Investigators:

Dr James Fong, *Ministry of Health and Medical Services, Fiji*

Professor John Kaldor, *University of New South Wales, Australia*

Co-Investigators:

Dr Mike Kama, *Fiji Centre for Communicable Disease Control*

Dr Torika Tamani, *Ministry of Health and Medical Services, Fiji*

Dr Lucia Romani, *University of New South Wales, Australia*

Dr Daniel Faktaufon, *Fiji Centre for Communicable Disease Control*

Dr Dashika Balak, *Ministry of Health and Medical Services, Fiji*

Associate Professor Rebecca Guy, *University of New South Wales, Australia*

Sophie Phelan, *University of New South Wales, Australia*

Associate Professor Andrew Steer, *Murdoch Childrens Research Institute, Australia*

Merelesita Rainima-Qaniuci, *Ministry of Health and Medical Services, Fiji*

Dr Luisa Cikamatana, *Ministry of Health and Medical Services, Fiji*

Dr Anaseini Cama, *Fred Hollows Foundation*

Permission has been granted by Principal Investigator Professor John Kaldor to include this protocol in this MAE Bound Volume.

CONTENTS

1. INTRODUCTION

1.1 Background Information and Literature Review

Chlamydial infection (or chlamydia), caused by the bacterium *Chlamydia trachomatis* (CT) and gonococcal infection (or gonorrhoea), caused by the bacterium *Neisseria gonorrhoeae* (NG) are curable sexually transmitted infections (STIs). Infections with CT and NG represent a considerable global public health problem, with an estimated 256 million cases among adults aged 15–49 years in 2012 (1). CT and NG are important causes of pelvic inflammatory disease, infertility, ectopic pregnancy and adverse birth outcomes such as premature rupture of membranes, pre-term birth, and still birth (2-4). CT and NG had the highest prevalence in the most recent global data, with much of the STI burden borne by sexually active adolescents and young adults in resource limited countries (5).

The prevalence of CT and NG has been reported to be very high in the Pacific. A study in 2008 found that among women aged under 25 attending ANCs across Fiji, Kiribati, Samoa, the Solomon Islands, Tonga, and Vanuatu, 30.1% had evidence of at least one STI when tested for CT, NG, syphilis and HIV (6). A study among women aged 18-35 in Papua New Guinea in 2016 found the prevalence of CT to be 22.9%, and the prevalence of NG to be 14.2% (7). Another study of antenatal women aged 16-49 years in the Solomon Islands in 2015 reported the prevalence of CT to be 20.3% and NG to be 5.1% (8). The above mentioned study from 2008 also found the prevalence of CT and NG in antenatal women less than 25 years in Fiji to be 34% and 3.1% respectively (6). Most studies of antenatal women in Pacific countries show the prevalence of CT and NG to be highest among those aged less than 25 years, with CT prevalence higher than that of NG.

Most CT infections are asymptomatic, with a minority presenting as cervicitis in females (9). NG infections are also generally asymptomatic, with some women experiencing mucopurulent cervicitis (10). The main control strategies for these infections are health promotion for safe sex, and effective diagnosis and antimicrobial treatment. For chlamydia, antimicrobial treatment usually involves azithromycin (1g PO, stat) or doxycycline (100mg PO, BD 7 days), and gonorrhoea is treated with ceftriaxone (500mg IMI, stat in 2mL 1% lignocaine PLUS azithromycin 1g PO, stat) (11). In most low and middle income countries laboratory diagnostic services are not widely available. In these settings, syndromic management is adopted used with various combinations of antimicrobial treatment depending on symptoms (12). This approach does not work well for some important syndromes, particularly vaginal discharge, and does not facilitate the identification of those with asymptomatic infection (13), leaving a potentially large untreated population pool at risk of complications and sources of ongoing transmission.

Standard approach to treatment of pregnant women with gonococcal or chlamydial infections in Fiji involves a combination of antibiotics as shown in Table 2 (14). Fiji has implemented syndromic reporting for STIs since 2011 (15). Six syndromes are reported from the three sexual and reproductive health (SRH) clinics: urethral discharge, vaginal discharge, lower abdominal pain, genital ulcers, scrotal swelling and neonatal conjunctivitis. The three SRH clinics based in the three health divisions in Fiji (Central/Eastern, Western, and Northern Divisions) report syndromic cases on a quarterly basis. In 2014, the Fiji STI Action Plan was developed. The Fiji STI Action Plan focuses on prevention, care, and monitoring and evaluation of research related to STIs. A number of ongoing challenges have been noted including availability of medication for STI treatment. The Republic of Fiji National Strategic Action Plan on HIV and STIs 2016-2020 mentioned the importance of political commitment, policies, prevention, continuum of care, system strengthening, research, and monitoring and evaluation.

Mass drug administration (MDA) has been investigated to a limited degree as a strategy for control of STIs. The objective of MDA is to provide therapeutic concentrations of antibiotics to as large a proportion of the population as possible in order to cure any asymptomatic infections and prevent new infections and reinfection during the period of post-treatment prophylaxis. Several studies have indicated that MDA can significantly reduce the prevalence of STIs including CT and NG in particular populations at high risk (16-20), but a number of issues have not been well explored, including duration of benefit, and the impact in general population settings.

Certain strains of CT are responsible for ocular trachoma, a neglected tropical disease prevalent in the Pacific Region (21). Ocular trachoma is transmitted through direct contact with infectious ocular or nasopharyngeal discharges on fingers, or indirect contact with contaminated fomites (21). WHO is currently coordinating the Global Elimination of Trachoma by 2020 Program, which relies on the use of the SAFE strategy. The SAFE strategy involves the following four components (which make up the acronym): Surgery for trichiasis, Antibiotic therapy, Facial cleanliness and Environmental impact (22). The antibiotic therapy component comprises of annual MDA of single oral dose azithromycin (20mg/kg, to a maximum of 1g in adults) (23). Azithromycin is the drug of choice for trachoma programs because of its therapeutic activity against CT, good safety profile, oral usage, and long half-life. Annual azithromycin MDA is delivered to the whole community, and is recommended where the prevalence of “trachomatis inflammation-follicular” (TF) is ≥ 10% in children aged 1-9 years. A recent national survey in Fiji has found that the prevalence of ocular trachoma in 1-9 year olds is high enough to justify the use of MDA with azithromycin, under the WHO SAFE Strategy. Trachoma MDA is scheduled to begin in September/October 2017 in Fiji.

Azithromycin is an effective drug for treatment of all strains of CT and is also used in combination with other antibiotics to treat NG (11). As azithromycin is delivered to the whole community in trachoma MDA, it could be expected to reduce STIs as well. A small-scale study in Honiara, Solomon Islands measured CT and NG prevalence at ten months after azithromycin MDA for trachoma in 2015 (24). There was a clear reduction in CT prevalence (around 40%) and a non-significant reduction in NG. In Australia, a conference abstract in 2006 reported that a routine STI control activity following 6 weeks after a trachoma control program found a substantial difference in the rates of CT and NG in those who had received azithromycin under the trachoma program compared with those who had not (6.6% v 27.4%) (25).

Fiji is about to implement MDA as a key component of control strategies for ocular trachoma. Given the public health importance of STIs in Fiji, it is appropriate and timely to evaluate the impact of azithromycin MDA for trachoma on the occurrence of these STIs. The findings will provide important information in Fiji and internationally on the role of trachoma MDA for STI control.

1.2 Statement of the Problem

Opportunity: the upcoming MDA for trachoma presents an opportunity to investigate the effect of MDA for trachoma on the high prevalence of CT and NG in Fiji.

2. AIMS AND OBJECTIVES

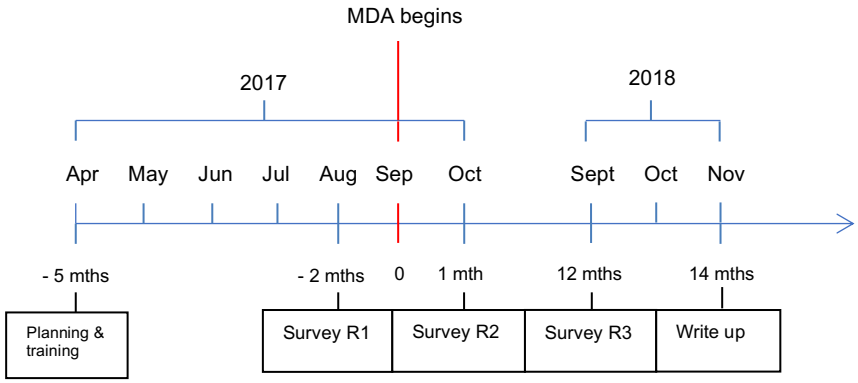
I. To conduct a baseline survey of the prevalence of CT and NG among women aged 18-29 years attending ANCs in Fiji.
II. Estimate the change in prevalence of CT and NG one month and one year after MDA for trachoma in Fiji.

3. METHODOLOGY

3.1 Study type

The study design will be repeat cross-sectional, with three identical prevalence surveys conducted from 2017 to 2018 in pregnant women attending selected clinical services in Fiji. The study will aim to recruit women attending each of the participating clinics over three points in time as follows: 1) Prior to the implementation of the trachoma MDA; 2) Immediately following completion of the trachoma MDA and 3) Twelve months after the completion of the trachoma MDA. Trachoma MDA is estimated to begin in Fiji in September/October 2017. The schedule of our study will be based around the dates of trachoma MDA (TBC). See Figure 1 below.

Figure 1. Study timeline



Setting

To provide a broad representation of the Fijian population, six ANCs in Fiji have been selected for the study: one divisional and one subdivisional hospital from each of the three divisions as follows.

Table 1: Study sites for proposed study

Division	Divisional hospital	Sub-divisional hospital
Central/Eastern	Colonial War Memorial Hospital, Suva	Nausori Hospital
Western	Lautoka Hospital	Nadi Hospital
Northern	Labasa Hospital	Savusavu Hospital

By recruiting participants from the above six hospitals, we will achieve a broad representation of STI prevalence in Fiji from all divisions.

Participants

Participants will be pregnant women aged 18-29 years attending their Booking Visit in Fiji. We have focused on 18-29 year olds as the prevalence of STIs in this age group is highest, attendance at ANCs is highest (26) and because CT and NG infections in pregnancy can lead to adverse outcomes. Participants will be recruited by study staff based at each participating clinic for the duration of the survey. The study staff will approach women in the waiting area and explain the study. For women who agree to participate and provide informed consent, eligibility criteria will be assessed, and the study procedures will be undertaken.

Recruitment procedures

The study will be explained on a group basis to the women in the waiting area so as not to disrupt the work flow at the ANC. The specifically hired and trained retired midwives will provide the women with general information about the study through a 5-10 minute talk.

- The talk will cover key study objectives and procedures, eligibility criteria, and the benefits and potential risks of study participation.
- At the end of the talk, copies of the study Participant Information Sheet (see Annex 5) will be provided to participants.
- If a woman is eligible and willing to participate, formal informed consent procedures will be followed. This will involve the signing of the Informed Consent Form (see Annex 6) by the study participant and the staff member obtaining and recording consent.
- The number of non-participants will be recorded along with the reason for not participating.
- Participants who are unable to read and/or write will be required to have an impartial witness present during the above procedures in order to ensure that there is no risk of misunderstandings or possible coercion.
- All participants will be given a copy of the informed consent form and participant information sheet to take home.

3.2 Variables of the study

In addition to submitting a urine specimen, study subjects will be asked to provide some basic details according to the specific study Data Collection Sheet (see Annex 3). Most of this data is already collected by the usual nurse at the Booking Visit, and will therefore simply be copied by the designated study specific retired midwife. Questions on all three surveys will include:

- Date of birth
- Ethnicity
- Years of education
- Village/town of residence
- Parity
- Gestation
- Living with current partner
- Most recent diagnosis of CT, NG or TV
- Whether the participant received treatment for the STI
- Any current STI symptoms (vaginal discharge, lower abdominal pain, itching, genital ulcers or none)

- Study ID number (according to study site and survey round)

Following trachoma MDA, survey two and three will also include an additional question asking if the woman received trachoma MDA (see Annex 3, Q17). Separate to the survey, laboratory technicians will record the STI results by Study ID number to be included as variables in the analysis (see Annex 4).

3.3 Testing procedures

After enrolment, participants will self-collect a urine specimen at the ANC and hand this straight to the study midwife. The urine specimen will be checked on the Urine Collection Log (see Annex 2). The woman will be asked to collect her specimen in the clinic toilet. The specimen collection container provided will be pre-labelled with both the participant's Study ID number and a unique Laboratory Sticker Number that will contain a bar code to be scanned prior to the testing phase.

The specimen will then be transported to an in-country "GeneXpert" machine for CT, NG and *Trichomoniasis vaginalis* (TV) testing by the laboratory technicians employed for this study. TV prevalence will be measured to serve as a control in our study as TV is an STI that is not affected by treatment with azithromycin. The GeneXpert CT/NG® (Cepheid) provides fully automated, easy-to-use point of care molecular tests for CT, NG and TV with the accuracy of laboratory-based nucleic acid amplification tests (27, 28). We will be using four GeneXperts. One will be at Lautoka, one at Labasa and two at Mataika House. Samples from Divisional and Sub-divisional hospitals will be transported to the divisional GeneXpert facility for processing. At the end of each clinic day, urine samples will be transported in an ice box to the processing facility where they will be stored in a designated refrigerator until they are tested. We will employ two technicians per GeneXpert processing facility, therefore six in total.

CT and NG are tested in a single module as a dual assay with results available in 90 minutes, while TV is tested alone taking 60 minutes. Samples can be refrigerated for up to 60 days, between 2-8 degrees Celsius. The GeneXpert CT/NG point of care test has been demonstrated in laboratory and field evaluations in Australia (27) and the USA (28) to have similar sensitivity and specificity to routine laboratory based NAAT tests, and is easy to use. The test has 5 targets, including a specimen processing control, specimen adequacy control, one CT target and two targets for NG. Using two separate targets for NG allows for more specific detection and confirmation of NG. The GeneXpert CT/NG test was approved by the Therapeutic Goods Administration for diagnostic purposes in Australia in March 2013, and obtained Conformité Européenne (CE) marking and US Food and Drugs Administration (FDA) clearance in 2012.

A laminated Quick Reference Guide will be packed into the GeneXpert carry case and placed in the testing area on each clinic day for ease of reference. GeneXpert test cartridges will also be pre-labelled with both the participant's Study ID Number and a unique Laboratory Sticker Number. GeneXpert CT/NG and TV test results will automatically be stored by Laboratory Sticker Number on the computer and at the end of each clinic day, the electronic test results database will be backed-up on the laptop computer and on a removable USB drive.

3.4 Sample size

We have determined that including approximately 1000 women per survey period will provide an adequate sample size to detect a significant reduction in CT between the first and subsequent 12-month round. Our initial calculations showed that only 417 women were needed per round to detect a significant difference in CT, with 80% power, based on an expected baseline prevalence of CT of 20% and an expected reduction of 37% at 12 months after trachoma MDA. However we increased the sample size to 1000 women per round to increase the possibility of detecting a significant difference in NG in case the prevalence of NG was higher than expected, and also to increase the precision. Based on a NG prevalence estimate of 3.1% in women aged <25 in Fiji (6), a sample size of >2300 is needed to detect an estimated reduction of 43% (24) in NG prevalence between rounds, which is not feasible. However if the prevalence of NG is 7% then a sample size of 1000 will be sufficient. Based on a sample size of 1000, the 95% confidence intervals around the baseline prevalence estimate of 20% will be 18-23%. Overall, approximately 3000 women will be tested for our study.

3.5 Treatment

Sexually transmitted infections

Any participant who receives a positive result for CT, NG or TV will be provided with treatment according to the Fiji STI treatment guidelines from the Fiji Ministry of Health Comprehensive Management Guidelines for STIs free of charge (14). See Table 2 for treatment guidelines. As per current Fiji guidelines, the women receive the results of the STI test at their next clinic visit approximately 2 weeks after the booking visit, with the clinic doctor providing treatment and addressing the issue of partner notification if necessary. Symptoms-based syndromic STI management will not be provided i.e. only those with a positive STI result will be treated.

Table 2: Fiji STI treatment guidelines from the Fiji Ministry of Health Comprehensive Management Guidelines for STIs (14).

STI	Recommended Treatment
Chlamydia	Azithromycin 1g single oral dose OR Erythromycin 500mg orally 6 hourly for 7 days
Gonorrhoea	Probenecid 1g orally as a single dose AND Augmentin 1 tablet single dose AND Amoxycillin 2.5g orally as a single dose
Trichomoniasis	Metronidazole 2g STAT OR 400mg twice daily for 7 days.

Trachoma MDA

For the trachoma mass drug administration, the entire population irrespective of age or gender, is provided with oral azithromycin (20mg/kg, to a maximum of 1g in adults). This will be administered through Fiji Ministry of Health.

Staff training

All staff will attend a briefing and discussion about the proposed study. Retired midwives will be employed as study clinical staff, and will receive specific study training. Laboratory staff will be required to complete a formal competency assessment and/or external accreditation before they are allowed to operate the GeneXpert machine as part of this study.

3.6 Data collection

All details collected from the patient survey and results from the STI test will be hand written by study staff onto paper templates. These details will then be entered into a password protected database entered by study clinical staff in the Suva study office. The paper data forms will be kept in a locked and secured filing system. Only the investigators and the study staff will have

access to the raw data during and after the study. Results from the STI test will be returned to the patient as per current national guidelines in Fiji.

3.7 Data processing and analysis

Data processing

Data will be coded and de-identified, and held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, and a password protected copy of the full database will be provided to Fiji Ministry of Health.

Data analysis

The prevalence of CT, NG and TV will be calculated for each of the three study periods, overall and by 5-year age subgroups. Prevalence will be calculated as the proportion of women who participated and were tested, who had a positive result. Prevalence will be calculated for each individual STI and also combined, with 95% confidence intervals. Prevalences will initially be compared between the three time points, using logistic regression. We will also compare the demographics of the study populations, and if there are any differences, we will include these variables in an adjusted analysis.

3.8 Ethical consideration

Ethics approval will be sought from the following organisations prior to study commencement:

- Fiji National Research Ethics Review Committee
- The University of New South Wales Ethics Commitee
- Australian National University Ethics and Integrity Services

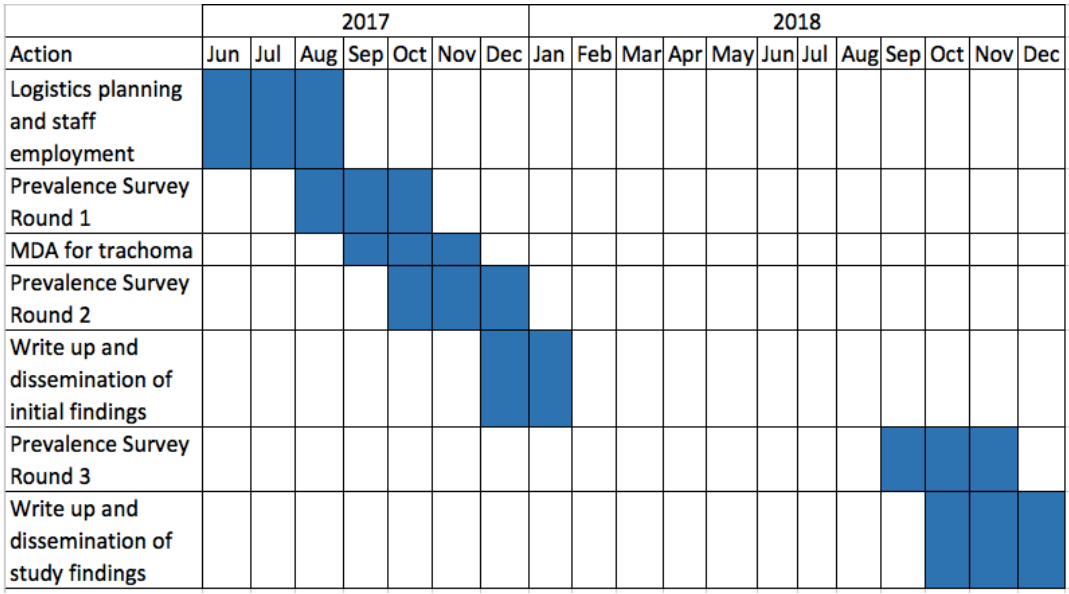
The main ethical issues will be the need to maintain privacy and confidentiality, and to ensure that women offered testing for STIs are able to receive their results and treatment as indicated, with appropriate support. All participants will be 18 years or over and will be required to understand and sign informed consent forms. These forms must be approved by the above listed ethics committees. Subject confidentiality will be maintained by study staff. Specimens can be kept for a few days after being analysed if needed, and will then be disposed of. Any participant receiving a positive result for an STI will be notified and provided with treatment free of charge for themselves and sexual partners according to current Fijian guidelines.

4. WORK PLAN

The work plan is based around the MDA for trachoma. Exact dates for the trachoma MDA are still to be confirmed, however it is estimated to begin in September/October 2017. Figure 2 below is subject to change depending on the dates for trachoma MDA, and is an estimate of the

work flow assuming that trachoma MDA will begin in either September, October or November 2017.

Figure 2: Work plan for proposed study



5. BUDGET

Figure 3: Budget for proposed study

BUDGET Project: Impact of MDA for trachoma on STIs in Fiji		
Salaries	Fijian Staff (12 retired midwives, 6 laboratory technicians)	$280,000
Medications		$8,000
Lab Consumables		$275,000
Travel and Accommodation		$ 30,000
Training costs		$ 4,000
Printing/other		$ 3,000
TOTAL (FJD)		**$ 600,000**

This study will be funded by the University of New South Wales, Australia.

6. ADMINISTRATION, MONITORING AND UTILISATION OF RESULTS

All results will be de-identified. Scientific publications and conference presentations related to the study and its findings will be sent to the investigator group of this study in draft form for approval. Authorship will follow standard guidelines for such publications and will be based on substantial contributions in a combination of: conception and design of the project; analysis and interpretation of research data; drafting significant parts of the work or critically revising it so as to contribute to the interpretation (29). Sites will have the opportunity to become involved in authorship by expressing interest to the Investigator Group on behalf of individual staff. Particular efforts will be made to ensure that Fiji-based investigators have the opportunity to participate in authorship in a lead capacity. A report with the results will be shared with the Fijian Ministry of Health.

Protocol Annex 1 REFERENCES

1. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. PloS one. 2015;10(12):e0143304.

2. Oakeshott P, Kerry S, Aghaizu A, Atherton H, Hay S, Taylor-Robinson D, et al. Randomised controlled trial of screening for Chlamydia trachomatis to prevent pelvic inflammatory disease: the POPI (prevention of pelvic infection) trial. BMJ (Clinical research ed). 2010;340:c1642.

3. Low N, Egger M, Sterne JA, Harbord RM, Ibrahim F, Lindblom B, et al. Incidence of severe reproductive tract complications associated with diagnosed genital chlamydial infection: the Uppsala Women's Cohort Study. Sexually transmitted infections. 2006;82(3):212-8.

4. Mullick S, Watson-Jones D, Beksinska M, Mabey D. Sexually transmitted infections in pregnancy: prevalence, impact on pregnancy outcomes, and approach to treatment in developing countries. Sexually transmitted infections. 2005;81(4):294-302.

5. World Health Organisation. Global incidence and prevalence of selected curable sexually transmitted infections - 2008. 2012 [Available from: http://www.who.int/reproductivehealth/publications/rtis/stiestimates/en/.

6. Cliffe SJ TS, Sullivan EA. Chlamydia in the pacific region, the silent epidemic. Sex Transm Dis. 2008;35(9):801-6.

7. Vallely LM, Toliman P, Ryan C, Rai G, Wapling J, Tomado C, et al. Prevalence and risk factors of Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis and other sexually transmissible infections among women attending antenatal clinics in three provinces in Papua New Guinea: a cross-sectional survey. Sexual health. 2016.

8. Marks M, Kako H, Butcher R, Lauri B, Puiahi E, Pitakaka R, et al. Prevalence of sexually transmitted infections in female clinic attendees in Honiara, Solomon Islands. BMJ open. 2015;5(4):e007276.

9. Gorowitz R, Torrone E. Chlamydial Infections. In: David L Heymann, editor. Control of Communicable Diseases Manual. 2nd ed. Washington: American Public Health Association; 2015.

10. Kidd S. Gonococcal Infections. In: David L Heymann, editor. Control of Communicable Diseases Manual. 2nd ed. Washington: American Public Health Association; 2015.

11. Australasian Sexual Health Alliance. Australian STI Management Guidelines for use in primary care 2016 [Available from: http://www.sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea - management.

12. World Health Organisation. Guidelines for the Management of Sexually Transmitted Infections 2003 [Available from: http://apps.who.int/iris/bitstream/10665/42782/1/9241546263_eng.pdf?ua=1.

13. Badman SG VL, Toliman P, et al. A novel point-of-care testing strategy for sexually transmitted infections among pregnant women in high-burden settings: results of a feasibility study in Papua New Guinea. BMC Infect Dis. 2016;16:250.

14. Fiji Ministry of Health. Comprehensive Management Guidelines for Sexually Transmitted Infections.

15. Fiji Ministry of Health. Republic of Fiji National Strategic Action Plan on HIV and STIs 2016-2020. 2016 [Available from: http://www.aidsdatahub.org/sites/default/files/publication/Republic_of_Fiji_National_Strategic_Action_Plan_on_HIV_and_STIs_2016-2020.pdf.

16. Labbe AC, Pepin J, Khonde N, Dzokoto A, Meda H, Asamoah-Adu C, et al. Periodical antibiotic treatment for the control of gonococcal and chlamydial infections among sex workers in Benin and Ghana: a cluster-randomized placebo-controlled trial. Sexually transmitted diseases. 2012;39(4):253-9.

17. Cowan FM, Hargrove JW, Langhaug LF, Jaffar S, Mhuriyengwe L, Swarthout TD, et al. The appropriateness of core group interventions using presumptive periodic treatment among rural Zimbabwean women who exchange sex for gifts or money. Journal of acquired immune deficiency syndromes (1999). 2005;38(2):202-7.

18. Olsen GA. Epidemiological measures against gonorrhoea. Experience in Greenland. The British journal of venereal diseases. 1973;49(2):130-3.

19. Wawer MJ, Sewankambo NK, Serwadda D, Quinn TC, Paxton LA, Kiwanuka N, et al. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. Rakai Project Study Group. Lancet (London, England). 1999;353(9152):525-35.

20. Steen R, Chersich M, Gerbase A, Neilsen G, Wendland A, Ndowa F, et al. Periodic presumptive treatment of curable sexually transmitted infections among sex workers: a systematic review. AIDS (London, England). 2012;26(4):437-45.

21. Mariotti SP SA. Trachoma. In: David L Heymann, editor. Control of Communicable Diseases Manual. 20th ed. Washington: American Public Health Association; 2015.

22. Emerson PM, Burton M, Solomon AW, Bailey R, Mabey D. The SAFE strategy for trachoma control: Using operational research for policy, planning and implementation. Bulletin of the World Health Organization. 2006;84(8):613-9.

23. Solomon AW ZM, Kuper H, Buchan JC, Mabey DC, Foster A. Trachoma Control: A Guide for Program Managers Geneva: World Health Organisation; 2006 [Available from: http://www.who.int/blindness/publications/tcm who_pbd_get_06_1.pdf.

24. Marks M, Bottomley C, Tome H, Pitakaka R, Butcher R, Sokana O, et al. Mass drug administration of azithromycin for trachoma reduces the prevalence of genital Chlamydia trachomatis infection in the Solomon Islands. Sexually transmitted infections. 2016;92(4):261-5.

25. A L. Effect of community-based trachoma mass treatment on chlamydia and/or gonorrhoea rates. Melbourne Australasian Sexual Health Conference; 2006.

26. Gubhaju B JE, Raikoti M. Fertility focused census data analysis in Fiji. . Suva, Fiji: Bureau of Statistics 2014; 2014.

27. Causer LM, Hengel B, Natoli L, Tangey A, Badman SG, Tabrizi SN, et al. A field evaluation of a new molecular-based point-of-care test for chlamydia and gonorrhoea in remote Aboriginal health services in Australia. Sexual health. 2015;12(1):27-33.

28. Gaydos CA, Van Der Pol B, Jett-Goheen M, Barnes M, Quinn N, Clark C, et al. Performance of the Cepheid CT/NG Xpert Rapid PCR Test for Detection of Chlamydia trachomatis and Neisseria gonorrhoeae. Journal of Clinical Microbiology. 2013;51(6):1666-72.

29. Australian National University. ANU Code of Research Conduct 2017 [Available from: https://policies.anu.edu.au/cs/groups/confidential/@rs/documents/edrms/dxbf/mda3/~edisp/anup_007403.pdf.

Protocol Annex 2: URINE COLLECTION LOG

STUDY ID	SEX (M or F)	DATE OF BIRTH (DD/MM/YYYY)	SAMPLE COLLECTED (Y or N)

Protocol Annex 3: DATA COLLECTION SHEET

To be completed by study midwives during participant's Booking Visit.

Check:
- ☐ Eligibility criteria met for participant.
- ☐ Informed consent form obtained from participant.
- ☐ Urine sample collected, labelled and logged.

Q1. Midwife ID: _ _ _ _

Q2. Participant Study ID Number: _ _ _ _ _

Q3. Study site: ……..

Q4. Date of booking visit (DD/MM/YYYY): _ _ / _ _ / _ _ _ _

Q5. Participant date of birth (DD/MM/YYYY): _ _ / _ _ / _ _ _ _

Q6. Ethnicity (Indigenous Fijian=F, Fijian-Indian=I, other=O):

Q7. Village/town of residence:

Q8. Number of previous births:

Q9. Gestation weeks of current birth:

Q10. Symptoms:

(none=N, vaginal discharge=VD, lower abdominal pain=AP, genital ulcers=GU, itching=I)

Q11. How many years of education have you completed?

Q12. Are you living with your current partner (Yes/No)?

Q13. Have you recently been diagnosed with an STI?

If the participant answered "yes" to Q13:

Q14. What STI were you diagnosed with (CT/NG/TV/other)?

Q15. How many months ago did you receive this diagnosis?

Q16. Did you receive treatment for this (Yes/No)?

*To add after MDA for trachoma:

Q17. Have you received MDA for trachoma? (yes=Y, no=N, don't know=DN)

Protocol Annex 4: LABORATORY RESULTS LOG

					RESULTS (Y or N)			
Study ID	GeneXpert barcode number	Participant D.O.B	Date of booking visit	Date of sample testing	*C. trachomatis*	*N. gonnorhoea*	*T. vaginalis*	Sample destroyed (Y or N)

Protocol Annex 5: PARTICIPANT INFORMATION SHEET

Research Project Title: Mass Drug Administration for Trachoma and STIs

You are invited to participate in a research project that is explained below. Thank you for taking the time to read this Information Statement. This Information Statement is four pages long. Please make sure you have read all the pages.

What is an information Statement?

These pages tell you about the research project. It explains to you clearly and openly all the steps and procedures of the project. The information is to help you decide whether or not you would like to take part in the research.

Please read this Information Statement carefully. You can ask us questions about anything in it. You may want to talk about the project with your family, friends or health care worker.

Participation in this research project is voluntary. If you don't want to take part, you don't have to. You can withdraw from the project at any time without explanation and this will not affect your access to the best available treatment options and care from your local health centre or any other health facility in Fiji.

Once you have understood what the project is about, if you would like to take part please sign the consent form at the end of this information statement. You will be given a copy of this information and consent form to keep.

1. What is the research project about?

The main purpose of this study is to find out the best strategy for reducing the amount of sexually transmitted infections (STIs) in Fiji.

Please see Question 1, Annex 5: One STI that is seen a lot in Fiji is chlamydia. The bacteria that causes genital chlamydia (*Chlamydia trachomatis*) is also known to cause the eye infection, trachoma. Because both infections are caused by the same bacteria, it means that they can be treated with the same medication. However, while both chlamydia and trachoma are caused by the same bacteria, they are caused by different types, or "strains", of this bacteria. This means that the diseases are transmitted in different ways, and effect different body parts: ocular trachoma is transmitted mostly by contact with the eye and nasal fluids from an infected person, and genital chlamydia is transmitted through sexual intercourse.

Mass drug administration (MDA) for the eye disease trachoma has been shown to reduce the amount of chlamydia and gonorrhoea in pregnant women in the Solomon Islands. MDA for trachoma is about to start in Fiji, so this is the perfect time to have a look and see if it can also reduce the amount of chlamydia and gonorrhoea? in pregnant women in Fiji.

In our study we will first of all have a look at the level of STIs in women attending their Booking Visit in Fiji. Next, we will have a look at the level of STIs in women attending their Booking Visit one month after trachoma MDA in Fiji. Finally, we will have a look at the level of STIs in women attending their Booking Visit twelve months after trachoma MDA in Fiji, to see how long the effect lasts.

2. *Why am I being asked to be in this research project?*

Most of the time, women who have an STI are unaware they have a treatable infection. Complications of untreated STIs can be especially serious for pregnant women.

3. *What STIs are you testing for?*

We are testing for chlamydia, gonorrhoea and trichomoniasis. These are regular tests that have been used in many countries for many years. In Fiji, these tests are not regularly conducted as they are very expensive. Therefore, STIs in Fiji are usually only treated if a person has any symptoms. However, only 2 in 10 women who have an STI have any symptoms. Your doctor will provide medicine if you have any of these diseases.

4. *What is MDA for trachoma?*

MDA for trachoma means that the whole community is given a single dose of the antibiotic medication known as azithromycin, by mouth. The dosage of azithromycin for MDA for trachoma is 20 mg/kg, to a maximum of 1g in adults, which is similar to the dosage of 1g of azithromycin to treat chlamydia. This is being organized by the Fiji Ministry of Health.

5. *Who is funding this research project?*

This research project is simply the “looking” part – to see what happens to the amount of STIs as a result of MDA for trachoma. This project is funded by The Kirby Institute, University of New South Wales, Australia.

6. *What do I need to do to be in this research project?*

If you agree to be a part of this research project, you will need to sign the consent form after reading this information. Then, when you attend your Booking Visit you will need to provide some basic information to the study nurse and collect a urine sample.

7. *What are my alternatives to taking part in this project?*

You do not have to take part in this project if you do not want to. If you take part and you change your mind, you can stop at any time without telling us why. If you want to withdraw from the project we will use any information collected unless you tell us not to. Your decision will not affect any treatment or care you receive, or your relationship with your nurse or your doctor. Please remember that at any time before and during the study, you can ask the

research team to clarify any doubts you may have.

8. What are the possible benefits for me?

If you have one of the STIs we are testing for, you will be informed and be provided with treatment free of charge.

9. What are the benefits for other people in the future?

By participating in this study, you will be assisting with our research investigating whether MDA for trachoma can help reduce the amount of STIs in pregnant women in Fiji. If MDA for trachoma does reduce the amount of STIs in pregnant women in Fiji, this strategy may be implemented to ensure that the amount of STIs in pregnant women and other populations in Fiji is reduced.

10. What are the possible risks, side-effects and/or discomforts?

If you are found to have chlamydia, gonnorrhoea or trichomoniasis you will be provided with the antibiotics per usual standard in Fiji. These are safe to use during pregnancy. Your doctor will discuss the option of treatment for any sexual partners.

11. Ethics Approval

Ethics approval will be sought by the Fiji National Research Ethics Review Committee, The Australian National University Human Ethics Review Committee and the University of New South Wales Ethics Review Committee.

12. Injury

In the unlikely event that you suffer an injury as a result of participating in this study, hospital care and treatment will be provided by the public health service at no extra cost to you.

13. Termination of study

This research project may be stopped in the unlikely event that there are unacceptable side effects due to any of the medications.

14. What will be done to make sure my information is confidential?

Any information we collect for this research project that can identify you will be treated as confidential. We can disclose the information only with your permission, except as required by law. The information will be de-identifiable. This means that we will remove your name, address, convert your date of birth to age and give the information a special code number. Only the research team can match your name to the code number, if it is necessary to do so. The information will be entered in a password-protected computer database. The paper data forms will be stored securely in a locked room at the Fiji Centre for Communicable Disease Control

(FCCDC) in Suva. The following people may access information collected as part of this research project: The research team involved with this project, two Australian Human Research Ethics Committees, and the Fiji National Research Ethics Review Committee. We will keep the information for seven years. After this time, it will be destroyed. After test results are confirmed, samples will be destroyed. In accordance with relevant Australian and Fijian privacy laws, you have the right to access and correct the information we collect and store about you. Please contact us if you would like to access your information. When we write or talk about the results of this project, only group results will be analysed and information will be provided in such a way that you cannot be identified. Reports and publications will not disclose the identity of participants. All results will be presented in a way which does not allow individuals to be identified. No information concerning the study or the data will be released to any unauthorized third party.

15. Will you be informed of the results when the research project is finished?

Once the results have been analysed, a poster explaining the de-identified results will be sent to your antenatal clinic and displayed on the noticeboard there. A more detailed report containing de-identified results will be sent to your antenatal clinic and the Fiji Ministry of Health. All results will be presented in a way which does not allow individuals to be identified.

Protocol Annex 6: PARTICIPANT INFORMED CONSENT FORM

Study ID number: _ _ _ _

Research project: MDA for Trachoma and STIs

Local Principal Investigator: Dr James Fong

Participant: I have read/been read the participant information sheet for this study, and I understand what will be expected of someone taking part in this study.
My questions concerning this study have been answered.
I understand that an individual taking part in this study may withdraw from it at any time without giving a reason and that this will not affect her normal care.

I consent/give consent for (name of participant) _____
to take part in this study.

Signature: _____

Date: _ _ / _ _ / _ _

Witness: I have read this form and the information form to the above person and am sure that he/she has understood what is required of someone enrolling in this study.

Signature: _____

Date: _ _ / _ _ / _ _

If you would like more information about the project or if you need to speak to a member of the research team in an emergency please contact at any time:

Name: Dr James Fong
Contact telephone: XXXXX
Contact email: XXXXX

Name: Sophie Phelan
Contact telephone: XXXXX
Contact email: XXXXX

If you have any concerns about the project or the way it is being conducted, and would like to speak to someone independent of the project, please contact:

Fiji National Health Research Ethics Review Committee

Telephone: XXXX

ANNEX 2B: Field Report of visits to antenatal clinics and laboratories

Sophie Phelan
Master of Applied Epidemiology Scholar
The Kirby Institute, University of New South Wales,
and The Australian National University

BACKGROUND

From Monday 12th June to Friday 16th June 2017, four out of six proposed study sites for the study "Impact of Mass Drug Administration for Trachoma on the Prevalence of Sexually Transmitted Infections in Fiji" were visited, as arranged by Dr Daniel Faktaufon. This study is currently subject to ethics approval from the Fiji National Health Research and Ethics Committee (FNHRERC) and the Australian National University Human Ethics Review Committee. The proposed study sites are six antenatal clinics across Fiji, and include a Divisional and Sub-divisional hospital from each Division as follows:

- Central/Eastern Division: Colonial War Memorial Hospital Suva and Nausori Hospital
- Western Division: Lautoka Hospital and Nadi Hospital
- Northern Division: Labasa Hospital and Savusavu Hospital

The above study sites were chosen to achieve a representative sample of the population of Fiji and to ensure that the required amount of urine samples per survey (1000) could be processed in a timely manner. Table 1 shows the numbers of participants that were estimated to be recruited from each ANC by the Investigator group prior to the site visits.

Table 1: Expected number of participants per survey, per ANC site.

ANC Site	Expected number of participants per survey
Colonial War Memorial Hospital Suva	300
Nausori Hospital	120
Lautoka Hospital	250
Nadi Hospital	150
Labasa Hospital	150
Savusavu Hospital	60

The purpose of the site visits was to meet with ANC staff in person, introduce the proposed project, and answer any questions clinic staff might have. Additionally, it was important to get an idea of the patient flow through the clinics so that appropriate logistic arrangements could be initiated. Another topic to investigate during the site visits was the opportunity to use the

GeneXpert machines located at Twomey Hospital, Suva, Lautoka Hospital and Labasa Hospital. Permission to investigate this was given by Dr Frank Underwood. Currently there are two GeneXpert machines available to use for this study: one at Mataika House, and one that will be transported to Fiji from the Kirby Institute. However, the more machines available, the more efficient sample processing can be, meaning that results and treatment are delivered to participants in a timely manner.

FINDINGS

This section provides a summary of what was found out at each site. Table 2 shows a summary of the days of Booking Visits, and average numbers of women per Booking Visit per ANC site visited as discussed with ANC staff. On average, each visit took approximately 30 minutes.

Table 2: Summary of ANC days of Booking Visit and average numbers of women per Booking Visit.

ANC Site	Days of Booking Visit	Average number of women per Booking Visit	Average number of women presenting for a Booking Visit per week
Colonial War Memorial Hospital Suva	Monday to Friday	30-40	150-200
Nausori Hospital	Thursday	30-50	30-50
Lautoka Hospital	Friday	75-90	75-90
Nadi Hospital	Thursday	30-40	30-40
Labasa Hospital	Wednesday	30-40	30-40
Savusavu Hospital	Wednesday	30-40	30-40

<u>Colonial War Memorial Hospital, Suva</u>

CWM was visited on Monday 12th of June. Dr Daniel provided a tour around the Labour Ward and Antenatal Clinic, and introduced Sister Mitka. The waiting area in the ANC was large and could seat approximately 50 people. The area for conducting the initial paper work for the Booking Visits consisted of four open style booths and a table that could easily conduct four booking visits, meaning that at peak times 8 or more booking visits could be conducted at once. Sister Mitka noted that the Booking Visit usually takes all day, with women arriving in the morning and completing their paperwork (Booking Folder) first of all. This proceeded to be the norm for all ANCs visited. Following this, the women go on to visit other rooms in the ANC and CWM to go through a series of clinical tests for the Booking Visit. Sister Mitka also noted that urine samples are no longer collected.

Nausori Hospital

Nausori Hospital was visited on Friday 16th of June. Dr Vini Kalougivaki introduced Staff Mary. Mary gave a tour of the Booking Visit waiting area which was a small room that could seat approximately 20 people. On Booking Visit days, women wait in turn and then proceed to a table at the front of the room where they go through the Booking Folder with the ANC nurse one at a time. Mary also noted that urine samples are no longer collected.

Twomey Hospital Laboratory

Twomey Hospital Laboratory was visited on Friday 16th of June. Mr Uraiya from Mataika House Laboratory conducted the tour and introduced the ladies responsible for running the GeneXpert. The GeneXpert in use at Twomey Hospital Laboratory was donated by the Global Fund for use in the TB Program. As Twomey Hospital is a specialist TB Hospital, the ladies noted that the GeneXpert has samples running all day, Monday-Friday, with a large backlog of samples. Therefore, it won't be possible to use the GeneXpert at Twomey Hospital Laboratory for this study.

Lautoka Hospital

Lautoka Hospital was visited on Thursday 15th of June. Sister Luisa and Sister Veena showed Sophie around the ANC waiting area. A midwife from Australia, Felicity, was working at Lautoka and was interested to hear about the study as well. The ANC waiting area looked big enough to seat about 40 people, with enough desk space to conduct the initial paperwork for two Booking Visits at a time. The Sisters noted that while Booking Visits are usually conducted on a Friday, women often come in on other days for their Booking Visits and the staff at Lautoka ensure that they are looked after. The sisters also noted that urine samples are no longer collected.

Lautoka Hospital Laboratory

Lautoka Hospital Laboratory was visited on Thursday 15th of June. Ritam was in Suva for a workshop, so Ritam's colleague Markita kindly assisted on the day. The GeneXpert in Lautoka was in use during the visit and it could be seen that only three out of four modules were working. The staff responsible for the GeneXpert were not around at the time. The next step is to confirm how frequently the Lautoka GeneXpert is used to analyse TB samples.

Nadi Hospital

Nadi Hospital was visited on Thursday 15th of June. Dr Lice provided a tour of the Maternity ward and Antenatal Clinic waiting area. The waiting area looked as if it could seat 20 people maximum. A small table at the front could seat one patient at a time to go through the paperwork required for the Booking Folder. Dr Lice noted that urine samples are no longer taken at Nadi.

Labasa and Savusavu Hospitals

An update was provided over email for the hospitals in the North. Rejieli Vuniduvu, Surveillance Officer for the Northern Division provided the information given in Table 2, and noted that urine samples are collected at the first booking for high risk mothers.

SUMMARY

Based on the numbers of women presenting for Booking Visits estimated by the ANC clinic staff and the days allocated for Booking Visits, study methods will have to either allow more time for sample collection from clinics like Nausori, Nadi and the Northern Division, or adjust the numbers of samples to be collected from each clinic.

All ANCs had a waiting area large enough for our study midwives to conduct the group information sessions for our studies. Seeing as the ANC visit takes all day, and most patients arrive in the morning, it would be best for our study midwives to conduct a few information sessions each Booking Visit morning.

Some ANCs such as Lautoka and CWM had enough room to conduct more than one Booking Visit at once. This is important to consider when allocating numbers of study midwives to each ANC, as we would be wise to allocate more midwives to clinics with higher patient flow to make use of these numbers.

Access to the GeneXpert at Lautoka is currently being determined. We also need to investigate how often the GeneXpert at Labasa is used to analyse TB samples. While the GeneXpert at Twomey is overwhelmed with TB analyses, two GeneXperts are available for this study: one at Mataika House and one to be transported from Australia.

Finally, all ANC staff were very interested in our study. They were all extremely welcoming and said they were happy to help in any way. It was a great experience to meet with them and discuss the proposed study.

Assisting site personnel and contact details were excluded from this thesis for privacy reasons.

Annex 2C: Slides from PowerPoint Presentations to PHIRG, SERP and SHP programmes at the Kirby Institute.

Impact of trachoma MDA on STIs in Fiji:
A repeat survey in antenatal women

James Fong, John Kaldor, Mike Kama, Torika Tamani, Lucia Romani, Daniel Faktaufon, Dashika Balak, Rebecca Guy, Sophie Phelan, Andrew Steer, Merelesita Rainima-Qaniuci, Anaseini Cama

Background: STIs and reproductive health

- STIs (chlamydia and gonorrhoea) are particularly prevalent in the Pacific Region
- Most are as asymptomatic in women (80%)
- Treated with single dose antibiotics like azithromycin
- If untreated, can cause extensive reproductive tract morbidity and adverse pregnancy outcomes in women

Table 1: Recent PCR determined prevalence of chlamydia and gonorrhoea in Pacific countries

Country	Year	Chlamydia prevalence (%)	Gonorrhoea prevalence (%)
Fiji	2008	29.0	1.7
Kiribati	2008	13.0	0
Samoa	2008	26.8	2.3
Tonga	2008	14.5	2.5
Vanuatu	2008[1]	13.2	2.4
Solomon Islands	2015[2]	20.7	5.2
Papua New Guinea	2016[3]	22.9	14.2

Notes:
[1]2008 estimates for pregnant women aged 15-44 years attending antenatal clinics. Cliffe et al 2005.
[2]2015 estimates for women attending outpatient clinics. Marks et al 2015.
[3]2016 estimates for pregnant women aged 18-35 years attending antenatal clinics. Vallely et al 2016.

Background: link to Trachoma

- The bacteria that causes chlamydia also causes ocular trachoma
  - *Chlamydia trachomatis*
- Trachoma treatment involves mass drug administration (MDA)
  - Azithromycin
- **MDA for trachoma proposed in Fiji September/October 2017…**

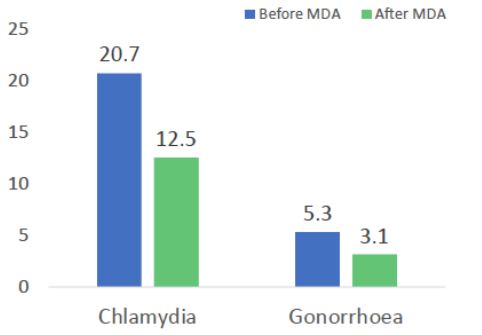
What is MDA for trachoma?

- Trachoma mass drug administration involves treating the **entire** population, irrespective of age or gender, with oral azithromycin (20mg/kg, to a max. of 1g in adults)
- Trachoma MDA is the "A" part of the WHO recommended SAFE strategy consisting of:
  - Surgery
  - Antibiotics
  - Facial cleanliness
  - Environmental improvement

Can MDA reduce STIs?

- Before and after study conducted 2015-2016[4]
- 298 women attending outpatient clinics in Honiara, Solomon Islands
- 10 months after azithromycin MDA for trachoma
- 40% reduction in prevalence of genital chlamydia
- 40% reduction in prevalence of gonorrhoea, however was not significant

Age-adjusted prevalence (%) of Chlamydia and Gonorrhoea before and after MDA for trachoma in Honiara



Marks et al 2016. Mass drug administration of azithromycin for trachoma reduces the prevalence of genital Chlamydia trachomatis infection in the Solomon Islands. *Sex Transm Infec* 92;261-265.

Our study

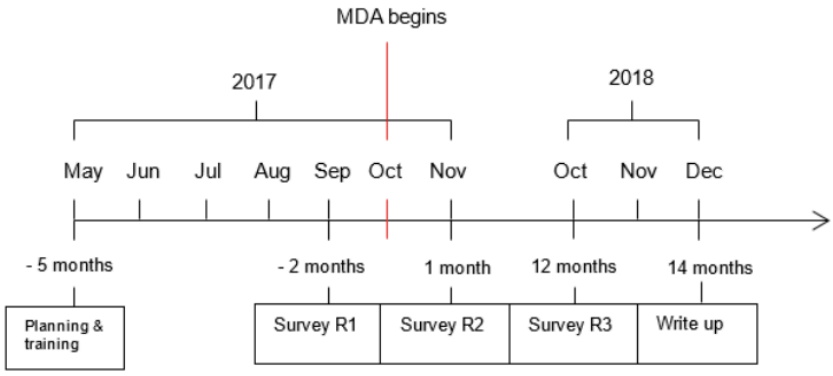
- **Conduct**: three cross sectional prevalence surveys of chlamydia and gonorrhoea in antenatal women
  1. Immediately before national MDA
  2. One month after MDA
  3. 12 months after MDA

- **Compare**: the prevalence of chlamydia and gonorrhoea at three time points to evaluate the impact of MDA.

Study objectives

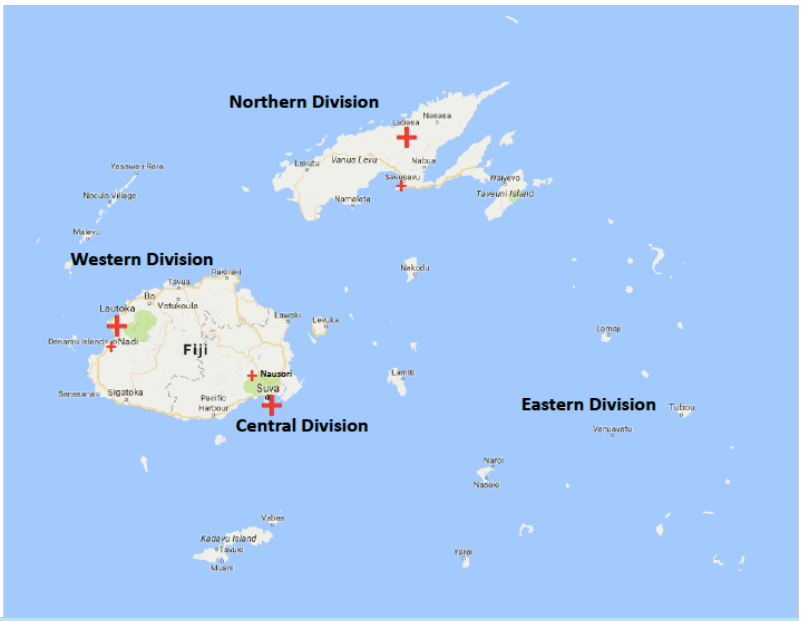
- To assess the prevalence of chlamydia and gonorrhoea among women aged 18-29 years attending antenatal clinics in Fiji.
- To estimate the change in prevalence of chlamydia and gonorrhoea ONE month after MDA for trachoma in Fiji.
- To estimate the change in prevalence of chlamydia and gonorrhoea TWELVE months after MDA for trachoma in Fiji.
- To assess the potential for MDA to contribute to STI control programs in the Pacific

Study design



Setting

Central/Eastern Division
CWM Hospital
Nausori Hospital
Western Division
Lautoka Hospital
Nadi Hospital
Northern Division
Labasa Hospital
Savusavu Hospital



Study participants

Who?

Pregnant women in Fiji

- Aged 18-29 years
- Attending their first antenatal clinic visit "Booking visit"

Why?

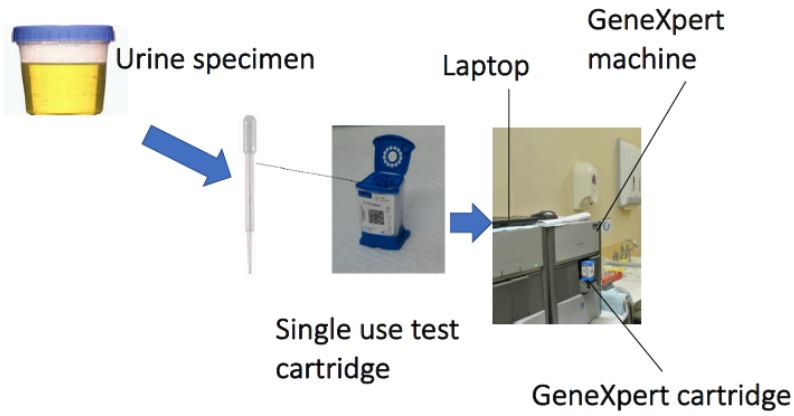
- STI prevalence in this age group is highest
- Booking visits most commonly attended by 18-29 year olds
- Chlamydia and gonorrhoea infections in pregnancy can lead to adverse outcomes

Further details: STI testing procedures

Collected from the participant:
- Urine specimen
- Brief survey

Next, specimens transported to laboratory
- **For**: chlamydia, gonorrhoea and trichomoniasis testing
- **Using**: "GeneXpert"

GeneXpert Point-of-Care Test for Chlamydia and Gonorrhoea



Above slide credit from Basil Donovan

Further details: Sample size

- 417 women is the minimum (based on a baseline prevalence of CT of 20%, reduction of 37% at 12 months, and 80% power)
- 1000 is ideal: increases the precision, and also increases the possibility of detecting a significant reduction in NG

Further details: Treatment

Any participant who receives a positive result for chlamydia, gonorrhoea or trichomoniasis will be provided with treatment according to the Fiji Ministry of Health Antibiotic Guidelines 2011 (costs covered by study)

The potential benefit

- More women tested and treated
- Reduce risk of reproductive morbidity for the women
- Provide PCR estimates of STI prevalence
- Determine the potential use of MDA for control of STIs
  - Duration of benefit
  - Significant reduction for chlamydia and/or gonorrhoea

Field trip report

Challenges

…so far

- Agreement on study base
- Locating/accessing GeneXperts

Future challenges…

- Dates of trachoma MDA
- Timely ethical approval
- …not forgetting the importance of improved education, environmental and sanitation conditions in the control of trachoma and sexually transmitted diseases.

References

1. Cliffe SJ, Tabrizi S, Sullivan EA. 2008. Chlamydia in the Pacific Region, the Silent Epidemic. *Sexually Transmitted Diseases*, 35(9);801-806.
2. Marks M, Kako H, Butcher R, Lauri B, Puiahi E, Pitakaka R, Sokana O, Kilua G, Roth A, Solomon AW, Mabey DC. 2015. *BMJ Open Access* 2015;5:e007276.doi:10.1136/bmjopen-2014-007276.
3. Vallely LM, Toliman P, Ryan C, Rai G, Wapling J, Tomado C, Huliafi S, Munnull G, Rarau P, Phuanukoonnon S, Wand H, Siba P, Mola GDL, Kaldor JM, Vallely AJ. 2016. Prevalence and risk factors of Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis and other sexually transmissible infections among women attending antenatal clinics in three provinces in Papua New Guinea: a cross-sectional survey. *Sexual Health* 13;420-427.
4. Marks M, Bottomley C, Tome H, Pitakaka R, Butcher R, Sokana O, Kako H, Solomon AW, Mabey DC. 2016. Mass drug administration of azithromycin for trachoma reduces the prevalence of genital Chlamydia trachomatis infection in the Solomon Islands. Sex Transm Infec 92;261-265.

Table 1.1: Recommended treatment of chlamydia, gonorrhoea and trichomoniasis for pregnant women in Fiji according to the Ministry of Health Government of Fiji Antibiotic Guidelines 2011.

STI	Recommended Treatment
Chlamydia	Azithromycin 1g single oral dose OR Erythromycin 500mg orally 6 hourly for 7 days
Gonorrhoea	Probenecid 1g orally as a single dose, plus either: • Augmentin 1 tablet single dose OR • Amoxycillin 2.5g orally as a single dose
Trichomoniasis	Severe infections in the first trimester: • Econazole pessaries 150mg at night for 3 days

Annex 2D: RISE: Regimens of Ivermectin for Scabies Elimination - Initial study protocol version submitted to ethics

Protocol Version 2

A Cluster Randomised Non-Inferiority Trial of One Versus Two Doses of Ivermectin for the Control of Scabies Using a Mass Drug Administration Strategy.

Or

RISE: Regimens of Ivermectin for Scabies Elimination

VERSION 2, 10th April 2018

Revision Chronology

Date of change	Summary of changes
No changes as yet.	

STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

Permission has been granted by Chief Investigator Professor Andrew Steer to include this protocol in this MAE Bound Volume.

CONTENTS

PROTOCOL SYNOPSIS

Title	A Cluster Randomised Non-Inferiority Trial of One Versus Two Doses of Ivermectin for the Control of Scabies Using a Mass Drug Administration Strategy
Objectives	Primary Objective: 1. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing the prevalence of scabies at 12 months after the intervention. Secondary Objectives: 1. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing the prevalence of scabies at 24 months; 2. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing the prevalence of impetigo at 12 and 24 months; 3. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing presentations to health clinics with scabies and impetigo; and 4. To determine the safety of one compared to two doses of ivermectin for ivermectin-based MDA.
Design	Prospective comparison of the efficacy and safety of two different treatment regimens for scabies in 20 villages in the Western Province of the Solomon Islands. One treatment arm involves a single dose of oral ivermectin delivered through MDA, and the other treatment arm involves two doses of oral ivermectin (one week apart). The prevalence of scabies and impetigo will be measured before treatment at baseline, then at 12 and 24 months post treatment.
Outcomes	Primary Outcome Measure: 1. The prevalence of scabies at month 12 compared to month 0 by study treatment arm. Secondary Outcome Measures: 1. The prevalence of scabies at month 24 compared to month 0 by study treatments. 2. The prevalence of impetigo at month 24 and 12 compared to month 0 by study treatments.

	3. The prevalence of presentations to primary health clinics by age group (less or greater than 1 year) with scabies and impetigo at month 24 compared to month 0 by study treatments. 4. The number of adverse events measured by passive surveillance in the 12 months after MDA.
Study Duration	24 months.
Interventions	Each of the 20 villages will be randomised in a 1:1 ratio to one of the following two treatment arms (10 in each arm): Group 1 - Oral ivermectin-based MDA (single dose): Participants will be offered 1 dose of oral ivermectin at 200 ug/kg unless contra-indicated. Individuals with a contra-indication will be offered topical permethrin. Group 2 - Oral ivermectin-based MDA (two-doses): Participants will be offered the first dose of MDA treatment as in the single dose group, and then a second dose 7 to 14 days later, identical to the first.
Number of subjects	Approximately 5000.
Population	All individuals living in the selected study sites, agreeing to participate.

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
AE	Adverse Event
AIM	Azithromycin Ivermectin MDA
DSMC	Data Safety Monitoring Committee
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
MCRI	Murdoch Children's Research Institute
MDA	Mass Drug Administration
NHMRC	National Health and Medical Research Council
NT	Northern Territory
NTD	Neglected Tropical Disease
SAE	Serious Adverse Event
SHIFT	Skin Health Intervention Fiji Trial
SID	Subject Identification Number
SUSAR	Suspected Unexpected Serious Adverse Reaction
UNSW	University of New South Wales
WHO	World Health Organization

ADMINISTRATIVE INFORMATION

1.1. Trial registration

1.1.1. Registry

We are in the process of registering our trial on ANZCTR (http://www.anzctr.org.au/).

1.2. Sponsor

Study Sponsor	Murdoch Children's Research Institute.
Contact name	Professor Andrew Steer
Address	Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Road, Parkville Victoria 3052 Australia.

Funding and resources: This study is funded by the National Health and Medical Research Council (NHMRC). It is based on the collaboration of a number of research institutes including Murdoch Children's Research Institute, the Kirby Institute UNSW, the Australian National University, the London School of Hygiene and Tropical Medicine and the Solomon Islands Ministry of Health.

1.3. Expected duration of study

The study will run for 24 months, with participant screening beginning on the 1st September 2018.

1.4. Contributorship

Name	Summary of contribution
Sophie Phelan (Study Coordinator)	Writing and collation of protocol.
Andrew Steer (Study Principal Investigator)	Study concept, design and proof reading of protocol.
Daniel Engelman (Study Investigator)	Study concept, design and proof reading of protocol.
Michael Marks (Study Investigator)	Study concept, design and proof reading of protocol.
Margot Whitfeld (Study Investigator)	Study concept, design and proof reading of protocol.
Ross Andrews (Study Investigator)	Study concept, design and proof reading of protocol.
Oliver Sokana (Study Investigator)	Study concept, design and proof reading of protocol.
John Kaldor (Study Investigator)	Study concept, design and proof reading of protocol.
Dickson Boara	Study concept, design and proof reading of protocol.
Lucia Romani (Study Investigator)	Study concept, design and proof reading of protocol.
Anneke Grobler (Study Statistician)	Statistical methods and proof reading of protocol.

For affiliations, qualifications and contact details of all investigators please see separate Investigator Details document.

2. INTRODUCTION AND BACKGROUND

2.1. Background and rationale

Global burden of Scabies

Scabies is a neglected tropical disease that is a substantial contributor to global morbidity and mortality. Caused by infestation with a microscopic mite (Sarcoptes scabiei) that burrows under the skin of hosts and is transmitted through close personal contact (1), scabies has recently been added to the World Health Organization (WHO) list of neglected tropical diseases (2). WHO estimates that over 100 million people worldwide have the disease every year, the vast majority living in tropical developing countries (3). A systematic review of global scabies prevalence published in 2015 found that countries of the Pacific have a particularly high burden of scabies with a prevalence in children in some areas approaching 50% (4). In a recent study conducted in 10 villages in the Western Province of the Solomon Islands, the proposed setting of this study, an all-ages scabies prevalence of 19.2% was estimated (5).

Health, social and economic consequences of scabies

The heavy burden of scabies in endemic countries has major health and social consequences, largely through its contribution to serious bacterial infection. Scabies is the most common cause of impetigo in developing countries, through its link to infection of the skin with Streptococcus pyogenes and Staphylococcus aureus, which arises when these bacteria gain access into skin broken by scratching due to the intense itchiness. The previously mentioned survey of scabies and impetigo in the Western Province of the Solomon Islands found a prevalence of impetigo of 32.7%, and was highest in children aged less than 4 years (42.6%). In this study scabies was identified as a major risk factor for impetigo (population attributable risk of 41%). Impetigo provides a key portal of entry for bacterial pathogens to lead on to more severe skin and soft tissue infections including abscesses, cellulitis and necrotising fasciitis, as well as invasive bacterial diseases of high prevalence in the Pacific (6).

Scabies also has a direct and significant impact on quality of life due to its itchiness, which causes sleep disturbances in up to 70% of cases and thus potentially contributes to delays in development and learning (7). Scabies also imposes a considerable economic cost on individuals, families and health services. Scabies and impetigo account for between 12% and 24% of primary health care centre presentations in tropical countries (4). In Fiji, 52% of children attending health clinics present with impetigo, scabies or both (8). In a study in Mexico, the average period of absence from school for scabies was 8 days and for skin infection 15 days, with the average costs

of treatment being US$24 and US$52 respectively (9), a substantial imposition in poor communities, especially when incurred repeatedly.

Standard approaches to scabies control

Standard approaches to scabies control have focussed on people with symptoms and their household contacts, and involved the use of topical cream (permethrin or benzoyl benzoate) with follow up review in 2 weeks. However, while these treatments have high cure rates at an individual level, they have no impact on community prevalence, with reinfestation occurring rapidly in endemic settings. Accordingly, attention has shifted in recent years to the potential role of MDA, a strategy that has been highly effective in the control of several other major neglected tropical diseases, including onchocerciasis, lymphatic filariasis, trachoma and soil-transmitted helminths. MDA is supported by WHO and multiple partners through large regional and global programmes. The five pharmaceutical agents that have been particularly prominent in MDA are ivermectin, albendazole, diethylcarbamzine, azithromycin and praziquantel, with ivermectin by far the most frequently delivered.

MDA for scabies

Ivermectin MDA for scabies has recently proven to be a highly promising control strategy. In the recently concluded Skin Health Intervention Fiji Trial (SHIFT), reported in the New England Journal of Medicine in 2015, ivermectin-based MDA was compared to permethrin based topical MDA and standard care (10). In the ivermectin arm, one dose of ivermectin was given to all participants, with a second dose for those clinically diagnosed with scabies. At 12 months scabies prevalence had declined by 94% in the ivermectin arm, compared to 62% and 49% in the permethrin and standard care arms respectively. The prevalence of impetigo declined similarly, with the greatest reduction in the ivermectin arm (67%). Unpublished data at 24 months show that the benefit of ivermectin MDA was sustained, with a prevalence of 3.7% in this arm, compared to 13.4% and 15.4% in the permethrin MDA and standard care arms.

However, before scabies MDA with ivermectin can be convincingly advocated as a public health strategy in national and global guidelines, key additional questions need to be addressed. One is the extent to which the substantial reduction in the prevalence of superficial skin infections (impetigo) seen in the SHIFT trial is translated into reductions in the more serious infectious complications of scabies. This is being investigated by this research team in a parallel study in Fiji. The second key question relates to the dose regimen of ivermectin that is needed for effective MDA – which will be investigated in this study.

Double dose regimen of ivermectin for scabies MDA

While the biology of scabies suggest that two doses may be better than one for treatment in individual patients, the difference may be less relevant for community level MDA. It has long been understood that effective treatment of scabies requires a second dose around 1-2 weeks after the first to kill eggs unhatched at the time of initial treatment, however this assumption is not based on quality evidence. Currently, clinical guidelines for scabies therapy are based on this assumption and recommend the second dose. This approach has therefore been incorporated into ivermectin MDA trials. SHIFT offered a second dose to all those with clinical scabies at baseline, while the much larger AIM trial, that was recently conducted in the Solomon Islands (under review), offered two doses to all participants because it was not feasible to screen over 25,000 participants to identify those with clinical scabies at baseline. However, the second dose is a complicating factor for MDA. It doubles the drug cost, and adds considerable logistic complexity to the delivery strategies. It also sets scabies MDA apart from other MDA programs, including those based on ivermectin for onchocerciasis and lymphatic filariasis, all of which use a single dose.

Proposed single dose regimen of ivermectin for scabies MDA

In fact, it is biologically plausible that by treating all community members with a single dose of ivermectin, the burden and transmission of scabies will be reduced sufficiently to achieve community prevalence of both scabies and impetigo similar to that achieved with two doses. In Zanzibar, where single-dose ivermectin-based MDA for lymphatic filariasis was conducted in more than 1.3 million people over 5 years, there was a 68% reduction in clinic presentations with scabies (11), suggesting that this regimen can have a very substantial effect on community scabies burden. However, the study was retrospective, had no comparison group, did not report on impetigo prevalence and relied on clinic reports of scabies treatment rather than the systematic, community wide skin examination that is the gold standard for assessing scabies prevalence. There is therefore a need for a definitive comparison of one versus two doses of ivermectin as MDA for scabies control.

Why this trial will be conducted in the Solomon Islands

This study is a priority for the Solomon Islands Ministry of Health, as the prevalence of scabies in the Solomon Islands presents a significant public health problem to the country. As mentioned above, a recent study conducted in 10 villages in the Western Province of the Solomon Islands found an all-ages scabies prevalence of 19.2% (5). Reducing the prevalence of scabies will also help to reduce the prevalence of impetigo. This is also highly prevalent in the Solomon Islands, with the previous study also finding a prevalence of impetigo of 32.7%. Other invasive bacterial

diseases that occur as a consequence of impetigo are highly prevalent in the Pacific (6). Staff of the Solomon Islands Ministry of Health have recognised this huge burden and have collaborated closely in the development of this study.

Additionally, this group of investigators have recent, extensive experience conducting scabies interventional and observational scabies research in the Solomon Islands. They have recently conducted three major projects on scabies in the Solomon Islands. The prevalence survey in Western Province, referred to previously, showed that a high participation rate in the setting of the current proposed trial can be achieved. A second project was a survey in Malaita Province, of a small population successfully treated with ivermectin MDA in 1997, which found that scabies remained virtually non-existent, some 15 years after the last treatment (12). Finally, the AIM trial, also referred to above, is the largest prospective MDA for scabies conducted anywhere in the in the world.

Given the potential large advantages of using a single dose of ivermectin for ivermectin-based MDA, the need for a properly conducted trial, and the study team's extensive experience in the Solomon Islands, the study team now propose a cluster randomised trial to determine whether a single dose of ivermectin MDA is as effective as a two dose ivermectin-based MDA in reducing the prevalence of scabies and impetigo.

Rationale

The main purpose of this study is to investigate if one dose of oral ivermectin delivered through MDA is as effective as two doses in reducing the population prevalence of scabies. This is the first study to investigate this. The intervention is at the village/community level because the objective is to determine the best strategy for reducing or eliminating scabies within whole communities. A cluster randomised, open-label, non-inferiority design is the ideal study type for this research question and will be adopted in this study. It is the ideal study type because firstly, the randomisation minimises the possibility of the anticipated difference in the outcome between the single dose and two dose villages being confounded. Second, randomisation must be at the level of the cluster, rather than individuals, because the primary outcome is population prevalence of scabies – not an individual outcome. The open label design will be used rather than a dummy or placebo second dose in the single dose arm, because one of the characteristics that might favour the single dose is better adherence.

2.2. Research Question

This study will answer the question of whether one dose of oral ivermectin delivered through MDA is non-inferior to two doses in reducing the population prevalence of scabies. Currently, MDA strategies used for other globally important neglected tropical diseases (NTDs) have been integrated as they only require one dose of medication. If one dose of oral ivermectin proves to be as effective as two doses, scabies MDA could be combined with MDA for other NTDs. The drug cost of scabies MDA could also be halved.

3 STUDY OBJECTIVES

3.1 Primary objective

1. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing the prevalence of scabies at 12 months after the intervention.

3.2 Secondary objectives

1. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing the prevalence of scabies at 24 months;
2. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing the prevalence of impetigo at 12 and 24 months;
3. To determine if MDA with one dose of ivermectin is as effective as MDA with two doses in reducing presentations to health clinics with scabies and impetigo; and
4. To determine the safety of one compared to two doses of ivermectin for ivermectin-based MDA.

4 STUDY DESIGN

4.1 Type of Study

This trial is a prospective comparison of 1 vs 2 doses of ivermectin MDA treatment for scabies. Using a cluster randomised design, each of the 20 villages will be randomised to one of two intervention arms (comparing 1 vs 2 doses), in a 1:1 ratio. After the communities are randomised to one of the two study arms, the study will be conducted in an open-label, prospective fashion. The proposed study will then determine the prevalence of scabies and impetigo before the intervention, 12 months after the intervention, and 24 months after the intervention, allowing the researchers to assess the effect of one dose of ivermectin MDA compared to 2 doses over time.

4.2 Study Setting

Twenty isolated village communities from the Western Province, Solomon Islands, will be selected as study sites. Each village has a population range of 200-300 people, and are culturally, geographically and demographically similar. These villages will be selected after consultation with senior representatives of the Solomon Islands Ministry of Health because of their population size, geographic location (particularly relative to other study villages and willingness to participate.

Figure 1. Map of the Solomon Islands (with the Western Province indicated in the box).

5 PARTICIPANTS AND RECRUITMENT

5.1 Number of Participants

Twenty villages have been selected for participation in this study based on population size of approximately 250 people per village, meaning an approximate total sample size of 5000.

5.2 Eligibility Criteria

As a community-based study of mass drug administration, all community members who have given consent to participate and meet all of the inclusion criteria and none of the exclusion criteria, are eligible for participation in this study.

5.2.1 Inclusion criteria

All community members of selected villages are able to be included in this study.

5.2.2 Exclusion criteria

If a potential participant meets any of the following exclusion criteria, they will not be able to participate in our study:

- Allergy to any of the components of the allocated drug regimen,
- Currently on, or has taken ivermectin in the previous 7 days,
- Has had topical 5% permethrin applied within previous 7 days .

5.3 Recruitment and identification of potential participants

Twenty isolated communities will be selected to be included in the study. The study team has had extensive preliminary discussions with a number of key stakeholders in the Solomon Islands, following an established process that is undertaken for the introduction of new community health initiatives. Following the initial endorsement granted for the overall concept by the Solomon Islands Ministry of Health, engagement at the community level will include discussion with senior district nurses who visit the communities, nurses at the island health centres, and local community leaders and village chiefs. More detailed discussion between study investigators and community leaders and key stakeholders as well as the community/island representatives is planned at study meeting in Gizo, 2018.

In each of the 20 communities, residents will be identified from the most recently available population lists, and invited to participate in the study through community leaders and members followed by a visit from the local District Nurse. The study will also establish a comprehensive community awareness program of information dissemination to ensure that community members are aware of the study, and have the opportunity to raise issues that may be of concern. The study team will arrive at the village at a pre-agreed date and conduct the screening and drug administration components of the study over a period of 1-2 days at a central location of the village (or a village health care centre if available).

Prior to performing any study specific procedure at each of the three planned community visits, a signed consent form will be obtained for each participant. For participants below the legal age, a parent, legal guardian, or person with power of attorney, must also sign a consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The project coordinator and a study nurse will conduct the informed consent discussion and will check that the participant and their legally acceptable representative comprehend the information provided and answer any questions about the study. Consent will be voluntary and free from coercion. The investigator that conducted the consent discussion will also sign the informed consent form. A copy of the consent form will be given to the participant

or their legally acceptable representative and the fact that the participant has been consented to the study will be documented in the participant's record.

5.4 Consent

Survey teams will be primarily composed of personnel from the local health services, who are fluent in local dialects. These individuals will be tasked with obtaining written informed consent from participants prior to their participation in this study at each of the three planned community visits, and will also sign the informed consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Consent will be voluntary and free from coercion. When the all the inclusion/exclusion criteria have been addressed and the eligibility of the participant confirmed, the participant may be assigned to a randomisation treatment in the study. Adults will give consent for themselves if they are competent to do so. For participants aged less than 18 years of age, written consent will be obtained from their parent/guardian. If participants are illiterate or unable to sign, the signature section on the study informed consent forms is large enough to accommodate a thumb print or personal sign. A copy of the consent form will be given to the participant or their legally acceptable representative and the fact that the participant has been consented to the study will be documented in the participant's record.

A record of all participants who were screened but not enrolled will be kept by survey team members (documenting ineligible participants and reasons for non-participation).

5.5 Community awareness and local involvement

Prior to study commencement a research workshop will be held and attended by both participating staff but also key community leaders from communities involved in the study. We also plan to engage local staff to conduct thorough community awareness campaigns among selected villages prior to our study. In addition, several high-level members of the Solomon Islands Ministry of Health have been involved in the development of the research question, outcome measures, study design, and conduct of the study from the start (see Investigator List).

6 INTERVENTION

6.1 Treatment arms

This study investigates the efficacy of two alternative MDA strategies of oral ivermectin for scabies control, namely one dose (Group 1) and two doses (Group 2).

1. Group 1 - Oral ivermectin-based MDA (single dose): Participants will be offered 1 dose of oral ivermectin at 200ug/kg unless contra-indicated. Ivermectin will be replaced by topical permethrin cream in "ivermectin contra-indication" groups (described in Section 5.5) as per guidelines for onchocerciasis programmes. No treatment will be given to participants who are considered by the study nurse to be extremely ill.

2. Group 2 - Oral ivermectin based MDA (two-doses): Participants will be offered the first dose of MDA treatment as in the single dose group, and then a second dose 7 to 14 days later, identical to the first. Contra-indication guidelines will be followed as per group 1.

6.2 Intervention(s)

Ivermectin is a registered, routinely manufactured and marketed drug produced respectively by Elea Laboratories (APPENDIX A, B).

Ivermectin 200μg/kg

Ivermectin is a white to yellowish-white non-hygroscopic crystalline powder which is practically insoluble in water, freely soluble in methanol, and soluble in 95% ethanol. It also contains microcrystalline cellulose, pregelatinised maize starch, magnesium stearate, butylated hydroxyanisole and citric acid anhydrous. Prepared as 3 mg tablets, the product is packaged in a small blister pack containing 6 tablets and will be stored at room temperature.

Ivermectin is considered to have a very good safety profile, with over 1 billion single doses distributed for control of onchocerciasis and lymphatic filariasis at doses of 100-200 μg/kg with little or no adverse outcomes beyond minor, reversible events (13-15). In these programmes, pregnant women and young children have been excluded from taking ivermectin in the absence of formal safety studies (13), but observational evidence indicates that the drug is safe in both of these populations. Ivermectin is on the Solomon Islands essential drug list for scabies.

6.2.1 Dosage and route of administration

Ivermectin will be taken orally as directly observed therapy either swallowed whole or crushed and mixed with yoghurt/custard. The dose of ivermectin will be determined according to body weight and/or height, and treatment will be administered under direct supervision before

participants leave the clinic. The recommended dose for scabies is 200 μg/kg. The dose range of 160–250 μg/kg is being used so the tablets can be cut evenly for distribution. The weight range used in this study is narrower than that recommended on the Product Information booklet so that a more accurate dose equivalent to 200 μg/kg can be delivered. The ivermectin dosage per weight for scabies MDA (dose 1 and dose 2) will be as follows:

15–18 kg 3.0 mg 19–27 kg 4.5 mg

28–36 kg 6.0 mg 37–55 kg 9.0 mg

56–74 kg 12.0 mg 75–100 kg 15.0 mg >100kg 18.0 mg

6.2.2 Dose modification

For practical reasons, a height-based dosing system may be used in line with programmatic dosing of ivermectin.

6.2.3 Preparation and administration of study drug

Drugs will be stored by the pharmacy until the initial survey period. They will be administered by the survey team nurses during the first village visit.

6.2.4 Dispensing and product accountability

Medications will arrive by plane and will reach the islands by boat at the provincial pharmacy / medical store. The order request will be checked with the supplies delivered. The delivery notice number, delivery date and the medications batch number will be recorded in a log book. Medications will be taken out of the pharmacy in bulk by the study teams for dispensing in the community. Study teams will maintain a log of all medicines dispensed that can be cross-checked against participants study records. As medication will be administered on the spot during our study, there will be no leftover product.

6.2.5 Measurement of participant compliance

All medication will be directly observed.

6.2.6 Excluded medications and treatments

Ivermectin will be replaced by topical permethrin cream in the following cases:

- pregnant women
- mothers nursing infants during the first week of life
- children under 12.5kg or 90cm

Any medication that participants are taking will be cross checked against the list of medications that interact with ivermectin and are contraindicated.

6.2.7 Treatment of participants with crusted scabies

Participants with severe or crusted scabies will be treated with 2 doses of ivermectin (except if ivermectin is contraindicated as outlined above) in conjunction with twice weekly permethrin cream for 1 month, with review at 1,2,3,12 and 24 months. Efforts will be made to control these cases intensively to prevent the high force of infection associated with these crusted cases from diminishing the effect of the MDA.

7 RANDOMISATION AND BLINDING

Islands will be randomly assigned to one of the treatment arms in a 1:1 ratio. A randomised list will be prepared by the study statistician.

7.1 Concealment mechanism

This is an open-label study.

7.2 Breaking of the Study Blind

7.2.1 On study

Not applicable.

7.2.2 On completion of the study

Not applicable.

8 STUDY VISITS AND PROCEDURES

8.1 Study timeline

Figure 2. Study Design Diagram

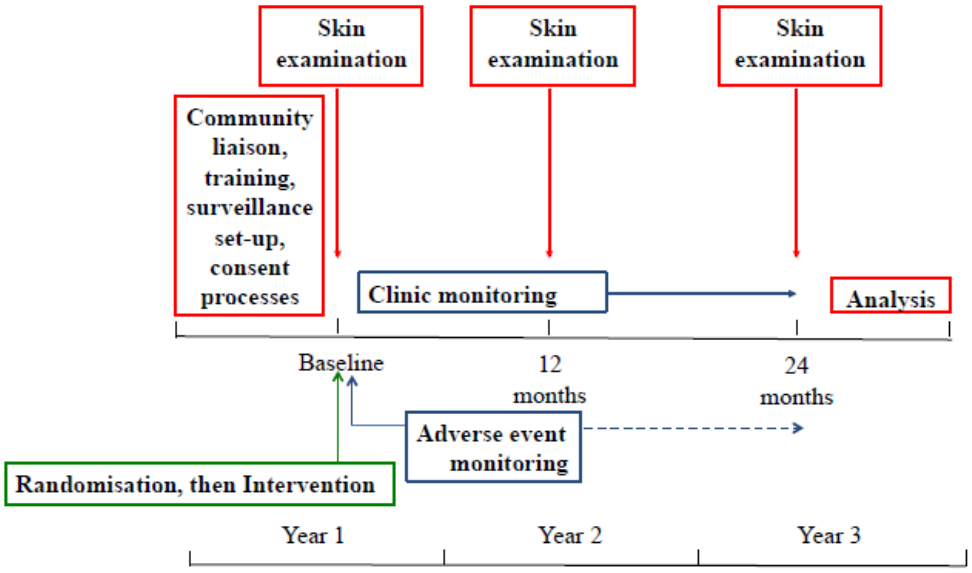
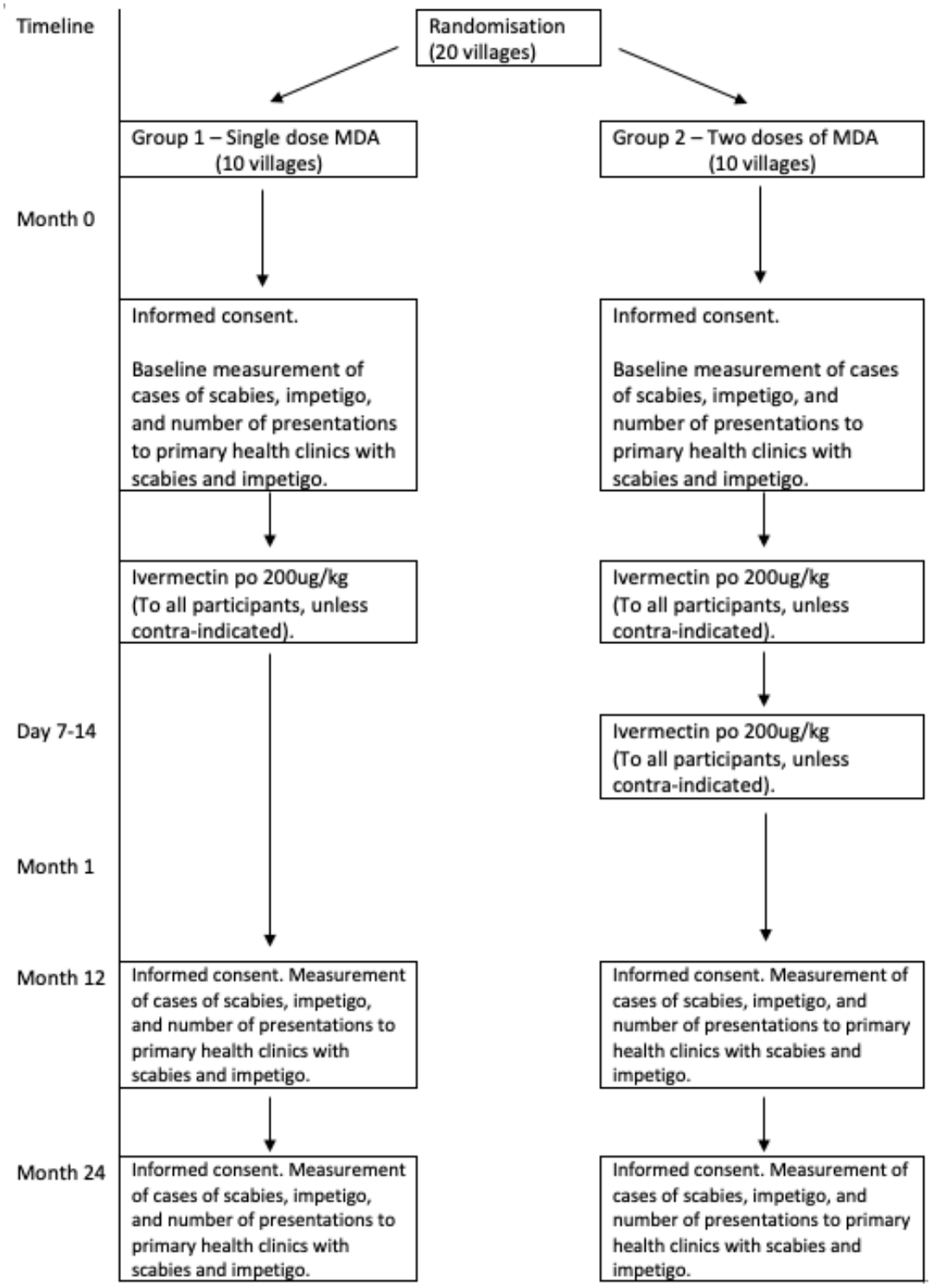


Figure 3. Study design and treatment flowchart from baseline to 24 months



8.2 Schedule of assessments

Figure 4: Study visit and procedure schedule

VISIT NUMBER	Visit 1	Visit 2	Visit 3	Visit 4
TIMING	Day 1	Day 8-15	12 months	24 months
Informed Consent	X		X	X
Demographic Information	X		X	X
Physical Examination	X		X	X
Contra-indication check	X			
Study drug dispensing	X	X (2-dose villages only)		
Medical illness / Adverse event check	X	X (2-dose villages only)		

8.3 Screening

We expect that the screening, scabies examination and drug administration (only at visit 1) component will take approximately 15 minutes per participant, per visit. For each participant, the screening process will be conducted by a study team member prior to the potential participants examination by the study nurse. The study team member responsible for screening will ensure they:

- Obtain and document consent from potential participant.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.

8.4 Baseline

At Visit 1, we will obtain the following information from participants for comparison to later visits:

- Record participant name, head of household name, age, sex, weight, height, and treatment (ivermectin (and second dose if applicable) or permethrin). Date, zone name, village name will be recorded at the top of the study record.
- Record results of scabies and impetigo clinical examination.

8.5 Visits

Please refer to Section 8.2, Schedule of assessments, above.

8.6 Final study visit

Please refer to Section 8.2, Schedule of assessments, above.

8.7 Withdrawal visit

Not applicable.

8.8 Unscheduled visit

Unscheduled visits are not anticipated but will be handled and documented by the TSC if they are deemed necessary.

8.9 Participant Withdrawal

8.9.1 Reasons for withdrawal

Study participation within villages is voluntary and study participants can withdraw at any time. The number of withdrawals will be recorded. An entire village can decide not to participate any more.

8.9.2 Handling of withdrawals and losses to follow-up

No data from participants s or villages who have withdrawn will be used. Due to the village-based study design, there will not be any losses to follow up.

8.9.3 Replacements

Not applicable.

8.10 Trial Closure

The trial is planned to run over a 24-month period. The primary outcome analysis of efficacy will be undertaken at 12 months (as described in Section 10.3). If any one of the two arms is clearly more effective than the other arms (defined as relative difference > 2 and statistically significant at alpha = 0.05 level or an absolute difference >20% and statistically significant at alpha = 0.05 level), then the study will be stopped and the most efficacious treatment regimen will be offered to participants in the other arm in consultation with the Provincial Ministry of Health.

Stopping rules

1. There is an unusual cluster of SAE's that, in the view of the Principal Investigator or the DSMC, is attributable to the study drug/treatment and poses a risk to other study participants.
2. Evidence emerges that indicates one or both regimens being investigated in this study are unsafe.

8.11 Continuation of therapy

No study medication will be issued to a participant after Visit 1.

9 OUTCOMES

9.1 Primary outcome

1. The prevalence of scabies at month 12 compared to month 0 by study treatment arm.

9.2 Secondary outcome(s)

1. The prevalence of scabies at month 24 compared to month 0 by study treatments.
2. The prevalence of impetigo at month 24 and 12 compared to month 0 by study treatments.
3. The prevalence of presentations to primary health clinics by age group (less or greater than 1 year) with scabies and impetigo at month 24 compared to month 0 by study treatments.
4. The number of adverse events measured by passive surveillance in the-12 months after MDA compared by study treatments.

For further information, see Section 10.4.

10 CLINICAL AND LABORATORY ASSESSMENTS

10.1 Clinical assessment of scabies

Scabies will be defined clinically without the use of microscopy, based on typical clinical findings, that is, pruritic inflammatory papules with a typical distribution of lesions. These include webs of the fingers, hands, wrists, elbows, knees, trunk and ankles. Diagnosis will follow methods used in scabies trials in Fiji and the Solomon Islands (5, 10).

Categories of scabies severity will be determined based on the nature and distribution of characteristic scabies lesions, with specific differentiation of infected scabies and crusted scabies. Screening for scabies will be conducted in the community from visible skin and skin that the participant is comfortable to expose. Infected scabies will be identified as pus-filled sores or crusted sores within the collection of scabies lesions. The severity of skin sores will be determined by the number of lesions identified.

10.2 Clinical assessment of skin sores

Impetigo is an infection by bacteria of the top layers of the skin. Impetigo starts as red or pimple-like sores surrounded by reddened skin. The sores can be anywhere on the body, but mostly on the face, arms, and legs. They fill with pus, then break open after a few days and form a crusted scab. Itching is common.

Diagnosis of skin sores in endemic areas is based upon clinical findings of discrete sores/lesions with pus or crusts. The above-mentioned nurses will also conduct the clinical assessment of skin sores.

10.3 Training of examiners

Nurses nominated by the Western Province will be trained in the diagnosis of scabies and impetigo by experts in scabies diagnosis and tropical dermatology. Training will be conducted in the weeks prior to commencement of the study. Training will consist of classroom teaching and supervised training in a community. Nurses will be required to pass a standardised assessment before commencing the fieldwork. An expert will supervise the initial period of fieldwork to continue training and ensure appropriate diagnosis.

During the training period, written consent will be obtained from all community participants. All participants will be examined by an expert, not just a training nurse. Any person found to have scabies or impetigo will be referred to the local clinic for treatment as per the Solomon Island standard treatment manual and the protocol used in a previous study in the Western Province (5).

10.4 Measurement of Secondary Outcomes 3 and 4

For Secondary Outcome 3, we will also document other skin and soft tissue infections such as abscesses, cellulitis and necrotising fasciitis.

For Secondary Outcome 4, passive surveillance will entail reviewing routinely collected summary data from hospital records at Gizo Hospital for the following adverse events: all deaths, unexplained deaths, and any emergency presentations 1 month after MDA. We will review routinely collected summary data on all still births from hospital records at Gizo Hospital for 12 months after MDA.

10.5 Assessment of contra-indications to ivermectin including pregnancy

All participants will be screened for contraindications for ivermectin. Participants will be asked whether they think they are pregnant (as described in section 8.6) and/or breastfeeding. If a participant is pregnant or unsure if pregnant, topical permethrin cream will be offered instead of oral ivermectin. Children under 12.5kg / 90cm will be offered permethrin cream. Participants with neurologic diseases such as Parkinson's Disease or cerebral palsy, and people taking medication that is metabolised by the cytochrome p450 pathway will be offered permethrin cream. Any medication that participants are taking will be cross checked against the list of medications that interact with ivermectin or permethrin and are contraindicated.

If a participant is allergic or hypersensitive to any component of ivermectin, permethrin or crotamiton, that medication will not be offered.

10.6 Measurement of weight and height

Participants will have their weight and height checked using standardized methods. Calibrated digital scales will be used to weigh participants, and height will be measured with standardised measuring tapes. Weight will be measured in kilograms and height will be measured in metres. Records will be taken on the appropriate form.

10.7 Pregnancy testing

During the consenting/assenting process, female participants will be asked whether they are, or think they might be, pregnant. If a participant is pregnant or unsure if pregnant, topical permethrin cream will be offered instead of oral ivermectin.

10.8 Study procedures at 12 and 24 months

At 12 and 24 months, participants' will undergo a physical examination. There are no laboratory assessments in this study and no tissue samples of any kind are being collected.

11 ADVERSE EVENTS AND RISKS

The Project Steering Committee will supervise and monitor the project at all times and if adverse events are experienced the committee will make sure that appropriate care is available. If present, the committee will report side effects to the Data Safety Monitoring Committee (DSMC) and the ethics committees.

11.1 Definitions

Adverse Event (AE): AEs will be assessed using the NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods 2016 definition of AEs: "Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and does not necessarily have a causal relationship with this treatment" (16).

Serious Adverse Event (SAE): SAEs will be assessed using the following NHMRC definition of SAEs: "Any adverse event/adverse reaction that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect" (16).

Note: Life-threatening refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in this definition should also be considered serious.

11.2 Assessment and documentation of adverse events

Given the short duration of the on-study period of the study (14 days), and the well-known adverse event profiles of single and two dose ivermectin, the DSMC will meet prior to the study, in the first 3 months after the MDA intervention and at the end of the study. The DSMC will review participant enrolment, AE's and address any problems within the study or any matter raised from a source external to the study. The DSMC will meet at additional timepoints if requested by a participating community or investigator.

11.3 Eliciting adverse event information

Any adverse events will be reported to community health care workers in the selected villages for 14 days following administration of the first dose of ivermectin. The community health care

workers will relay this information to the study team who will document the AE and send a report to the DSMC who will meet as outlined above.

11.4 Serious adverse event reporting

Any SAEs and SUSARs will be handled as described in Section 11.3 above. After they have been discussed by the DSMC, they will be reported to all study HRECs by the Study Coordinator.

11.4.1 Assessment of AEs and SAEs

Assessment of adverse events will be performed according to the Common Toxicity Criteria for Adverse Events (CTCAE v3.0) (17). Adverse events will be graded according to severity:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe – requiring medical care or hospitalization
- Grade 4: Life-threatening or disabling
- Grade 5: Death

Adverse events will be assessed for the likely relationship to treatment:

- Not related to treatment
- Unlikely to be related to treatment
- Possibly related to treatment
- Probably related to treatment
- Definitely related to treatment

Serious adverse events (SAE) will be reviewed by the DSMC. These will be defined as grade 3+ (irrespective of relationship to treatment) and grade 2 adverse events possibly related or related to treatment. Adverse events (AE) not categorized as serious will be documented and reported to the Principal Investigator and the Investigator responsible for trial site medical decisions. They will be compiled and reported to the DSMC at the next meeting date.

11.4.2 SUSARS

All SUSARs occurring in a study participant will be reported to the DSMC (i.e. within 15 calendar days of first knowledge), or for fatal or life-threatening events, an initial or full report within 7 calendar days and a follow-up report if necessary within the 15 calendar day timeframe. An investigator will complete, sign and submit the SUSAR report.

11.4.3 Surveillance of Adverse Events

Adverse events will be monitored through passive surveillance for 24 months after the intervention by review of clinic records. Clinic records will be reviewed 24 months after MDA, and the number of AEs reported by study participants in the time period between MDA and the 24-month point will be collected.

12 DATA MANAGEMENT

12.1 Data Collection

12.1.1 Source Data

All data will be directly entered electronically into the appropriate REDCap form. When internet is available these forms will be uploaded onto the study REDCap database. During the period before the data is uploaded to the REDCap database, this data will be referred to as “source data”. It will be backed up every night onto an external hard drive by the Survey team leader until it can be uploaded to the REDCap database.

12.1.2 Data Capture Methods

In the field all data will be directly entered into custom built REDCap databases on android devices. REDCap is a highly reputable electronic research database, which is highly secure and requires specific user access with password protection. It was originally built by Vanderbilt University, USA, and the REDCap consortium is now composed of institutions in 92 countries. REDCap has been used for over 180,000 projects and cited in over 1500 publications. The data will be checked and cleaned before analysis. No investigation of the data will begin until an accurate database has been assured.

12.2 Data Storage

Electronic data collected and stored on the android devices, and will be downloaded directly to the REDCap database as soon as there is internet signal. The REDCap database will be able to be accessed by investigators (including at MCRI) using a password protected log-in that will only be known to the investigators. The REDCap database files will be downloaded onto a separate password-protected computer and the original files on the handheld devices will be deleted. Data collected about the participants will be coded and de-identified and held in strict confidence. All results will be presented in a way, which does not allow individuals to be identified. No information concerning the study or the data will be released to any unauthorized third party. A password protected copy of the full database will be provided to the Solomon Islands Ministry of Health.

12.3 Record Retention

The paper data forms will be kept in a locked room in a locked and secure filing system at an office in Gizo Hospital, Solomon Islands. Only the investigators and the study staff will have access to the raw data during and after the study. Data from this study will be destroyed after 15 years as per local guidelines.

If data are published, only aggregate results will be reported. Reports and publications will not disclose the identity of participants.

12.4 Collection of additional health economic data

We also plan to collect basic health economic data from a random sample of participants at Visit 1. This will include a short questionnaire on the monetary cost of any current or past scabies or impetigo treatment, and non-medical costs such as time off work, school absenteeism and "presenteeism" (working but not as efficiently as usual). We also plan to assess quality of life with a standardised questionnaire. All questionnaires will be piloted by a small sample of participants during Community Awareness visits prior to the study.

13 STUDY OVERSIGHT

13.1 Governance structure

The trial will be coordinated by a research team, led by the Principal Investigator, a study doctor and a study coordinator. The study coordinator will be delegated responsibility for participant follow-up visits, data collection and maintenance of study documentation. Handling of investigational products will be the responsibility of the study coordinator, under supervision from the Principal investigator.

13.2 Trial Steering Committee

A Trial Steering Committee will be established to provide general oversight of the trial including decisions on protocol development and protocol deviations, response to issues arising throughout trial and interpretation of findings.

13.3 Independent Data Monitoring Committee

An independent data monitoring committee will be established to oversee the safety and progress of the trial.

13.4 Quality Control and Quality Assurance

Standard Operating Procedures (SOPs) will be developed to ensure the quality and consistency of the survey and drug administration procedures at each village. Electronic data will be reviewed and cleaned by the Study Coordinator once it has been uploaded to the study database after each survey period. Electronic study records and logs will be reviewed by the Survey team lead at the end of each village visit and backed up to an external harddrive. Survey team leaders will discuss any quality assurance procedures with the Study Coordinator who will correct minor issues at their discretion and address any major issues with the Trial Steering Committee.

See Section 10.3 for nurse training.

14 STATISTICAL METHODS

14.1 Sample Size Estimation

Primary Outcome

Sample size calculations were based on the primary outcome, the difference in prevalence of scabies between month 0 and month 12 in each arm. A standard Monte Carlo simulation method with 1000 repetitions was used to estimate the required sample size and number of villages to achieve statistical power of 80% (18). Based on preliminary data, it was conservatively assumed that scabies prevalence across villages varies between 10% and 30% (mean 20%, standard deviation, SD, 5%) at baseline. Using the effect size measured in SHIFT, it was assumed that in the two-dose regimen, the prevalence of scabies in villages measured at 12 months would be between 1% and 5% (mean 3%, SD 1%), while in the one-dose regimen a prevalence between 3% and 9% was assumed (mean 6%, SD 2%). The average cluster (village) size was assumed to be 250 individuals with a range of 200 to 300.

Clinical relevance

A non-inferiority margin of + 5% (12-month scabies prevalence one-dose regimen minus 12-month scabies prevalence two-dose regimen) was considered to be clinically relevant. In other words, the one-dose regimen would be described as non-inferior to the two-dose regimen if the upper-bound of the two-sided 95% confidence interval for the difference in prevalence was less than or equal to 5%. Based on these assumptions, 20 villages randomised equally (10 in each arm) would be sufficient to achieve the required power.

Secondary Outcomes

There is sufficient sample size to measure all secondary outcomes.

14.2 Statistical Analysis Plan

Primary outcome

A standard approach for analysis of cluster randomised clinical trial data will be employed. In each village, the prevalence of scabies will be calculated at baseline, 12 months and 24 months, as the proportion of participants who show signs of scabies. The calculation will be based on all participants at each time point that participated in the study. The same participants will not necessarily attend at all 3-time points. For each village, the difference in prevalence between baseline and 12 months will be calculated. The means of these differences will be calculated in the two treatment arms and compared between the two treatment arms by calculating the difference between the means and the ratio of the means. If the upper limit of the two-sided 95% confidence interval of the mean difference between the two study arms is less than or equal to 5% (the clinically relevant non-inferiority margin) the one-dose regimen would be described as non-inferior.

The analysis will be based on the intention to treat population, including all participants in each village regardless of actual treatment status. The secondary study outcomes will be analysed using the same methodology.

14.2.1 Population to be analysed

The study population will be all those residing in the selected 20 villages at month 0, 12 and 24 who have consented to enrol in this study.

14.2.2 Handling of missing data

Any missing data will be handled by the study statistician whose judgement will determine how the data is handled.

14.3 Interim Analyses

No interim analysis is planned.

15 ETHICS AND DISSEMINATION

15.1 Research Ethics Approval

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the relevant human research ethics committee (HREC). A letter of protocol approval by HREC will be obtained prior to the commencement of the study, as well as approval for other study documents subject to HREC review. This protocol is being considered by

the MCRI/RCH HRE, the National Research Ethics Review Committee, Solomon Islands, and will be submitted to the Australian National University HREC.

15.2 Modifications to the protocol

Modifications from the original protocol are not anticipated, however if this does occur approval will be sought for amendments to the protocol and these will be described in the final reports. Protocol modifications will be reported to study investigators in accordance with standard GCP processes.

15.3 Protocol Deviations

Deviation from the original protocol and statistical plan is not anticipated, however if this does occur approval will be sought for amendments to the protocol and these will be described in the final reports. Protocol deviations will be reported to study investigators in accordance with standard GCP processes.

15.4 Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and the clinical information relating to participating participants. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsoring institution. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records. All evaluation forms, reports and other records that leave the site will be identified only by the Subject Identification Number (SID) to maintain participant confidentiality. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by HREC or regulatory agencies.

15.5 Participant Reimbursement

Not applicable.

15.6 Financial Disclosure and Conflicts of Interest

There are no relevant financial or other conflict of interests to be disclosed.

15.7 Dissemination and translation plan

Publication and reporting of results and outcomes of this study will be accurate and honest, undertaken with integrity and transparency. Publication of results will be subjected to peer-review. Authorship will be given to all persons providing significant input into the conception, design, and execution or reporting of the research. No person who is an author, consistent with this definition, will be excluded as an author without their permission in writing. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation. All conflicts arising through disputes about authorship will be reviewed by the director. Acknowledgement will be given to collaborating institutions and hospitals and other individuals and organisations providing finance or facilities.

Individual data will not be made available publicly, but de-identified data may be made available for further analysis. Results of the study will be presented locally (including to the community) and made available to health policy decision makers and clinical staff.

In terms of the dissemination of results to study participants, community health workers in all participating villages will receive newsletters and posters containing the results. Posters will be displayed in village clinics and the community health workers will ensure that participants are told that results are available and describe them to anyone who cannot read.

16 REFERENCES

1. Heukelbach J, Feldmeier H. Scabies. Lancet 2006; 367(9524): 1767-74.
2. World Health Organization. Neglected Tropical Diseases. 2015. http://www.who.int/neglected_diseases/diseases/en/ (accessed 16/3/2015).
3. World Health Organization. Epidemiology and management of common skin diseases in children in developing countries. Geneva, 2005.
4. Romani L, Steer A, Whitfeld M, Kaldor J. Systematic review of the global prevalence of scabies and impetigo. The Lancet Infectious Diseases 2015;15:960-967.
5. Mason DS, Marks M, Sokana O, et al. The Prevalence of Scabies and Impetigo in the Solomon Islands: A Population-Based Survey. PLoS Neglected Tropical Diseases. 2016;10(6). Baroux N, D'Ortenzio E, Amedeo N…Steer AC. The emm-cluster typing system for Group A
6. Streptococcus identifies epidemiologic similarities across the pacific region. Clin Infect Diseases 2014; 59(7): e84-92.
7. Jackson A, Heukelbach J, Filho AF, et al. Clinical features and associated morbidity of scabies in a rural community in Alagoas, Brazil. Trop Med Internat Health :2007; 12(4): 493-502.
8. Steer AC, Tikoduadua LV, Manalac EM, Colquhoun S, Carapetis JR, Maclennan C. Validation of an Integrated Management of Childhood Illness algorithm for managing common skin conditions in Fiji. Bull World Health Organ 2009; 87(3): 173-9.
9. Hay RJ, Estrada Castanon R, Alarcon Hernandez H, et al. Wastage of family income on skin disease in Mexico. BMJ 1994; 309(6958): 848.
10. Romani L, Whitfeld MJ, Koroivueta J, et al. Mass Drug Administration for Scabies Control in a Population with Endemic Disease. N Engl J Med 2015; 373(24): 2305-13.
11. Mohammed KA, Deb RM, Stanton MC, Molyneux DH. Soil transmitted helminths and scabies in Zanzibar, Tanzania following mass drug administration for lymphatic filariasis--a rapid assessment methodology to assess impact. Parasit Vectors 2012; 5: 299.
12. Marks M, Satorara L, et al. Long Term Control of Scabies Fifteen Years after an Intensive Treatment Programme. PLOS Neglected Tropical Diseases 2015; (9:e0004246).
13. Mectizan Donation Program. www.mectizan.org (accessed 17/03/2010).
14. Tielsch JM, Beeche A. Impact of ivermectin on illness and disability associated with onchocerciasis. Trop Med Internat Health 2004; 9(4): A45-56.
15. Ottesen EA, Hooper PJ, Bradley M, Biswas G. The global programme to eliminate lymphatic filariasis: health impact after 8 years. PLoS Negl Trop Dis 2008; 2(10): e317.

16. NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (dated November 2016). Accessed on April 10, 2018 from: https://www.nhmrc.gov.au/guidelines-publications/eh59
17. RS. F. Ivermectin use in scabies. . Am Fam Physician. 2003;68:1089-92.
18. Boos D, Stefanski LA. Monte Carlo Simulation Studies. Springer Text in Statistics; 2012: 363-83.

Annex 2E: Participant Information and Consent Form

HREC Project Number:	38099A		
Research Project Title:	RISE: Regimens of Ivermectin for Scabies Elimination		
Local Principal Investigator:	Mr Oliver Sokana		
Version Number:	1	**Version Date:**	10/04/2018

Thank you for taking the time to read this **Participant Information Statement and Consent Form**. We would like to invite you to participate in a research project that is explained below.

This document is 3 pages long. Please make sure you have all the pages.

What is an Information Statement and Consent Form?

An Information and Consent Form tells you about the research project. It clearly explains exactly what the research project will involve. This information is to help you decide whether or not you would like to take part in the research. Please read it carefully.

Before you decide if you want to take part or not, you can ask us any questions you have about the project. You may want to talk about the project with your family, friends or health care worker.

Taking part in the research is up to you

It is your choice whether or not you take part in the research. You do not have to agree if you do not want to. If you decide you do not want to take part, it will not affect the treatment and care you get.

Signing the form

If you want to take part in the research, please sign the consent form at the end of this document. By signing the form you are telling us that you:

- understand what you have read
- had a chance to ask questions and received satisfactory answers
- consent to taking part in the project.

We will give you a copy of this form to keep.

1. What is the research project about?

The aim of this programme is to get rid of the skin infection known as scabies. People often don't know they have this infection. To get the best results we try to treat everyone to make sure we don't miss anyone with infection. Usually you need to take the same medicine twice to get rid of this infection, but you may only need to take it once. We are trying to figure out if we can get rid of scabies if everyone in your community takes this medicine once.

2. Who is funding this research project?

The programmes are organised by the Solomon Islands Ministry of Health, the London School of Hygiene & Tropical Medicine, The Kirby Institute, the Australian National University, and the Murdoch Childrens Research Institute, Melbourne.

3. Why am I being asked to take part?

Twenty villages in the Western Province of the Solomon Islands have been selected at random to their skin checked and be provided with medication for scabies. Everyone living in the village will be asked to participate.

4. What do I need to do in this research project?

If you agree to take part, we will record information about your age and gender and will take your height and weight. Depending on what study treatment your community has been allocated, we may organise a second dose of treatment for scabies one or two weeks after the first dose for 10 out of the 20 villages. We will also examine your skin for signs of scabies and other skin problems. (Note: for visits 2 and 3, treatment component will be taken out of this answer – and replaced with something like "if you have scabies or other skin problems, you will receive standard treatment for this).

5. Can I withdraw from the project?

You can stop taking part in the project at any time. You just need to tell us so. You do not need to tell us the reason why. If you leave the project we will use any information already collected unless you tell us not to.

6. What are the possible benefits for me and other people in the future?

You and your community will receive treatment for scabies. If our study shows that this is an effective strategy, we may be able to provide this treatment to help other people in the Solomon Islands and many other countries.

7. What are the possible risks, side-effects, discomforts and/or inconveniences?

Treatment for scabies is very effective and side effects are uncommon and quickly go away. Ivermectin occasionally causes dizziness or tummy upset. Azithromycin occasionally causes tummy upset. Pregnant women should not take ivermectin and will be offered a cream instead. Having your skin examined for scabies is not uncomfortable or painful. The whole process, including asking questions and examination should take less than 10 minutes.

8. What will be done to make sure my information is confidential?

Any information we collect for this programme that can identify you will be treated confidentially, except as required by law. Nothing that could reveal your identity will be disclosed outside the programme.

9. Will I be informed of the results when the research project is finished?

Results of the programme will help us understand the best way to treat scabies in communities in the Solomon Islands and elsewhere. Results will be published in the medical literature, and a report summarizing the results will be sent to your community health worker. You and your family will not be personally identified in any report or publication.

10. Who should I contact for more information?

If you would like more information about the project, please contact:

Name:	Mr Oliver Sokana
Contact telephone:	XXX XXXX
Email:	XXX XXXX

OR

Name:	Miss Sophie Phelan
Contact telephone:	XXX XXXX
Email:	XXX XXXX

If you:

- have any concerns or complaints about the project
- are worried about your rights as a research participant
- would like to speak to someone independent of the project.

You can contact the Solomon Islands National Health Research Ethics Committee by telephone on (+677) 37295, or you can contact the Director of Research Ethics & Governance at The Royal Children's Hospital Melbourne by telephone on (03) 9345 5044.

CONSENT FORM

HREC Project Number:	38099A		
Research Project Title:	RISE: Regimens of Ivermectin for Scabies Elimination		
Version Number:	1	**Version Date:**	10/04/2018

- I have read this information statement and I understand its contents.
- I understand I have to do to be involved in this project.
- I understand the risks I could face because of my involvement in this project.
- I voluntarily consent to take part in this research project.
- I have had an opportunity to ask questions about the project and I am satisfied with the answers I have received.
- I understand that this project has been approved by The Solomon Islands National Health Research Ethics Committee and the Royal Children's Hospital Melbourne Human Research Ethics Committee. I understand that the project and any updates will be carried out in line with the National Statement on Ethical Conduct in Human Research (2007).
- I understand I will receive a copy of this Information Statement and Consent Form.

I consent/give consent for _____to take part in this study.
(Participant Name)

_____	_____
Participant Signature	Date

_____	_____	_____
Name of Witness to Participant's Signature	Witness Signature	Date

Declaration by researcher: I have explained the project to the participant who has signed above. I believe that they understand the purpose, extent and possible risks of their involvement in this project.

_____	_____	_____
Research Team Member Name	Research Team Member Signature	Date

Note: All parties signing the Consent Form must date their own signature.

Annex 2F: Scoping Trip Report

RISE Study, Western Province

16-17th May 2018 Visit Trip Report

Visiting Study Team

- Matthew Parnaby – MCRI
- Oliver Sokana – Focal Person Eye Health, MHMS
- Sophie Phelan – UNSW/ANU

16th May Morning Meeting

Attendees:

- Dickson (Gizo Hospital Transport Coordinator)
- Dr Dickson Boara (Provincial Health Director, Western Province)
- Christina Galona (Head of Nurse Education)
- Selina Maena (Gizo Hospital Finance Team)
- Frederick Neqo (Gizo Hospital Pharmacy)
- Jeffrey Kovini (Head of Nursing, Western Province)
- Visiting study team

Introductions, Study timelines and Village Selection

Key points:

- Sophie gave a short presentation summarizing the RISE study
- The following study timelines were confirmed:
    - Study team visit June 11-16th 2018
    - Baseline prevalence survey and MDA Sept-Oct 2018
    - 12 month prevalence survey Sept-Oct 2019
    - 24 month prevalence survey Sept-Oct 2020.
- A shortlist of 40 potential study villages was discussed amongst the group. This list consisted of villages of approximately 200 people from the 2009 Western Province census (sub regions that Oliver and Daniel Engelman previously advised to exclude were excluded here also).
- The group mapped out the villages and collaboratively discussed the pros and cons of including/excluding certain villages.
- The list was narrowed to 28 villages.
- The need for an accurate census of these villages was agreed by all.

16th May Afternoon Meetings

Pharmacy meeting with Frederick

- Frederick advised that it is possible to store the study drugs in Gizo, however storage room in the hospital pharmacy and oxygen room is minimal. Matthew was able to visit the storage space.
    - Action: look into alternative packaging options for the study drugs that takes up less room.
- Frederick advised that it was best to speak with Willie at NMS, Honiara about the initial importation of the study drugs into the country.
    - Action: Oliver to follow up with Willie, and liaise with Matthew regarding the necessary procedures.
- Frederick advised that the Solomon Islands usually source permethrin from Fiji or Australia.
    - Action: Sophie to liaise with Matthew (Fiji permethrin contact).

Finance meeting with Selina

- 2 Banks in Gizo: ANZ and Bank of South Pacific (BSP)
- ANZ bank has best exchange rate.
- Bookkeeping
    - Action: need to create study receipt books and study stamp. Study logo?

Study Census meeting with Clemence (Community Nursing Coordinator)

- No other sources of population data are available (from community health clinics, other programs eg malaria bednets).
- If a census were to be conducted, this should be discussed with Freda (Assistant Director of Nursing PHC).

17th May Morning Meetings

Study Census meeting with Freda Havea (Assistant Director of Nursing PHC)

- Freda agreed to assist with conducting a census in the 28 villages that were shortlisted the previous day.
- The logistics, timing, cost, and personnel involved in such a census were discussed.
    - 6 Public Health graduate students could be hired for the study teams (2 teams of 3, with 1 boat each).
    - Tina and Freda would conduct a training day.

    - Approximately two weeks would be needed to conduct the census.
    - A data collection sheet was created. Paper data collection forms will be used for the census.
    - Oliver has a data collection assistant who will enter the data electronically (will take 4-5 days).
- Community Awareness strategies for the census were discussed. These will include a radio message once a day for 1 week before the census, and letters to be sent to village pastors.
    - Action: Sophie propose a census budget to Aus study team
- Community Awareness strategies for the RISE study were discussed. Oliver reassured the group that the health education programs in the village health clinics will ensure this is done.

General Study logistics discussion (among visiting study team)

- Cost of boat hire was discussed. We are able to use one Hospital boat for free – however if there is an emergency, the hospital will require this boat immediately. Each boat can carry 6-7 people along with supplies.
- Oliver suggested that we have two study teams. The first team visits all villages, but will only give the first dose for 2 dose villages. The second team will come back and deliver the second dose for each 2 dose villages. Preferable to use the same boat drivers as the census, and to get the geographic coordinates for each village to find it again in 2019 and 2020.
- Redcap/Android data collection acceptable.
    - Action: Aus team, what is the study budget for this?
- Field jackets discussed as a better option than study t-shirts for identifying study team.
- Waterproof spray jackets will be needed for team members.
- Tina agreed to assist with nurse training for the study.
- Phone service: coverage patchy and intermitted for both “Our Telecom” and “Bmobile” in Gizo. “Our Telecom” appeared to have better coverage.
- All agreed on the need for a local study team leader on each team.

Oliver and Tina’s capacity for involvement

- Oliver busy with work in Honiara yet can assist from there. He will not be able to work in the field.
- Tina can assist from Gizo, and can assist with field work but only for 2-3 weeks.

17th May Afternoon Meetings

Gizo Primary School – Meeting with Principal (Nester Thugea: +XXXX)

- 700 primary children, 30 teachers.
- The principal tentatively agreed to conducting the nurse training.
- August would be a good time to conduct the training.
- The principal looks forward to discussing this more on our visit in June.

Long term accommodation scoping trips

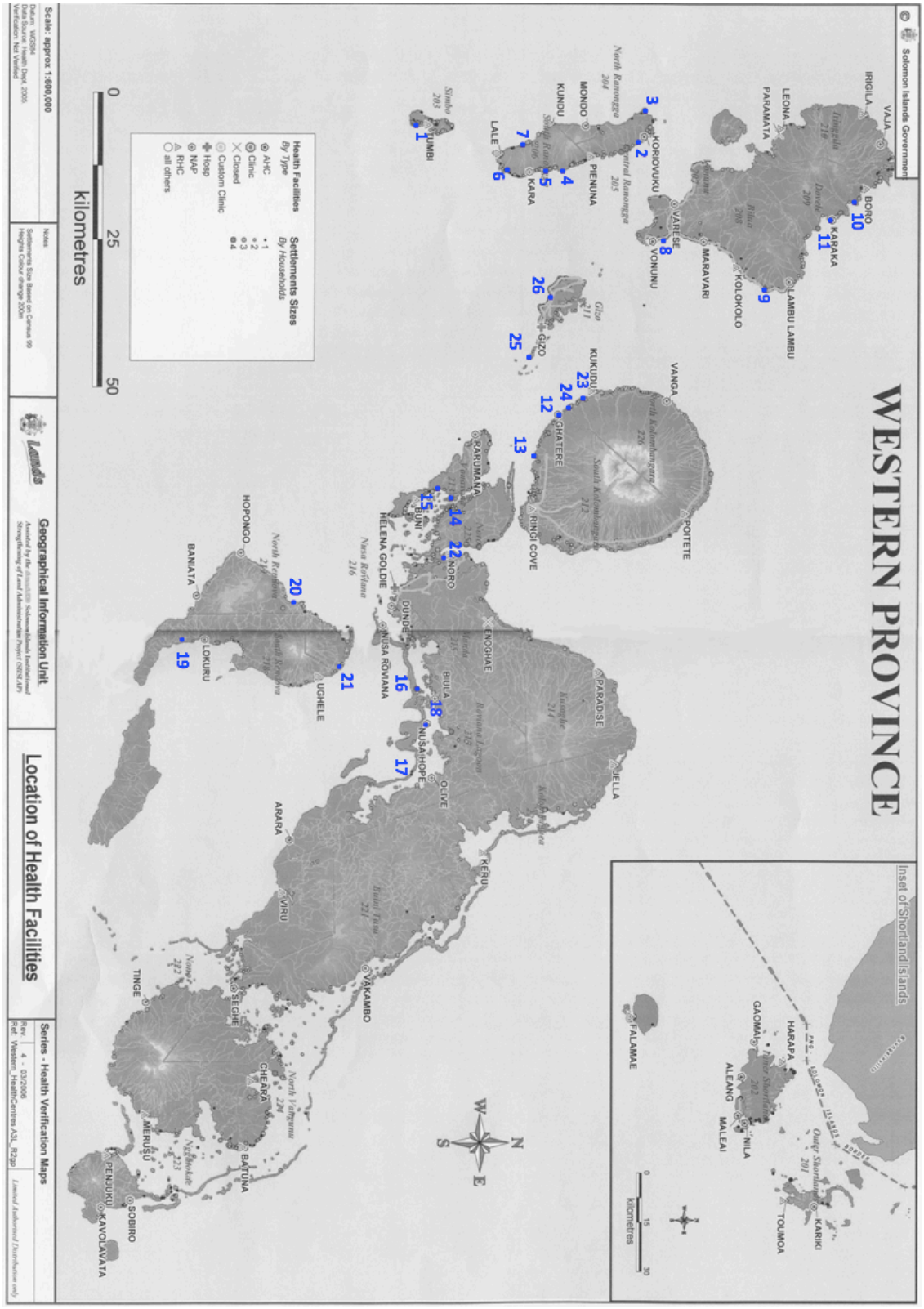
- Cegily's Guesthouse (p: 60035, m: 7467982): shared bathroom, lounge and kitchen. Fan. On hill behind hospital. Some areas still under construction. Approx $50 Aus a night.
- N'agua Resthouse (p: 60012): shared bathroom, lounge and kitchen. Air con. On hill behind hospital. Approx $50 Aus a night.
- WSM Rest Haus (p: 60945, m: 7901096, m: 7430410, e: wsmresthouse@gmail.com). Self-contained rooms with bathroom, kitchen, balcony and kitchen utilities. $765 Aus per month. Women only.

Trip Report Appendices

Trip Report Annex 1: Contact details of Participants

(Excluded for privacy reasons).

Trip Report Annex 2: Map of shortlisted villages



**note: village locations are very approximate!*

See next page for legend.

Legend #	Village	Population (2009)
1	TAPURAI	295
2	KOLOMALI	218
3	BURI SOUTH	266
4	SUAVA	267
5	PAQE	259
6	KOQU-WESTERN 6	236
7	KEARA	285
8	BARAKOMA	255
9	KUAVA	239
10	KARO KESA	269
11	KARAKA	267
12	GHATERE	267
13	KUZI	264
(Unknown location)	NAQILEANA	269
14	NEW MALA-WETSERN 13	205
15	BARASIPO	226
16	TUNGUIVILI	190
(Unknown location)	PIHARIKI	250
17	SASAVELE	283
18	NUSA HOPE	203
19	RANO-WESTERN 18	224
20	RENDOVA HBR	226
21	AGAGANA	267
22	Part of Noro Base P4	220
23	IRIRI	234
24	VAVANGA-WESTERN 26	182
25	BABANGA	296
26	TITIANA-WESTERN 11	269

Trip Report Annex F: Census data collection form

Population Profile by Village Summary

Village:……Page number:……Date:…… Total households per page:……

	Household Name	<1 yr		1-4 yrs		5-14 yrs		15-49 yrs		50+ yrs		Total	
		M	F	M	F	M	F	M	F	M	F	M	F
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													
13													
14													
15													
16													
17													
18													
19													
20													
21													
22													
23													
24													
25													
26													
27													
28													
29													
30													
31													
32													
33													
34													
35													
36													
37													
38													
39													
40													
	TOTAL												

Annex 2G: Extracted version of REDCap Database

Confidential

Demographics

Study ID	_____
Demographics	
DOB known?	◯ Yes ◯ No
Date of birth (DD/MM/YYYY)	_____
Age (whole years)	_____
Class	_____
Sex	◯ Male ◯ Female

Confidential

Examination

Study ID	_____
Examiner ID	◯ Doctor 1 ◯ Doctor 2 ◯ Nurse 1 ◯ Nurse 2 ◯ Nurse 3 ◯ Nurse 4 ◯ Other
Other Examiner initials	_____
Day of examination	◯ Tues W1 ◯ Wed W1 ◯ Thurs W1 ◯ Fri W1 ◯ Mon W2 ◯ Tues W2 ◯ Wed W3 ◯ Other
Skin Examination	
1. Any abnormal skin lesions or rash?	◯ Yes ◯ No (If no, END examination)
2. TYPICAL LESIONS: Do the skin lesions look like the common scabies rash?	◯ Yes ◯ No
3. TYPICAL DISTRIBUTION: Are the lesions or rash in the common areas for scabies?	◯ Yes ◯ No
4. Are there definite burrows?	◯ Yes ◯ No
5. ITCH: Any itch?	◯ Yes ◯ No
Contact History	
6A. Do you live with someone with itch?	◯ Yes ◯ No
6B. Do any of your classmates or friends have itch?	◯ Yes ◯ No
6C. Do you live with someone who has a rash that looks like scabies?	◯ Yes ◯ No
6D. Do any of your classmates or friends have a rash that looks like scabies?	◯ Yes ◯ No

Confidential

7. IACS Criteria subcategory:	○ Other Diagnosis ○ B3 ○ C1 ○ C2
Other diagnosis, specify	_____
8. How many scabies lesions present?	○ 1-10 ○ 11-49 ○ >=50
9. Any infected sores or infected scabies?	○ Yes ○ No
10. How many infected lesions?	○ ≤ 5 lesions ○ 6-10 lesions ○ 11-49 lesions ○ >= 50 lesions
11. Other serious skin infection?	○ No ○ Cellulitis ○ Abscess/boils ○ Crusted scabies ((If other, include under Q12 Referral))
Referral	
12. Treatment or referral required?	☐ Scabies ☐ Impetigo - mild (home treatment) ☐ Impetigo - moderate or severe (referral) ☐ Other ☐ None
Other referral description	_____

Confidential

Consensus

Study ID	_____
7. IACS Criteria subcategory:	◯ Normal skin ◯ Other Diagnosis ◯ B3 ◯ C1 ◯ C2
Other diagnosis, specify	_____
8. How many scabies lesions present?	◯ 1-10 ◯ 11-49 ◯ >=50
9. Any infected sores or infected scabies?	◯ Yes ◯ No
10. How many infected lesions?	◯ ≤ 5 lesions ◯ 6-10 lesions ◯ 11-49 lesions ◯ >= 50 lesions
11. Other serious skin infection?	◯ No ◯ Cellulitis ◯ Abscess/boils ◯ Crusted scabies
Referral	
12. Treatment or referral required?	☐ None ☐ Scabies ☐ Impetigo - mild (home treatment) ☐ Impetigo - moderate or severe (referral) ☐ Other
Other referral description	_____

Chapter 3: Analysis of a public health dataset

Association between clean faces and trachoma in remote Australian communities prior to implementation of community-wide control strategies

Contents

3.1 List of Abbreviations

CDNA	Communicable Diseases Network Australia
GET 2020	The Alliance for the Global Elimination of Blinding Trachoma by 2020
HREC	Human Research Ethics Committee
MAE	Master of Applied Epidemiology
MDA	Mass Drug Administration
NTSRU	National Trachoma Surveillance and Reporting Unit
NT	Northern Territory
SAFE	Surgery (to correct trichiasis), Antibiotic treatment, Facial cleanliness and Environmental improvements
SA	South Australia
TF	Trachomatous inflammation - follicular
TI	Trachomatous inflammation - intense
WA	Western Australia
WHO	World Health Organization

3.2 Prologue

I acknowledge the traditional owners of the lands that provided the data for this analysis. I acknowledge their continuing connection to land, sea and community. I pay my respects to them, their cultures and their elders, past, present and emerging.

My role: The National Trachoma Management Program was initiated in Australia in 2006 (Kirby Institute 2018). Since then, the Australian Government has funded the National Trachoma Surveillance and Reporting Unit (NTSRU) to provide a national mechanism for monitoring and evaluating trachoma control. The NTSRU is responsible for coordinating data collection, analysis and reporting related to the ongoing evaluation of trachoma control strategies in Australian jurisdictions endemic for trachoma. Currently, the Kirby Institute manages the NTSRU and has done so since 2010. Prior to this, the NTSRU was managed by the Centre for Eye Research Australia and the Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, the University of Melbourne.

This project came about as a result of my interest in trachoma prior to the Master of Applied Epidemiology (MAE) program. My field supervisor, John Kaldor, suggested that I investigate the association between clean faces and trachoma as this is something that has never been investigated in the Australian context, and as the NTSRU, the Kirby Institute has access to the entire national and historical database. For this project, my role included drafting a number of briefs for jurisdictions, creating a data analysis plan in consultation with the team biostatistician Gordana Popovic, learning about mixed effects binomial models, cleaning the dataset, and conducting the data analysis.

Lessons learned: In this project, I learnt about mixed effects logistic regression, which was a challenging extension of my knowledge of regression prior to the MAE and the MAE course POPH8913: Analysis of Public Health Data. I enjoyed learning a new statistical method because one of the things I had hoped to obtain through the MAE was to further my skills in advanced statistics. Besides learning a new skill, it was interesting to learn about the history of trachoma surveillance in Australia, and about the role that the NTSRU plays in this. Through this project, I learnt a lot about the management and governance of national public health datasets in general. A key part of learning about the governance of national public health datasets involved participating in the negotiation process between the Kirby Institute and trachoma endemic jurisdictions regarding the level of depth of this analysis. As there are a number of limitations of the Australian trachoma dataset (to be discussed in more detail in this chapter) it is easy for the prevalence data to be misinterpreted. Because of the concerns of jurisdictions, a tightly restricted analysis at the national level only was agreed upon for the final version of this

chapter. The final lesson I learnt from this project was the importance of the caution of the well recognised problem of interpreting association too easily to mean causation. This caution will remain in the back of my mind for all future population based research I contribute to.

Public health impact: This was the first time that the association between clean faces and trachoma has been investigated in Australia at the national level. While facial cleanliness is already endorsed by the World Health Organization (WHO) in their strategy to eliminate trachoma as a public health problem, recent debates and a lack of strong evidence of this association have shed some doubt onto the necessity of the inclusion of facial cleanliness in the WHO strategy. The evidence from this analysis will continue to support trachoma control nationally and internationally.

Acknowledgements: I would like to acknowledge John Kaldor, Kathryn Glass and Ross Andrews for their supervision and technical advice for this project. I would like to thank Gordana Popovic from the University of New South Wales for her biostatistical advice, and Carleigh Cowling for her assistance with the set up and coordination of this project. I would also like to thank Anthony Solomon, Medical Officer for Trachoma from the World Health Organisation Geneva for his consultation regarding this analysis. I would also like to acknowledge the Trachoma Surveillance Officers from the Northern Territory, South Australia and Western Australia.

3.3 Abstract

Introduction: The association between clean face prevalence and trachoma prevalence has not been formally investigated in the Australian setting. The objective of this analysis is to determine if there is an association between clean face prevalence and trachoma prevalence in remote Australian communities where trachoma has been endemic.

Methods: We used screening data prior to community control strategies from Aboriginal and Torres Strait Islander children aged 5-9 years old who were living in remote communities in regions of Northern Territory, Western Australia and South Australia. Data were extracted from the National Trachoma Registry managed by the Kirby Institute. A logistic regression model was used to examine the relationship between the prevalence of clean faces and the prevalence of trachoma in Australian communities, adjusting for screening year and for region as a random effect.

Results: The first screening results from years 2007-2017 were included for 185 Australian communities. A significant association was found between higher prevalence of clean faces and lower prevalence of trachoma. Median trachoma prevalence was 21.4% for communities with a clean face prevalence of ≤25%, 31.7% for communities with a clean face prevalence of >25 to ≤50%, 16.7% for communities with a clean face prevalence of >50 to ≤75%, and 0.0% for communities with a clean face prevalence of >75%. In the binomial model which adjusts for community size and reporting year, compared to communities with a clean face prevalence of ≤25%, communities with a clean face prevalence ranging from >25 to ≤50% had 0.66 times the odds of having trachoma (95% CI 0.45-0.96), communities with a clean face prevalence ranging from >50 to ≤75% had 0.48 times the odds (95% CI 0.33-0.70), and communities with a clean face prevalence greater than >75% had 0.21 times the odds (95% CI 0.14-0.31).

Conclusions and public health implications: In this first, baseline analysis of clean faces and trachoma data for Australia, higher prevalence of clean faces was associated with a lower prevalence of trachoma. This association needs to be interpreted in terms of several caveats. These include uncertain direction of causality between clean faces and trachoma; the lack of a standardized definition of a clean face, particularly in earlier years; and the fact that the measurement of clean faces may vary according to the setting in which it takes place. Based on jurisdictional preference, this analysis will remain confidential, however the discussions it generates at jurisdictional level could pave the way for future analyses to provide evidence to either support or discourage the continued inclusion of facial cleanliness in the WHO strategy and therefore continue to support trachoma control nationally and internationally.

3.4 Introduction

Trachoma is an ocular infection that primarily affects underprivileged populations and continues to be the world's leading cause of infectious, preventable blindness[1]. Associated with limited water supplies and sanitation, trachoma is a disease of poverty and is defined by WHO as a neglected tropical disease. The disease is caused by the bacteria *Chlamydia trachomatis*, and manifests as inflammation of the conjunctiva. There are two phases of trachoma disease. This analysis will focus on the first phase, known as active trachoma, which is frequently seen in infancy and childhood and involves repeated attacks of conjunctivitis[2].

Clinically, there are two conditions that can be seen in the active trachoma phase (with increasing severity): trachomatous inflammation - follicular (TF) and trachomatous inflammation - intense (TI)[3]. Active trachoma is associated with ocular and nasal secretions that are particularly noticeable on the faces of children, but the active stage may also be asymptomatic in children and adults[2]. Close facial contact, hand-to-eye contact, flies and fomites (towels, clothing and bedding) are transmission pathways for trachoma[4]. The disease is more prevalent in dry, dusty and overcrowded environments linked to poor living conditions and inadequate personal hygiene behaviors. The highest prevalence of trachoma is commonly seen in children, who are believed to be the main reservoirs of infection.

Trachoma is a public health problem in 37 countries globally, with over 1.9 million people currently blind or visually impaired because of the disease[1]. Australia is the only high-income country where trachoma is still endemic[5]. In Australia, trachoma occurs primarily in remote and very remote Aboriginal communities in the Northern Territory (NT), South Australia (SA) and Western Australia (WA). Prevalence among children aged 5-9 years in affected remote communities of Australia has steadily declined from 2007-2012, following the implementation of the National Trachoma Management Program in 2006[5] and has been relatively stable since then.

The Alliance for the Global Elimination of Blinding Trachoma by 2020 (GET 2020), supported by the WHO, advocates for the implementation of the SAFE strategy, with its key components of surgery (to correct trichiasis), antibiotic treatment at community level to reduce the pool of infection in communities, facial cleanliness and environmental improvements, particularly focusing on water and sanitation access[6]. Australia has adopted a modified form of the SAFE strategy. This investigation will focus on the facial cleanliness component of the SAFE strategy. The facial cleanliness component of the SAFE strategy aims to maintain clean faces in the community in order to reduce eye-seeking flies and person-to-person transmission of *C. trachomatis*[8].

Children with potentially infective ocular and nasal discharge who are covered with flies are those assumed to be the source of most new infections[8]. Hence, increasing the prevalence of clean faces through the promotion of face-washing in particular and hygiene promotion in general are targets of most national trachoma control programmes[9]. Face washing promotion as a community intervention can be combined with mass drug administration (MDA) with antibiotics in areas with high trachoma endemicity. MDA with antibiotics (the A component of SAFE) aims to reduce the reservoir of *C. trachomatis* in the community, while face washing aims to interrupt the cycle of infection and re-infection in the long term. The proposed assessment of the effect of facial cleanliness is by estimation of the prevalence of clean faces in children aged 1-9 years.

An integral assumption of the SAFE strategy is that clean faces are protective against trachoma, however data on the direct impact of improvements in facial cleanliness are limited[7]. Findings consistently show that an unclean face is associated with trachoma and that flies, a possible physical vector of *C. trachomatis*, are attracted to an unclean face[10]. There is considerable evidence that people with clean faces are less likely than people with dirty faces to have active trachoma[11-18]. However, most of the data were obtained from observational studies and the methodological quality of the few controlled trials was not reported. Several studies have attributed changes in the prevalence of active trachoma to facial cleanliness programmes without adequately accounting for chance variation, seasonal effects, or secular trends[19].

Interpretation of the association between clean faces and trachoma must take into account a number of issues. The first is that it is unclear whether “dirty” faces lead to trachoma, or whether trachoma results in dirty faces, via the production of ocular and nasal discharges that can be symptoms of trachoma[10]. Second, there is no globally standardized definition of a clean face, and definitions have varied across the years and geographic locations. This lack of a standardized definition means that ocular and nasal discharge caused by respiratory infections associated with bacterial conjunctivitis[20] can be misinterpreted as a “dirty face” associated with trachoma. The third and final issue relates to the fact that the prevalence of clean faces varies by of the setting in which the assessment takes place. For example, measurements taken in clinics have been found to overestimate the prevalence of clean faces compared to measurements taken at home[10].

The association between clean face prevalence and trachoma prevalence has not been systematically examined in the Australian context. This analysis aims to investigate this association, and to interpret the results in light of the aforementioned caveats.

3.5 Methods

Objective

The objective of this analysis was to determine if there is an association between clean face prevalence and trachoma prevalence in rural/remote Australian communities that were endemic for trachoma at baseline prior to implementation of community wide control strategies.

Study population

The study population was comprised of Aboriginal and Torres Strait Islander children aged 5-9 years old, resident in a remote community of NT, SA or WA in a region endemic for trachoma, and who were screened at the first community survey prior to implementation of community wide control strategies (from 2007-2017 depending on the community). While WHO recommends that children aged 1-9 years old are screened, in Australia screening focusses on 5-9 year old's due to ease of access through schools. Only two other states (New South Wales and Queensland) collected data on clean face/trachoma prevalence, however this data was very minimal so it was excluded from this analysis.

Data extraction

The data used for this analysis were drawn from the National Trachoma Database maintained by the Kirby Institute. The data in this database were collated from annual jurisdictional reports from 2007-2017, and were collected according to the Communicable Diseases Network Australia (CDNA) *National guidelines for the public health management of trachoma in Australia*[21]. Data from 2006 were excluded from this analysis as collection methods in this first year of the National Trachoma Management Program differed substantially from those subsequently adopted.

Variables

The following variables were extracted from the National Trachoma Database: screening year, state (NT, SA and WA only), region, community, number screened for clean faces, number with clean faces, number screened for trachoma, number with trachoma, and treatment strategy. For data confidentiality reasons, the trachoma team at the Kirby Institute generated a dataset with community names and jurisdictions deleted for this analysis. This analysis only included prevalence data from communities at their baseline screening prior to community wide control strategies, as these may have included treatment with antibiotics. Therefore, each community is included once in this analysis, at its year of baseline screening.

Definitions

The definitions used in this analysis are consistent with those used in the national guidelines[21].

Clean face: For data collected between 2006-2009, there was no standardised definition for a clean face. For data collected between 2010-2012, the definition of a clean face was "absence of dirt, dust and crusting on cheeks and forehead". For 2013-2014, the definition of a clean face was "absence of dirt, dust and crusting (nasal and ocular discharge) on cheeks and forehead". For data collected between 2015-2017, the definition of a clean face according to the CDNA guidelines was "the absence of nasal and ocular discharge on the face"[21].

Community: A geographic location where people reside and where there is at least one school.

Community wide treatment: Antibiotic administration to all Aboriginal and Torres Strait Islander people in the community who weigh >3kg and who live in houses with children < 15 years.

Endemic trachoma: Prevalence of trachoma at 5% or higher in children aged 1-9 years.

Trachoma (or active trachoma): The presence of chronic inflammation of the conjunctiva caused by infection with *C. trachomatis*; includes WHO simplified grading: TF and TI.

Trachomatous inflammation - follicular (TF): Presence of five or more follicles in the central part of the upper tarsal conjunctiva, each at least 0.5 mm in diameter, as observed through a loupe.

Trachomatous inflammation - intense (TI): Pronounced inflammatory thickening of the upper tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels.

Measurement of study variables

Clean faces: clean faces were measured by specifically trained graders who assessed a clean face dependent on the definition for the year of data collection as above.

Active trachoma: active trachoma was measured by specifically trained graders according to the WHO Trachoma Grading classification criteria[22].

Data analysis

Data analysis was completed using Microsoft Excel 2018 version 16.9 (Microsoft Corporation, Washington, USA) and Stata version 15.1 (StataCorp, Texas, USA).

A new variable for clean face prevalence was created based on the following four prevalence categories: ≤25%, >25 to ≤50%, >50 to ≤75% and >75%.

A new variable to categorise the definition of clean face at time of screening was also created, comprising the following four categories: "No standardised definition" (screening years 2007-

2009), “absence of dirt, dust and crusting on cheeks and forehead” (screening years 2010-2012), “absence of dirt, dust and crusting (nasal and ocular discharge) on cheeks and forehead” (screening years 2013-2014), and “the absence of nasal and ocular discharge on the face” (screening years 2015-2017).

Firstly, a descriptive analysis was conducted. The aims of this were to:

1. Calculate the number of baseline communities included per year, by clean face definition.
2. Calculate the median, interquartile range (IQR) and range of the number of children screened for trachoma and clean faces in communities by clean face prevalence category.
3. Calculate the median prevalence of trachoma by clean face prevalence category.
4. Create a scatterplot of clean face prevalence by trachoma prevalence.

Secondly, a logistic regression model was created to examine the relationship between the prevalence of clean faces and the prevalence of trachoma in screened communities in Australia, adjusting for region as a random effect (within state) and the covariate screening year. Communities were weighted according to size in the model. Screening year was included as a covariate (instead of the clean face definition variable that was derived from the screening year variable) as trachoma prevalence is affected by dry and wet years. Assumptions of the model were checked and found to be reasonable.

Thirdly, a sensitivity analysis was conducted to examine the strength of the association between clean faces and trachoma for communities examined over a time period in which there was no standardised definition of a clean face. This was created using the same logistic regression model as above, including the 136 communities screened from 2007-2009. However, it did not adjust for the covariate screening year, as this was not a significant addition to the model (Likelihood ratio (LR) test >0.05).

Ethics approval processes

The ethics approval process for this project was complex. The Kirby Institute is covered by UNSW Human Research Ethics Committee (HREC) (under approval no. 9-14-042) to collate and analyse data from the National Trachoma Database. SP was added to this protocol to undertake this analysis. Additionally, jurisdictional approval from the NT, SA and WA was required to present this project in SP’s MAE bound volume. Obtaining jurisdictional approval required jurisdictions to see a fairly late draft, and SP could not apply for ANU ethics until this was obtained. Once the jurisdictions approved this chapter, SP applied for and received ANU HREC approval (under approval no. 2019/035).

No individual-level data are available in the National Trachoma Database. Communities and jurisdictions were de-identified, and data is presented at the national level.

Dissemination of results

A report summarising the key results will be distributed to jurisdictions.

3.6 Results

Baseline prevalence data from children in 185 communities endemic for trachoma across NT, SA and WA from 2007-2017 were included in this analysis (Table 1). Most communities included in this analysis were screened in the earlier years, when there was no standardized definition of a clean face (136 communities).

Table 1: Number of baseline communities included in analysis by screening year and clean face definition

Clean face definition	Screening year	No. communities
No standardized definition of clean face	2007	93
	2008	30
	2009	13
	2007-9	**136**
The absence of dirt, dust and crusting on cheeks and forehead	2010	9
	2011	14
	2012	20
	2010-12	**43**
Absence of dirt, dust and crusting (nasal and ocular discharge) on cheeks and forehead	2013	4
	2014	1
	2013-14	**5**
Absence of nasal and ocular discharge on the face	**2016**	**1**
	Overall total	**185**

Overall, the median number of children screened for trachoma per community was 14 (IQR 7-26, range 1-219), and the median number of children screened for clean faces per community was 13 (IQR 4-25, range 1-219). The overall median trachoma prevalence was 6.9%. Most communities (71%) had a clean face prevalence of over 75% (Table 2), with 89 communities having a clean face prevalence of 100%. The median trachoma prevalence for communities with a prevalence of over 75% of clean faces was 0.0%.

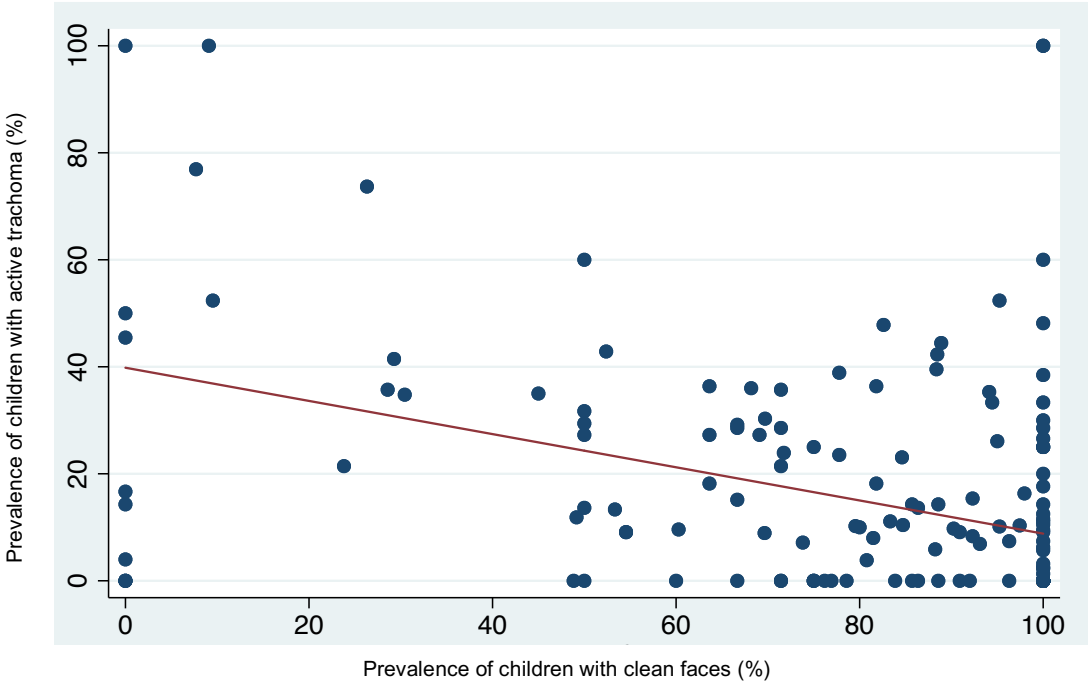
Table 2: Median trachoma prevalence by clean face prevalence for 185 communities across the NT, SA, and WA prior to community wide treatment (2007-2017)

	No. communities		No. children screened for trachoma per community			No. children screened for clean faces per community			M. trachoma prevalence (%)
Clean face prevalence	n	%	M	IQR	R	M	IQR	R	
≤25%	13	7	11	4-21	1-126	6	3-21	1-126	21.4
>25 to ≤50%	13	7	22	19-41	9-49	20	10-34	2-59	31.7
>50 to ≤75%	28	15	14.5	10-33	4-219	15	10-33	4-219	16.7
>75%	131	71	14	4-26	1-144	11	4-24	1-144	0.0
Total	185	100	14	7-26	1-219	13	4-25	1-219	6.9

** M=median, IQR=inter quartile range, R=range*

The association between clean face prevalence and trachoma prevalence is shown graphically in the scatterplot in Figure 1. As the proportion of children with clean faces increases, the proportion of children with trachoma decreases, which is indicated by the line of best fit in Figure 1. A significant, weak, negative correlation was calculated (Pearson's correlation coefficient = -0.41, P<0.001).

Figure 1: Scatterplot of the prevalence of active trachoma by the prevalence of clean faces in 185 communities across the NT, SA, and WA prior to community wide treatment (2007-2017)



The results from the binomial logistic regression model confirm that this observed trend of a decrease in trachoma with an increase of clean faces in a community is statistically significant (Table 3). Compared to communities with a clean face prevalence of ≤25%, communities with a clean face prevalence ranging from >25 to ≤50% had 0.66 times the odds of having trachoma (95% CI 0.45-0.96), communities with a clean face prevalence ranging from >50 to ≤75% had 0.48 times the odds of having trachoma (95% CI 0.33-0.70), and communities with a clean face prevalence greater than >75% had 0.21 times the odds of having trachoma (95% CI 0.14-0.31).

Table 3: Results from mixed effects model including all communities

Clean face prevalence	Odds ratio	P-value	95% CI
≤25%	1	-	-
>25 to ≤50%	0.66	P=0.031	0.45-0.96
>50 to ≤75%	0.48	<0.001	0.33-0.70
>75%	0.21	<0.001	0.14-0.31

**adjusted for random effect of region and covariate screening year*

The final analysis was a sensitivity analysis. The same model created for Table 3 was run to examine the strength of the association between clean faces and trachoma for communities examined over the time period in which there was no standardised definition of a clean face (Table 4). This involved 136 communities examined between 2007 and 2009. The odds ratios from this analysis show a similar trend of a decrease of trachoma with an increase of clean faces, however this trend was not significant for all categories, and confidence intervals were wider.

Table 4: Results from mixed effects model only including 136 communities screened between 2007 and 2009

Clean face prevalence	Odds ratio	P-value	95% CI
≤25%	1	-	-
>25 to ≤50%	0.71	>0.05	0.46-1.11
>50 to ≤75%	0.42	<0.001	0.27-0.67
>75%	0.21	<0.001	0.14-0.34

**adjusted for random effect of region*

3.7 Discussion

In this analysis of the association between clean faces and trachoma in the Australian setting, data from 185 communities at baseline between 2007 and 2017 showed that, prior to any community-wide control strategy being implemented, a higher prevalence of clean faces was significantly associated with a low prevalence of trachoma. There was very little trachoma in communities with prevalence of clean faces between 75 and 100%.

These community level results reflect and build on the individual level results found in the current literature. Significant associations between clean faces and trachoma have been found in studies of children in South Sudan[12] (odds ratio (OR) of 0.3 comparing trachoma in relation to clean faces), Ethiopia [13-14] (OR 0.6[13]; OR 0.55[14]) and Tanzania[15] (OR 0.58). However, there are substantial differences in the methodology of these studies. Clean faces were measured according to different definitions and among children of different age groups. Likewise, "dirty" faces have been associated with trachoma in children in Tanzania[16] (OR 1.30), Mali[17] (OR 3.67) and Niger[18] (OR 3.13). However, substantial differences between studies in dirty face definition and age group were found again.

Like our study, most of the studies in the literature are observational studies. An exception was the report of West and colleagues[15] who conducted a randomized controlled trial (RCT) and found a significant OR of 0.62 (95% CI 0.40-0.97) when investigating the effect of clean faces on trachoma. However, there are practical and ethical reasons why it is difficult to conduct an RCT to investigate the association between a clean face and trachoma, specifically the difficulty of asking one group of participants to refrain from face washing for the study period.

While I found a significant association between clean face and trachoma prevalence, I must also consider this finding in light of limitations of clean face data noted in the introduction, along with the additional limitations of this analysis. These are considered in the numbered sections below.

1. *Direction of causality between clean faces and trachoma*

As noted in the Introduction, there has been debate about the causal direction between facial cleanliness and trachoma. This is a limitation which cannot be addressed in this study, because of its cross-sectional nature.

2. *Lack of a standardized definition of a clean face*

With regard to the lack of a standardized definition of a clean face, a limitation of this study is that this definition has changed four times during our study period 2007-2017. This has possibly

resulted in more or less clean faces being picked up over the years, depending on the definition at the time of screening. It also means that these study results are difficult to compare with other studies in the literature with a different definition of a clean face. The sensitivity analysis attempted to consider the effect of multiple changes by restricting analysis to the time period 2007-2009 in which there were no changes in definition, however over this time period, there was no standardised definition of a clean face. While the sensitivity analysis showed a decrease in trachoma with an increase in clean faces, not all categories were statistically significant.

These limitations and variations of definitions for clean faces used to collect this data may have incorrectly defined some faces as dirty when they were actually caused by the ocular and nasal discharge from upper respiratory infections with bacterial conjunctivitis, rather than by trachoma[20].

3. *Variation of prevalence of clean faces by setting*

As evidence shows that measurements of clean faces taken in clinics tend to overestimate the prevalence of clean faces compared to measurements taken in at home[10], it would have been useful to control for this in my analysis. Information regarding the location of trachoma assessment was not available for this analysis.

4. *Limitations of this analysis*

In addition to these issues of interpretation of clean face data, there were other limitations to this analysis. Firstly, facial cleanliness screening did not necessarily occur at the same time as screening for trachoma, as indicated in the difference in number of children screened for a clean face and screened for trachoma within each community. Also, I was not able to adjust for sex in this analysis as these data were not available. Importantly, these data do not contain information to adjust for the occurrence of face washing and health promotion activities that could have had an effect on the prevalence of clean faces. Additionally, while Australia collects screening data on children aged 1-14 years, and the WHO Trachoma guidelines recommend screening of clean face in children aged 1-9 years, this analysis only included children aged 5-9 years. A limitation of trachoma data in Australia is that it is difficult to collect accurate data on the numbers of children in a community due to population movement between some Indigenous communities[23] – another reason why the data used in this analysis may not be totally representative of clean face and trachoma prevalence. Finally, the fact that data used are from the community level, and not the individual level, means that these results are less amenable to adjustment for individual confounders.

3.8 Conclusion and public health implications

In this analysis of Australian communities, a high prevalence of clean faces was significantly associated with a low prevalence of trachoma. While the limitations of this analysis are important to consider in the interpretation of the results, the results are still useful for trachoma control in Australia. Strengths of this analysis include that it was based on a large number of communities, and that it is the first analysis of this association with national data in the Australian context. Future analyses could focus on longitudinal changes in clean face prevalence over time, and adjust for the differences in the definition of clean faces.

3.9 References

1. World Health Organization. 2018. Trachoma. Accessed on 15th Jan 2018 from https://www.who.int/en/news-room/fact-sheets/detail/trachoma
2. Evans J, Solomon A. 2011. Antibiotics for Trachoma. *Cochrane Database of Systematic Reviews*. 3:CD001860.
3. Thylefors B, Jones B, West S et al. 1987. A simple system for the assessment of trachoma and its complications. *Bulletin of the World Health Organization* 65:477-83.
4. Mariotti S, Solomon A. 2015. Trachoma. Control of Communicable Diseases Manual. 20th ed. Heymann D. *American Public Health Association*, Washington 2015.
5. The Kirby Institute, UNSW Sydney, WHO Collaborating Centre in Trachoma. 2018. Australian Trachoma Surveillance Report 2017. Accessed on 16th December 2018 from http://www.health.gov.au/internet/main/publishing.nsf/content/1B9028E9FD71332ACA257BF00018CCD6/$File/Australian-Trachoma-Surveillance-Report-2017.pdf
6. World Health Organization. 2013. Report of the 17th Meeting of the WHO Alliance for the Global Elimination of Blinding Trachoma, 22-24 April 2013. Geneva. Accessed on the 16th December 2018 from: https://www.who.int/blindness/publications/GET17Report_final.pdf?ua=1
7. Ejere H, Alhassan M, Rabiu M. 2015. Face washing promotion for preventing active trachoma. *The Cochrane database of systematic reviews*. 2:Cd003659.
8. Mathew A, Turner A, Taylor H. 2009. Strategies to control trachoma. *Drugs* 69(8):953-70.
9. King J, Ngondi J, Kasten J et al. 2011. Randomised trial of face-washing to develop a standard definition of a clean face for monitoring trachoma control programmes. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 105(1):7-16.
10. Zack R, Mkocha H, Zack E et al. 2008. Issues in defining and measuring facial cleanliness for national trachoma control programs. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 102(5):426-31.
11. Bailey R, Lietman T. 2001. The SAFE strategy for the elimination of trachoma by 2020: will it work? *Bulletin of the World Health Organization* 79(3):233-6.
12. Ngondi J, Matthews F, Reacher M et al. 2008. Associations between active trachoma and community intervention with Antibiotics, Facial cleanliness, and Environmental improvement (A,F,E). *PLoS Neglected Tropical Diseases* 2(4):e229.
13. Ngondi J, Gebre T, Shargie E et al. 2010. Estimation of effects of community intervention with antibiotics, facial cleanliness, and environmental improvement (A,F,E)

in five districts of Ethiopia hyperendemic for trachoma. British Journal of Ophthalmology 94(3):278-281.

14. Ferede A, Dadi A, Tariku A et al. 2017. Prevalence and determinants of active trachoma among preschool-aged children in Dembia District, Northwest Ethiopia. *Infectious Diseases of Poverty* 6(1):128.
15. West S, Munoz B, Lynch M et al. 1995. Impact of face-washing on trachoma in Kongwa, Tanzania. *The Lancet* 345(8943):155-158.
16. Taylor H, West S, Mmbaga B et al. 1989. Hygiene factors and increased risk of trachoma in central Tanzania. *Archives of Ophthalmology* 107(12):1821-1825.
17. Schemann J, Sacko D, Malvy D et al. 2002. Risk factors for trachoma in Mali. *International Journal of Epidemiology* 31(1):194-201.
18. Abdou A, Nassirou B, Kadri F et al. 2007. Prevalence and risk factors for trachoma and ocular Chlamydia trachomatis infection in Niger. *British Journal of Ophthalmology* 91(1):13-17.
19. Emerson P, Cairncross S, Bailey R et al. 2000. Review of the evidence base for the 'F' and 'E' components of the SAFE strategy for trachoma control. *Tropical Medicine and International Health* 5(8): 515-527.
20. Mohammadpour M, Abrishami M, Masoumi A et al 2016. Trachoma: Past, present and future. *Journal of Current Ophthalmology* 28(4):165-169.
21. Communicable Diseases Network Australia. 2014. Trachoma: CDNA National Guidelines for the Public Health Management of Trachoma. Accessed on the 16th December 2018 from: http://www.health.gov.au/internet/main/publishing.nsf/Content/D02F0C1C2AB90509CA257C66001C089C/$File/Trachoma-SoNG.pdf
22. Thylefors B. 1987. Trachoma Simplified Grading Card. World Health Organization, Department of Neglected Tropical Diseases. Accessed on the 16th December 2018 from https://www.who.int/trachoma/resources/SAFE_documents/en/
23. Centre for Eye Research in Australia. 2006. Trachoma Surveillance Report 2006. Accessed on 15th Jan 2019 from http://www.health.gov.au/internet/main/publishing.nsf/Content/trachoma-surveillance-reports/$File/NTSRU_TrachomaSurveillanceReport2006_12Oct2007.pdf

Chapter 4: Investigation of an acute public health problem

Characteristics of females with gonorrhoea in NSW, 2018 – a case series investigation

Contents

4.1 List of abbreviations

ANU	Australian National University
ASGC-RA	Australian Standard Geographical Classification – Remoteness Area
BBV	Blood borne virus
CDB	Communicable Diseases Branch
ELR	Electronic Laboratory Record
HIV	Human immunodeficiency virus
IDU	Injecting Drug User
IT	Information Technology
IUSTI	International Union against Sexually Transmitted Infections
LGV	Lymphogranuloma venereum
LHDs	Local Health Districts
MAE	Master of Applied Epidemiology
MSM	Men who have sex with men
NCIMS	Notifiable Conditions Information Management System
NSW	New South Wales
PCR	Polymerase chain reaction
PHU	Public Health Unit
RCT	Randomised controlled trial
SAPHaRI	Secure Analytics for Population Health Research and Intelligence
SHC	Sexual health clinic
SOPs	Standard Operating Procedures
SSHC	Sydney Sexual Health Clinic
STI	Sexually transmitted infection
USYD	University of Sydney
VIC	Victoria
WHO	World Health Organization

4.2 Prologue

My role: Sexually transmitted infections (STIs) form a key pillar of research at the Kirby Institute. As a reflection of this research interest, it was suggested that I investigate the current increase of gonorrhoea notifications in New South Wales (NSW) women in collaboration with NSW Ministry of Health for my Master of Applied Epidemiology (MAE) outbreak investigation. This sounded like an interesting learning experience to me as none of our case studies at MAE course block were of STI outbreaks; they mostly focussed on gastrointestinal disease and influenza outbreaks. In addition, I felt that I could use my experience with sexual health survey data in Uganda prior to the MAE in application to this public health issue.

Lessons learned: For this project, I was based at NSW Ministry of Health for approximately 1-2 days per week over several months during 2018. It was a great experience to be welcomed into the Blood borne viruses/Sexually transmitted infections group within the Communicable Disease Branch, and to learn more about the government side of public health in NSW. Throughout this project, it was interesting to learn about how the public health units (PHUs) in NSW work together in response to public health issues – either through pre-established systems or innovative mechanisms. Due to the sensitive nature of investigating an STI, I also learnt a lot about the ethical requirements of public health investigations using state notification data, and the application of the NSW *Public Health Act* 2010.

Public health impact: The results from this study helped NSW Ministry of Health to better understand the recent increase in gonorrhoea in this population, and to inform public health action. The proportions of low condom use for all types of sex highlight the need for condom promotion in heterosexual females. The relatively high recruitment rate that we achieved is reflective of sensitive study methodologies, which can be utilised in future STI outbreak investigations in females.

Acknowledgements: First of all, I would like to thank the investigation team from Health Protection, New South Wales Ministry of Health: Tove Lysa-Fitzgerald, Christine Selvey, Vicky Sheppeard and Jeremy McAnulty, and members of the investigation team from the Kirby Institute: Basil Donovan, Rebecca Guy, and John Kaldor. I would also like to acknowledge my academic supervisor, Kathryn Glass for helping me with the structure and flow of this chapter. From the Kirby Institute, I would like to thank Louise Causer with her assistance with the clarity of this chapter, and Jana Sisnowski, Praveena Gunaratnaram and Larissa Lewis, who provided insights from a similar study they were working on. For their help in piloting the survey, I would like to thank the MAE 2018 cohort, and Tambri Housen and Kamalini Lokuge from the Australian National University (ANU). I would also like to thank MAE 2017 Alumni Meru Sheel for her

assistance with the online survey deployment system used at NSW Ministry of Health, and insights from a similar investigation she conducted for her MAE.

4.3 Abstract

Introduction: Gonorrhoea notification rates have increased substantially in heterosexuals in urban areas across Australia over the past decade. The objective of this investigation was to describe the characteristics of women notified to NSW Ministry of Health with gonorrhoea and their partners.

Methods: Women aged ≥18 years who resided in NSW, for whom a gonorrhoea notification had been made to NSW Ministry of Health from 21 May to 17 June 2018, were asked to complete a questionnaire on personal and partner risk behaviours (sex workers were asked about non-paying partners). Participants could complete the investigation questionnaire with their clinician, via a questionnaire sent through text message or email, or by phone. A descriptive analysis was conducted based on responses regarding the first partner only and stratified by sex worker status.

Results: 68 questionnaires were received from 118 women, giving a response rate of 58%. Of the 68 participants, 31% identified as sex workers, 3% as Aboriginal, 63% were Australian born and 91% resided in an urban area. In the three months prior to their gonorrhoea diagnosis, most respondents did not have sex overseas (82%), and their last sexual partner was male (84%). Of these partners, 19% were not Australian born, 32% were non-regular partners, and 10% had travelled overseas. Most participants (76%) believed their partner was heterosexual, 6% bisexual, and 3% did not know. Condom use was low for all types of sex; for vaginal, anal and oral sex was: 38%, 0% and 0% (sex workers), and 5%, 0% and 8% (non-sex workers), respectively.

Conclusion and public health impact: Sex overseas and sex with bisexual men do not appear to be major risk behaviours in this population. Low condom use highlights the need for further condom promotion.

4.4 Introduction

Gonorrhoea is a sexually transmitted infection (STI) caused by the bacterium *Neisseria gonorrhoeae (N. gonorrhoeae)*[1]. Gonococcal infection causes genital tract infections that are frequently asymptomatic in women[2]. Untreated infections can also result in disseminated infection, pelvic inflammatory disease in women, and infertility in both men and women[1]. In addition, the risk of both acquisition and transmission of human immunodeficiency virus (HIV) is elevated in those with gonococcal infections[1]. Gonorrhoea is a common infection worldwide with an estimated 78 million new cases in 2012 according to the World Health Organization (WHO)[3]. Gonorrhoea is recognised to be of global significance because of its adverse health effects (particularly pelvic inflammatory disease, sequelae in pregnancy, and sequelae for newborns), and the propensity of the causative bacterial species to acquire antibiotic resistance.

In Australia, gonorrhoea is one of a number of notifiable infections, and is consistently ranked among the five most frequently notified communicable diseases. Gonorrhoea has been long documented at elevated rates among men who have sex with men (MSM)[4], female sex workers[5] and in young Aboriginal and Torres Strait Islander people, particularly those living in remote communities[6]. Clinic-based studies have shown that the incidence of gonorrhoea in MSM is 6.48 per 100 person-years[4], and 4.50/100 PY among female sex workers[5]. Incidence in 16-19 year old Aboriginal and Torres Strait Islander people living in remote communities is 26.10/100 PY and 23.40/100 PY for males and females respectively[6]. National gonorrhoea guidelines advise testing according to individual risk, with regular testing recommended for sex workers[7] and three monthly screening recommended for MSM at high risk[8]. Gonorrhoea screening guidelines vary between Australian jurisdictions, however generally recommend annual screening for priority populations including young sexually active people and Aboriginal people[9].

Among heterosexuals in urban and regional areas, earlier studies show that the prevalence of gonorrhoea was very low (<1%)[10, 11-12]. Over the past ten years, gonorrhoea notification rates have increased in men and women aged 15-34 years, and people living in urban areas. Crude rates increased by 63% (62 to 101 per 100 000) from 2012 to 2016, with an increase in both males (72%) and females (43%), and metropolitan areas (99%)[13]. While there is limited data at the national level on sexual orientation for gonorrhoea notifications, data collected though enhanced surveillance in Melbourne, Victoria (VIC)[14] suggest that endemic heterosexual transmission of gonorrhoea is increasing.

Until recently, increases in gonorrhoea notification rates in all Australian at risk groups have been attributed to an increase in testing rates. Chlamydia testing has long been recommended,

and as duplex polymerase chain reaction (PCR) testing for chlamydia and gonorrhoea has become standard practice, there has been a consequent increase in gonorrhoea tests[15]. In addition, PCR tests for gonorrhoea are more sensitive than the previously used culture based tests, resulting in more true positive results than the culture based tests. However, the notification rate has continued to rise since the implementation of duplex testing in 2012[15]. Gonorrhoea testing information (using chlamydia PCR tests as a proxy) from the Medicare Benefits Scheme is routinely collected and analysed by the Kirby Institute annually. While the number of Medicare-rebated tests has continued to increase in the past five years, the number of notifications has risen more rapidly[13], suggesting that transmission of gonorrhoea has increased, screening has been better targeted to people at higher risk of infection, or both.

NSW accounted for 29% of Australian gonorrhoea notifications in 2016, with increases in both males and females compared to 2015[13]. In 2017, the annualised gonorrhoea notification rate was 116 notifications per 100,000 population, 29% higher than 2016[16], with a 32% relative increase in males and an 15% relative increase in females[16]. While 83% of the 7,660 notifications in 2017 were in men, a high proportion of these are believed to be associated with male to male sex. Rates among females in NSW have been increasing since 2016, suggesting that heterosexual transmission may be increasing, as observed in WA and VIC.

In order to identify control measures to reduce the risk of heterosexual gonorrhoea transmission, risk factors need to be identified in women. Risk factors already identified include injecting drug use (IDU) among female sex workers[5] and females attending sexual health clinics (SHCs)[10], and travel-associated sex among females attending SHCs (sexual contact overseas, sexual contact with an overseas partner or being a known contact of someone with gonorrhoea[10], or sex with a partner from a high prevalence country[17]). A case series study found high proportions of women attending SHCs for gonorrhoea had acquired the infection locally (73%) or through unprotected vaginal sex (94%)[19]. A recent study suggested that heterosexual female sexual contact with bisexual men could explain the increase in gonorrhoea positivity in women without any alteration in the women's sexual behaviour[17]. In addition, a biologically plausible and proven association exists between saliva use (as a sexual lubricant and through kissing) and gonorrhoea (particularly throat gonorrhoea[19, 20-21]) in MSM populations that may be contributing to the rise in gonorrhoea infections in Australian heterosexual women.

In the context of increasing case numbers, an investigation of characteristics of NSW women with newly diagnosed gonorrhoea infection was recommended by NSW Ministry of Health to better understand the recent increase in infection rates in this population and inform public health action. This chapter reports on a descriptive analysis of NSW notifications data from 2013-2018 (over the past five years) and a case series investigation to explore characteristics

and potential risk factors associated with the recent increase in gonorrhoea infections among women.

4.5 Methods

Study type

We conducted a case series investigation in order to determine the prevalence of risk factors among gonorrhoea cases and their characteristics (see ANNEX 4A for approved ministerial brief).

Initially, we considered the alternative approach of a case control study (see ANNEX 4B for the original study protocol). The ideal study type for the investigation of this outbreak is a case control study that recruits controls from two sources – SHCs and the general population. This approach would avoid any bias that may result from over-matching which happens when one control that has very similar characteristics to cases is used in sexual health studies. We considered recruiting controls from the following alternative options: the general population, gonorrhoea test-negative notifications, and age-matched chlamydia notifications.

Each of these sources of controls had a number of associated problems. For general population controls, limitations included the extensive amount of time required to identify and contact controls, as well as the selection biases and sensitivity issues that would be introduced from general population recruitment methods such as Facebook advertising and random digit dialling. If we recruited gonorrhoea test-negative notifications, additional ethics approvals would be required as test-negative gonorrhoea results are not notifiable, which would take up a substantial amount of time. In the end, we decided to use age matched female chlamydia notifications as they were the most accessible control population to our study investigation team (see Annex 4B for original matching criteria and sample size calculations for the case control study).

However, age matched female chlamydia notifications also had some important limitations. Firstly, there was the risk that the chlamydia controls would potentially be overmatched to cases as they share similar risk factors. Secondly, there was the risk that we would cause unnecessary discomfort (by asking sensitive questions) to a population with a disease that was not the public health concern we were investigating. After assessing the ethical and logistical limitations that the controls for a case control study investigating this outbreak would entail, we decided a case series investigation would be the most sensitive and practical.

Study population

Inclusion criteria were women aged ≥18 years residing in NSW who were notified to NSW Ministry of Health as having newly diagnosed gonorrhoea from 21 May – 17 June 2018. Newly diagnosed gonorrhoea refers to a positive result from a screening test only (positive results from tests of cure were excluded). Three notifications aged 17 and under were excluded because of the time that would have been required to obtain the additional approvals necessary to recruit this population. We placed no upper bound on the age for inclusion in order to maximise numbers of participants and understand the nature of the outbreak in older age groups. The study recruitment period was limited in order to facilitate rapid completion of the study.

Cases

Case definition: Women aged ≥18 years residing in NSW and notified to NSW Ministry of Health with newly diagnosed gonorrhoea from 21 May – 17 June 2018 inclusive.

Gonorrhoea notification requirements in NSW

Under the 2010 NSW *Public Health Act*, gonorrhoea is listed as a Schedule 1, Category 3 infection which means that laboratories making a diagnosis of the condition are required to notify public health authorities. Confirmed gonorrhoea cases in NSW and nationally require "laboratory definitive evidence", which can be via isolation of *N. gonorrhoeae* (culture), or detection of *N. gonorrhoeae* by nucleic acid testing (PCR).

After a notification is made, follow up of the case is not mandatory by NSW public health authorities. They must however verify demographics and test results of cases. Some PHUs in NSW such as Hunter New England and Nepean Blue Mountains conduct enhanced follow up of gonorrhoea cases in the form of a questionnaire which gathers information on demographics, factors that may be relevant to sexual acquisition of infection (e.g. sex work, travel), symptoms and treatment.

Laboratory testing

Most local laboratories in NSW can test patient samples for the presence of *N. gonorrhoeae* using PCR and culture. When a sample is found to be positive for *N. gonorrhoeae*, laboratories either send the notification and patient details through to the NCIMS system automatically (via Electronic Laboratory Record (ELR)) or notify the corresponding NSW PHU, who then enters the data into NCIMS within 5 working days.

Sample size

Approximately 120 cases were expected based on the same calendar period in 2017. We expected to recruit at least 50% of these (60 cases) based on the recruitment rate for a similar questionnaire in an investigation of lymphogranuloma venereum (LGV) in men led by MAE scholar Meru Sheel and TLF, CS and the rest of the Blood Bourne Virus (BBV)/STIs team at NSW Health Protection in 2017[22].

Recruitment

Given the sensitive nature of this study, we initially contacted each doctor responsible for the eligible notification by fax (the usual mode of communication between NSW Ministry of Health and clinicians). The fax contained the study questionnaire and three options for completion: (i): complete the questionnaire in consultation with the patient; (ii) give approval for NSW Ministry of Health to contact the patient and offer to administer the questionnaire via the patient's preferred method (text message or email questionnaire link, or over the phone), or (iii) opt out on behalf of the patient. If the doctor nominated NSW Ministry of Health to administer the questionnaire, the doctor provided their patient's mobile number (not a mandatory reporting field in the NSW Notifiable Conditions Information Management System (NCIMS). NSW Ministry of Health advised the diagnosing doctor to inform their patient to expect NSW Ministry of Health to be in contact with them if the doctor selected option (ii).

In the event of non-response from a diagnosing doctor, we followed up with a reminder fax 1 week after the original fax was sent. If there was still no response 1 week after the reminder fax, we followed up with a call to the diagnosing doctor. If we were unable to get in contact with the doctor, we recorded that the case was lost to follow up.

Furthermore, in the event of non-response from a case within 48 hours of contact, we followed up with a reminder text. If no response was obtained within 48 hours after the reminder text, NSW Ministry of Health sent a third link, and if there was still no response 48 hours after this, a phone call was made to the patient. If they did not answer, they were listed as lost to follow up.

Data collection

If the doctor agreed to administer the questionnaire themselves, they completed the questionnaire on the faxed form and sent it back to NSW Ministry of Health, where the responses were manually entered into NCIMS. The online questionnaire for text/email responses was hosted by NCIMS, so the results were automatically sent to NCIMS upon completion. At the end of the study period, a linked dataset containing information collected from NCIMS (below) and study variables was extracted from NCIMS.

Information collected from NCIMs

Initial review of gonorrhoea cases: for the review of male and female gonorrhoea cases in NSW from 2013-2018, notification data was extracted from NCIMS by TLF on the 19th September 2018 using the NSW Ministry of Health Secure Analytics for Population Health Research and Intelligence (SAPHaRI) system and put into an Excel spreadsheet. This included the following variables:

- Age
- Date of birth
- Gender
- Date of notification
- Site of infection

This data excluded non-NSW residents, persons whose residential postcode was not known, persons reported as transgender (due to small numbers) and persons whose age or sex was not reported.

Case series investigation: for the case series investigation, gonorrhoea notification data on all eligible cases was extracted from NCIMS by TLF using the SAPHaRI system and put into an Excel spreadsheet. This included the following variables:

- NCIMS ID number
- Date of birth
- Age
- Date of notification
- Local health district (LHD)
- Practice type

Age was categorised into the following age-groups consistent with NSW Ministry of Health reports: 18-19, 20-24, 25-29, 30-39, 40-49, 50-59, and 60+ years.

Patient questionnaire

Questionnaire design

We designed the questionnaire to be brief (to allow completion in under 10 minutes in order to maximise participation) and to capture key information on sex work and travel-associated sex. The most sensitive questions were placed towards the end and we included sensitive answer options (eg the option “Prefer not to say” for most questions).

We included some questions adapted from previously used questionnaires because of their demonstrated success: the previously mentioned LGV questionnaire[22], gonorrhoea enhanced surveillance questionnaires from Nepean Blue Mountains and Hunter New England PHUs, the questionnaire from the Second Australian Study of Health and Relationships[23], the questionnaire from the Australian Chlamydia Control Effectiveness Pilot (ACCEPt)[24], and the draft questionnaire of a similar case control study planned in WA by the Kirby Institute in collaboration with WA Department of Health[25].

The final questionnaire contained a combination of multiple choice and short answer questions: seven questions on personal risk factors (Section 1) and nine questions on partner risk factors (Section 2). See ANNEX 4D for the final questionnaire. To obtain information about partner risk factors in Section 2, we asked participants about characteristics of up to 10 sexual partners in the three months prior to gonorrhoea diagnosis. While the incubation period of gonorrhoea is 2-7 days[1], we chose to ask about risk factors in the time frame of three months as gonorrhoea frequently presents asymptomatically in women, and wanted to allow for a longer exposure period without drastically increasing the risk of recall bias.

Questionnaire piloting and review

We piloted and reviewed the questionnaire within our internal study group, and then piloted it with the MAE 2018 cohort during one of their course block periods. The MAE scholars had a broad range of epidemiological and questionnaire experience, and 94% (16/17) of students were females over 18 (who proved to be an ideal pilot group as most met the age/sex criteria for inclusion in our study). We also distributed the questionnaire to the NSW Sexual Health Directors for comment.

Questionnaire deployment

Once we had finalised the questionnaire, we ensured it could be deployed in several ways: fax, text message/online questionnaire, and over the phone. The faxable version of the questionnaire (ANNEX 4D) was worded in such a way that it could be administered by a clinician in person with a participant, administered verbally by an investigation team member over the phone, or filled in by a participant alone during a consultation. The text message/online version of the questionnaire was created manually in the NCIMS system using branching logic, a feature that creates a custom path through a questionnaire based on a respondent's answers.

Data storage

Variables from notification data and the questionnaire data were stored within NCIMS and extracted from NCIMS in deidentified form for analysis on a password protected server at the

NSW Ministry of Health which complies with NSW Ministry of Health Information Technology (IT) privacy standards.

Data analysis

Microsoft Excel version 16, 2018 was used for all data analyses. For the descriptive analysis of NSW gonorrhoea notifications from 2013-2018, SP created graphs in Excel showing trends in gonorrhoea notifications over time. Rates were calculated in Excel using notifications as the numerator, the mid-point of Australian Bureau of Statistics population estimates as the denominator, and multiplied by 100,000.

For the case series results, SP conducted a descriptive analysis of questionnaire results for section 1 and 2 of the questionnaire and calculated the prevalence of proposed gonorrhoea risk factors among cases was calculated. Analyses were conducted separately for two groups based on sex worker status, as sex workers were overrepresented in the responses we received (while it is difficult to estimate the number of female sex workers in the NSW population, estimates range from 1,500 working at any one time to 10,000 in the whole of NSW[26]).

The analyses of partner characteristics for the second part of the questionnaire in this chapter is limited to the characteristics of the first partner listed by respondents.

Definitions

Sex worker status: was defined by participants' answer to the question "Have you been paid for sex work in the past 12 months?".

Remoteness: was defined according to the Australian Standard Geographical Classification – Remoteness Area (ASGC-RA 2011).

Stakeholder engagement

The key stakeholders involved in this study were NSW Sexual Health Directors, NSW PHUs, the Sydney Sexual Health Clinic (SSHC) and the diagnosing clinicians. NSW Sexual Health Directors were informed about the study during their monthly meeting by Christine Selvey (CS), provided with the study protocol and questionnaire, and given the opportunity to ask questions or provide feedback. The NSW PHUs were informed via email by Tove Lysa-Fitzgerald (TLF), provided with the protocol and questionnaire and given the opportunity to ask questions or provide feedback. A number of PHUs also volunteered to assist with study administration of cases within their LHDs. Based on previous notification counts, a large proportion of cases were expected to come from SSHC. For this reason, we contacted SSHC to discuss the study and work out how to assist with the potential workload.

Case management

To coordinate the study administration between PHUs, study Standard Operating Procedures (SOPs) were developed to cover the routines of faxing clinicians and following up with cases. A live Excel spreadsheet template was kept on the NSW Ministry of Health platform PopNet (an online platform accessible by all PHUs in NSW) throughout the study so that study team members and PHU staff could update and track the progress of the investigation.

Study timeline

The increase in notifications of gonorrhoea in NSW women was of public health concern but not considered to be an acute public health problem, demanding immediate resolution. The priority was conducting a thorough, considered, and sensitive scoping investigation to pave the way for future work. To ensure this, a substantial amount of time was put into the development and execution of this outbreak investigation (see Table 1), with initial development and approval taking four months.

Table 1: Study timeline for gonorrhoea in NSW women case series investigation

Date	Study Milestone
20 November 2017	Initial concept discussion, study design and questionnaire design
18 April 2018	Rejection of initial protocol and brief (case control study)
27 April 2018	Approval of adapted protocol and brief (case series study)
28 April – 20 May	Study set up
21 May – 17 June 2018	Recruitment period
18 June – 16 July 2018	Study follow up
17 July – December 2018	Data analysis and write up

Ethics approvals

This study was undertaken as public health follow-up of people notified to NSW Ministry of Health with a notifiable condition. As the provision of such information by doctors is authorised under the *Public Health Act 2010*, human research ethics committee approval was not required. Women could decline consent to participate in the study at any stage.

As this investigation formed the outbreak component of a member of the study team's MAE (SP), it was covered by the ANU Human Research Ethics Committee under protocol 2017/909 for outbreak investigation and surveillance evaluation projects for MAE scholars.

Dissemination of results

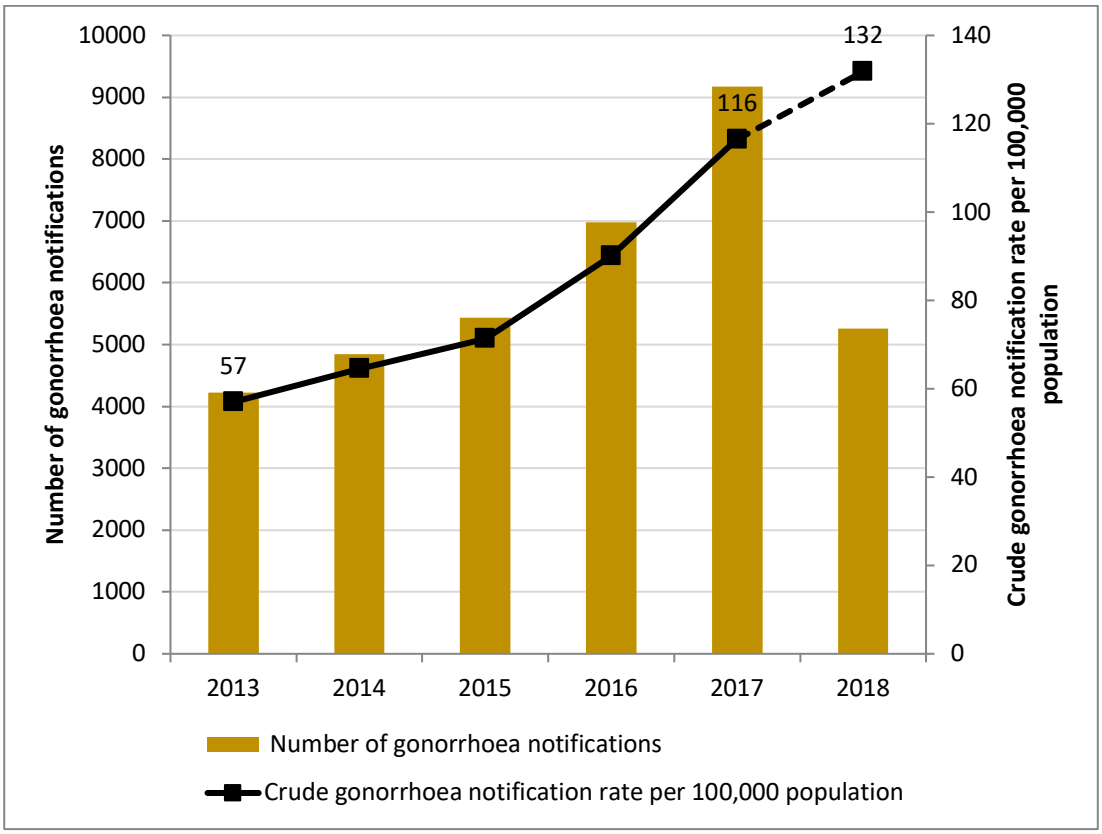
During the study period, ad hoc updates were provided to NSW Ministry of Health Communicable Diseases Branch (CDB) during their weekly epidemiology meetings. At the end of the investigation period, a short report summarising the descriptive statistics was provided to the Blood Bourne Viruses/Sexually Transmitted Infections (BBV/STIs) team. A member of the investigation team (SP) gave a presentation on the investigation to NSW Ministry of Health CDB and to the Public Health Interventions Research Group (PHIRG) at the Kirby Institute. A Rapid Fire 3-minute Oral presentation was given by SP at the International Union against Sexually Transmitted Infections (IUSTI) Asia Pacific conference in Auckland, New Zealand (ANNEX 4E) on 2 November 2018.

4.6 Results

Descriptive analysis of NSW gonorrhoea notifications from 2013-2018

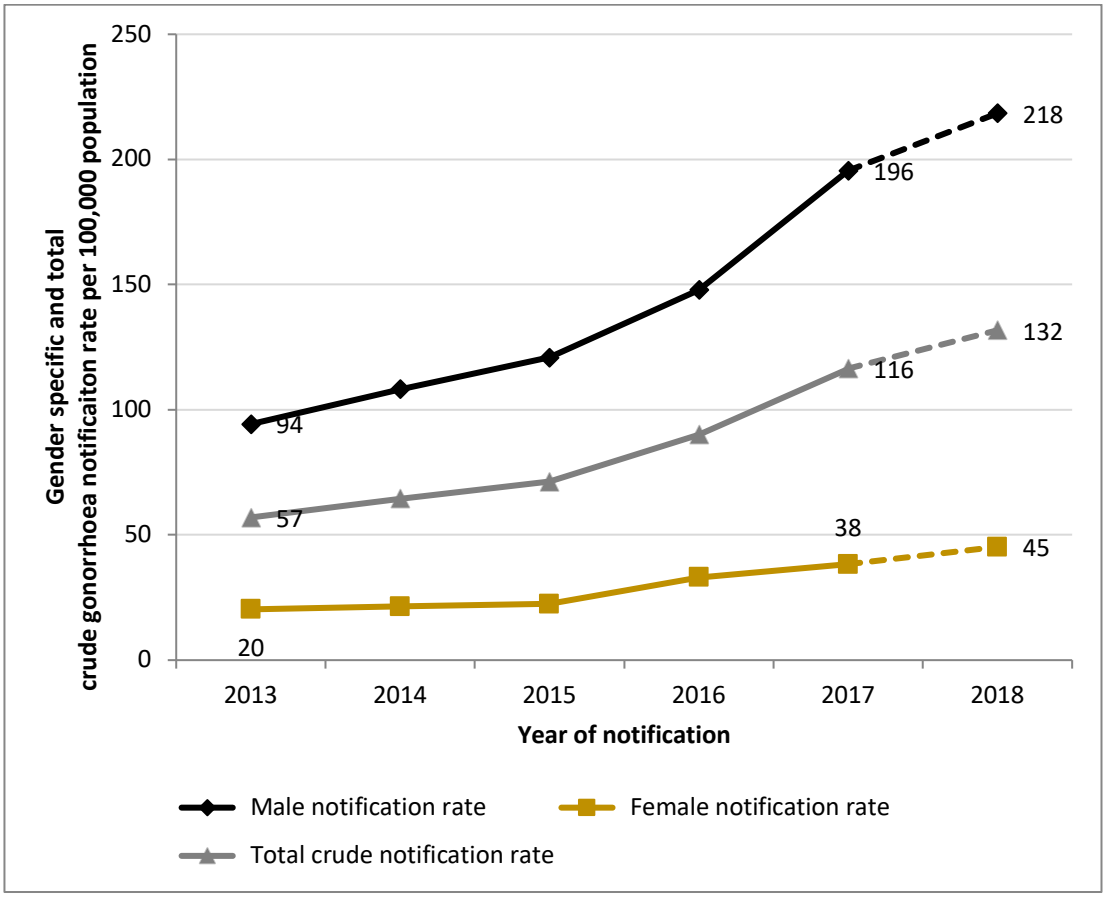
The crude gonorrhoea notification rate has been steadily increasing in NSW since 2013 (Figure 1). In 2017, the annualised gonorrhoea notification rate was 116 notifications per 100,000 population, 29% higher than 2016. The projected gonorrhoea notification rate for 2018 based on data from January-June and ABS population estimates shows a 14% increase from 116 notifications in 2017 per 100,000 to an estimated 132 notifications in 2018.

Figure 1: Number and crude rate of gonorrhoea notifications, NSW, 1 January 2013-30 June 2018



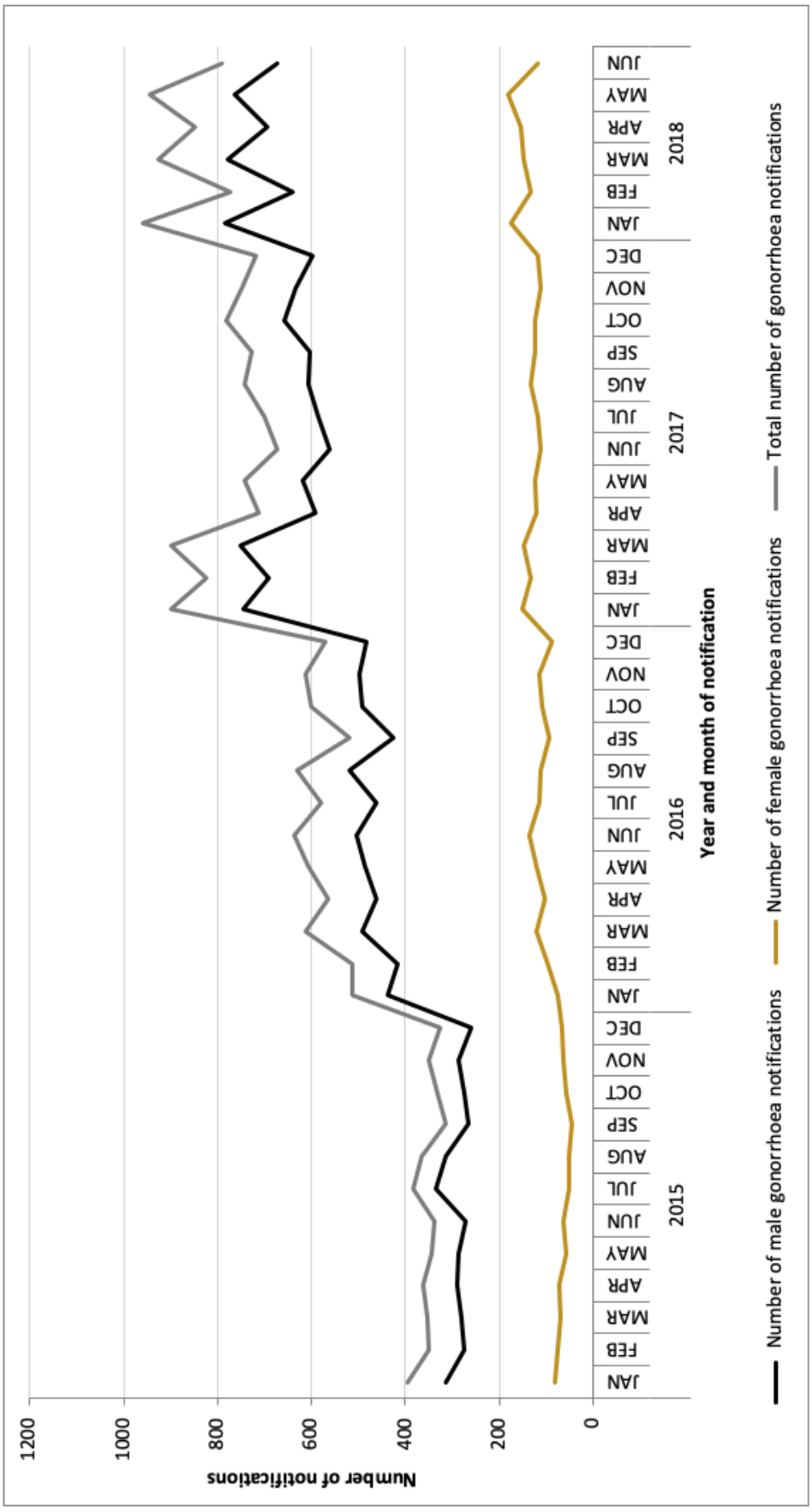
When stratified by gender, there is a 32% increase can be seen in males and a 15% relative increase can be seen in in females between 2016 and 2017 (Figure 2). Projected relative increases for 2018 based on data from January to June indicate an 11% relative increase for males and an 18% relative increase for females.

Figure 2: Gender specific gonorrhoea notification rate, NSW, 1 January 2013-30 June 2018



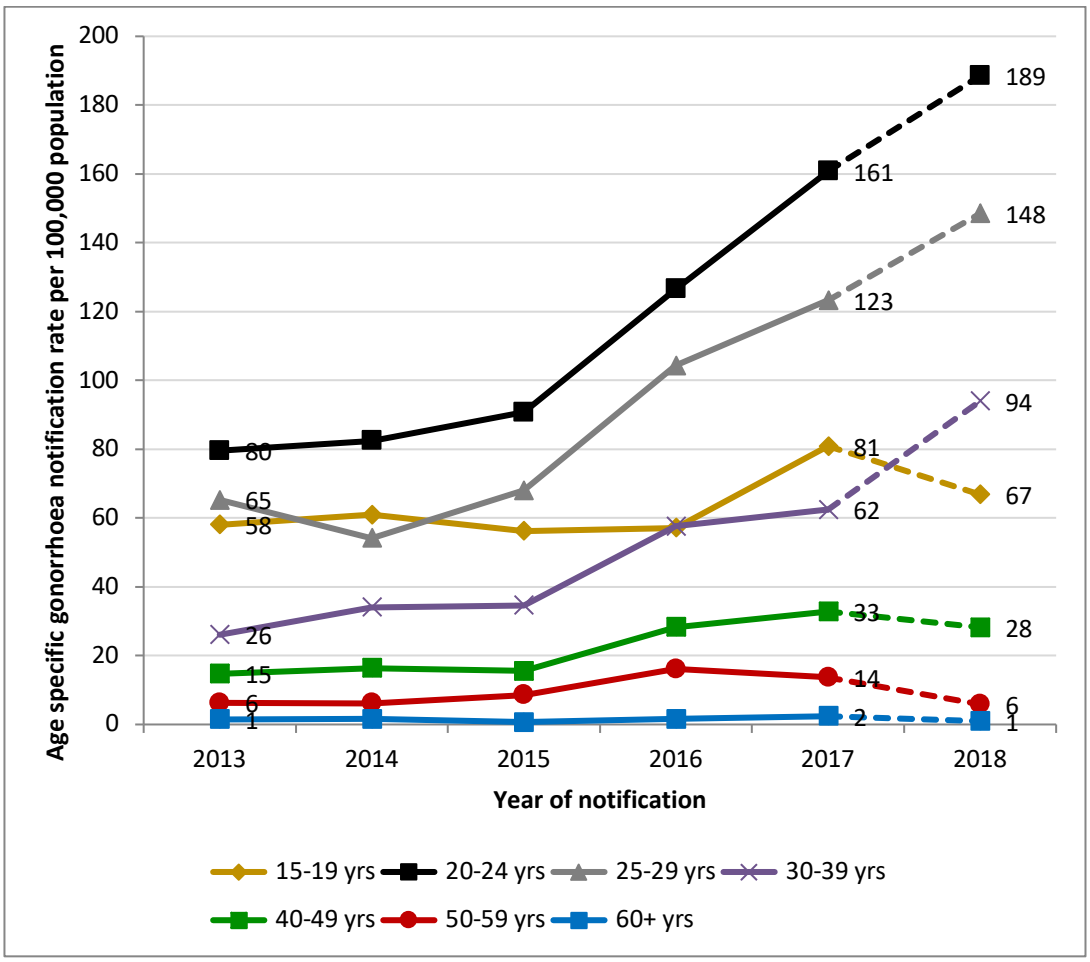
The gonorrhoea notification rate in NSW has not shown any evidence of seasonality over the past 3.5 years. However, there have been increases in gonorrhoea notifications in January 2017-18 among males and females (Figure 3) which is thought to reflect targeted testing and or transmission at this time.

Figure 3: Count of gonorrhoea notifications by year, month and gender NSW, 1 January 2013-30 June 2018



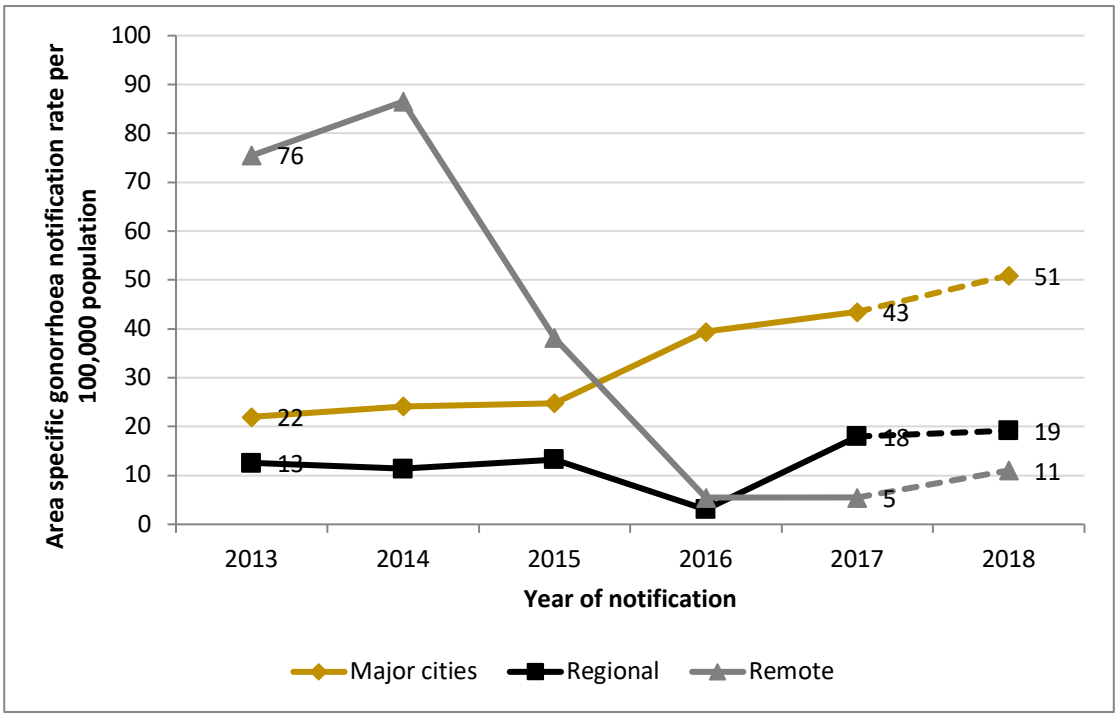
Over the past 4.5 years, 20-24 year old and 25-29 year old (YO) females have had the highest rates of gonorrhoea notifications, with rates increasing each year (Figure 4). The notification rate among 30-34 YO females has also been increasing each year. The notification rate for 15-19 YOs, 40-49 YOs, 50-59 YOs and 60+ YOs decreased in the first 6 months of 2017.

Figure 4: Age specific gonorrhoea notification rates in females aged 15 years and over, NSW, 1 January 2013-30 June 2018



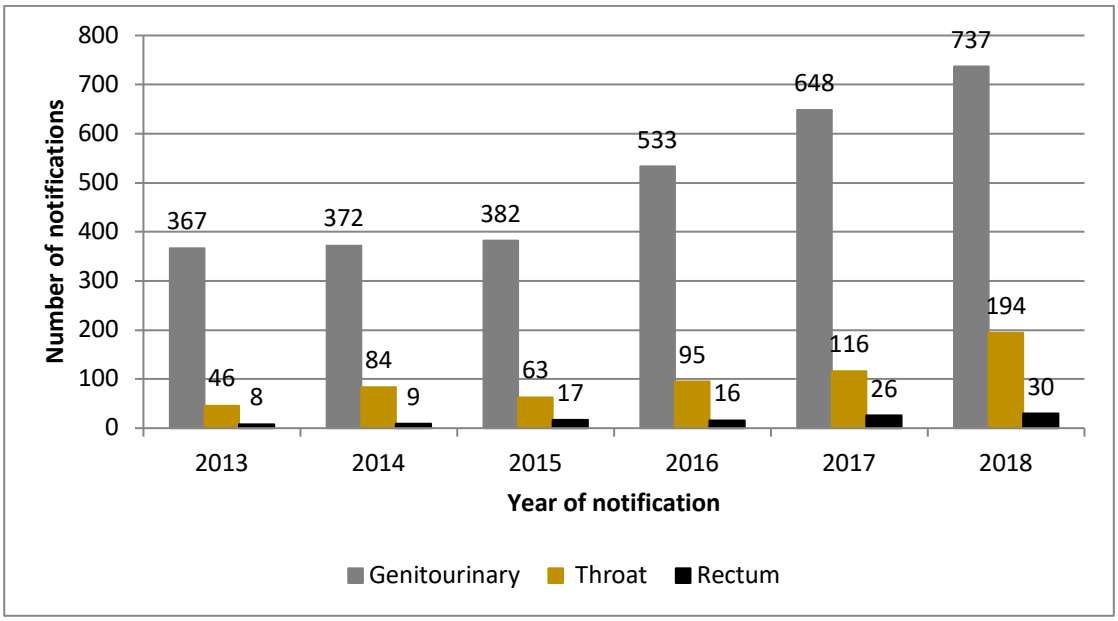
By remoteness category, the gonorrhoea notification rate has appeared to increase in NSW females in urban and regional areas (Figure 5), while in remote areas it has dropped off between 2014-2016 and then stabilised.

Figure 5: Area specific gonorrhoea notification rates in females living in major cities, urban and regional areas, NSW, 1 January 2013-30 June 2018



Most gonorrhoea infections in NSW females have been at genitourinary sites over the past six years, with numbers steadily increasing at this site. The throat has been the second most common site of infection over the past six years, and has increased many times more than rectal infections, the least common site of infection (Figure 6).

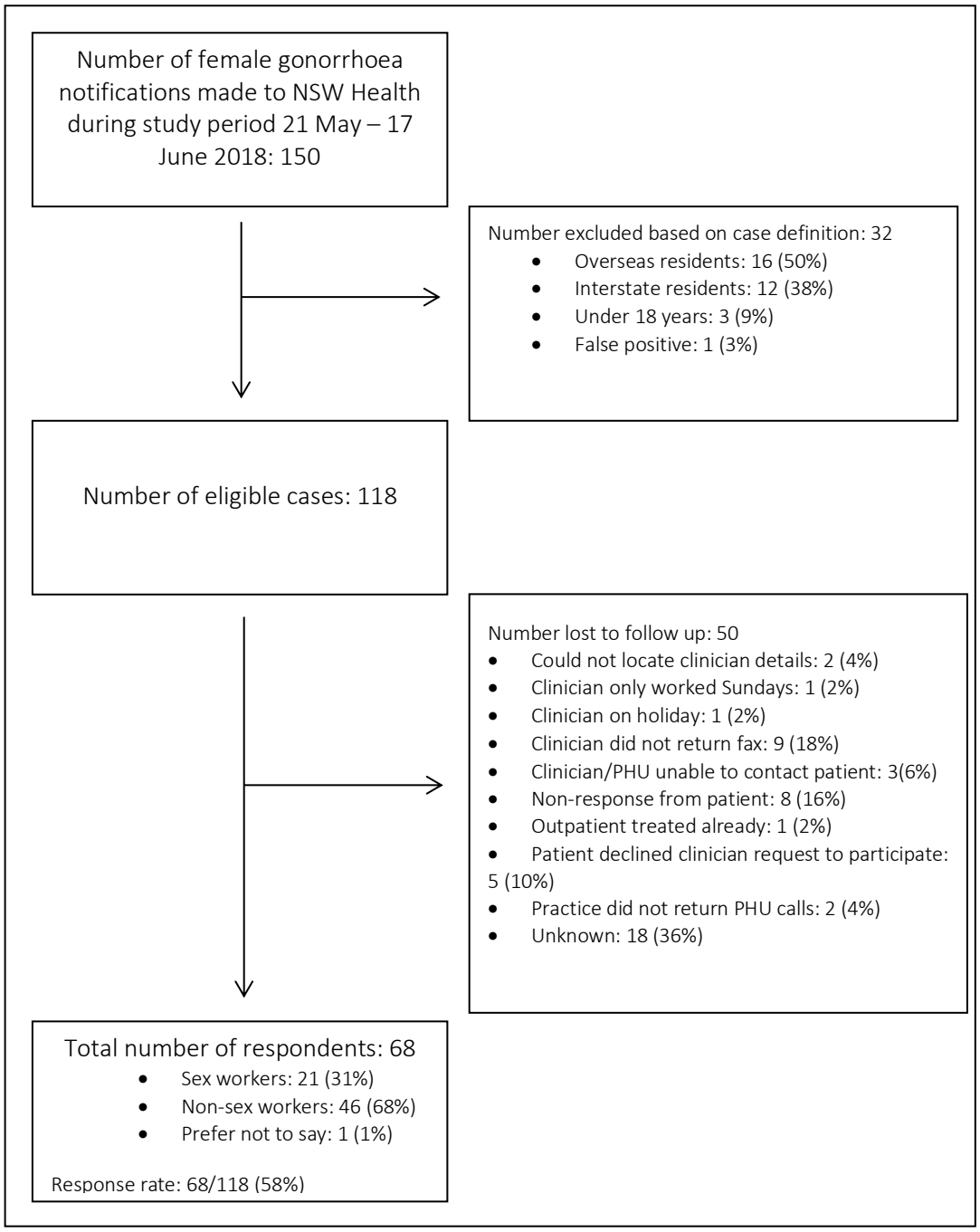
Figure 6: Number of female gonorrhoea infections by site of infection, NSW, 1 January-30 June 2013 - 2018



Questionnaire Responses

During the study period of 21 May – 17 June 2018, 150 gonorrhoea notifications in women were received by NSW Ministry of Health (Figure 7). Of these 150 notifications, 32 were excluded because they did not meet the case definition: being overseas or interstate residents, under 18 years, or a false positive result. Of the 118 eligible cases remaining, questionnaires were received from 68 women giving a response rate of 58% (68/118). While repeated attempts were made to follow up all eligible cases as outlined in the methods section, 50 were lost to follow up for a range of reasons (see Figure 7).

Figure 7: Study flow chart of participants



Just under one third of questionnaire responses received were from women self-described as sex workers (Figure 7). The participant who preferred not to state their sex worker status was excluded from this analysis, bringing the total number of responses analysed from this point forward to 67.

For all participants, the preferred administration method was an in-person clinician administered questionnaire, with 64% of respondents choosing this option (see Table 2). This was followed by the text message method, with 30% of respondents choosing this option.

Table 2: Number of questionnaires returned, by method

Method	No. questionnaires	% total
Clinician administered	43	64%
Text sent to patient	20	30%
Email sent to patient	3	4%
Phone call to patient	1	1%
TOTAL	67	NA

Most questionnaire responses (61%) were among women diagnosed at a general practice clinic (Table 3). Most sex worker respondents (81%) were diagnosed through an SHC, while most non-sex worker respondents (83%) were diagnosed through a general practice facility.

Table 3: Proportion of responses, by practice type

	Sex workers (N=21)		Non-sex workers (N=46)		TOTAL (N=67)	
Practice type	n	%	n	%	n	%
Sexual Health	17	81%	4	9%	21	31%
General Practice	3	14%	38	83%	41	61%
Public Hospital	0	0%	1	2%	1	1%
Family Planning	0	0%	0	0%	0	0%
Other	0	0%	1	2%	1	1%
Missing	1	5%	2	4%	3	4%

The highest response rate (75%) was from women diagnosed at SHCs, followed by general practices (55%) (Table 4).

Table 4: Response rate, by practice type

Practice type	No. responses	No. eligible cases	Response rate (%)
Sexual health clinic	21	28	75%
General practice	41	75	55%
Public hospital	1	5	20%
Family planning clinic	0	1	0%
Other	1	2	50%
Missing	3	7	43%
TOTAL	67	118	57%

Demographic characteristics and risk behaviors

Overall, the most frequently represented age group was 30-39 years (34%) (Table 5.1). This differed by sex worker status with the proportion of sex workers (43%) being 30-39 years of age, and a higher proportion of non-sex workers being 20-24 years (35%). Most participants came from an urban area (91%), both for sex workers (95%) and non-sex workers (89%) (Table 5.1).

The reporting of Aboriginal and Torres Strait Islander status was complete for all participants, with 3% identifying as Aboriginal (4% non-sex workers, and no sex-workers) (Table 5.1).

Over a third (36%) of participants were born overseas, with a substantially higher proportion (71%) of sex workers in this category versus 20% of non-sex workers and 13% of participants born overseas had arrived recently (within the last three years).

All participants were recorded as having been assigned female gender at birth (99%) apart from one for whom the response to this question was missing (Table 5.1). All participants identified as females (Table 5.1). Most participants said they were currently heterosexual or straight (91%) with a small percentage reporting being bisexual (7%) (Table 5.1), with a similar breakdown for sex workers and non-sex workers.

The most common reasons for being tested for gonorrhoea were: having symptoms (42%), a routine STI check (27%) or because a sexual partner had an STI (25%) (Table 5.1). When stratified by sex worker status, the proportions differed slightly but the same reasons were still the most common, at 29%, 57%, 14% respectively among sex workers and 48%, 13% and 30% among non-sex workers.

Table 5.1: Demographic characteristics and personal risk behaviors

	Sex workers (N=21)		Non-sex workers (N=46)		TOTAL (N=67)	
Variable	n	%	n	%	n	%
Gender assigned at birth						
Female	21	100%	45	98%	66	99%
Missing	0	0%	1	2%	1	1%
Current gender identity						
Woman	21	100%	46	100%	67	100%
Missing	0	0%	0	0%	0	0%
Age-group						
18-19	0	0%	3	7%	3	4%
20-24	4	19%	16	35%	20	30%
25-29	5	24%	6	13%	11	16%
30-39	9	43%	14	30%	23	34%
40-49	1	5%	3	7%	4	6%
50-59	2	10%	2	4%	4	6%
60+	0	0%	2	4%	2	3%
Missing	0	0%	0	0%	0	0%
Remoteness category						
Urban	20	95%	41	89%	61	91%
Regional	0	0%	4	9%	4	6%
Remote	0	0%	0	0%	0	0%
Missing	1	5%	1	2%	2	3%
Indigenous Status						
Non-Aboriginal	21	100%	44	96%	65	97%
Aboriginal	0	0%	2	4%	2	3%
Missing	0	0%	0	0%	0	0%
Country of birth						
Australia	6	29%	36	78%	42	63%
Overseas	15	71%	9	20%	24	36%
Prefer not to say	0	0%	1	2%	1	1%
Missing	0	0%	0	0%	0	0%
Sexual orientation						
Heterosexual or straight	18	86%	43	93%	61	91%
Bisexual	3	14%	2	4%	5	7%
Different identity	0	0%	1	2%	1	1%

Missing	0	0%	0	0%	0	0%
Reason for STI test						
Symptomatic	6	29%	22	48%	28	42%
Routine STI check	12	57%	6	13%	18	27%
Other consultation	0	0%	2	4%	2	3%
Sexual partner had an STI	3	14%	14	30%	17	25%
Other	0	0%	2	4%	2	3%
Missing	0	0%	0	0%	0	0%

Table 5.2: Year of arrival to Australia among overseas born women

	Sex workers (N=15)		Non-sex workers (N=9)		TOTAL (N=24)	
Year of arrival in Australia	n	%	n	%	n	%
< 3 years	2	13%	1	10%	3	13%
3+ years	3	20%	4	44%	7	29%
Missing	10	67%	4	44%	14	58%

Partner risk behaviors

The median number of partners reported in the three months prior to gonorrhoea diagnosis by all participants was 1 (range: 0-20) (Table 6.1). Only the range differed slightly between sex workers (0-20) and non-sex workers (1-12).

Table 6.1: Median number of sexual partners

Variable	Sex workers (N=21)	Non-sex workers (N=46)	TOTAL (N=67)
No. of sex partners			
Median (range)	1 (0-20)	1 (1-12)	1 (0-20)
Missing	3	1	4

All results from Tables 6.2-6.9 relate to the participants' partner in the three months prior to gonorrhoea diagnosis. Most participants (52%) completed this questionnaire in relation to a "regular" partner (Table 6.2), and when stratified by sex worker status the highest proportion of responses were also regarding a regular partner (43% sex workers and 57% non-sex workers).

Table 6.2: Relationship to partner

Variable	Sex workers (N=21)		Non-sex workers (N=46)		TOTAL (N=67)	
Relationship to partner						
Regular partner	9	43%	26	57%	35	52%
Casual partner	0	0%	13	28%	13	19%
One-night stand	2	10%	4	9%	6	9%
Other	2	10%	1	2%	3	4%
Missing	8	38%	2	4%	10	15%

For the 22 participants who had a non-regular partner (casual, one-night stand, or other in Table 6.2), most met through friends (36%) or a dating application (app) (23%) (Table 6.3).

Table 6.3: How met non-regular partner

Variable	Sex workers (N=4)		Non-sex workers (N=18)		TOTAL (N=22)	
Method of meeting non-regular partner						
Dating website	0	0%	1	6%	1	5%
Dating app	1	25%	4	22%	5	23%
Through friends	0	0%	8	44%	8	36%
Through work	1	25%	0	0%	1	5%
Educational institute	0	0%	1	6%	1	5%
Bar/nightclub	1	25%	0	0%	1	5%
Other	0	0%	1	6%	1	5%
Prefer not to say	1	25%	2	11%	3	14%
Missing	0	0	1	6%	1	5%

Those who met through a dating application app did so via Tinder (80%) or Bumble (20%) (Table 6.4).

Table 6.4: Dating application used to meet partner

Variable	Sex workers (N=1)		Non-sex workers (N=4)		TOTAL (N=5)	
Dating app						
Tinder	1	100%	3	75%	4	80%
Bumble	0	0%	1	25%	1	20%
Missing	0	0%	0	0%	0	0%

The reported partners of most participants were male (84%) with 1% of partners reported as "other" (Table 6.5). However, this question had a comparatively low response rate of 85%. The question on sexual orientation of partner also had an 85% response rate. Of all partners, 76% were heterosexual, 6% were bisexual, 3% of participants did not know the sexual orientation of their partner, and 15% of respondents did not answer the question on sexual orientation. Among sex workers, most partners (62%) were heterosexual and none were reported as bisexual or unknown. The remaining 38% were missing data. Among non-sex workers, again most partners were heterosexual (83%) while 9% were bisexual, 4% unknown and 4% were missing.

Table 6.5: Gender identity and sexual orientation of partner

	Sex workers		Non-sex workers		TOTAL	
Variable	(N=21)		(N=46)		(N=67)	
Gender identity of partner						
Male	13	62%	43	93%	56	84%
Other	0	0%	1	2%	1	1%
Missing	8	38%	2	4%	10	15%
Sexual orientation of partner						
Heterosexual	13	62%	38	83%	51	76%
Bisexual	0	0%	4	9%	4	6%
Don't know	0	0%	2	4%	2	3%
Missing	8	38%	2	4%	10	15%

When participants were asked if they believed if their partner was the source of gonorrhoea transmission, 51% said yes, 22% said no, 12% were unsure, and 15% of responses to this question were missing (Table 6.6). Of those who believed that the partner in mention was the source, most (24%) believed that this partner acquired the infection from another sexual partner.

Table 6.6: Participant opinion on personal gonorrhoea transmission

Variable	Sex workers (N=21)		Non-sex workers (N=46)		TOTAL (N=67)	
Do you believe this person passed gonorrhoea on to you?						
Yes	3	14%	31	67%	34	51%
No	6	29%	9	20%	15	22%
Unknown	4	19%	4	9%	8	12%
Missing	8	38%	2	4%	10	15%
If yes, where do you think they acquired the infection? *(Free text response).*						
		n=3		n=31		n=34
Another sexual partner	0	0%	8	26%	8	24%
Another woman	0	0%	1	3%	1	3%
Another man	0	0%	1	3%	1	3%
Australia	1	33%	0	0%	1	3%
China	0	0%	1	3%	1	3%
New Zealand	0	0%	1	3%	1	3%
Darwin	0	0%	1	3%	1	3%
Cairns	0	0%	1	3%	1	3%
Unknown	0	0%	7	23%	7	21%
Missing	2	67%	10	32%	12	35%

Most partners were Australian born (54%) with 6% unknown and 21% of responses to this question missing (Table 6.7). Overall 3% of participants reported having had sex overseas in the 3-month period of questioning – with 5% of sex workers and 2% of non-sex workers reporting having sex overseas. The response rate to this question was again low (85%). Further, 10% reported that their partner had travelled overseas in the three months prior to the participant's gonorrhoea diagnosis (10%), and 16% of participants did not know if their partner had travelled overseas. This breakdown was similar for non-sex workers, while no sex workers reported that their partner had travelled overseas. Among non-sex workers whose partner had travelled overseas, the largest proportion had travelled to China (29%), while 14% of partners each travelled to Japan, New Zealand, Thailand and USA.

Table 6.7: Travel associated sexual behaviors

Variable	Sex workers (N=21)		Non-sex workers (N=46)		TOTAL (N=67)	
Sex in Australia						
Yes	12	57%	43	93%	55	82%
No	1	5%	1	2%	2	3%
Missing	8	38%	2	4%	10	15%
If no, specify: country		n=1		n=1		n=2
China	1	100%	0	0%	1	50%
Missing	0	0%	1	100%	1	50%
Did partner travel overseas						
Yes	0	0%	7	15%	7	10%
No	8	38%	31	67%	39	58%
Unknown	5	24%	6	13%	11	16%
Missing	8	38%	2	4%	10	15%
If yes, specify: country		n=0		n=7	n=7	
China	0	0%	2	29%	2	29%
Japan	0	0%	1	14%	1	14%
New Zealand	0	0%	1	14%	1	14%
Thailand	0	0%	1	14%	1	14%
USA	0	0%	1	14%	1	14%
Missing	0	0%	1	14%	1	14%
Partner country of birth						
Australia	5	24%	31	67%	36	54%
Brazil	1	5%	0	0%	1	1%
China	2	10%	2	4%	4	6%
Thailand	1	5%	0	0%	1	1%
England	0	0%	2	4%	2	3%
Italy	0	0%	1	2%	1	1%
Lebanon	0	0%	1	2%	1	1%
New Zealand	0	0%	1	2%	1	1%
Turkey	0	0%	1	2%	1	1%
USA	0	0%	1	2%	1	1%
Unknown	4	19%	0	0%	4	6%
Missing	8	38%	6	13%	14	21%

Vaginal sex was reported most frequently, (84% of partners, Table 6.8), followed by giving oral sex to men (fellatio) (54%), females receiving oral sex (cunnilingus) (45%), kissing (34%), and anal sex (10%). Responses were similar between sex workers and non-sex workers.

Table 6.8: Types of sex practiced

Variable	Sex workers (N=21)		Non-sex workers (N=46)		TOTAL (N=67)	
Type of sex *(calculated as a % total group, note that participants could select multiple options).*						
Vaginal	13	62%	43	93%	56	84%
Anal	2	10%	5	11%	7	10%
Fellatio	12	57%	24	52%	36	54%
Cunnilingus	11	52%	19	41%	30	45%
Kissing	11	52%	22	48%	23	34%
Missing	8	38%	2	4%	10	15%

Condom use was low among participants for vaginal, anal and fellatio; 38%, 0% and 0% respectively among sex workers and 5%, 0% and 8% among non-sex workers (Table 6.9).

Table 6.9: Condom use by type of sex

Variable	Sex workers		Non-sex workers		TOTAL	
Condom use, vaginal sex	n=13		n=43		n=56	
Yes	5	38%	2	5%	7	13%
No	7	54%	28	65%	35	63%
Sometimes	1	8%	6	14%	7	13%
Missing	0	0%	7	16%	7	13%
Condom use, anal sex	n=2		n=5		n=7	
Yes	0	0%	0	0%	0	0%
No	2	100%	3	60%	5	71%
Sometimes	0	0%	1	20%	1	14%
Missing	0	0%	1	20%	1	14%
Condom use, fellatio	n=12		n=24		n=36	
Yes	0	0%	2	8%	2	6%
No	7	58%	21	88%	28	78%
Sometimes	0	0%	1	4%	1	3%
Missing	5	42%	0	0%	5	14%

4.7 Discussion

General discussion of study and results

Our study did not provide evidence to support the proposed hypothesis that the increase in gonorrhoea in NSW females was associated with travel associated sex or sex with a bisexual partner. Our results however indicate that the outbreak could be related to local, heterosexual condomless transmission.

In our study only a small proportion of participants reported sexual contact overseas, or had sexual contact with an overseas partner. This finding was in contrast to previous studies in which travel associated sex was a risk factor for gonorrhoea in women[10, 17]. When asked about partner travel overseas, only a small proportion of participants reported that their partner had travelled overseas. Other behaviours that have been suggested as potential risk factors including kissing and sexual contact with bisexual men. Approximately one third of participants in our study reported kissing, however no participant reported kissing only, making it difficult to determine whether kissing alone was a risk factor for gonorrhoea for females in our study. We found that only a small proportion of participants had sexual contact with bisexual men. Unprotected vaginal sex was common among study participants, and has also previously been confirmed as a risk factor for gonorrhoea in women[18]. Most cases in our study were heterosexual, which is consistent with current trends[14].

Consistent with characteristics of notified gonorrhoea cases in NSW females, most participants in this case series were urban residing. However, most participants in this case series were also much older (most cases aged 30-39 years) than age trends in NSW notified cases (most notifications aged 20-24 years).

While most non-sex workers were Australian born, a higher proportion of sex workers were born overseas, again consistent with other reports[26, 5]. One quarter of participants were tested for gonorrhoea because they were a contact of someone with an STI, which has previously been confirmed as a risk factor for gonorrhoea[10]. The most frequent reason for testing among non-sex workers was having symptoms, which given that gonorrhoea is often asymptomatic in women, indicates that a large proportion of infections are likely to remain untreated. Among sex workers the most frequent reason for testing was a routine STI check, reflecting the fulfilment of the national recommendation for the regular screening of sex workers in Australia[7]. The higher reported reason for testing (that is, screening) of sex workers compared to non-sex workers may reflect the overrepresentation of sex-workers in our study participants.

Compared to condom use for vaginal and anal sex in the sexual health survey ASHR2[27], condom use for vaginal and anal sex was low in our study, for sex workers and non-sex workers. A relatively high recruitment rate (61%) was achieved for this study compared to another study investigating increases an STIs through a similar method[22].

Practical challenges in conducting the investigation

Design: There was prolonged discussion on study design issues because of the personal and sensitive nature of this investigation – that is, the investigation of an STI in females. STIs in MSM have been researched extensively, so this population is generally used to participating in research and hence potentially more comfortable with the idea of sharing personal details pertinent to the epidemiology of STIs. Women on the other hand have been less involved in such research, so extra caution was advised in our approach, particularly considering the stigma and entrenched gender norms and stereotypes associated with these infections.

Contacting doctors and participants: It was difficult to initially contact diagnosing clinicians through fax because the fax number field is not mandatory for notifications in NCIMS, and the central register of NSW clinician/medical practice fax numbers only covers approximately 70% of NSW clinicians. This meant that the investigation team had to search for the numbers via the internet, or phone the practice if these details were not displayed on practice websites. Once a fax number was located, many clinicians needed to be followed up with a reminder fax or phone. Another bottleneck was retrieving the mobile number/email of patients. Again, this field is not mandatory on NCIMS notifications.

Electronic platform: Because of data storage and privacy issues, it was required that the electronic questionnaire design and deployment be through NCIMS. The NCIMS electronic questionnaire design platform had limited functionality compared to other questionnaire platforms such as REDCap and SurveyMonkey. In addition, a side investigation into the low response rate by clinicians in the first week revealed that the fax machine used to deploy the faxes was distorting the faxes we sent into unreadable documents. Finally, as the data analysis component of this investigation had to be completed at NSW Ministry of Health due to data storage issues, the investigation team member doing the analysis (SP) had to use the software available only there. As a descriptive analysis was originally planned, Excel was deemed suitable but ultimately proved to have limitations in regard to the type of analysis it could support. Accordingly the analysis for this bound volume (BV) was restricted to the first partner only.

Epidemiological limitations

The application and use of the results from this study are limited for a number of reasons. Firstly, the descriptive nature of case series studies means that there was no direct comparison group. So, while some risk factors were highly prevalent among study participants, without a control group the comparative prevalence in the general population is not known, let alone whether any difference was statistically significant. In addition, the sample size was small (<100), so for some categories of risk factors there was minimal data. Also, a large proportion of eligible cases were lost to follow up. There could have been differences between those who responded and those who did not. Among those who agreed to participate, the response rates to questions within the questionnaire were generally high, however more sensitive questions probing sexual risk factors had a lower response rate.

There were also several limitations to the study questionnaire itself. Socioeconomic status, alcohol and drug use are known to be risk factors for gonorrhoea infection in women, yet we decided not to include them in our questionnaire in order to keep it succinct and focused on under-researched and new risk factors. Some aspects of the questionnaire would have had a higher content validity if they were better defined – for example, we did not define the categories within the variable "Relationship to partner". In addition, we specifically asked about the means of meeting non-regular partners only, whereas it would have been more beneficial to ask everyone how they met their partner regardless of whether they were regular or not.

The results from section 2 of the questionnaire on partner characteristics need to be interpreted with caution as they were completed by the participant as a proxy for their partner(s). It is possible, indeed likely, that participants did not know the true answer to some of these questions (especially the sexuality and travel questions). It was also difficult to determine which partner (if any) of the nominated partners was the source of gonorrhoea infection in the participant as we had no objective measure of this. We chose to ask about up to 10 partners in the three months prior to gonorrhoea diagnosis based on practicality, previous study methods[10], and the incubation period of gonorrhoea. In addition, as this analysis is based on the first partner listed by participants only, there is the possibility that the characteristics of the partner who was the source of gonorrhoea were missed. Recall bias could be present (at least to the same extent in all participants) as all participants were cases. Screening bias was previously discussed in reference to sex workers, therefore certain risk factors may have been disproportionately weighted in the descriptive analysis.

4.8 Conclusion and public health implications

In response to the increase in gonorrhoea notifications among NSW females, this investigation has provided further information on the characteristics of women and potential risk factors. Travel associated sex and sex with a bisexual partner were hypothesised to be major risk factors, however we did not find clear evidence to support this in our study based on the small proportions of cases reporting these characteristics. However, our results indicate the outbreak could be related to local, heterosexual, condomless transmission. Low condom use for all types of sex among sex workers and non-sex workers highlights the need for condom promotion. A relatively high recruitment rate was achieved, which is indicative of sensitive study methods that could be utilised in future studies on this topic.

4.9 Recommendations for improving the public health response to gonorrhoea in NSW

- Raise awareness and promote regular STI screening among in NSW females.
- Promote condom use in NSW females.
- Update the completeness of the register of fax and mobile numbers for clinicians in NSW, and/or make the reporting of diagnosing clinicians fax numbers mandatory in NCIMS.
- For future investigations planning electronic questionnaires, consider using a more sophisticated platform than NCIMS such as REDCap, Qualtrics or Secure Data Kit, which also allow secure data storage.
- Conduct a further analysis of the study results including all partners listed for each participant.
- Conduct further research considering the following study adaptations:
    - A longer study recruitment period to enable a larger sample size;
    - A future case control study with test-negative gonorrhoea notifications, or chlamydia notifications as controls to assist in evaluating the significance of risk factors; and
    - A future study with a qualitative aspect to delve further into the detail of potential risk factors.

4.10 References

1. Kidd S. 2015. Gonoccocal Infections. Control of Communicable Diseases. Heymann D. Washington, *Alpha Press:* 237-242.
2. Walker C, Sweet R. 2011. Gonorrhoea infection in women: prevalence, effects, screening and management. *International Journal of Womens Health* 3:197-206.
3. Newman L, Rowley J, Vander Hoorn S, Wijesooriya N, Unemo M, Low N, Stevens G, Gottlieb S, Kiarie J and Temmerman M. 2015. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. *PLOS ONE* 10(12):e0143304.
4. Selvey L, Slimings C, Adams E et al. 2018. Incidence and predictors of HIV, chlamydia and gonorrhoea among men who have sex with men attending a peer-based clinic. *Sexual Health* doi 10.1071/SH17181.
5. Callander D, McManus H, Guy R et al. 2018. Rising chlamydia and gonorrhoea incidence and associated risk factors among female sex workers in Australia: a retrospective cohort study. *Sexually Transmitted Diseases* 45(3):199-206.
6. Silver B, Guy R, Wand H et al. 2015. Incidence of curable sexually transmissible infections among adolescents and young adults in remote Australian Aboriginal communities: analysis of longitudinal clinical service data. *Sexually Transmitted Infections* 91(2):135-141.
7. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). 2016. Australian STI Guidelines for Use in Primary Care – Sex Workers. Accessed on 20th Nov 2018, from: http://www.sti.guidelines.org.au/populations-and-situations/sex-workers#testing-advice
8. STIs In Gay Men Action group (STIGMA). 2014. Australian Sexually Transmitted Infection & HIV Testing Guidelines 2014. Accessed on 13th December 2018 from https://stipu.nsw.gov.au/wp-content/uploads/STIGMA_Testing_Guidelines_Final_v5.pdf
9. Western Australia Department of Health. 2019. STI screening recommendations for priority populations. Accessed on 20th Nov 2018, from: https://ww2.health.wa.gov.au/Silver-book/STI-screening-recommendations-for-high-risk-populations
10. McDonagh P, Ryder N, McNulty A et al. 2009. Neisseria gonorrhoeae infection in urban Sydney women: prevalence and predictors. *Sexual Health* 6(3):241-244.

11. Chow E, Fehler G, Read T et al. 2015. Gonorrhoea notifications and nucleic acid amplification testing in a very low-prevalence Australian female population. *Medical Journal of Australia* 202(6):321-323.
12. Mannion P, Fairley C, Fehler G et al. 2016. Trends in gonorrhoea positivity by nucleic acid amplification test versus culture among Australian heterosexual men with a low prevalence of gonorrhoea, 2007-2014. *Sexually Transmitted Infections* 92(8):625-628.
13. The Kirby Institute. 2017. HIV, Viral Hepatitis and Sexually Transmissible Infections in Australia: Annual Surveillance Report 2016. Accessed on 11 March 2018 from https://kirby.unsw.edu.au/sites/default/files/kirby/report/SERP_Annual-Surveillance-Report-2016_UPD170627.pdf
14. Jasek E, Chow E, Ong J, et al. 2017. Sexually transmitted infections in Melbourne, Australia from 1918 to 2016: nearly a century of data. *Communicable Disease Intelligence* 41(3):e212-e222.
15. Donovan B, Dimech W, Ali H et al. 2015. Increased testing for Neisseria gonorrhoeae with duplex nucleic acid amplification tests in Australia: implications for surveillance. *Sexual Health* 12(1):48-50.
16. New South Wales Department of Health. 2018. NSW Sexually Transmitted Infections Strategy 2016-2020: Data Report January to December 2017. Accessed on 26th October 2018 from https://www.health.nsw.gov.au/Infectious/Reports/Publications/sti/nsw-2017-sti-report.pdf
17. Misson J, Chow E, Chen M et al. 2018. Trends in gonorrhoea infection and overseas sexual contacts among females attending a sexual health centre in Melbourne, Australia, 2008-2015. *Communicable Disease Intelligence* 42:pii S2209-6051(18)00024-6
18. Lusk M, Uddin R, Lahra M et al. 2013. Pharyngeal Gonorrhoea in Women: An Important Reservoir for Increasing Neisseria gonorrhoea Prevalence in Urban Australian Heterosexuals? *Journal of Sexually Transmitted Diseases* e967471.
19. Chow E, Cornelisse V, Read T et al. 2016. Saliva use as a lubricant for anal sex is a risk factor for rectal gonorrhoea among men who have sex with men, a new public health message: a cross-sectional survey. *Sexually Transmitted Infections* 92(7):532-536.
20. Butler L, Osmond D, Jones A et al. 2009. Use of saliva as a lubricant in anal sexual practices among homosexual men. *Journal of Acquired Immune Deficiency Syndromes* 50(2):162-167.
21. Fairley C, Zhang L, Chow E. 2018. New thinking on gonorrhoea control in MSM: are antiseptic mouthwashes the answer? *Current Opinion in Infectious Diseases* 31(1):45-49.

22. Sheel, M. 2017. Chapter 3: Field Investigation of a Public Health Problem. In: "Island Dreaming: Applied Epidemiology in the Pacific Region". Thesis (MPhil) accessed on 20th October 2018 from https://openresearch-repository.anu.edu.au/handle/1885/143531
23. Richters J, Badcock P, Simpson J et al. 2014. Design and methods of the Second Australian Study of Health and Relationships. *Sexual Health* 11(5):383-396.
24. Hocking J, Low N, Guy R et al. 2010. Australian Chlamydia Control Effectivenss Pilot (ACCEPt): a cluster randomised controlled trial of chlamydia testing in general practice. Study protocol. Accessed on 20th Oct 2018 from http://www.accept.org.au/images/Protocol/THELANCET-D-12-09010.pdf.
25. The Kirby Institute. 2017. Case-control study to investigate risk factors for gonorrhoea in heterosexuals residing in metropolitan areas in WA (DRAFT protocol, Version 1, internal document).
26. Donovan B, Harcourt C, Egger S et al. 2012. The Sex Industry in New South Wales: A report to the NSW Ministry of Health. Sydney, The Kirby Institute, University of New South Wales. Accessed on 18th March 2018 from https://www.acon.org.au/wp-content/uploads/2015/04/NSW-Sex-Industry-Report-CSRH-2012.pdf
27. De Visser R, Badcock P, Rissel C et al. 2014. Safer sex and condom use: findings from the second Australian study of health and relationships. *Sexual Health* 11(5):495-504.

ANNEX 4A: Brief to Chief Health Officer (CONFIDENTIAL, examiners only)

(Brief page 1)

(Brief page 2)

ANNEX 4B: Outbreak Investigation Proposal: Risk factors for gonorrhoea in females in NSW - a case control study.

Investigators: Sophie Phelan, Tove-Lysa Fitzgerald. Christine Selvey, John Kaldor, Rebecca Guy, Basil Donovan

1. OBJECTIVE

To determine the risk factors for gonorrhoea in females in NSW.

2. BACKGROUND

Gonorrhoea is a sexually transmitted infection (STI) caused by the bacterium *Neisseria gonorrhoeae* (1). Gonococcal infection causes symptomatic and asymptomatic genital and extra-genital tract infections. Untreated infections can result in pelvic inflammatory disease in women, and infertility in both men and women[1]. In addition, the risk of both acquisition and transmission of HIV is elevated in those with gonococcal infections[2]. Gonorrhoea is a common infection worldwide with an estimated 78 million new cases (95% confidence interval 53-110 million) in 2012 according to the World Health Organization[3].

Those predominantly affected include MSM, female sex workers, sexually active adolescents and younger adults, and people of low socioeconomic status[1]. In Australia, gonorrhoea is consistently ranked among the top five most notified communicable diseases and is largely concentrated among MSM and young Aboriginal and Torres Strait Islander people living in remote communities. However, in the past ten years, notification rates have increased in men and women aged 15-34 years living in urban areas. Between 2012 and 2016 in Australia, gonorrhoea notification rates increased by 63% (62 to 101 per 100 000), with an increase in both males (72%) and females (43%)[4]. Although notification data do not routinely collect the gender of the sexual partner for all cases, the increase in women suggests heterosexual acquisition.

Until recently, increases in gonorrhoea notification rates have been thought to reflect an increase in testing rates[5], duplex PCR testing for chlamydia and gonorrhoea becoming standard practice[5], and the fact that PCR tests are more sensitive than culture. However, duplex testing has been in place since 2012, so this does not explain the continued rise. Medical Benefits Scheme gonorrhoea testing information is collected and analysed by the Kirby Institute annually. The number of Medicare-rebated tests has increased in the past 5 years, and in 2016 there were two diagnoses for every 100 Medicare-rebated tests done, 64% higher than in 2012[4]. This suggests that transmission of gonorrhoea has increased and/or screening is better targeted to people at high risk of infection.

New South Wales accounted for 29% of Australian gonorrhoea notifications in 2016, with increases in both males and females[4]. From January to June 2017, the annualised gonorrhoea notification rate was 120 notifications per 100,000 population, 33% higher compared to 2016[6]. When stratified by gender, a 34% relative increase was observed in males and an 18% relative increase was observed in females[6]. The transmission of gonorrhoea in NSW is thought to be mainly associated with male-to-male sex, with 83% of the 4,717 notifications from January to June 2017 being in men. However, an increasing proportion of notifications have been in women since 2016, suggesting that heterosexual transmission may be increasing.

In order to reduce the number of gonorrhoea notifications in heterosexual people, risk factors need to be identified so that control measures can be implemented.

Recent studies have identified various risk factors for gonorrhoea in different groups. A high number of casual sex partners was found to be a risk factor for pharyngeal gonorrhoea in MSM attending a sexual health centre in Melbourne[7]. Recent injection drug use, and being born in Australia or New Zealand were found to be risk factors for gonorrhoea in female sex workers[8]. Being aged 15-29 years, and being a resident of particular Local Government Areas was found to be a risk factor for gonorrhoea in people aged over 15 years in greater western Sydney[9]. Among MSM in Melbourne, saliva use as a lubricant for anal sex was found to be a risk factor for gonorrhoea[10]. Chow et al., 2017[11], demonstrated that overseas sexual contact in countries where gonorrhoea prevalence is high was a significant risk factor for women attending a Melbourne SHC who were diagnosed with gonorrhoea. Sexual contact with bisexual men, use of dating websites/apps, kissing, oral sex and saliva use were also cited as potential risk factors for the transmission of gonorrhoea among women. A study conducted by Sydney Sexual Health centre of gonorrhoea diagnoses 1997-2007 identified being a known contact of someone with gonorrhoea, recent sex overseas, and recent sex with a partner from overseas to be risk factors for cervical gonorrhoea in women[11].

An investigation examining risk factors for gonorrhoea infection in women in NSW is required to better understand the recent increase in disease rates in this population and inform public health action.

3. METHODS

3.1. Design

A matched case control study is proposed as the study population is not well defined

3.2. Study population

The study base will be comprised of females aged ≥18 years who reside in NSW and were notified to NSW Ministry of Health with a gonorrhoea or chlamydia infection from 1 October 2017 - 30 April 2018. Females aged 17 and under will be excluded; only a small number of female gonorrhoea notifications are under 18 years of age. The proposed time period will ensure we can recruit enough participants and reduce recall bias.

Cases

Case definition: a female aged ≥18 years residing in NSW and notified to NSW Ministry of Health with gonorrhoea from 1 October 2017 to 30 April 2018. Confirmed gonorrhoea cases in NSW require laboratory definitive evidence, which could be any of the following: isolation of *N. gonorrhoeae*, detection of *N. gonorrhoeae* by nucleic acid testing, or detection of typical Gram-negative intracellular diplococci in a smear from a genital tract specimen [ref: NSW Health gonorrhoea control guidelines].

Case eligibility: cases will be excluded from the case control study if:

- Cases do not wish to participate
- Cases do not have a mobile number recorded on their notification
- Cases doctors request that we do not contact them
- Cases cannot be contacted after 1 repeat text plus one phone call
- Cases have been notified with chlamydia from 1 October 2017 to 30 April 2018

Controls

Control definition: a female aged ≥18 years residing in NSW and notified to NSW Ministry of Health with chlamydia from 1 October 2017 to 30 April 2018. Confirmed chlamydia cases in NSW (excluding eye infections) require laboratory definitive evidence, which could be any of the following: isolation of *Chlamydia trachomatis,* detection of *C. trachomatis* by nucleic acid testing, or detection of *C. trachomatis* antigen [ref: NSW Health gonorrhoea control guidelines].

Control eligibility: controls will be excluded from the case control study if:

- Controls do not wish to participate

- Controls do not have a mobile number recorded on their notification
- Controls doctors request that we do not contact them
- Controls cannot be contacted after 1 repeat text plus one phone call
- Controls have been notified with gonorrhoea from 1 October 2017 to 30 April 2018

Matching

In NSW, female gonorrhoea cases are slightly older (approximately 5-6 years) than female chlamydia cases. For this reason, controls will be matched to cases by age (with a 2-3 year margin). Controls will also be matched to cases based on epi week (calculated onset date). Due to the statistically small number of cases, we will recruit 2 controls to 1 case to increase the power of the study.

3.3. Sample size

Sample size calculations are reported in Table 1 below based on the following assumptions.

1. Risk factor prevalence: in the respective study populations, the prevalence of risk factors commonly identified in previous research (12-16) ranged from <5% for the most extreme category of a variable (e.g. as <1 months duration of sexual relationship with most recent sexual partner [14]) to 10% - >20% for most variables).
2. Effect size: previous case-control studies, using different study populations, have found odds ratios ≥ 2.0 in multivariate analyses, with the effect size being considerably larger for most socioeconomic and behavioural characteristics of individuals and their partners.

*Table 1: Minimum sample size at different levels of risk factor prevalence (Epi Info7)**

Ratio of cases to control	Risk factor prevalence	Effect size (OR)	Total sample size	Cases	Controls
1:1	10%	2.0	566	283	283
	15%	2.0	416	208	208
	20%	2.0	344	172	172
1:2	10%	2.0	615	205	410
	15%	2.0	453	151	302
	20%	2.0	378	126	252

**All calculations based on 80% power, 0.05 significance level*

In order to optimise the detection of an effect size where the risk factor prevalence is low, a ratio of one case to two controls (1:2), and a total sample size of 615 participants (minimum 205 cases and 410 controls) has been selected from the sample size calculations in Table 1. In order to achieve these numbers, we estimate that we will need to recruit participants who were notified during a period of seven months from 1 October 2017 to 30 April 2018. These estimates are based on the number of female gonorrhoea and chlamydia notifications received from 1 January 2017 to 31 January 2018 with a conservative assumption of 50% of notifications having a mobile number, and a further 50% response rate.

3.4. Data collection

Case and control recruitment

Gonorrhoea and chlamydia notifications for this study period have already been collected under the NSW *Public Health Act 2010*. Prior to the commencement of the study, a fax will be sent to all general practitioners in NSW notifying them of the study rationale and methods. All NSW SHCs will be informed through the sexual health director's forum. The NSW public health network will also be notified and informed via e-mail and teleconference.

Study participants will be accessed retrospectively through the Notifiable Conditions Information Management System (NCIMS) by Sophie Phelan, MAE scholar (Kirby Institute) who will be based at NSW Ministry of Health for this study. Controls will be recruited ad hoc to case recruitment to ensure they are appropriately matched. People who fit the case or control criteria will be sent a text message via PRODOCOM, a secure online electronic communication platform inviting them to participate in our study. If they wish to participate, they will be sent another text message containing a link to an online survey hosted by NCIMS. The online survey will be sent out through NCIMS, and the results are sent directly back to NCIMS.

Data to collect

A new data set will be created, in which the following variables from consenting notifications will be extracted from the notification data:

- calculated onset date
- epi week
- epi year
- age at event years
- age at event months

- age at event decimal
- postcode
- residential LHD
- residential local government area
- anatomic site of infection
- test type
- test result
- susceptibility test
- susceptibility result
- disease (chlamydia or gonorrhoea)

The following information will be extracted through the survey questionnaire and merged with the notification data:

- country of birth
- Aboriginality
- gender assigned at birth
- current gender identity
- sexual orientation
- injection drug use ever
- reason for test
- number of sexual partners
- condom use
- previous STI diagnoses
- recreational drug use within the previous 12 months
- sex work within the previous 12 months
- travel within the previous 12 months
- sexual contact whilst travelling
- country of sexual contact
- gender of sexual partner/s
- sexual orientation of partner/s
- sexual practices with partner/s
- other sexual partners of sexual partner/s
- method of meeting sexual partner/s eg dating app
- country of birth of sexual partner/s
- travel exposure of sexual partner/s

3.5. Data storage

The raw notification and survey data will be stored within NCIMS and extracted from NCIMS for analysis on a password protected server at the NSW Ministry of Health. De-identified data sets generated by analysis will be stored within the NSW Ministry of Health network drive which complies with NSW Ministry of Health IT standards.

3.6. Data analysis

Following a descriptive analysis, a univariate analysis of risk factors for cases versus controls will be conducted. This will produce odds ratios, p-values and 95% confidence intervals for risk factor variables. Risk factors that were found to be significant ($P<0.05$) in the univariate analysis will be included in a multivariate analysis which will also produce odds ratios, p-values and 95% confidence intervals for included risk factor variables.

The STATA 17 software package will be used for all data analyses.

4. COMMUNICATION AND GOVERANCE ARRANGEMENTS

4.1. Communication

Prior to the commencement of the study, a fax will be sent to all general practitioners in NSW notifying them of the study rationale and methods. All NSW SHCs will be informed through the sexual health director's forum. Doctors will be given the opportunity to indicate that they do not wish their patients to participate. The NSW public health network will also be notified and informed via e-mail and teleconference.

4.2. Governance

A steering committee chaired by the Executive Director, Health Protection NSW or the Director, CDB will be formed to provide oversight and advice regarding the investigation. Membership will include a SHC director and a PHU director.

5. ETHICAL CONSIDERATIONS

This investigation will be undertaken as public health follow-up of people notified to NSW Ministry of Health with a notifiable condition for which rates of notification have increased substantially. The objective of the investigation is to identify risks for infection to enable better gonorrhoea control strategies to be developed and implemented. Therefore, human research ethics committee approval is not required.

6. TIMELINE

February 2018:

- finalise research proposal and questionnaire
- notify GPs and PHUs, SHCs

March 2018:

- pilot and adjust survey.

April 2018:

- send out survey.
- follow up non-responses
- data entry

May 2018:

- data analysis and write up

June 2018:

- dissemination of results

7. DISSEMINATION PLAN

The results of this case control study will be shared with NSW Ministry of Health through the distribution of an epidemiological report on the investigation. The investigators may summarise the study in a manuscript for submission to a peer reviewed journal. This investigation will also be written up as an Outbreak Investigation chapter in Sophie Phelan's MAE thesis.

8. REFERENCES

1. SK. Gonoccoccal Infections. In: DH, editor. Control of Communicable Diseases Manual. 20th ed. Washington DC: American Public Health Association; 2015. P. 237-42.
2. Victorian Department of Human Services. The blue book: guidelines for the control of infectious diseases. 2011. Available from https://www2.health.vic.gov.au/getfile/?sc_itemid=%7B7A1F05A1-64B0-4B8C-A730-D4F8F107AA52%7D&title=The%20blue%20book [last accessed 26th Feb 2018]
3. Newman L et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. *PLOS ONE*. 2015.10(12):e0143304
4. The Kirby Institute, UNSW. HIV, Viral Hepatitis and Sexually Transmissible Infections in Australia: Annual Surveillance report 2016.
5. Donovan B et al. Increased testing for Neisseria gonorrhoeae with duplex nucleic acid amplification tests in Australia: implications for surveillance. *Sex Health* 2015. 12(1):48-50
6. NSW Health. NSW Sexually Transmissible Infections Strategy 2016-2020: Data Report January-June 2017 (UNPUBLISHED). 2017.
7. Cornellisse et al. Risk factors for oropharyngeal gonorrhoea in men who have sex with men: an age-matched case-control study. *Sex Transm Infect*. 2018. Published Online First: 22 January 2018. doi: 10.1136/sextrans-2017-053381
8. Callendar et al. Rising Chlamydia and Gonorrhoea Incidence and Associated Risk Factors Among Female Sex Workers in Australia: A Retrospective Cohort Study. *Sex Transm Dis*. 2018. 45(3):199-206
9. Gale et al. Demographic and geographical risk factors for gonorrhoea and chlamydia in greater Western Sydney, 2003-2013. *Commun Dis Intell Q Rep* 2018. 30;41(2):E134-E141.
10. Chow et al. Saliva use as a lubricant for anal sex is a risk factor for rectal gonorrhoea among men who have sex with men, a new public health message: a cross-sectional survey. *Sex Transm Infect*. 2016;92:532-536.
11. Chow et al. Risk factors for gonorrhoea in heterosexuals. Australasian HIV & AIDS conference joint with Australasian Sexual Health conference, Canberra, 6-9 November 2017, viewed 5/2/2018, https://az659834.vo.msecnd.net/eventsairaueprod/production-ashm-public/23dfdf15afa247b0974116d3941d983a
12. McDonagh et al. Neisseria gonorrhoeae infection in urban Sydney women: prevalence and predictors. *Sex Health*. 2009. 6(3): 241-4.

13. Barry PM et al. Risk factors for gonorrhea among heterosexuals--San Francisco, 2006. *Sex Transm Dis*. 2009. 36(2 Suppl): p. S62-6.
14. Mertz KJ et al. Gonorrhoea in male adolescents and young adults in Newark, New Jersey: implications of risk factors and patient preferences for prevention strategies. *Sex Transm Dis*. 2000. 27(4): p. 201-7.
15. Ross JD et al. Reducing the risk of gonorrhoea in black Caribbean men: can we identify risk factors? *Sex Transm Infect*. 2003. 79(2): p. 119-23.
16. Azariah, S. and Perkins N. Risk factors and characteristics of patients with gonorrhoea presenting to Auckland Sexual Health Service, New Zealand. *N Z Med J*. 2007. 120(1252): p. U2491.
17. Manhart LE et al. Influence of study population on the identification of risk factors for sexually transmitted diseases using a case-control design: the example of gonorrhoea. *Am J Epidemiol*. 2004. 160(4): p. 393-402.

ANNEX 4C: Clinician Fax Template

Dr [insert name]
Address
Address NSW PCDE

Dear Dr [insert name]

NSW Health has been notified that your patient [insert name], date of birth [DD/MM/YYYY], has tested positive for gonorrhoea.

We are seeking your help in completing the attached questionnaire with this patient to obtain information on factors that may have led to their gonococcal infection. Alternatively, if you would like NSW Health to send the questionnaire via SMS or e-mail to your patient for self-completion, tick the appropriate box below and provide the mobile phone number and/or email address for your patient. Please tell your patient to expect someone from NSW Health to be in contact with them.

Due to a recent increase in gonorrhoea notifications among women in NSW, NSW Health are conducting enhanced follow up of women notified with gonorrhoea. This will help us to better understand risk factors that may be contributing to the increase, which in turn will inform prevention strategies.

Section 55(4) of the *Public Health Act 2010* requires medical practitioners to provide available information requested by NSW Health concerning their patient's notifiable condition and risk factors for infection.

Upon completion of this form (and questionnaire if you have administered this yourself), please return it to NSW Health by secure fax on 02 xxxx xxxx. If you have any questions or concerns, please contact Dr Christine Selvey (02) 9391 9195 or Christine.Selvey@doh.health.nsw.gov.au .

Thank you for your help in this important matter.

Yours sincerely

Director, Public Health Unit

Please tick the appropriate box below to indicate your choice of questionnaire administration:

- ☐ I have administered the questionnaire and attached it to this fax.
- ☐ I request NSW health to administer the questionnaire to my patient, using contact details:
  - mobile phone number:.....
  - email address:.....
- ☐ It is not appropriate for the above patient to complete the questionnaire in any manner. Do not contact this patient. Please provide reason:.....

Return to NSW Health on fax (02) xxxx xxxx

NSW Ministry of Health
ABN 92 697 899 630
73 Miller St North Sydney NSW 2060
Locked Mail Bag 961 North Sydney NSW 2059
Tel. (02) 9391 9000 Fax. (02) 9391 9101
Website. www.health.nsw.gov.au

ANNEX 4D: Questionnaire Template (Clinician fax version)

CONFIDENTIAL

NSW Health Female Gonorrhoea Enhanced Follow Up Questionnaire

NSW GOVERNMENT Health

SECTION 1: PERSONAL INFORMATION

Please ask your patient the following questions, and tick the appropriate answers.

1. What is your country of birth?
   - ☐ Australia
   - ☐ Overseas
     If your patient was born overseas, what year did they arrive in Australia? .....
   - ☐ Prefer not to say

2. Are you of Aboriginal or Torres Strait Islander origin?
   - ☐ No
   - ☐ Yes, Aboriginal ☐ Yes, Torres Strait Islander ☐ Yes, Aboriginal and Torres Strait Islander
   - ☐ Prefer not to say

3. What gender were you assigned at birth?
   - ☐ Female ☐ Male ☐ Prefer not to say

4. Which of the following best describes your current gender identity?
   - ☐ Woman
   - ☐ Man
   - ☐ Non-binary
   - ☐ Different identify
     If you selected "different identity" please state your identity: .....
   - ☐ Prefer not to say

5. Do you consider yourself to be:
   - ☐ Heterosexual or straight
   - ☐ Gay or lesbian
   - ☐ Bisexual
   - ☐ Queer
   - ☐ Different identity
     If you selected "different identity" please state your identity: .....
   - ☐ Prefer not to say

6. What was the reason you thought you should get tested for a sexually transmitted infection?
   - ☐ I had symptoms
   - ☐ I was undertaking a routine sexually transmitted infection check
   - ☐ The sexually transmitted infection check was offered to me as part of another consultation (eg pap smear, antenatal check-up, contraception consultation, etc)
   - ☐ A sexual partner had an STI
   - ☐ Other
     Please specify the reason you thought you should get tested: .....
   - ☐ Prefer not to say

7. Have you ever been paid for sex in the past year?
   - ☐ Yes
     If yes, please circle: Private, Massage, Street, Brothel, Other
   - ☐ No
   - ☐ Prefer not to say

THIS COMPLETES SECTION 1. PLEASE CONTINUE TO SECTION 2.

SECTION 2: PARTNER INFORMATION

In this section, you will ask your patient about their sexual partners. For a patient who has identified as a sex worker, please ask them to complete this section in reference to their non-paying sexual partners. **Please photocopy and complete a new version of Section 2 for each (maximum 10) sexual partner that your patient had during the 3 months prior to their gonorrhoea diagnosis.**

Please ask your patient the following questions.

1. How many sexual partners did you have in the 3 months prior to your diagnosis:.....

Please ask your patient to answer the following questions in reference to each partner.

2. What is your relationship to this partner?
   ☐ Regular partner ☐ Occasional/casual partner ☐ One-night stand ☐ Other ☐ Prefer not to say

If this partner was a regular partner, please continue to Question 3. If not, please answer Question 2a.

2a. Where did you meet this partner?
   ☐ Dating website. Please specify which dating website.....
   ☐ Dating app. Please specify which dating app.....
   ☐ Through work ☐ Through friends ☐ Bar/nightclub ☐ University/TAFE/Community college etc
   ☐ Travelling ☐ Other ☐ Prefer not to say

3. What is the gender identity of this partner?
   ☐ Male ☐ Female ☐ Other ☐ Prefer not to say ☐ Unknown

4. What do you believe is the sexual orientation of this partner?
   ☐ Heterosexual ☐ Bisexual ☐ Other ☐ Don't know ☐ Prefer not to say

5. Did you have sex with this partner in Australia?
   ☐ Yes ☐ No
   If no, please specify the country where you had sex with this partner.....
   ☐ Prefer not to say

6. Did this partner travel overseas in the three months prior to your diagnosis?
   ☐ Yes ☐ No
   If yes, please specify the country or countries where this partner travelled in the three months prior to your diagnosis.....
   ☐ Unknown ☐ Prefer not to say

7. What is the country of birth of this partner? .....

8. Do you believe that this partner passed gonorrhoea to you?
   ☐ Yes If yes, where do you think they acquired the infection? .....
   ☐ No

9. What sort of sex did you have with this partner?
   ☐ Vaginal intercourse
   Did you use condoms with this partner during vaginal intercourse?
   ☐ Yes ☐ No ☐ Sometimes
   ☐ Anal intercourse
   Did you use condoms with this partner during anal intercourse?
   ☐ Yes ☐ No ☐ Sometimes
   ☐ Giving oral sex
   Did you use condoms with this partner when you gave oral sex?
   ☐ Yes ☐ No ☐ Sometimes
   ☐ Receiving oral sex
   ☐ Kissing
   ☐ Other
   ☐ Prefer not to say

THANK YOU FOR YOUR TIME

May 2018

ANNEX 4E: IUSTI Rapid Fire Oral Presentation

IUSTI ASIA PACIFIC SEXUAL HEALTH CONGRESS 2018

Characteristics of Women with Gonorrhoea in NSW, 2018: a Case Series Investigation

PHELAN S[1 2], FITZGERALD T[3], KALDOR J[1], GUY R[1], DONOVAN B[1], SHEPPEARD V[3], MCANULTY J[3], SELVEY C[3].

[1] *THE KIRBY INSTITUTE, UNIVERSITY OF NEW SOUTH WALES*
[2] *NATIONAL CENTRE FOR EPIDEMIOLOGY & POPULATION HEALTH, RESEARCH SCHOOL OF POPULATION HEALTH, AUSTRALIAN NATIONAL UNIVERSITY*
[3] *HEALTH PROTECTION NSW, NSW HEALTH*

Acknowledgements: Kathryn Glass[2], NSW Public Health Network and study participants

Disclosure of interest statement: None to declare

Join the Conversation @ASHMMEDIA #IUSTIAP18

BACKGROUND/AIMS AND METHODS

- **Background:** Gonorrhoea notification rates increasing across Australia
- **Issue:** Risk factors in women need to be identified. Travel associated sex?
- **Research question:** What are the characteristics of women notified to New South Wales (NSW) Health with gonorrhoea, and their partners?
- **Study design:** Case series
- **Participants:** NSW women aged ≥18 years, for whom a gonorrhoea notification had been made from 21 May to 17 June 2018
- **Method:** Questionnaire. Sex workers reported on non-paying partners only
- **Statistical analysis:** A descriptive analysis was conducted

Join the Conversation @ASHMMEDIA #IUSTIAP18

RESULTS

- **Response rate:** 58% - 68/118 eligible women
- **Personal characteristics:**
  - 31% sex workers, 3% Aboriginal, 63% Australian born and 91% urban residents
  - Median age: 30
  - Routine STI check: 57% sex workers, 13% non-sex workers
  - In 3 months prior to diagnosis, only 3% respondents had sex overseas
- **Partner characteristics:**
  - 84% male, 54% Australian born, 32% non-regular partners, and 10% travelled overseas
  - 76% heterosexual, 6% bisexual, and 3% did not know (missing 15%)
- **Condom use:** was low

Join the Conversation @ASHMMEDIA #IUSTIAP18

CONCLUSION

- **Conclusion:** increase appears to be related to local, heterosexual, condomless transmission
- **Limitations:** incomplete follow up, missing data, no control group
- **Next steps:**
  - Raise awareness and promote regular STI screening among this population
  - A future study with a control group
  - A future study with a qualitative aspect

Chapter 5: Evaluate a surveillance system or other health information system

In search of a denominator: a systematic review of the source and public health utility of data on numbers tested for chlamydia and influenza

"What's an epidemiologist?"

"Someone in search of a denominator".

Contents

5.1 List of abbreviations

APPRISE	Australian Partnership for Preparedness Research on Infectious diSease Emergencies
CDC	Centre for Disease Control
CDNA	Communicable Disease Network Australia
MAE	Master of Applied Epidemiology
NNDS	National Notifiable Diseases System
NAAT	Nucleic acid amplification testing

5.2 Prologue

My role: For my evaluation of a surveillance system, my field placement supervisors suggested I conduct a systematic review on the access and utility of testing denominator data in order to highlight the importance of this resource to communicable disease surveillance systems. I led the systematic review, with support from the Australian Partnership for Preparedness Research on Infectious diSease Emergencies (APPRISE) Centre for Research Excellence (CRE); notably with the APPRISE investigators John Kaldor, Stephen Lambert and Ross Andrews. We narrowed the scope of the review to the examples of two specific infectious diseases of public health importance to Australia, chlamydia and influenza, and kept the review focused on Australian papers only. I was able to present the methodology of this review to the APPRISE Annual General meeting in 2017 and obtain feedback.

I took a different approach to demonstrating my MAE competency with respect to understanding disease surveillance. While MAE students in the past have evaluated a wide range of diseases reported through the National Notifiable Diseases Surveillance System, essentially assessing the Centre for Disease Control and Prevention (CDC) Guidelines against the case count (numerator), I have taken a different approach and assessed an important gap in national surveillance data by investigating the access to and utility of testing denominator data. In this chapter, the systematic review format (structured by the PRISMA and Cochrane guidelines) evaluates the surveillance systems used in 35 peer reviewed papers and ten publicly available reports. This presented a challenge when it came to apply the CDC Guidelines for Evaluating Public Health Surveillance Systems, which are not designed to evaluate surveillance systems in peer reviewed papers. In response to this challenge, I designed a system to score each individual peer reviewed paper against four key CDC surveillance system attributes: representativeness, timeliness, data quality and stability. Due to the systematic review format, the layout of this chapter is slightly different to the previous three chapters: following the prologue, this chapter will consist of the final draft version of the systematic review paper. We intend to submit this paper to the international journal, Eurosurveillance, meeting the MAE requirement of a draft peer reviewed paper. No ethics approvals were required for this project.

Lessons learned: Throughout this project, I learnt about the different types of surveillance systems utilised in Australia, and the pros and cons of each when it comes to accessing and utilising denominator data. Prior to the MAE, I attended a Cochrane Systematic Review workshop as training for a previous systematic review I worked on with the Kirby Institute. Both the systematic nature and ability to synthesize important public health evidence are aspects of systematic reviews that appeal to me, and this MAE project provided another opportunity to apply the skills I learnt at the Cochrane workshop. The detailed search component of this review

strongly instilled in me the importance of record keeping. As this project was the most autonomous and the least urgent of my MAE projects, I constantly re-prioritised other projects of higher urgency above this review. Through this process of dipping in and out of such a detail-intensive project, I learnt the hard way that in situations like this it is essential to leave comprehensive notes to yourself, as I often assumed I could easily jump straight back into the project. Through experiencing the strengths and weaknesses of various reference software packages, I also learnt that it is vital to always conduct due diligence and double check the storage, entry and reference format of peer-reviewed papers in the package yourself. Lastly, while I was reflecting on the bigger picture of this project, I learnt about an interesting paradox known as the "inverse evidence law"[1, 2] in population based research. This paradox refers to the fundamental problem that there is generally the strongest evidence for the least important public health policies, and weaker evidence for the most important ones. I believe the inverse evidence law applies to this project: as while the strengths and weaknesses of using different denominators for interpreting disease rates are well known to epidemiologists, there is limited evidence on this topic. As this is the first systematic review on the importance of testing denominator data, it will be an important resource for public health policy.

Public health impact: This is the first systematic review to investigate the access and use of testing denominator data. While testing denominator data may seem an obvious and important resource for interpreting infectious disease trends, the paucity of literature on this subject makes it difficult for stakeholders in public health to advocate for its necessity, let alone access and utilise it. A key issue found through conducting this review is that an effective system for the reporting of line listed test negative results is not in place. This systematic review will be an important resource going forward in efforts to make testing denominator data for infectious diseases notifiable in Australia, thus ensuring that stakeholders in public health can interpret epidemiological trends based on comprehensive data.

Acknowledgements: Firstly, I would like to acknowledge the second reviewer, Skye McGregor, and co-authors of this systematic review: John Kaldor, Rebecca Guy, Ross Andrews, Stephen Lambert, Ross Andrews. I would also like to acknowledge members of the APPRISE CRE for their feedback. My academic supervisor, Kathryn Glass, was a great support in ensuring that this project met the MAE competencies for a surveillance project. Thanks to MAE alumni Emma Field for sharing her experiences from a similar MAE project of her own. Cheng Siu, Medical Librarian at UNSW Library, was a huge help with the systematic search strategy. Thanks must also go to Gabi Willis, Ximena Tolosa, Patiyan Andersson, Kaitlyn Vette, Ross Andrews, Amy Bright, Callum Thirkell, Cushla Coffey, Jana Sisnowski, Tanyth deGooyer, Nasra Higgins and Peter Markey who were a great help with the grey literature search.

Prologue References:

1. Nutbeam D. 2003. How does evidence influence public health policy? Tackling health inequalities in England. *Health Promotion Journal of Australia*; 143:154-8.
2. Westin S. 2015. Epidemiology and Health Policy: How to avoid becoming prisoners of the proximate. *Norsk Epidemiology* DOI:10.5324/nje.v25i1-2.1888

5.3 In search of a denominator: a systematic review of the source and public health utility of data on numbers tested for chlamydia and influenza

Final draft peer-reviewed paper

Authors: Sophie Phelan, Skye McGregor, Rebecca Guy, Ross M Andrews, Stephen Lambert, John Kaldor

Acknowledgements: APPRISE Centre for Research Excellence, Kathryn Glass, Emma Field

Intended Journal: Eurosurveillance

Abstract

Objective: Review how counts of infectious disease tests (testing denominator data) have been accessed and utilised in disease surveillance in Australia, using the examples of chlamydia and influenza.

Methods: A systematic search of peer reviewed and grey literature was conducted for reports containing chlamydia and influenza testing denominator data. Australian papers that were at the jurisdictional or national level that reported data from more than a single clinic, used a population based sampling scheme, described the occurrence of chlamydia and influenza using positivity rates, and contained laboratory confirmed data on chlamydia or influenza were included. The full text of 74 peer-reviewed papers and 18 reports from jurisdictional websites were examined. All available data were analysed using descriptive methods. In addition, a scoring system using four key surveillance system attributes promulgated in the Centre for Disease Control and Prevention (CDC) Guidelines for Evaluating Public Health Surveillance Systems (timeliness, representativeness, stability and data quality) was designed and applied to peer reviewed papers.

Results: A total of 45 peer-reviewed papers and reports were included in this review: 14 on influenza and 31 on chlamydia. From the peer-reviewed literature search, 35 peer-reviewed papers met the inclusion criteria for this review, including 26 for chlamydia and 9 for influenza. Median study population testing coverage for chlamydia was 29% of the notional target population (range 3.4-84.9%); one influenza paper reported coverage as 61%. The most common source of testing denominator data was existing sentinel surveillance networks (5/9 or 56% influenza papers and 14/25 or 56% chlamydia papers - two chlamydia papers used the same dataset and were treated as one study). For chlamydia papers, the most frequent reason cited by authors to use testing denominator data was to “describe testing practices” (9/26 or 35% papers – the two papers using the same dataset were separated here), and for influenza papers, the most frequent reason was to “estimate disease burden” (6/9 or 67% papers). A search for publicly available reports containing testing denominator data on chlamydia and influenza on the Commonwealth and jurisdictional Department of Health websites found that 5/9 websites had reports containing influenza testing denominator data, and 5/9 websites had reports containing chlamydia testing denominator data. The most common source of testing denominator data from grey literature reports was also existing sentinel surveillance networks (4/5 or 80% of influenza reports and 3/5 or 60% of chlamydia reports). In all grey literature reports, testing denominator data was used to estimate disease burden. For the evaluation of testing denominator data from the peer reviewed papers against the CDC Guidelines, the

median scores for influenza and chlamydia were respectively: 5.0 and 4.0 for timeliness, 3.0 and 5.0 for representativeness, 4.0 and 4.0 for stability, and 3.0 and 5.0 for data quality.

Conclusions and implications for public health: The collection and analysis of testing denominator data for chlamydia and confirmed-influenza has had public health benefits. More systematic use of testing denominator data for these and other infections can significantly improve our ability to control diseases of public health importance.

Introduction

In Australia, the surveillance of communicable diseases at the national level is primarily conducted through aggregation of unit records of case reports in the form of de-identified data provided by the six states and two territories[1]. The jurisdictions are responsible for public health action necessary in response to these notifications. Since 1991, de-identified case notification data for the communicable diseases and disease groups defined on the National Notifiable Disease List have been transmitted to Australia's National Notifiable Diseases System (NNDSS)[1]. Case definitions generally require laboratory evidence of infection. National data on most notifiable conditions are usually reported as counts, or as rates per capita estimated population.

These rates are currently calculated using notifications as the numerator, with the denominator per 100,000 estimated population at a suitably chosen time point in the reporting period (adjusted for Australian Bureau of Statistics population estimates). This method of rate calculation is convenient and efficient. However, the interpretation of disease trends using this approach is biased by the lack of data on the total number of tests performed[2-7].

Notification counts can be influenced by a number of factors besides changes in disease occurrence, particularly for infections that frequently occur without clinical symptoms and are therefore detected by screening. Such factors may include changes in patient health seeking behaviour, testing guidelines (resulting in changed levels of testing), sensitivity of test methods, and surveillance methods (notification practices, case definitions, sources of reporting). The use of population counts as denominators for rates can lead to misleading interpretations of the epidemiology of a disease, and sometimes causes unnecessary alarm. For example, what may look like an outbreak based on increased notification rates per head of population may actually be due to increased testing.

Prevalence and incidence are two common measures used to describe the burden of disease. Prevalence indicates the total disease burden in a population, while incidence indicates the amount of new cases in a population, the latter typically calculated as a frequency count, rate or proportion[8]. Notification rates may also be hybrids of prevalence and incidence, depending on the case definition. For example, the calculation of the global incidence of tuberculosis is complex, and involves a combination of prevalence and incidence data[9]. The ideal way to calculate infection (prevalence/incidence/crude) rates in a population is to screen everyone in the population, or a representative sample. Ideally, this rate calculation would involve the number of notifications as the numerator, and the total population as the denominator – where the total population is tested. However, this approach is not generally feasible as it is very

expensive, resource intensive, and prone to sampling issues including non-response that might be linked to infection status.

In the absence of population level surveys, an alternative approach to the aforementioned ideal one is to keep the same notifications numerator, but to use the total number of diagnostic tests performed as the denominator (hereon referred to as "testing denominator data"). This calculation is also referred to as "positivity". Such rates have the potential advantage of compensating to some extent for variations in testing patterns, but still have methodological limitations as indicators of population prevalence, because of the uncertain representativeness of those tested. Nevertheless, use of testing denominator data may offer a significant and attainable improvement over the current approach, without adding a major resource burden.

While the testing denominator data approach is potentially attractive, it has not been used or promoted widely in disease surveillance, and there have been few publications on its methodological strengths and weaknesses. In order to develop an understanding of when and how the method has been used in public health surveillance, we undertook a systematic review for Australia. Additionally, we evaluated the utility of the approach against four key surveillance system attributes promulgated in the Centre for Disease Control and Prevention (CDC) Guidelines for Evaluating Public Health Surveillance Systems (referred to here onwards as "CDC Guidelines")[10]. These four key system attributes were timeliness, representativeness, stability and data quality. This systematic review of the use of testing denominator data is intended to support consideration of how such data can be made more useful and accessible for disease control.

Methods

Included diseases

The infections chlamydia and influenza were chosen for several reasons. Firstly, they are the two most frequently notified diseases nationally for the past 5 years[11]. Secondly, they provide a contrast in that chlamydia analyses focus on long-term trends, while influenza is generally viewed from an outbreak or seasonal perspective. Thirdly, both infections can occur with limited symptoms, or symptoms that could be due to a range of other infections, so case detection is strongly dependant on screening, with substantial potential for misinterpretation of notification data.

C*hlamydia – the infection*

Chlamydia is a sexually transmitted infection caused by the bacterium *Chlamydia trachomatis*[12]*.* The disease often presents asymptomatically, especially in females. In symptomatic males, chlamydia most often presents as urethritis, and in females cervicitis. Both of these syndromes may also be due to other bacterial infections such as gonorrhoea. Untreated chlamydia in females can lead to pelvic inflammatory disease and pregnancy complications, and it is associated with an increased risk of HIV infection[12].

Chlamydia – testing and notification guidelines

The Australian STI management guidelines[13] recommend chlamydia testing for a number of groups because of their increased risk of chlamydial infection. These groups include people: under 30 years and sexually active, with a partner change in the last 12 months, who had an STI in the past 12 months, who have a sexual partner with an STI, who are at increased risk of complications of an STI e.g. termination of pregnancy or intrauterine device insertion, who have signs or symptoms suggestive of chlamydia, or who request a sexual health check. Depending on the patient's sexual history and specimen preference, a swab (ano-rectal, pharyngeal, endocervical, or vaginal) or a first pass urine sample is collected and sent for laboratory nucleic acid amplification testing (NAAT). The Communicable Disease Network Australia (CDNA) Guidelines dictate that only confirmed chlamydia cases are notifiable (CDNA 2013). A confirmed chlamydia notification requires laboratory definitive evidence only, through either: isolation of *C. trachomatis*, detection of *C. trachomatis* through NAAT, or detection of *C. trachomatis* antigen[14].

Influenza – the virus

Influenza is an acute virus of the respiratory tract, transmitted by aerosol droplets or contact with an infected person[15]. There are three recognised types of influenza: A, B and C. Within

these types exist a number of ever evolving subtypes and distinct lineages which can cause seasonal or sporadic outbreaks. Influenza is characterised by fever, cough, headaches, myalgia, prostration, coryza and/or a sore throat. Influenza infection can lead to lower respiratory tract complications, and increased risk of death in people aged over 65. Again, these symptoms may arise due to a number of other viral infections.

Influenza – testing and notification guidelines

While there are no national guidelines for influenza laboratory testing in Australia, there are four general practice sentinel surveillance systems (three state based and one national) that collect throat or nasal swab samples for laboratory testing from a proportion of patients presenting with influenza like illness at the discretion of the clinician[16]. These are: the Australian Sentinel Practices Research Network (ASPREN); the Sentinel Practitioners Network of Western Australia (SPN(WA)), the Victorian Sentinel Practice Influenza Network (VicSPIN), and the New South Wales Electronic General Practice Surveillance (eGPS).

The CDNA Guidelines require that only laboratory confirmed influenza infections are notifiable[17]; it is recognised that only a small proportion of potential cases are tested[18]. Confirmed cases of influenza require laboratory definitive evidence only, which include any of the following: isolation of influenza virus by culture from appropriate respiratory tract specimen, detection of influenza virus by nucleic acid testing from appropriate respiratory tract specimen, laboratory detection of influenza virus antigen from appropriate respiratory tract specimen, IgG seroconversion or a significant increase in antibody level or a fourfold or greater rise in titre to influenza virus, or single high titre by CFT or HAI to influenza virus.

Search strategy

We used the PRISMA statement for preferred reporting of systematic reviews and meta-analyses[19] and the Cochrane Collaboration Handbook on Systematic Reviews of Health Promotion and Public Health Interventions[20] to guide the protocol, search and reporting of this review. Our search strategy comprised two steps: a search of the peer reviewed literature followed by a grey literature search.

A search of the peer-reviewed literature included the two electronic databases, Medline and Embase, was designed with the assistance of the UNSW Medical Librarian. Both databases were searched through the UNSW Ovid platform using the MeSH heading functionality, and a keyword search was also used in Medline. Synonyms for the following terms were joined using the Boolean operators AND/OR as follows: “denominator data” AND “Australia” AND “chlamydia OR influenza”. The specific terms used in these search strings can be found in Annex 5A. The search was limited to papers published from 1st January 2008-13th July 2018 to ensure

we captured the most up to date articles that have been informed by previous research and were from an era of consistent testing technologies.

The grey literature was also searched for reports of the use of testing denominator data by the jurisdictional and national government departments of health in Australia. One study team member (SP) searched nine web sites (one from each of the eight Australian jurisdictions: Northern Territory, Queensland, New South Wales, Australian Capital Territory, Victoria, Tasmania, South Australian, Western Australia, and one from the Commonwealth) for their most recent publicly available report containing testing denominator data for chlamydia or influenza in the review period. If no report could be found, SP liaised with contacts at jurisdictions to confirm their findings. For instances where more than one report was available on each website, only the latest one within the study period (1st January 2008-13th July 2018) was included.

Eligibility criteria

The titles and abstracts of the peer reviewed articles were screened independently by two authors (SP and SM). To be eligible, articles needed to:

a) Be at the Australian jurisdictional or national level
b) Report data from more than a single clinic setting
c) Use a population based sampling scheme
d) Describe the occurrence of chlamydia or influenza using positivity rates
e) Contain laboratory confirmed data on chlamydia or influenza.

Studies that met the above criteria were included, with no minimum sample size specified.

Quality assessment

A quality assessment tool was developed based on the GRADE criteria[21], the Joanna Briggs Institute critical appraisal tools[22], and our study objectives (see Annex 5B). Two authors (SP and SM) completed the quality assessment for all included studies.

Data extraction

Data independently were extracted from reports that met inclusion criteria by SP and SM using a predefined data extraction tool, which was piloted with 2 papers (one chlamydia paper[4] and one influenza paper[24]) to ensure ease of use and that all pertinent data items were included. Results were compared and resolved between the two reviewers.

The following variables were extracted from each peer reviewed publication: Study ID (First author surname, year of publication), time period of data collection, setting, study population

testing coverage (proportion of study population tested), source of testing denominator data, stratifications of data (Indigenous status, age, sex and other e.g. risk factors), and use of testing denominator data in the study. We did not assess or compare the study outcomes as such, but focused on the study methodology. Multiple studies using the same dataset were treated as one study for all analyses except those regarding use of testing denominator data, where we treated multiple studies using the same dataset as individual studies.

The following variables were extracted from each report found in the grey literature and managed in a separate database: jurisdiction, source of testing denominator data available, title of report, time period of data collection, source of testing denominator data in report, and frequency of the report.

In order to classify the source of surveillance data within the paper or online report for the variable "source of testing denominator data", SP and SM applied the definitions in Table 1 below to the testing denominator data in the papers and reports. The definitions in Table 1 have been adapted from definitions in surveillance literature[8, 24].

Table 1: Sources of denominator data

Type of testing denominator data	*Source of testing denominator data*	*Definition*
Sentinel surveillance data (numerator and denominator data from the same source)	Existing sentinel surveillance networks	One or more formal reporting units, each of which is made up of a facility that has responsibility for some aspect of testing for one or more specific infectious diseases. Reporting units can include laboratory or clinical facilities.
	Ad hoc sentinel surveillance networks	Infectious disease data routinely collected and recorded by individual clinics that are not part of formal public health surveillance mechanisms. Data accessed and analysed on an ad hoc basis.
Laboratory testing data (denominator) (numerator and denominator from different sources)	Laboratory data collected in bulk from laboratories and analysed without linking to specific notifications	Infectious disease testing data routinely collected and recorded by individual laboratories that are not mandatory to report to public health authorities.
	Lab data collected and linked to individual notifications data	Formal data linkage of separate datasets using common identifiers (in this instance lab data and notifications data). Enhances bulk lab data by providing further information on reasons for testing and the facility at which testing was undertaken.

In order to describe the use of testing denominator data within selected papers for the variable "use of testing denominator data", SP and SM classified the paper into one or more of the

following five categories below based on the objectives of the paper and specific reason for using testing denominator data:

- Describe testing practices,
- Demonstrate use of positivity in disease surveillance,
- Identify risk factors,
- Estimate disease burden; or
- Describe another epidemiological relationship.

Data management

- Search results were managed in a library in Endnote X8, and data were extracted into Microsoft Excel 2018 v16.2.1 for analysis.

Data analysis

Graphs

Graphs were created using Microsoft Excel 2018 v16.2.1 to visually summarise the source and use of testing denominator data for chlamydia and influenza reports.

Study population testing coverage

Study population testing coverage is the proportion of the study population which is tested. This provides an indication of testing practices, and also shows how representative the data are. This measure was extracted from all studies that reported it, and the median was calculated by disease in Microsoft Excel 2018 v16.2.1.

Evaluation of peer-reviewed articles based on CDC Guidelines for Evaluating Public Health Surveillance Systems.

Peer-reviewed articles were subjected to an evaluation by two authors (SP and SM) against four key surveillance system attributes from the CDC Guidelines[10] (Table 2): data quality, timeliness, stability and representativeness. The authors developed guidelines to score included reports against the aforementioned criteria for quality (Table 3).

Table 2: Definitions of CDC surveillance system attributes assessed in this review

CDC surveillance system attribute[10]	Definition
Data quality	Data quality reflects the completeness and validity of the data recorded in the public health surveillance system.
Timeliness	Timeliness reflects the speed between steps in a public health surveillance system.
Stability	Stability refers to the reliability (i.e., the ability to collect, manage, and provide data properly without failure) and availability (the ability to be operational when it is needed) of the public health surveillance system.
Representativeness	A public health surveillance system that is representative accurately describes the occurrence of a health-related event over time and its distribution in the population by place and person.

For the scoring system designed for this study, all studies started with 5 points for each CDC surveillance system attribute. Points were then deducted if the study used methods prone to bias for each attribute, which were assessed using selected extracted study variables separately by SP and SM. Any disagreement was resolved through discussion. Variables extracted for this

review that are assessed against the CDC surveillance system attributes are highlighted red in the table below (Table 3).

Table 3: Scoring system used to evaluate CDC surveillance system attributes for included studies

CDC surveillance system attribute	Study method assessed	Scoring criteria	Deduction
Representativeness	Study period. (Does study period (Time period of data collection) cover sufficient seasonality of disease?)	Less than one year for chlamydia, less than one pandemic/flu season for flu	3
		One year for chlamydia, one pandemic/flu season for flu	2
		Two years for chlamydia, two pandemic/flu seasons for flu	1
		More than two years for chlamydia, more than two pandemic/flu seasons for flu	0
	Sample size	Insufficient sample size (numerator of Crude population coverage <1000 people); or Sample size missing (numerator of Crude population coverage)	1
Stability	Source of testing denominator data	Existing sentinel surveillance networks (Source)	1
		Laboratory data collected in bulk (Source)	2
		Ad hoc sentinel surveillance networks (Source)	3
		Linked laboratory data (Source)	4
Timeliness	Last year of study Data collection period within:	Same year as publication (= 1 year) to year before publication (= 2 years) (Study ID)	0
		3-4 years of publication	1
		5-6 years of publication	2
		7-8 years of publication	3
		9-10 years of publication	4
Data quality		No denominator of Crude population coverage	2
		Does not stratify positivity (Stratifications of positivity) by at least one variable	2

Results

Peer-reviewed and grey literature results

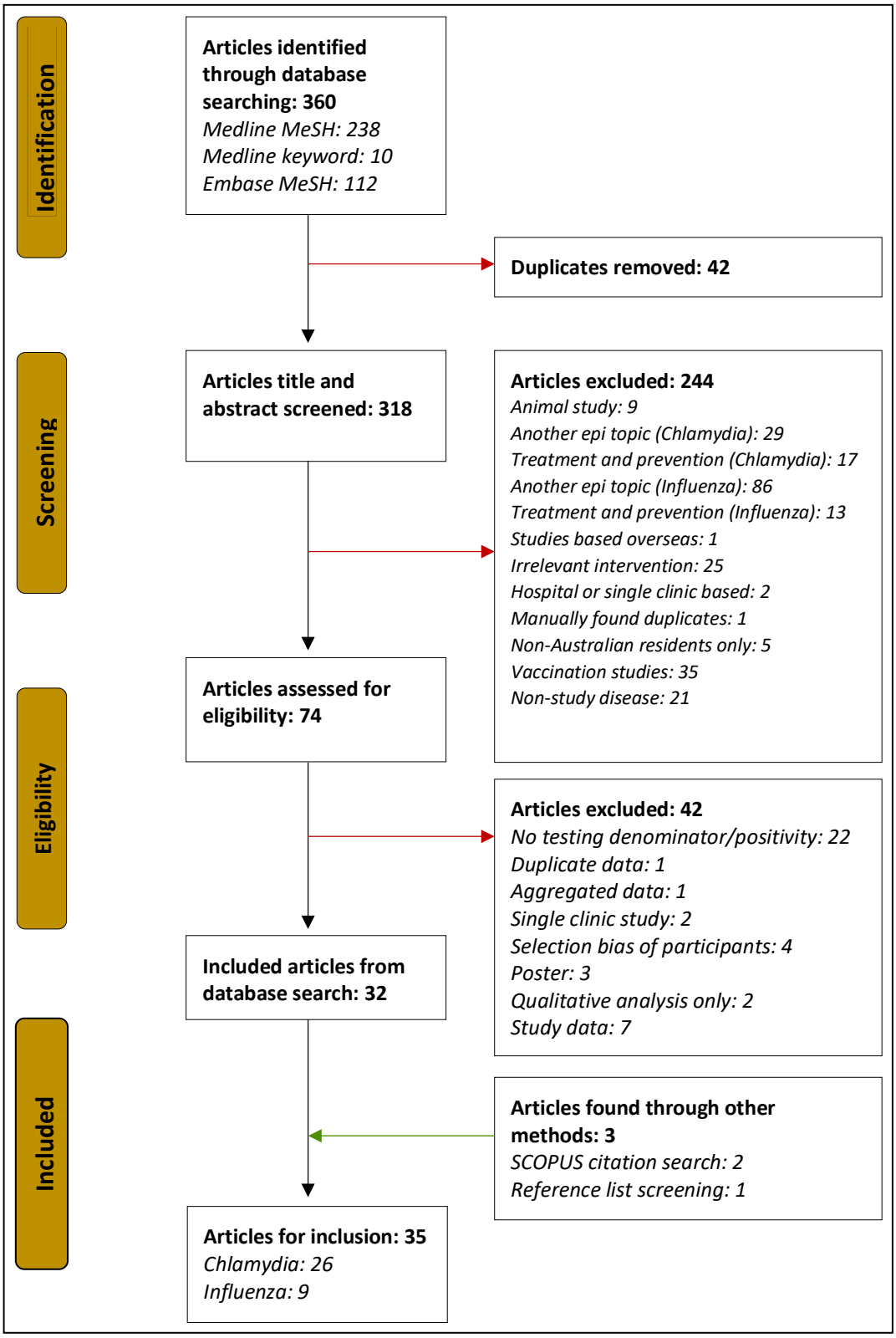
The database search returned 360 papers (see Figure 1). After 42 duplicates were removed, the titles and abstracts of 318 papers were screened. After 244 papers were excluded, the full text of 74 papers was examined. Following a full text review, a further 42 papers were excluded, leaving 32 papers to include in the review. A SCOPUS citation search of the included papers returned two relevant papers, and a reference list screening returned one further relevant paper. This resulted in 35 papers for final inclusion: 26 papers on chlamydia (74%) and 9 on influenza (26%).

The grey literature search of nine websites returned eight reports: four on influenza and four on chlamydia. Contacting jurisdictions yielded two more reports, bringing the total of non-peer reviewed reports to ten: five on influenza (50%) and four on chlamydia (50%). Detailed tables of data extraction can be found in Annex 5C, separately for peer reviewed articles (Annex 5C, Table 1 and 2) and grey literature reports (Annex 5C, Table 3).

Population testing coverage was not provided in grey literature reports. Less than half of the peer reviewed papers included the proportion of the population tested. The median population testing coverage for the 12/26 chlamydia peer reviewed papers that measured testing coverage was 29% (range 3.4-84.9%). Only one out of the nine peer reviewed papers on influenza reported testing coverage, and this was 61%.

Grey literature reports presented data on jurisdictional rates of chlamydia and influenza (Annex 5C, Table 3). In total, 5/9 websites had reports containing influenza testing denominator data, and 5/9 websites had reports containing chlamydia testing denominator data. Only the Commonwealth Department of Health website and the Department of Health websites of two states (WA and NSW) published reports online containing testing denominator data for both chlamydia and influenza.

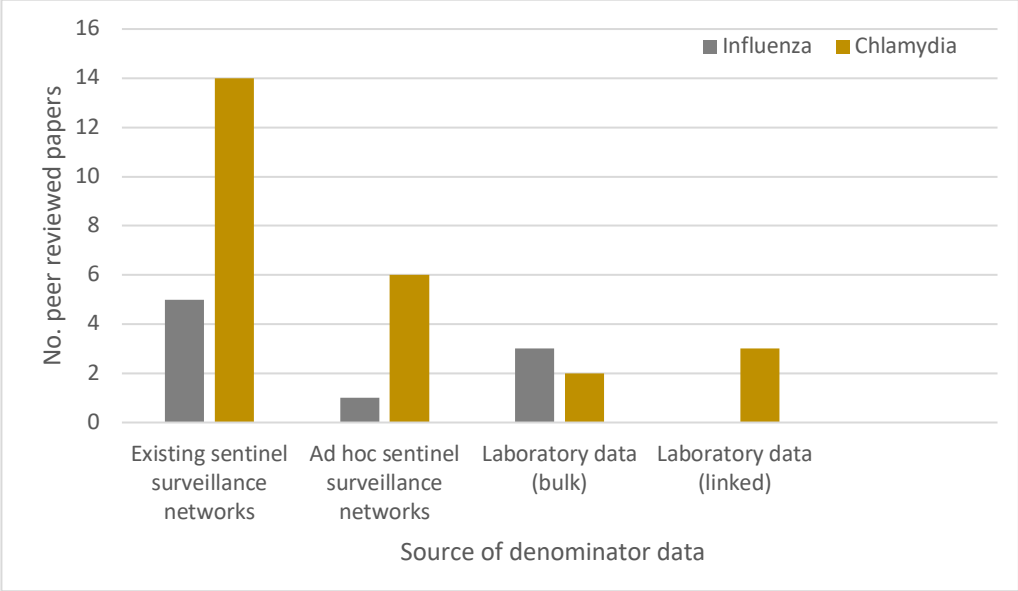
Figure 1: PRISMA flow diagram summarizing the systematic search used to identify peer-reviewed articles.



Source of testing denominator data

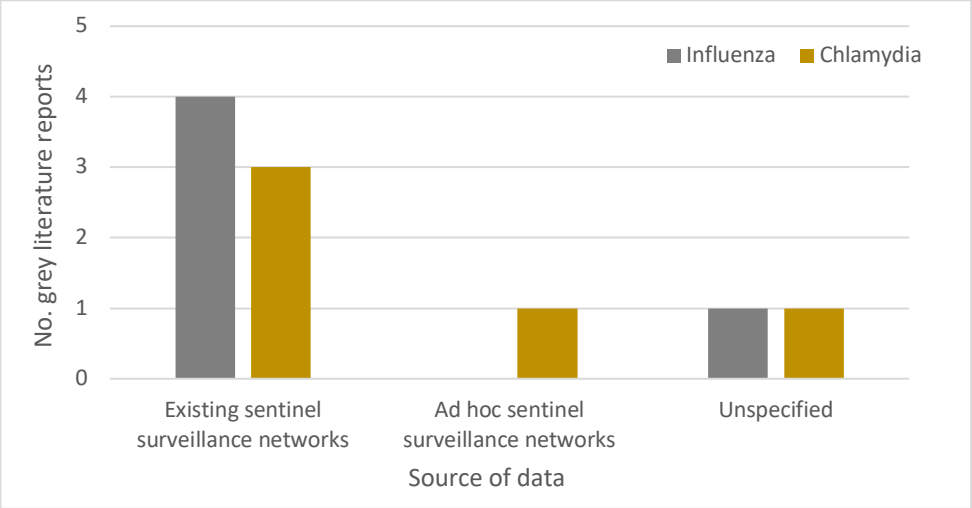
Two chlamydia peer reviewed papers[25, 26] used the same dataset, and were thus treated as one paper for the below analysis regarding source of testing denominator data. In peer reviewed papers, the most common source of testing denominator data was existing sentinel surveillance networks (5/9 or 56% influenza papers and 14/25 or 56% chlamydia papers) (Figure 2a). For chlamydia, ad hoc sentinel surveillance networks were the second most common source of testing denominator data (6/25 or 24% of papers), with the least common data source being laboratory data collected in bulk (2/25 or 8% of papers). For influenza, laboratory data collected in bulk was the second most common data source (3/9 or 33% of papers), with the least common data source being ad hoc sentinel surveillance networks (1/9 or 11% of papers). Linked laboratory data was only a source of testing denominator data for chlamydia papers (2/25 or 8% of papers).

Figure 2a: Sources of testing denominator data in peer reviewed papers



Within the grey literature, the most common source of testing denominator data was existing sentinel surveillance networks (4/5 or 80% of influenza reports and 3/5 or 60% of chlamydia reports) (Figure 2b). Two reports (2/10 or 20%) did not specify the source of testing denominator data (one influenza report and one chlamydia report), while one paper sourced testing denominator data through ad hoc sentinel surveillance networks (1/10 or 10% total reports, and 2/5 or 20% of chlamydia reports).

Figure 2b: Sources of testing denominator data in grey literature

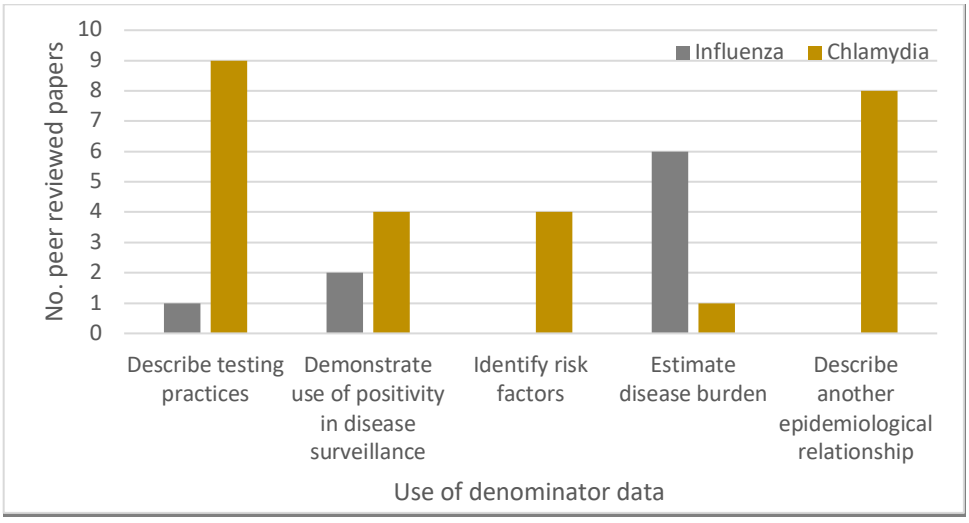


Use of testing denominator data

For chlamydia papers, the most frequent reason for using testing denominator data was to "describe testing practices" (9/26 or 35% papers) (Figure 3). This was followed by to "describe another epidemiological relationship" (8/26 or 31% papers), equally followed by to "identify risk factors" and to "demonstrate use of positivity in disease surveillance" (each 4/26 or 15% papers). To "estimate disease burden" was the least most frequent use of chlamydia testing denominator data (1/26 or 4%).

For influenza papers, the most frequent reason for using testing denominator data was to "estimate disease burden" (6/9 or 67% papers). This was followed by to "demonstrate use of positivity in disease surveillance" (2/9 or 22% papers), with to "describe testing practices" the least most frequent use of influenza testing denominator data (1/9 or 11% papers). In all grey literature reports, testing denominator data was used to estimate disease burden.

Figure 3: Use of testing denominator data in peer-reviewed papers



Scoring of papers against CDC surveillance system attributes

Only peer reviewed papers were scored against the CDC surveillance system attributes. Among the peer reviewed influenza papers, a median score of 5.0 was given for timeliness, a median score of 4.0 was given for stability, and a median score of 3.0 was given for data quality and representativeness (Table 4a). Overall, only 2/9 (22%) of influenza papers received an individual median score of 4.0 for all attributes, while the other 7/9 (78%) of papers received a median score between 2.5 and 3.5.

*Table 4a: Summary of author scores for the testing denominator data surveillance systems in included **influenza** peer-reviewed articles against key surveillance system attributes*

Article ID	Data quality	Representativeness	Timeliness	Stability	**Median score**
Cowie 2017[23]	3	5	4	4	4.0
Dawood 2010[27]	1	3	5	3	3.0
Dawson 2016[5]	3	2	4	4	3.5
Dowse 2011[28]	3	3	4	3	3.0
Fielding 2009[29]	1	2	5	4	3.0
Kelly 2009[30]	3	2	5	4	3.5
Kelly 2009[31]	3	2	5	2	2.5
Kelly 2013[32]	1	4	5	4	4.0
Lambert 2010[2]	3	4	4	3	3.5
Median score	3.0	3.0	5.0	4.0	NA

Two chlamydia peer reviewed papers[25, 26] used the same dataset, and were thus treated as one paper for the below scoring against key surveillance system attributes. Among the peer reviewed influenza papers, a high median score of 5.0 was received for data quality and representativeness, and a median score of 4.0 was received for timeliness and stability (Table 4b). Overall, just over a third of chlamydia papers had a median score of 4.5 (9/25 or 36% of papers) for all attributes, while the other papers had a median score between 2.5 and 4.0 for all attributes (16/25 or 64% of papers).

*Table 4b: Summary of author scores for the testing denominator data surveillance systems in included **chlamydia** peer-reviewed articles against key surveillance system attributes*

Article ID	Data quality	Representativeness	Timeliness	Stability	Median score
Ali 2012[4]	5	5	4	4	4.5
Bowring 2012[33]	5	5	4	4	4.5
Bowring 2013[34]	5	5	3	4	4.5
Dimech 2014[35]	3	5	3	4	3.5
Forrest 2009[36]	5	5	4	2	4.5
Franklin 2010[37]	5	5	4	2	4.5
Garton 2016[38]	3	5	4	2	3.5
Goller 2012[39]	5	5	4	4	4.5
Guy 2010[40]	5	4	4	4	4.0
Guy 2011[41]	5	5	4	4	4.5
Guy 2011[42]	5	5	4	4	4.5
Lim 2012[43]	3	5	4	1	3.5
Lim 2014[44]	3	5	4	4	4.0
O'Connor 2014[45]	5	5	4	4	4.5
Reekie 2017[46]	5	5	3	1	4.0
Reekie 2018[47]	5	4	3	1	3.5
Silver 2015[48]	3	5	3	2	3.0
Silver 2016[49]	3	5	2	2	2.5
Stephens 2015[50]	3	5	3	3	3.0
Stephens 2017[25], Stephens 2017[26]	4	5	3	3	3.5
Su 2008[51]	3	4	4	2	3.5
Ward 2014[52]	5	4	3	4	4.0
Weaver 2017[53]	3	5	3	4	3.5
Wilkinson 2012[54]	3	5	4	4	4.0
Wilkinson 2017[55]	3	5	4	4	4.0
Median score	5.0	5.0	4.0	4.0	NA

Discussion

Chlamydia and influenza have consistently been the top two notified diseases in Australia for the past five years. It is of public health importance to comprehensively understand fluctuations in these disease rates. We reviewed 46 publications (67% of which were on chlamydia) in an attempt to support consideration of how such data can be made more useful and accessible for infectious disease control. Testing denominator data are a major gap in infectious disease surveillance in Australia. While it is not the perfect surveillance tool, routine ascertainment of testing denominator data would be a substantial improvement, less subject to bias, than the current approach of counting only positive results.

Our results show that existing sentinel surveillance networks, which provide numerator and denominator data from the same source, were the most common source of testing denominator data for chlamydia and influenza peer reviewed papers and grey literature reports. The most frequent reason for using testing denominator data for chlamydia peer reviewed papers was to describe testing practices, and for influenza peer reviewed papers the most frequent reason for using denominator data was to estimate disease burden. In all grey literature reports, testing denominator data was used to estimate disease burden. Applying the scoring system that we created using the CDC surveillance system attributes, influenza papers prioritized timeliness and stability, while chlamydia papers prioritized representativeness and data quality. However, it is likely that some influenza papers prioritised timeliness over data quality as they were written during the 2009 pandemic, and were therefore more concerned with timely international sharing of data.

Less than half of all 35 of the included peer reviewed papers reported study population testing coverage (that is, the proportion of the study population who were tested). The median population testing coverage of chlamydia was 29%, and only one influenza paper reported testing coverage. While we have only crudely compared this measure across studies, it still provides a general indication of testing practices and representativeness of the data.

The generalisability of this review is limited because we only looked at two diseases of public health importance in Australia. Internationally, other countries are also making use of testing denominator data in the same way. The UK has recently begun to report chlamydia positivity rates with testing denominator data[56] at the national level. As summarised by Lambert 2010[2] (included in this review), sentinel surveillance systems for influenza have been implemented by the United Kingdom's Health Protection Agency[57] and the European Influenza Surveillance Network[58]. Testing denominator data collected from sentinel surveillance systems have also

been utilised to examine influenza vaccine effectiveness in the United States[59], and to define periods of peak influenza activity in Canada[60].

Another limitation was the grading of the included testing denominator data against the CDC surveillance system attributes. The method that we designed was unvalidated and relied on variables extracted for this review only. In addition, the CDC Guidelines were originally designed as a series of tasks and related activities to be applied to public health surveillance systems in real time to assess key surveillance attributes. It was therefore challenging to adapt them to evaluate a surveillance system based on the content of a peer reviewed paper or report. For example, an important measure of timeliness with regard to testing data is how quickly it can be received by public health authorities. If a public health unit is trying to track increases of disease in real time, they will need to know if the percentage positive is going up in real time also (or as close to real time as possible). In our criteria, the scoring of timeliness relies on how quickly the data were published. The detailed information that would be needed to evaluate the testing denominator data against the five other CDC surveillance system attributes was not available in the peer reviewed papers. However, the method we designed still offers valuable general descriptors of the surveillance systems for the purposes of this paper.

In order to make testing denominator data on chlamydia and influenza more relevant in the interpretation of time trends and other patterns of disease for stakeholders in disease surveillance in Australia, data collection systems need to be strengthened in various ways. The most important of these is timeliness – these data need to be available to disease surveillance authorities at the same time that positive notifications are available. In order to do this in the most cost effective and timely way, a method that is as minimally resource draining on laboratories and public health units as possible needs to be devised to ensure a sustainable data source.

Currently, all negative test results are already recorded into laboratory databases. What remains is to support the transfer of this data to public health authorities. As the workload for laboratories is highly seasonal for influenza, methods to reduce the workload could include the option of delayed notifiability of negative results for laboratories that lack the resources to update their system with testing denominator data concurrently with positive notifications, or a limitation of the initial data request to a number of larger laboratories with the capacity to fulfil it[2]. In addition, a pilot programme could be conducted in a smaller area on either chlamydia or influenza testing denominator data, for example a local health district, to gain further understanding of the resources and time needed to implement the notification of testing denominator data at a larger scale. While there would be an initial delay in the arrangement of appropriate logistics, the end result of eased access to testing denominator data would ensure

the end goal of a more robust and comprehensive system for the surveillance of chlamydia and/or influenza.

There are two key caveats to consider in the interpretation of testing denominator data. The first is a limitation that exists for all data on notifiable diseases in Australia - there are still large disparities in data collection methods, testing practices and case definitions between the six states and two territories[61]. Secondly, a method for accounting for repeat testing in the same individual within the surveillance period would need to be implemented. The results from the second post treatment test for chlamydia positive patients would need to be entered into data collection systems in a way that does not include them in the testing denominator data. Additionally, persons presenting over several occasions for chlamydia screening tests over the year would need to be accounted for so as not to overestimate population prevalence[50]. Use of a personal identifier code could assist in this.

Considering this, we propose that the collection of testing denominator data allows a practical medium for interpreting disease trends, subject to testing denominator data being made available to public health authorities using timely and cost efficient methods. It would be beneficial for the test negative results to be broken down by the same variables that are provided with a positive notification (sex, age, date of test, laboratory method etc), as well as reason for test in order to understand testing practices. It would also be helpful if testing denominator data from both private (Medicare funded) and public laboratory data were sourced to minimise bias in relation to socioeconomic status and location[6]. With the right support, this would be relatively simple and could be introduced rapidly. In future, the collection of testing denominator data on other notifiable diseases in Australia that have a case definition which requires laboratory evidence would be beneficial to consider.

In conclusion, this review has identified gaps in the literature with regard to the reporting of testing denominator data for two key diseases of public health importance. Testing denominator data for surveillance of chlamydia and influenza provide the resources to account for variations in testing practices within disease trends, which is vital as testing practices vary considerably within jurisdictions and surveillance systems for each of these diseases. We propose that the collection of testing denominator data for chlamydia and confirmed-influenza will significantly improve our understanding of the epidemiological trends of these diseases of public health importance in Australia. A uniform, national sentinel surveillance system for chlamydia and influenza is something that could be developed with relative ease, and provide important data to comprehensively understand fluctuations in these disease rates.

References

1. Australian Government Department of Health. 2015. Introduction to the National Notifiable Diseases Surveillance System. Accessed on 12th December 2018 from http://www.health.gov.au/internet/main/Publishing.nsf/Content/cda-surveil-nndss-nndssintro.html
2. Lambert S, Faux C, Grant K et al. 2010. Influenza surveillance in Australia: We need to do more than count. *Medical Journal of Australia* 193(1):43-45.
3. Ali H, Donovan B, Liu B et al. Chlamydia prevention indicators for Australia: review of the evidence from New South Wales. *Sexual Health* 2012; 9:399–406. doi:10.1071/SH11183.
4. Ali H, Guy R, Fairley C et al. 2012. Understanding trends in genital Chlamydia trachomatis can benefit from enhanced surveillance: findings from Australia.[Erratum appears in Sex Transm Infect. 2013 May;89(3):e1]. *Sexually Transmitted Infections* 88(7):552-557.
5. Dawson G, Gilmour R, Tobin S et al. 2016. Strengthening public health systems: assessing the attributes of the NSW influenza surveillance system. *Public Health Research and Practice*. 15;26(2) pii: 2621621.
6. Cretikos M, Mayne D, Reynolds R et al. 2014. Testing-adjusted chlamydia notification trends in New South Wales, Australia, 2000-2010. *Western Pacific Surveillance Response Journal*. 14;5(3):7-17.
7. Schmutz C, Burki D, Frei R et al. 2013. Testing for Chlamydia trachomatis: time trends in positivity rates in the canton of Basel-Stadt, Switzerland. Epidemiology and Infection 141:1953–64. doi:10.1017/S0950268812002567.
8. Porta M. 2014. A Dictionary of Epidemiology. Sixth Edition. *Oxford University Press*, New York, USA.
9. Glaziou P, Sismanidis C, Pretorius C et al. 2015. Methods used by WHO to estimate the global burden of TB disease. Accessed on 10th February 2018, from https://arxiv.org/ftp/arxiv/papers/1603/1603.00278.pdf
10. Centres for Disease Control (CDC) and Prevention. 2001. Updated Guidelines for Evaluating Public Health Surveillance Systems. Morbidity and Mortality Weekly Report. 50(RR13);1-35.
11. Australian Government Department of Health. 2019. National Notifiable Diseases Surveillance System. Notifications for all diseases by State & Territory and year. Accessed on 21st Jan 2019 from: http://www9.health.gov.au/cda/source/rpt_2_sel.cfm, (using national notification rates per 100,000 population (2014-2018)).

12. Gorwitz R, Torrone E. 2015. Chlamydial Infections; in; Control of Communicable Diseases Manual. 20th Edition. Ed: Heymann D.
13. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine. 2018. Australian STI Management Guidelines for use in primary care – Chlamydia. Accessed on 20th Jan 2019, from http://www.sti.guidelines.org.au/sexually-transmissible-infections/chlamydia
14. Communicable Diseases Network Australia (CDNA). 2013. Chlamydial infection case definition. Accessed on 21st Jan 2019, from http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_chlmyd.htm
15. Bridges C, Mounts A, Besselaar T et al. 2015. Influenza; in; Control of Communicable Diseases Manual. 20th Edition. Ed: Heymann D.
16. Sullivan S, Pennington K, Raupach J et al. 2016. A Summary of Influenza Surveillance Systems in Australia 2015. Accessed on 21st Jan 2019, from http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/$File/Influenza-Surveillance-Systems-Paper.pdf.
17. Communicable Diseases Network Australia (CDNA). 2008. Influenza laboratory-confirmed case definition. Accessed on 21st Jan 2019, from http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_flu.htm
18. Reed C, Chaves S, Daily Kirley P et al. 2015. Estimating influenza disease burden from population-based surveillance data in the United States. PLoS One. 2015;10(3):e0118369
19. Moher D, Liberati A, Tetzlaff J et al. 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *British Medical Journal* 339:b2535, doi: 10.1136/bmj.b2535
20. Armstrong R, Waters E, Jackson N et al. Guidelines for Systematic reviews of health promotion and public health interventions. Version 2. Melbourne University: Australia. October 2007.
21. Ryan R, Hill S. 2016. How to GRADE the quality of the evidence. Cochrane Consumers and Communication Group. Version 3.0 December 2016. Accessed on 31st January 2018 from http://cccrg.cochrane.org/author-resources
22. Joanna Briggs Institute. The University of Adelaide. Critical Appraisal Tools. Accessed on 19 February 2018, from http://joannabriggs.org/research/critical-appraisal-tools.html.

23. Cowie G, Cowie B, Fielding J. 2017. Influenza Testing trends in sentinel surveillance general practices in Victoria 2007-2014. *Communicable Disease Intelligence* 41(1):E4-E9.
24. Choi B. 2012. The Past, Present and Future of Public Health Surveillance. *Scientifica* vol. 2012, Article ID 875253.
25. Stephens N, Coleman D, Shaw K et al. 2017. Chlamydia retesting and retest positivity rates: results from a state-wide laboratory data linkage study in Tasmania, 2012-13. *Sexual Health* 14(3):261-267.
26. Stephens N, Coleman D, Shaw K et al 2017. Testing for chlamydial infection: Are we meeting clinical guidelines? Evidence from a state-level laboratory data linkage analysis for 15-to 29-year-olds. *Sexual Health* 14(6):507-513.
27. Dawood F, Hope K, Durrheim D et al. 2010. Estimating the Disease Burden of Pandemic (H1N1) 2009 Virus Infection in Hunter New England, Northern New South Wales, Australia 2009. *PLoS ONE* 5(3).
28. Dowse G, Smith D, Kelly H et al. 2011. Incidence of pandemic (H1N1) 2009 influenza infection in children and pregnant women during the 2009 influenza season in Western Australia - a seroprevalence study. *Medical Journal of Australia* 194(2):68-72.
29. Fielding J, Higgins N, Gregory J et al. 2009. Pandemic H1N1 influenza surveillance in Victoria, Australia, April - September, 2009. *Eurosurveillance* 14(42).
30. Kelly H, Carville K, Grant K et al. 2009. Estimation of Influenza Vaccine Effectiveness from Routine Surveillance Data. *PLoS ONE* 4(3):e5079.
31. Kelly H, Grant K. 2009. Interim analysis of pandemic influenza (H1N1) 2009 in Australia: surveillance trends, age of infection and effectiveness of seasonal vaccination. *Eurosurveillance* 14(31).
32. Kelly H, Grant K, Tay E et al .2013. The significance of increased influenza notifications during spring and summer of 2010-2011 in Australia. *Influenza and Other Respiratory Viruses* 7(6):1136-1141.
33. Bowring A, Gouillou M, Guy R et al. 2012. Missed opportunities - Low levels of chlamydia retesting at Australian general practices, 2008-2009. *Sexually Transmitted Infections* 88(5):330-334.
34. Bowring A, Goller J, Gouillou M et al. 2013. Chlamydia testing and retesting patterns at family planning clinics in Australia. *Sexual Health* 10(1):74-81.
35. Dimech W, Lim M, Van Gemert C et al. 2014. Analysis of laboratory testing results collected in an enhanced chlamydia surveillance system in Australia, 2008-2010. *BMC Infectious Diseases* 14: 325.

36. Forrest G, Boonwaat L, Douglas J et al. 2009. Enhanced chlamydia surveillance in New South Wales (Australia) prisons, 2005-2007. *International Journal of Prison Health* 5(4):233-240.

37. Franklin N, O'Connor C, Shaw M et al 2010. Chlamydia at an inner metropolitan sexual health service in Sydney, NSW: Australian Collaboration for Chlamydia Enhanced Sentinel Surveillance (ACCESS) Project. *Sexual Health* 7:478-483.

38. Garton L, Dyda A, Guy R et al. 2016. High chlamydia and gonorrhoea repeat positivity in remote Aboriginal communities 2009-2011: longitudinal analysis of testing for re-infection at 3 months suggests the need for more frequent screening. *Sexual Health* 13(6):568-574.

39. Goller J, Ward J, Saunders M et al. 2012. Chlamydia sentinel surveillance in Aboriginal Community Controlled Health Services finds higher testing and positivity rates among younger people. *Australian and New Zealand Journal of Public Health* 36(6):577-581.

40. Guy R, Kong F, Goller J et al. 2010. A new national Chlamydia Sentinel Surveillance System in Australia: evaluation of the first stage of implementation. *Communicable Disease Intelligence Quarterly Report.* 34(3):319-328.

41. Guy R, Wand H, Franklin N et al. 2011. Re-testing for chlamydia at sexual health services in Australia, 2004-08. *Sexual Health* 8(2):242-247.

42. Guy R, Wand H, Franklin N et al. 2011. Chlamydia trends in men who have sex with men attending sexual health services in Australia, 2004-2008. *Sexually Transmitted Diseases* 38(4):339-346.

43. Lim M, Goller J, Guy R et al. 2012. Correlates of Chlamydia trachomatis infection in a primary care sentinel surveillance network. *Sexual Health* 9(3):247-253.

44. Lim M, El-Hayek C, Goller J et al. 2014. Trends in chlamydia positivity among heterosexual patients from the Victorian Primary Care Network for Sentinel Surveillance, 2007-2011. *Medical Journal of Australia* 200(3):166-169.

45. O'Connor C, Ali H, Guy R et al. 2014. High chlamydia positivity rates in Indigenous people attending Australian sexual health services. *Medical Journal of Australia* 200(10): 595-598.

46. Reekie J, Donovan B, Guy R et al. 2017. Trends in chlamydia and gonorrhoea testing and positivity in Western Australian Aboriginal and non-Aboriginal women 2001–2013: a population-based cohort study. *Sexual Health* 14(6):574-580.

47. Reekie J, Donovan B, Guy R et al. 2018. Risk of Pelvic Inflammatory Disease in Relation to Chlamydia and Gonorrhea Testing, Repeat Testing, and Positivity: A Population-Based Cohort Study. *Clinical Infectious Diseases* 66(3):437-443.

48. Silver B, Guy R, Wand H et al. 2015. Incidence of curable sexually transmissible infections among adolescents and young adults in remote Australian Aboriginal communities: analysis of longitudinal clinical service data. *Sexually Transmitted Infections* 91(2):135-141.

49. Silver B, Kaldor J, Rumbold A et al. 2016. Community and clinic-based screening for curable sexually transmissible infections in a high prevalence setting in Australia: a retrospective longitudinal analysis of clinical service data from 2006 to 2009. *Sexual Health* 13(2):140-147.

50. Stephens N, Coleman D, Shaw K et al. 2015. Improving public health surveillance of chlamydia: analysis of population-level positivity trends. *Sexual Health* 12(4):369-371.

51. Su J, Skov S. 2008. An assessment of the effectiveness of the Tiwi Sexual Health Program 2002-2005. *Australian and New Zealand journal of public health* 32(6):554-558.

52. Ward J, Goller J, Ali H et al. 2014. Chlamydia among Australian Aboriginal and/or Torres Strait Islander people attending sexual health services, general practices and Aboriginal community controlled health services. *BMC Health Services Research* 14:285.

53. Weaver E, Bowring A, Guy R et al. 2014. Reattendance and chlamydia retesting rates at 12 months among young people attending Australian general practice clinics 2007-10: a longitudinal study. *Sexual Health* 11(4):366-369.

54. Wilkinson A, El-Hayek C, Fairley C et al. 2012. Incidence and risk factors associated with chlamydia in men who have sex with men: A cohort analysis of Victorian Primary Care Network for Sentinel Surveillance data. *Sexually Transmitted Infections* 88(5):319-324.

55. Wilkinson A, McNamee K, El-Hayek C et al. 2017. Utility of risk-based chlamydia testing in primary care: Analysis of retrospective surveillance data among women in Melbourne, Australia. *Sexual Health* 14(3):268-273.

56. Health Protection Agency (UK). HIV and Sexually Transmitted Infections Department Centre for Infections. Health Protection Weekly Report 2011. Accessed on 27th February 2019 from http://www.hpa.org.uk/hpr/.

57. Health Protection Agency (UK). HPA national influenza weekly reports 2008/09. Accessed on 27th February 2019 from http://www.hpa.org.uk/HPA/Topics/InfectiousDiseases/InfectionsAZ/1191942171484/

58. European Centre for Disease Prevention and Control (ECDC). 2019. Influenza Surveillance – Sentinel Surveillance. Accessed on 21st January 2019 from https://ecdc.europa.eu/en/seasonal-influenza/surveillance-and-disease-data/facts-sentinel-surveillance
59. Fireman B, Lee J, Lewis N, et al. 2009. Influenza vaccination and mortality: differentiating vaccine effects from bias. *American Journal of Epidemiology* 170:650-656.
60. Kwong J, Maaten S, Upshur R et al. 2009. The effect of universal influenza immunization on antibiotic prescriptions: an ecological study. *Clinical Infectious Diseases* 49:750-756.
61. Gibney K, Cheng A, Hall R et al. 2016. Sociodemographic and geographical inequalities in notifiable infectious diseases in Australia: a retrospective analysis of 21 years of national disease surveillance data. *The Lancet Infectious Diseases*. https://doi.org/10.1016/S1473-3099(16)30309-7
62. Kirby Institute. 2017. HIV, Viral Hepatitis and Sexually Transmissible Infections in Australia Annual Surveillance Report 2017. Accessed on 11th December 2018 from: https://kirby.unsw.edu.au/sites/default/files/kirby/report/SERP_Annual-Surveillance-Report-2017_compressed.pdf
63. Australian Government Department of Health. 2018. Australian Influenza Surveillance Report. No. 03, 2018, 18 June to 1 July 2018. Accessed on 12th October 2018 from http://www.health.gov.au/internet/main/publishing.nsf/Content/FBDA88CC40F930D4CA2582C200163E73/$File/flu-03-2018.pdf
64. Northern Territory Department of Health. 2018. Surveillance Update for Notifiable Sexually Transmitted Infections and Blood-Borne Viruses in the Northern Territory, Vol. 19, No. 1. Accessed on 11th Oct 2018 from https://digitallibrary.health.nt.gov.au/prodjspui/handle/10137/237
65. New South Wales Department of Health. 2017. NSW Sexually Transmissible Infections Strategy 2016-2020: January to December 2017 Data Report. Accessed on 11th Oct 2018 from https://www.health.nsw.gov.au/Infectious/Reports/Publications/sti/nsw-2017-sti-report.pdf
66. New South Wales Department of Health. 2018. Influenza Surveillance Weekly Report: Week 27: 2 to 8 July 2018. Accessed on 11th Oct 2018 from https://www.health.nsw.gov.au/Infectious/Influenza/Publications/2018/weekending-08072018.pdf
67. Queensland Health. 2018. State wide Weekly Influenza Surveillance Report: Reporting period: 1 January to 31 December 2017. Accessed on 11th Oct 2018 from

https://www.health.qld.gov.au/__data/assets/pdf_file/0034/656494/influenza-qld-2017.pdf

68. Department of Health, Western Australia. 2016. The Epidemiology of Notifiable Sexually Transmitted Infections and Blood-Borne Viruses in Western Australia 2016 Annual Report. Accessed on 11th Oct 2018 from https://ww2.health.wa.gov.au/Articles/A_E/Epidemiology-of-STIs-and-BBVs-in-Western-Australia.
69. Department of Health, Western Australia. 2018. Virus WAtch: Week ending 15th July 2018. Accessed on 15th September 2018, from https://ww2.health.wa.gov.au/~/media/Files/Corporate/general%20documents/Infectious%20diseases/PDF/VWAtch/20180715-virus-watch.pdf
70. Communicable Disease Control Branch, South Australia Health. Surveillance of sexually transmitted infections and blood-borne viruses in South Australia, 2015. Accessed on the 13th September 2018, from https://www.sahealth.sa.gov.au/wps/wcm/connect/36ced8804f954557af7caf0ba45b835a/Epidemiological+report+2015.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-36ced8804f954557af7caf0ba45b835a-mwNbebt.
71. Tasmanian Government. Department of Health and Human Services. 2018. fluTAS 2018 Report 3. Accessed on 13th October 2018, from https://dhhs.tas.gov.au/publichealth/communicable_diseases_prevention_unit/flutas_2018_report_3

Annex 5A: Electronic database search strategy

Table 1: MEDLINE MeSH search via Ovid at UNSW

Resource selected: "Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily, and Versions ® 1946 to July 13, 2018".

#	Search terms	Number of results
1	Australia/ or Australian Capital Territory/ or New South Wales/ or Northern Territory/ or Queensland/ or South Australia/ or Tasmania/ or Victoria/ or Western Australia	128,301
2	Influenza (Subject heading: Influenza, Human; Subheading: ep, mo, pc, sn, tm [Epidemiology, Mortality, Prevention & Control, Statistics & Numerical Data, Transmission])	28,396
3	Chlamydia/ or chlamydia trachomatis	13,993
4	Denominator data.mp	247
5	Surveillance data.mp	6592
6	Sentinel data.mp	59
7	Population surveillance/ or public health surveillance/ or sentinel surveillance/	62,319
8	Laboratory negative.mp	28
9	Denominator.mp	4808
10	Testing denominator data	1
11	Incidence/ or prevalence/	463,507
12	Disease surveillance.mp	4216
13	Testing-adjusted.mp	95
14	Surveillance trend*.mp	36
15	Epidemiological trend*.mp	908
16	Diagnosis rate*.mp	1223
17	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	519,311
18	2 or 3	42,387
19	1 and 17 and 18	301
20	Limit 19 to yr="2008-Current"	213

Table 2: MEDLINE keyword search via Ovid at UNSW

Resource selected: "Epub ahead of print" (till July 13, 2018).

#	Search terms	Number of results
1	Australia.mp	1821
2	Influenza.mp	1002
3	Chlamydia.mp	307
4	Denominator data.mp	1
5	Surveillance data.mp	118
6	Sentinel data.mp	1
7	Population surveillance.mp	13
8	Public health surveillance.mp	45
9	Sentinel surveillance.mp	36
10	Laboratory negative.mp	1
11	Denominator.mp	96
12	Testing denominator data.mp	0
13	Incidence.mp	10,988
14	Prevalence.mp	10,425
15	Disease surveillance.mp	96
16	Testing-adjusted.mp	5
17	Surveillance trend*.mp	1
18	Epidemiological trend*.mp	28
19	Diagnosis rate*.mp	45
20	2 or 3	1308
21	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 15 or 16 or 17 or 18 or 19	20,765
22	1 and 20 and 21	6

Table 3: EMBASE MeSH Search via Ovid at UNSW

Resource selected: Embase Classic+Embase 1947 to 2018 July 13.

#	Search terms	Number of results
1	Australia/ or Australian Capital Territory/ or New South Wales/ or Northern Territory/ or Queensland/ or South Australia/ or Tasmania/ or Victoria/ or Western Australia	151,815
2	Influenza/ep [Epidemiology]	1073
3	Chlamydia.mp	25,751
4	Denominator data.mp	375
5	Surveillance data.mp	7990
6	Sentinel data.mp	83
7	Population surveillance.mp	802
8	Laboratory negative.mp	45
9	Denominator.mp	7121
10	Testing denominator data.mp	2
11	Incidence/ep [Epidemiology]	1
12	Prevalence/ep [Epidemiology]	1
13	Disease surveillance/ or Epidemiology/	242,714
14	Testing-adjusted.mp	134
15	Surveillance trend*.mp	42
16	Epidemiological trend*.mp	1264
17	Diagnosis rate*.mp	2101
18	2 or 3	45,817
19	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	259,816
20	1 and 18 and 19	66
21	Limit 19 to yr=”2008-Current”	57

Annex 5B: Peer reviewed paper quality assessment tool

Criteria		Article ID
Study participants and setting: are these described in detail?		Response: Yes, No, Unclear, NA
Sample frame: is the sample frame appropriate to address the target population of the study?		
Sample method: are participants sampled in an appropriate way?		
Sample size: is the sample size adequate?		
Measurement of outcome: is the measurement of chlamydia or influenza valid, reliable and objective?		
Confounders: are any confounders identified and dealt with appropriately?		
DATA	Timeliness: are the data recent (within the past 10 years)?	
	Representativeness: do the data represent the group intended in the specific study methods?	
	Completeness: is the data complete (ie no missing data)?	
	Data analysis method: is the method of data analysis appropriate for the specific study research question?	
	Relevance: are the data generalizable to the topic of this review?	
OVERALL RISK OF BIAS		Low, Moderate, High

Annex 5C Data extraction of peer reviewed and grey literature

*Table 1: Descriptive summary of study details of peer reviewed papers containing testing denominator data on **influenza***

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Cowie 2017[23]	8 years (May-Oct for 2007-2014)	VIC	Sentinel general practice patients in Victoria.	4542/7421 ILI patients were tested (61%).	Existing sentinel surveillance networks (VicSPIN)	None	To describe testing practices. (To use positivity alongside other methods to evaluate the consistency of sentinel general practitioners' swabbing practice within and between influenza seasons).
Dawood 2010[27]	<1 year (Jun 1-Aug 30, 2009)	NSW	HNE laboratory compared to NSW laboratory	34177 specimens tested. Population denominato r not reported.	Laboratory data collected in bulk (HNE: Hunter Area Pathology Service laboratory) and sentinel surveillance data (NSW: SEALS, ICPMR, and five NSW government operated labs).	None	To estimate disease burden. (The proportion of pH1N1 positive specimens was calculated and applied to estimates of ILI, hospitalizations, and deaths to estimate pH1N1 associated disease burden during the first wave of pH1N1 circulate in HNE).
Dawson 2016[5]	1 year (2012-2013)	NSW	Sentinel laboratori es in NSW	Population testing coverage not reported.	Existing sentinel surveillance networks (11 labs, nine public and two private, including 2 reference labs).	Other	To demonstrate use of positivity in disease surveillance. (To provide an indication of the sensitivity of the NSW influenza surveillance system).

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Dowse 2011[28]	1 year (1 Nov 2008-30 Nov, 2009)	WA	Children 1-4 years, children 5-19 and pregnant women aged 21-45 in WA.	648 individuals in the pre-pandemic period and 736 in the post-pandemic period were tested. Population denominators not reported.	Laboratory data collected in bulk Use of historical laboratory specimens from PathWest were sent to the WHO C. Centre for Reference and Research on Influenza in Melbourne for testing.	Age	To estimate disease burden. (Positivity was used as an estimate of the prevalence of pH1N1 2009 influenza infection in children and pregnant women during the 2009 influenza season in WA).
Fielding 2009[29]	<1 year (27 Apr-27 Sep, 2009)	VIC	Sentinel general practice patients in Victoria	Population testing coverage not reported.	Existing sentinel surveillance networks (from the General Practice Sentinel Surveillance (GPSS), Victoria)	None	To estimate disease burden. (Positivity was one measure this study used to assess the 2009 H1N1 pandemic in Victoria).
Kelly 2009[30]	<1 year (Weeks 11-28, 2009)	VIC	Sentinel general practices in Victoria	682 patients tested. Population denominator not reported.	Existing sentinel surveillance networks (from GPSS Victoria)	Age, Other	To estimate disease burden. (Positivity was calculated to compare the proportion of total influenza detections and proportion of influenza detections due to pH1N1 in 2009. Positivity was also calculated in order to calculate vaccine effectiveness of the seasonal influenza vaccine against pH1N1 2009).

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Kelly 2009[31]	1 year (2009)	VIC	Sentinel surveillance practice patients in Victoria	Population testing coverage not reported.	Ad hoc sentinel surveillance networks (from selected general practices in Victoria)	Other	To estimate disease burden. (Positivity was just one epidemiological measure calculated to describe pH1N1 2009 and seasonal influenza infection in this study. Positivity was compared between total influenza detections and number of H1N1 2009 detections).
Kelly 2013[32]	5 years (2007-2011)	National	National	Population testing coverage not reported.	Existing sentinel surveillance networks (Laboratory data sent to the WHO Global Influenza Surveillance and Response System (GISRS) FluNet from the Australian Network of National Influenza Centres and other national influenza reference laboratories in Australia.)	None	To estimate disease burden. (Positivity was one measure used to estimate the significance of increase influenza notifications during spring and summer of 2010-11 in Australia).

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Lambert 2010[2]	5 years (2004-2008)	QLD, VIC, WA	State based laboratories and surveillance systems	Population testing coverage not reported.	Laboratory data collected in bulk (QLD Health Laboratories, VIDRL, PathWest)	Other	To demonstrate use of positivity in disease surveillance. (Influenza positivity was calculated for three different jurisdictions and the arguments for and against making negative influenza test results notifiable were discussed).

*Table 2: Descriptive summary of study details of peer reviewed papers containing testing denominator data on **chlamydia***

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Ali 2012[4]	5 years (1 Jan 2006-31 Dec 2010)	National	Patients from 18 Sexual health clinics across Australia	54,851/64,588 patients tested (84.9%).	Existing sentinel surveillance networks (Australian Collaboration for Chlamydia Enhanced Sentinel Surveillance programme – ACCESS)	Indigenous status, Sex, Age, Other	To demonstrate use of positivity in disease surveillance. (Positivity was calculated to understand trends in genital chlamydia trachomatis in Australia. Positivity rate was compared with the Medicare testing rate and the national notification rate).
Bowring 2012[33]	2 years (2008-2009)	National	Patients attending 5 Australian family planning clinics	6895/13,690 patients tested (50.4%).	Existing sentinel surveillance networks (ACCESS)	Age, Sex, Other	To describe testing practices. (Positivity was calculated and compared between first and re-test for chlamydia).
Bowring 2013[34]	2 years (2008-2009)	National	Patients from 25 participating general practice clinics in ACCESS	4894/50,408 patients tested (9.7%).	Existing sentinel surveillance networks (ACCESS)	Age, Sex, Other	To describe testing practices. (Positivity was calculated and compared between first and re-test for chlamydia).
Dimech 2014[35]	3 years (2008-2010)	National	15 laboratories representative of general practice and high-risk clinics	592,626 patients tested. Population denominator not reported.	Existing sentinel surveillance networks (ACCESS)	Age, Sex, Other	To describe testing practices. (Positivity was calculated and compared with testing rates to inform health promotion strategies).

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Forrest 2009[36]	3 years (2005-2007)	NSW	NSW prisons	16% prisoner population tested. (5865/36579)	Ad hoc sentinel surveillance networks	Other	To estimate disease burden. (Main outcome was prevalence).
Franklin 2010[37]	5 years (2004-2008)	NSW/ National	A sexual health clinic in inner west Sydney compared to national data from sexual health clinics.	2999/4564 patients tested (65.7%).	Ad hoc sentinel surveillance networks (SHC's own clinic data and sentinel surveillance network data (ACCESS)).	Indigenous status, Other	To describe testing practices. (Positivity and testing rates were calculated and compared between various population stratifications for the SHC and national data).
Garton 2016[38]	6 years (Jan 2009-Dec 2014)	NT	65 remote health services in Northern and Central Australia	18,280 patients tested. Population denominator not reported.	Ad hoc sentinel surveillance networks (Routinely collected laboratory data linked to STRIVE study data)	Age, sex	To describe testing practices. (Positivity was compared at initial test and at retest in 3 months to detect repeat chlamydia infections).
Goller 2012[39]	2 years (2008-2009)	National	Eight ACCHSs from five jurisdictions (Vic, WLD, NSW, WA and NT).	2883/19,854 patients tested (14.5%).	Existing sentinel surveillance networks (ACCESS)	Sex, Other	To describe testing practices. (Positivity and testing rates were compared among patients attending ACCHSs).

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Guy 2010[40]	5 years (2004-2008)	National	The entire ACCESS sentinel surveillance system: 6 separate networks; 5 clinical networks involving sexual health services, family planning clinics, general practices, antenatal clinics, Aboriginal community controlled health services, and 1 laboratory network.	% shown per priority population over 5 years (no crude %).	Existing sentinel surveillance networks (ACCESS)	Age, Sex, Other	To demonstrate the use of positivity in disease surveillance. (Positivity was calculated as part of the purpose of this article which was to conduct an evaluation on the first stage of the ACCESS chlamydia sentinel surveillance system).
Guy 2011[41]	5 years (Jan 2004-Dec 2008)	National	1 network of ACCESS: comprised of 25 sexual health services across Australia	9057/69,927 patients tested (13.0%).	Existing sentinel surveillance networks (ACCESS)	Age, Sex, Other	To describe testing practices. (The primary aim of this study was to describe the frequency of the 3-month test for re-infection among sexual health service patients in Australia. Positivity was calculated to show trends in chlamydia prevalence).

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Guy 2011[42]	5 years (2004-2008)	National	Men who have sex with men attending sexual health services in Australia	77.2% (9093 patients tested/11,777 eligible patients at first visit). Available by site and year.	Existing sentinel surveillance networks (ACCESS)	Other	To describe another epidemiological relationship. (Chlamydia positivity was compared with chlamydia testing rate and stratified by risk factors to better understand chlamydia trends).
Lim 2012[43]	3 years (Apr 2006-Jun 2009)	VIC	11 sentinel sites including SHCs, primary care clinics, general practices with a focus on gay men's health and a juvenile justice clinic.	44,199 patients tested Population denominator not reported.	Linked laboratory data (Sentinel surveillance data (The Victorian Primary Care Network for Sentinel Surveillance on BBVs and STIs.) linked to study data).	Indigenous status, Sex, Age, Other	To identify risk factors. (Chlamydia positivity was compared across a number of study questionnaire variables on chlamydia risk factors).
Lim 2014[44]	5 years (2007-2011)	VIC	Two sexual health clinics and six other primary care clinics that target young people and women at high risk.	55,453 patients tested. Population denominator not reported.	Existing sentinel surveillance networks (VPCNSS)	Age, Sex, Other	To demonstrate the use of positivity in disease surveillance. (Chlamydia positivity was calculated to describe the epidemiology of chlamydia in Victoria in a way that accounts for the amount of testing conducted).

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
O' Connor 2014[45]	6 years (Jan 2006-Dec 2011)	National	25 sexual health services in Australia.	168,729 eligible patients visited clinic (denominator). Numerators not reported (but some stratified %s).	Existing sentinel surveillance networks (ACCESS)	Indigenous status, Age, Sex, Other	To describe another epidemiological relationship. (Positivity was calculated to describe the clinical epidemiology of chlamydia among Indigenous people attending sexual health services around Australia).
Reekie 2017[46]	12 years (2001-2013).	WA	A cohort of 318,002 women, born between 1974 and 1995, residing in Western Australia (WA) was determined from birth registrations and the 2014 electoral roll.	134,980/318,002 women had at least one test (42%).	Linked laboratory data (Numerator data: routinely collected laboratory data. Denominator data: electoral roll. The two datasets were probabilistically linked).	Indigenous status, Age, Sex, Other	To describe another epidemiological relationship. (This study used a novel method to examine trends over 12 years in chlamydia and gonorrhoea testing and positivity to understand the epidemiology of these STIs in Aboriginal and non-Aboriginal women of reproductive age).

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Reekie 2018[47]	12 years (2002-2013)	WA	A population based cohort of Western Australian women, obtained from record linkage of the WA electoral roll and the WA Birth Registrations data collection.	Only the total number of tests was available as a proportion of all women included in the cohort: Chlamydia only: 10745/315,123 (3.4%) Chlamydia and gonorrhoea: 120,748 315,123 (38.3).	Linked laboratory data	Other	To describe another epidemiological relationship. The association between chlamydia positivity and pelvic inflammatory disease was calculated.
Silver 2015[48]	3 years (2009-2011)	National	Clinics across four geographical regions: 28 communities in Central Aus, 29 in the "Top End" of the NT, eight in the Kimberley region of WA and three in the Cape York region of QLD.	17,848 patients tested. Population denominator not reported.	Ad hoc sentinel surveillance networks (Routinely collected clinic data linked to STRIVE study data)	Sex, Age, Other	To identify risk factors. (Positivity was used to calculate chlamydia prevalence for a number of stratifications).

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Silver 2016[49]	Four years (2006-2009)	NT	Primary health care (PHC) clinics in remote regions of central Australian in the NT.	2792 individuals tested. Population denominator not recorded.	Ad hoc sentinel surveillance networks	Age, Sex, Indigenous status, Other	To describe another epidemiological relationship. (To compare the uptake and outcomes of two STI screening programs: a community wide screening program and PHC clinic testing).
Stephens 2015c[50]	10 years (2001-2010)	TAS	State wide notification and laboratory data	138 396 tests conducted. Population denominator not reported.	Laboratory data collected in bulk	Age, Sex, Other	To demonstrate use of positivity in disease surveillance. (This study examined the value of reporting positivity trends for chlamydia surveillance).
Stephens 2017[25] and Stephens 2017[26]	2 years (1 Jan 2012-31 Dec 2013)	TAS	Residents of Tasmania aged between 15 and 29 years inclusive.	31,899 tests conducted in 24,830 individuals. Population denominator not reported. (Slightly different numbers for Stephens 2016: 32,791 tests in 24,753 individuals).	Laboratory data collected in bulk	Age, Sex, Other	Stephens 2017: To describe testing practices. (This study used positivity to describe the epidemiology of and testing practices for chlamydia in young Tasmanians). Stephens 2017*: To describe another epidemiological relationship. (This study used positivity to assess if Tasmania is meeting clinical testing guidelines for chlamydia).

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Su 2008[51]	6 years (2001-2006)	NT	Remote Indigenous communities in the Tiwi Islands, Darwin Remote and Katherine regions, NT	No data on testing coverage.	Ad hoc sentinel surveillance networks	Other	To describe another epidemiological relationship. (Chlamydia positivity and other STI positivity was calculated over time to assess the effectiveness of the Tiwi Sexual Health Program).
Ward 2014[52]	1 year (2009)	National	25 GP clinics, 22 SHSs and six ACCHs within ACCESS	17,323/35,782 patients tested (48.4%).	Existing sentinel surveillance networks (ACCESS)	Indigenous status, Sex, Age, Other	To describe another epidemiological relationship. (Positivity was one measure calculated to describe the epidemiology of chlamydia among Australian Aboriginal and/or Torres Strait Islander people attending sexual health services, general practices and ACCHSs).
Weaver 2014[53]	4 years (Jan 2007-Dec 2010).	National	25 GP clinics within ACCESS	6498/55,318 patients tested (11.7%).	Existing sentinel surveillance networks (ACCESS)	None.	To describe testing practices. (The aim of this paper was to investigate the timing of attendance and chlamydia testing in GP clinics. Positivity was calculated by year to show trends in chlamydia prevalence).

Article ID	Time period of data collection	Jurisdiction	Setting	Crude population testing coverage	Source	Stratifications of positivity	Use of testing denominator data in study
Wilkinson 2012[54]	4 years (Apr 2006-Jun 2010)	VIC	Three general practices that specialise in gay men's health, a metropolitan sexual health centre and a regional sexual health centre.	6333 patients tested. Population denominator not reported.	Existing sentinel surveillance networks (VPCNSS)	Indigenous status, Sex, Age, Other	To identify risk factors. (Chlamydia positivity was calculated to investigate risk factors associated with chlamydia in men who have sex with men).
Wilkinson 2017[55]	8 years (2007-2014)	VIC	Women aged 16 years and over who attended one of 5 participating clinics including general practice, family planning and sexual health clinics	28,381 patients tested. Population denominator not reported.	Existing sentinel surveillance networks (VPCNSS)	Indigenous status, Sex, Age, Other	To identify risk factors. (Positivity was calculated to investigate risk factors associated with chlamydia among women in Melbourne, Australia).

*Table 3: Grey literature search results for the latest reports containing **influenza and/or chlamydia** testing denominator data accessible from jurisdictional website between 1st Jan 2008 to 13th Jul 2018)*

Jurisdiction	Disease	Testing denominator data within report	Title of report	Time period of data collection	Source of data in report	Frequency of report
National	Chlamydia	✓	HIV, Viral Hepatitis and sexually transmitted infections in Australia Annual Surveillance Report 2017[62]	Jan-Dec 2016.	Existing sentinel surveillance networks (ACCESS)	Annually
	Influenza	✓	Australian Influenza Surveillance Report, No. 3, 2018[63]	18th Jun – 1st Jul, 2018.	Existing sentinel surveillance networks (Pathology West ICPMR (NSW), VIDRL (VIC), PathWest (WA), Tasmania (no laboratory specified)).	Fortnightly/ Annually
NT	Chlamydia	✓	Surveillance Update for Notifiable Sexually Transmitted Infections and Blood-Borne Viruses in the Northern Territory, Vol. 19, No. 1[64]	Jan to Mar 2018	Existing sentinel surveillance networks (Western Diagnostic Pathology)	Quarterly
	Influenza	✗				
ACT	Chlamydia	✗				
	Influenza	✗				
NSW	Chlamydia	✓	NSW Sexually Transmittable Infections Strategy 2016-2020: January to December 2017 data report[65]	Jan to Dec 2017	Ad hoc sentinel surveillance networks (ACCESS Database, The Kirby Institute and the Burnett Institute).	Bi-annually/ Annually
	Influenza	✓	Influenza Surveillance Weekly Report. Week 27: 2 to 8 July 2018[66]	2nd to 8th Jul 2018.	Existing sentinel surveillance networks (11 NSW Sentinel Laboratories)	Weekly/ Monthly/ Annually
VIC	Chlamydia	✗				
	Influenza	✗				
QLD	Chlamydia	✗				

	Influenza	✓	Statewide Weekly Influenza Surveillance Report[67]	1st Jan – 31st Dec 2017	Existing sentinel surveillance networks (Public laboratory system).	Weekly (merged cumulatively to one available report).
WA	Chlamydia	✓	The Epidemiology of Notifiable Sexually Transmitted Infections and Blood Bourne Viruses in Western Australia[68]	1st Jan – 31st Dec 2016.	Unspecified.	Annually
	Influenza	✓	Virus WAtch[69]	Week ending 8th Jul 2018	Existing sentinel surveillance networks (Routine and sentinel samples processed by PathWest. Does not include samples referred to PathWest by other laboratories).	Weekly
SA	Chlamydia	✓	Surveillance of Sexually Transmitted Infections and blood-borne viruses in South Australia, 2015[70]	1st Jan – 31st Dec 2015.	Existing sentinel surveillance networks (Three sentinel laboratories (unnamed)).	Yearly
	Influenza	✗				
TAS	Chlamydia	✗				
	Influenza	✓	fluTAS 2018 Report 3[71]	1st Jan – 30th Jun 2018	Unspecified (Laboratory results - specific laboratories not specified).	Weekly

Chapter 6 – MAE Teaching Experience

Lesson from the Field and teaching session

Contents

Summary

This chapter summarises the activities undertaken as part of the peer-to-peer teaching requirements of the Master of Applied Epidemiology (MAE) Program. The MAE program includes two teaching requirements: a "Lesson from the Field" (LFF) and a Teaching Session. During the LFF, MAE scholars are required to prepare and deliver an interesting lesson from their field placement via teleconference to a group of students from their cohort. My LFF, titled "Ethical, Cultural and Practical Study Design Challenges in the Pacific", is outlined in the first section of this chapter. For the Teaching Session, the second year MAE cohort, as a group, are required to prepare and deliver a teaching session for the first-year MAE cohort over three hours. The contribution of my teaching group was a session on "Communicating as a Field Epidemiologist during Public Health Emergencies" which is outlined in the second section of this chapter.

I enjoy teaching epidemiology and biostatistics, and had experience in this prior to the MAE in my position as Associate Lecturer in Epidemiology and Biostatistics at the University of Sydney (USYD). I especially enjoy teaching culturally diverse audiences as it challenges me to simplify and adapt my explanations of concepts. Socratic questioning is a technique I embrace particularly in my epidemiology teaching style, as this helps students to break down complex concepts into simple first principles themselves. This not only leaves students feeling empowered and equipped with a sound understanding of epidemiological principles, but with a strategy they can use to deal with future challenges.

In addition to the MAE competencies, I was involved in the planning and facilitation of a three-day Systematic Review workshop held at UNSW for some of their collaborators in Indonesia in 2017. I also tutored the postgraduate courses "Epidemiology Methods and Uses" and "Introductory Biostatistics" at USYD throughout the first year of my MAE. In 2017, I was invited to give a guest lecture on Field Epidemiology to the postgraduate Advanced Epidemiology class at USYD. I based my LFF on components of this lecture. I was happy to be invited back in 2018 and present the lecture again. Collectively, my activities undertaken as part of the MAE teaching component and beyond demonstrate my skills and enthusiasm in teaching complex epidemiological methods to a variety of audiences, both via teleconference and face-to-face.

Acknowledgments

I would like to acknowledge the 2018 MAE Cohort; in particular my LFF group: Kaitlyn Vette, Patiyan Anderson, Aurysia Hii, Natalie Strobel, and Kelley Meder (and Jana Sisnowski for trialling my LFF). I would also like to acknowledge my MAE teaching session group: Ximena Tolosa, Aurysia Hii, and Patiyan Anderson. From the University of Sydney School (USYD) of Public Health, I would like to acknowledge Professor Tim Driscoll, Ms Anagha Killedar, Mr Ryan Pysar, Dr Erin Mathiew, and Dr Gemma Jacklyn for their assistance in putting together my guest lecture on Field Epidemiology at USYD, upon which my LFF was based.

Lesson from the Field: "Ethical, Cultural and Practical Study Design Challenges in the Pacific."

As the 2017 MAE cohort was quite large, we divided into small groups for the LFF sessions. My LFF group included Patiyan Andersson, Kelley Meder, Natalie Strobel, Kaitlyn Vette, and Aurysia Hii. My role within our group was to coordinate the LFF schedule of session times and dates for everyone. Between February and August 2018, I participated in the following five LFFs (as well as conducting my own):

- *Stratified Sample Sizes and Weighted Analysis*, Kelley Meder (National Centre for Immunization Research and Surveillance), 15th March 2018.
- *Understanding Your Population for Data Analysis*, Natalie Strobel (Faculty of Health and Medical Sciences, The University of Western Australia), 23rd April 2018.
- *Introduction to Burden of Disease Models,* Patiyan Andersson (Health Emergency Management Branch, Immunisation Branch, Office of Health Protection, Department of Health), 15th May 2018
- *Introduction to R: Using Influenza Data,* Kaitlyn Vette (Vaccine Preventable Diseases Surveillance Section, Office of Health Protection, Department of Health), 20th May 2018
- *Using Content Analysis to Analyse Qualitative Data,* Aurysia Hii (Integrated Systems for Epidemic Response, The Kirby Institute UNSW), 1st August 2018

I conducted my LFF titled "Ethical, Cultural and Practical Study Design Challenges in the Pacific" on the 22nd February 2018 (see Annex 6A for my LFF including answers and sample responses). Within my LFF, my role included lesson planning, piloting of the lesson, distribution of teaching material, coordination of lesson time and technical set up (Zoom/UNSW teleconference back up), and facilitation. I chose to focus my LFF on learning experiences from my Fiji epidemiology project that fell through. My LFF involved conducting a critical appraisal of the original study in the Solomon Islands (Marks et al 2016[1]) that my Fiji study was based on, and discussing how potential areas of bias could be improved in a new study - which was essentially what I did when designing my epidemiology project. I had based my guest lecture to the postgraduate Advanced Epidemiology students at USYD on a critical appraisal of the Marks et al 2016 study also, and adapted some parts of this for my LFF. I chose to focus the last part of my LFF on ethical and cultural challenges that I encountered to bring awareness of these issues to my cohort so that they would be prepared for similar situations in future.

Overall, I received very positive feedback from my LFF. On reflection however, I felt that I rushed through the lesson a little too quickly. I was aware that we had a lot to get through, so I tried to cram it all into the one-hour timeslot. I think it would have been more effective to

narrow the scope of my LFF, so that I could have managed the time to discuss less questions in more detail. In addition, the range of answers I received for each question made it apparent that I could have worded my questions more clearly. That said, I felt like I created an interesting, useful and enjoyable LFF for my group. I created a brief evaluation survey on Survey Monkey with the following questions:

> *"Did Sophie make you feel comfortable to ask questions in your LFF? If yes, how? If not, how could she improve on this?"*
>
> *"Did the lesson help deepen your understanding of ethical, cultural and practical study design challenges in the Pacific?"*
>
> *"Did Sophie explain answers clearly? If yes, how? If not, how could she improve on this?"*
>
> *"Was the timing of the lesson appropriate (did you feel that enough time was spent on difficult concepts)?"*
>
> *"Was there anything you think Sophie did particularly well?"*
>
> *"What could Sophie improve on?"*

Four out of five participants provided feedback (Annex 6B). It was great to receive very positive feedback overall. It seemed that I created an open environment in which participants felt comfortable to ask and answer questions. Participants' understanding of ethical, cultural and practical study design challenges in the Pacific was deepened through my LFF. The students were satisfied with the way that I explained answers and the fact that I could go into more detail if required. Participants were happy overall with the timing yet noted it would have been helpful to spend more time on some questions, as we finished early. Overall, they reported that my facilitation style was a great strength, and noted that in future something I could improve on would be drawing out the discussion around each question a little more.

Teaching Session: "Communicating as a Field Epidemiologist during Public Health Emergencies."

For our three-hour teaching session as second year MAE students, our whole cohort divided into four small groups based on the skills we wanted to teach. I played a key role in the design of the overall structure of the Teaching Session.

We decided to allocate 20 minutes to each group to conduct a formal classroom-based teaching session during the first 1.5 hours. This was followed by a short break, during which we shared a PowerPoint presentation with the first-year students which contained an "MAE Hot Tip" slide from each second year MAE. The next 1.5 hours after the PowerPoint presentation were a little more fun and practical. The second years facilitated an MAE "Pub Quiz" where each second year group would be allocated 20 minutes for a more "hands on" epidemiology themed teaching session during the last 1.5 hours. See Table 1 below for an outline of all the sessions.

Table 1: Outline of MAE Teaching Session 2018

Teaching session topic	Time allocated
Teaching Session 1	Allow 90 minutes
Communicating as a Field Epidemiologist in Public Health Emergencies	20 minutes
Writing tips	20 minutes
Logic models	20 minutes
Ethical considerations in surveys	20 minutes
Break	5 minutes
MAE Hot Tips from the Second Years	10 minutes
Teaching session 2 – Pub Quiz (1.5hrs-ish)	Allow 90 minutes
Personal Protective Equipment group	20 minutes
Communicable disease Playdough group	20 minutes
Communicable disease Pictionary group	20 minutes
Epidemiology charades group	20 minutes

I formed a group with Ximena Tolosa, Patiyan Andersson and Aurysia Hii as we all wanted to pass on our lessons learned from our MAE Pacific based field projects. Our formal classroom-based teaching session was on the topic "Communicating as a Field Epidemiologist during Public Health Emergencies" (see Annex 6C for slides). We had all experienced the complexities of scientific communication with a variety of stakeholders in our various field epidemiologist roles,

and wanted to prepare the second years for this as it is something important but not taught in course-block. Our teaching session involved a case study where second years had to imagine they were the field epidemiologist in a complex outbreak in a Pacific country, and needed to provide essential epidemiological updates to three different stakeholders.

For our hands-on teaching session, or "Pub Quiz", we designed a light-hearted activity about the correct application of Personal Protective Equipment (PPE). First years were allocated into small groups, and had to dress a group member correctly in PPE following the WHO PPE donning guidelines[2]. Once they were dressed in PPE, they were sprayed with glitter (see left: Sophie Phelan spraying a participant in glitter) and then had to follow the WHO PPE doffing guidelines[3]. It would be clear if anyone had not followed the guidelines correctly as they would have been covered in glitter – a comparatively harmless substitute for infected bodily fluids and aerosols.

Within our group, we equally shared roles of lesson planning, preparation of teaching materials and coordination of lesson timing. Aurysia Hii provided the PPE equipment. We each took turns at facilitating different parts of the classroom-based lesson; I introduced and concluded the session, while Aurysia, Patiyan and Ximena facilitated the small group discussions and fed back the answers to the rest of class.

In the process of planning and conducting the MAE teaching session, I learnt that simple learning objectives are best for this sort of thing. My group had so many ideas of what we wanted to teach, yet we realised to fit within the timeframe we had to simplify our learning objectives. It was quite challenging to plan and coordinate the entire teaching session among the large cohort of second year MAEs (17 students), yet every second year provided substantial contributions in their own way.

Overall, we felt like our Teaching Session was a great success – yet we needed an objective measure of evaluation. Therefore, the second-year cohort conducted a peer and class evaluation on Survey Monkey.

First years who undertook the activities and our fellow second-years who designed the activities were asked the following three questions about each of the four teaching sessions:

"Please rate how you found the format of the session"

"Please rate how you found the presenters style"

"Please rate how you found the session content"

Answer options were: Not of use, Minimal Use, Neutral, Useful, Highly Useful. Feedback from our session on communicating during public health emergencies showed that in regard to the format and presentation style, the most common response was that they were "Highly useful" (48%). There was room for improvement in our content however, as most students rated this as "Useful" (52%) (Annex 6D).

To obtain overall feedback, the following three questions were asked with the option to answer with free text:

"Overall, what did you learn from the session?"

"What did you think needed improvement?"

"Do you think the students had an opportunity to interact throughout the sessions?"

Most responses stated that they enjoyed learning practical tips from the second years, in particular with regard to our session on communicating during public health emergencies and writing tips for the final thesis. In terms of improvements, most responses stated that there was nothing the second years could improve on. Among the few suggested improvements, better time management and individual introductions from the second years were the most common. Finally, all responses were happy with the level of interaction facilitated in all sessions, especially in regard to the epidemiology themed Pub Quiz.

References

1. Marks M, Bottomley C, Tome H, et al. 2016. Mass drug administration of azithromycin for trachoma reduces the prevalence of genital *Chlamydia trachomatis* infection in the Solomon Islands. *Sexually Transmitted Infections* 92(4):261-265.
2. World Health Organization. 2015. Steps to put on personal protective equipment (PPE) including coverall. World Health Organization. Accessed on 15th December 2018, from http://www.who.int/iris/handle/10665/150116
3. World Health Organization. 2015. Steps to take off personal protective equipment (PPE) including coverall. World Health Organization. Accessed on 15th December 2018, from http://www.who.int/iris/handle/10665/150118

Annex 6A: Lesson from the Field: Ethical, Cultural and Practical Study Design Challenges in the Pacific

Facilitator: Sophie Phelan

This LFF will be conducted by teleconference on Thursday 22nd February 2018 from 8pm-9pm AEST/5pm-6pm AWST. Please save your responses to the questions in this word file template and send back to me (sphelan@kirby.unsw.edu.au) by COB Monday 19th February 2018. This session is focused on practical aspects of study design.

LEARNING OBJECTIVES

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

1. Critically review methodological limitations of epidemiological field studies in an international setting.
2. Evaluate strengths and weaknesses in epidemiological study design.
3. Develop improvements to the study design of epidemiological field studies.
4. Apply understanding of ethical issues in research to fieldwork.

BACKGROUND

Trachoma is a neglected tropical disease that affects the eyes. It is responsible for considerable morbidity in certain countries and in sub-populations within countries. The strategy of population-wide antibiotic distribution programs (also known as Mass Drug Administration (MDA) programs) has been adopted in an attempt to eliminate trachoma as an endemic disease. As this involves the widespread use of antibiotics, MDA programs may have additional beneficial (or harmful) health effects. One potential benefit is a reduction in the incidence and prevalence of certain sexually transmitted infections (STIs). This is because some of the bacteria which cause the STIs are also susceptible to the antibiotics used in the MDA for trachoma. A recent study by Marks et al (2016) investigated this issue in the Solomon Islands. The study had several methodological limitations. This LFF session will consider these methodological limitations and discuss the challenges of designing an improved study for another Pacific country.

RESOURCES

1. Cliffe S, Tabrizi S, Sullivan E. 2008. Chlamydia in the Pacific Region, the Silent Epidemic. *Sexually Transmitted Diseases* 35(9):801-806.
2. Lahra M, Lo Y, Whiley D. 2013. Gonococcal antimicrobial resistance in the Western Pacific Region. *Sexually Transmitted Infections* 89:iv19-iv23.
3. Marks M, Bottomley C, Tome H et al. 2016. Mass drug administration of azithromycin for trachoma reduces the prevalence of genital Chlamydia trachomatis infection in the Solomon Islands. *Sexually Transmitted Infections* 92(4):261-265.

TASK 1: Case study

Critically read the paper by Marks et al (2016). You are aware that another Pacific Island country is planning to conduct nationwide MDA for trachoma, and have been asked by your supervisor to consider the study methodology in Marks et al (2016) to plan a similar study in another Pacific country. Complete Tasks 2-5 to assist your planning.

TASK 2: Study design considerations

2.1 What is the study design used in the paper by Marks et al (2016)? Is this the best study design that could be used to answer the study question?

The study design used in the paper was a cross-sectional before/after study design. The most ideal study type would have been a randomized controlled trial (RCT), however in this case there were ethical and practical reasons that this was not possible. All participants answered this question correctly.

Responses to the best study design that could be used included:

"A randomised control trial is another design that can be used to measure the impact of an intervention, however, there can be ethical reasons to not selecting this design such as limiting treatment to a selected group of the population. In this study and RCT would not be appropriate as MDA was already being distributed for trachoma, so participants would not have been able to be randomly allocated to the treatment group."

"Could be improved by using a[n RCT] *design where defined population groups (e.g. villages) are randomised to receive MDA intervention or not; and comparing cross sectional data on STIs from before and after the intervention, with a representative sampling (send out sampling kits) of the entire sexually active population is conducted."*

2.2 Briefly research some of the advantages and disadvantages of using urine specimens vs vaginal swabs for PCR STI testing. To keep things simple, please answer this question in respect to your allocated rectangle in the table. Potential aspects to consider could include: cultural sensitivity, sample transportation, sample storage, cost, test sensitivity/specificity.

All participants hit the key advantages and disadvantages, as their responses show below:

	Advantages ✓	Disadvantages ✗
Urine specimen 	*"Easy to explain and technically easy to self-collect by patient. Non-invasive. Cheap sampling kit. Can be transported at room temperature (<48h), although other paper state refrigerated. Sens/Spec depends on analysis method, but acceptable for most (>90%).*	*"Requires for urine not to be passed 2hrs before. Requires accurate collection of the first pass urine. Needs immediate refrigeration"*
Vaginal swab 	*"Easy to explain. Can be completed straight away by the participant. No need for a pelvic examination. Potentially more acceptable than an invasive test.* *Storage can be at ambient temps"*	*"More false positives. Culturally less acceptable than urine samples, especially if conducted in the home. More invasive than urine samples. Acceptable specificity, but sensitivity is lower than urine specimen. Must return to the clinic or lab for analysis."*

2.3 How could you adapt your study methodology to prove that any significant reduction in chlamydia or gonorrhoea was a result of the trachoma MDA, and not a parallel activity such as a health promotion campaign?

In my study design, we planned to mitigate this by sampling participants for a sexually transmitted disease that was not affected by azithromycin – trichomoniasis vaginalis. None of the LFF participants gave this response, however there was no perfect answer to this question and many had some ideas I hadn't thought of. Some of these included:

"You could include a screening questionnaire which indicates whether the women are currently, or planning to, partaking in a health promotion campaign. You can include a follow-up questionnaire upon sample return with questions around involvement in such activities as well."

"Your initial step would be to identify if there are any current health promotion campaigns and other interventions that could have an impact on the study outcome."

2.4 The development of antimicrobial resistance in the causative bacterium of gonorrhoea, *Neisseria gonorrhoeae* is of increasing concern. Could you do anything in your revised study to contribute to scientific research in this area? (If you are interested and would like more information on antimicrobial resistance *in N. gonorrhoeae* in the Pacific, see paper by Lahra and coworkers (2013)).

In my study design, we planned to also perform molecular testing of genetic resistance to *N. gonorrhoeae*. All participants mentioned that they would also do this in their revised study, and provided some extra details as below:

"Do a nested study to test for antimicrobial resistance of N. gonorrhoeae*. In a certain area you could collect additional samples and complete the required analysis."*

"Assessing the resistance of any specimens where N. gonorrhoeae *is present would be ideal to contribute to further research in this area. As the paper explains, there aren't the lab facilities to perform gonococcal culture, however the possibility of developing an in-house molecular assay to detect resistance such as that described by Unemo et al in 2014 (http://cmr.asm.org/content/27/3/587.full) could be explored. If this is unfeasible, the possibility of taking samples off shore for resistance testing should be investigated."*

2.5 Convenience sampling was the recruitment strategy used in the paper by Marks et al. What other sampling strategies could you use to obtain a more representative study population in your revised study (consider the high population mobility across most Pacific Islands)?

In my revised study, we used clustered sampling across the four divisions of Fiji to get a more representative study population. Three participants gave this answer also. The two participants below gave great answers however they were not possible in this study context:

"Send out self-sampling kits together with a survey to randomised households. However, may end up with a low response rate and hence waste of sampling kits. Also, there may be culturally sensitive aspect to deal with, along with social welfare risks (family members may question why the individual has been "selected" to receive a STI testing kit)."

"Presumably it would be difficult to collect name lists or anything simple for random sampling when there is high movement of the population. With this high mobility there may be immigration records that enable simple random sampling from the list of people incoming and outgoing. There a whole host of accessibility and ethical points on that though. If there are good records of people receiving antenatal care, a list of names could be used to randomly sample and could be more broadly sourced if the information is available. This may be more random but still restricts the sample population."

2.6 The study by Marks et al lacked an objective measure of MDA treatment uptake (they relied on patient reports, which are subject to recall bias!). Can you think of an objective or a slightly better subjective measure to use in your improved study?

We couldn't actually think of an objective measure of MDA uptake for our study. Follow up of patients in Fiji was impossible due to high mobility, and no individual level coverage data of trachoma MDA is collected so that could not be linked to study data. I was interested to put this question to my LFF group. Some other methods participants suggested to verify treatment uptake included:

"Asking participants to record or mark off dates in a diary or calendar each time they took the medication over the course of treatment".

"Asking participants to retain all treatment packaging and return this to the study team on completion, including any tablets that were not consumed".

"Reviewing pharmaceutical dispensing data and patient medical records".

"Asking clinic staff to maintain treatment records for their patients".

2.7 Are there any additional aspects of the original study that you could improve in your study?

All participants responded with excellent additional aspects for consideration. Some examples included:

"One of the limitations of the study was that it did not collect information on MDA treatment of sexual partners. In an improved study, this information should be collected to assess whether there is an association between this and the study outcomes."

"I'm not sure but there appears to be better methods of measuring STIs so maybe considering whether it's feasible to do this. Also a qualitative study in conjunction would be good to determine sexual behaviours. A survey might not be appropriate but one-on-one interviews could be good to have a look at how you could get to the core of the problem."

TASK 3: Epidemiological considerations

For a source of bias in the Marks et al study that was discussed in Task 2, explain the likely effect on the main study outcomes (comparison of the prevalence of STIs before and after MDA for all participants, and comparison of the prevalence of STIs before and after stratified by those who said they had received the antibiotic and those who said they had not). Otherwise, indicate why you don't feel you can predict the likely effect.

All participants described the effects of recall bias. One participant also described the effect of selection bias, as below:

"The selection bias associated with the convenience sample of women attending the clinics may have several effects on the data seen downstream. By using the same clinics as the previous survey and sampling, some of these participants would have been informed and treated in the previous round, and as such can be considered more aware of STIs, which may account for a reduction in prevalence in both post-MDA groups compared with the pre-MDA group."

TASK 4: Biostatistical considerations

As part of the analysis, the authors compared the prevalence of two types of STI, *C. trachomatis* and *N. gonorrhoeae*, between those who had received the antibiotics and those who did not (revisit the Results section of the Abstract for the case study).

Based on the results (i.e. don't consider the potential sources of bias in the study), do you agree with the interpretation by the authors that there was an effect on *C. trachomatis* infection prevalence but not on *N. gonorrhoeae* infection prevalence? Why or why not?

One student agreed, and the other four students disagreed with the authors interpretation. Essentially the authors could have explained in more detail that there was an effect of MDA on N. gonorrhoeae prevalence, but the sample size was not sufficient to detect a significant effect.

Below is the justification from the participant who agreed with the authors, and a justification from a participant who did not agree with the authors.

"Yes, because of the increasing antibiotic resistance in N. gonorrhoeae*, it is possible that the MDA had no effect on the number of diagnosed cases, whereas the prevelance decreased in those infected with C. trachomatis."*

"The results section of the abstract state that there was no change in the prevalence of N. gonorrhoeae *following MDA treatment. This is not correct. Table 3. states that there was a 3% reduction in prevalence, however, this difference was not statistically significant. The authors should have clarified that there was no statistically significant change in prevalence."*

TASK 5: Ethical considerations

5.1 Knowledge of a positive STI result can sometimes result in partner conflict and violence. What measures could you take to ensure that this risk is reduced?

In our study plans, we took care to adhere to local STI notification guidelines. All participants provided measures that would ensure patient confidentiality as their answers. Examples included:

"You would ensure patient confidentiality. You could also inform the women of their outcome at a normal clinic visit, rather than having them schedule an additional visit which may arise suspicion."

"As part of the study, education and counselling support for both the participant and their partner should be provided if they test positive and even if they test negative. This should be provided in a culturally appropriate and safe way i.e. by trained staff, in a private location, in the local language etc. Education on STIs should be offered to the community and reduce the stigma associated with a positive result."

5.2 Considering the threat of gonococcal antimicrobial resistance, weigh up the advantages and disadvantages of this study with regard to its public health impact.

I wanted to use this question to start a discussion around the ethics of this issue. Students provided many advantages and disadvantages, and we were able to have a well-rounded discussion.

Some advantages included:

- *"Active case finding and treatment for community members who may not have otherwise had the opportunity to be tested and treated".*

- *"Reduction in negative health outcomes associated with undetected and untreated chlamydia infections such as pelvic inflammatory diseases, infections and infertility".*
- *"Contribute to the evidence around MDA use and reduction of Chlamydia".*

Some disadvantages included:

- *"May contribute to increased risk of antimicrobial resistance, however, this can be reduced by explaining the importance of following treatment routine to patients".*

END

Note: if you would like to read more about STIs in the Pacific region, please read Resource 1 (Cliffe et al 2008).

Annex 6B: Lesson from the Field Feedback

Question	Feedback
1. Did Sophie make you feel comfortable to ask questions in your LFF? If yes, how? If not, how could she improve on this?	**Participant 1:** Yes, she was very approachable and happy to take any questions from the group. **Participant 2:** Yes, she was very encouraging. She often would give the opportunity to ask questions and discuss further, before she moved onto the next question. **Participant 3:** Yes, you mentioned a number of times that you were happy to take questions either during or after. And I think you did this for each questions but my recall bias on this is quite poor (sorry!). you also created a relaxed and open environment. **Participant 4:** Yes. Sophie made sure everyone had a turn to answer questions and was supportive during the process.
2. Did the lesson help deepen your understanding of ethical, cultural and practical study design challenges in the Pacific?	**Participant 1:** Yes. Prior to the session I did not understand how much of a public health issue this was, and it really helped me understand more about the challenges of working in a remote region with a vulnerable population. **Participant 2:** Absolutely. Both the question themselves and the subsequent discussion was very helpful in terms of raising aspects that I would not have necessarily thought of on my own. **Participant 3:** Yes, it really did **Participant 4:** Yes. Especially for STIs. I wasn't aware of partner violence related to STIs so it was interesting to learn about that ethical issue.
3. Did your Sophie explain answers clearly? If yes, how? If not, how could she improve on this?	**Participant 1:** Yes, Sophie was very clear and easily understood with her explanations. She was happy to go into more depth if needed. **Participant 2:** Yes. I thought the model of letting someone provide their answer and then filling in or summarizing it afterwards worked very well. **Participant 3:** Yes - you added to our answers to fill in any gaps. You also provided answers to how you planned to do the study if they differed from our answers **Participant 4:** Yes Sophie explained the answers clearly and provided feedback on what happened within the context of her project.
4. Was the timing of the lesson appropriate (did you feel that enough time was spent on difficult concepts?)	**Participant 1:** Yes. More time was allocated on the more controversial question topics which was good for discussion. **Participant 2:** Yes **Participant 3:** No issue with timing as we finished early. We could have spent a bit more time discussing and debating some questions/answers **Participant 4:** Yes
5. Was there anything you think Sophie did particularly well?	**Participant 1:** Facilitate the session and get everyone to participate. **Participant 2:** I thought the lesson and the questions were very well designed. Sophie kept track of the time and made sure that we got through it all. **Participant 3:** You introduced the study and set the scene quite well. Made everyone feel welcome and that their contributions were useful and valuable. Great job!

	Participant 4: I thought she chaired the meeting very well. Sophie directed and gave everyone a chance to provide answers and ask questions. It was efficiently run.
6. What could Sophie improve on?	**Participant 1:** Sophie did really well. Perhaps just a quick summary of the article we were discussing in the beginning of the lesson as a refresher. **Participant 2:** Nothing that I can think of, she did a great job. **Participant 3:** Perhaps for each question you could have facilitated and prompted discussion a bit more by asking everyone as a group what they thought of certain aspects of the study or other's responses. Just to help with engaging everyone (or forcing) in discussion. **Participant 4:** Nothing. I really enjoyed the lesson.

Annex 6C: MAE Teaching Session PowerPoint

Communicating as a Field Epi during Public Health Emergencies

Learning objectives

1. **Understand** your role as a Field Epidemiologist investigating an outbreak within the context of a complex, fast evolving, humanitarian emergency.
2. **Communicate** to different audiences as a part of your role as Field Epidemiologist.
3. **Work** and **deliver** relevant information under time pressure.

Scenario

You are the Field Epi on deployment to a post disaster zone. **There has been a cholera outbreak following a tsunami in a coastal urban centre in a Western Pacific country.**

Today, you have three stakeholders that you need to communicate to:

1. Interagency members at daily Situation Report meeting
2. Data collectors at local health care clinic
3. Your incoming replacement Field Epi (another GOARN volunteer)

Lead Field Epi presenting at a daily interagency Situation Report meeting

1. Recent data (24 hours)
2. Any problems? Eg increase in cases in clinic 4 (they have asked for help), no reporting from clinic 2.
3. In-country situation (is there still an influx of people?)

Method: short talk, use PowerPoint/whiteboard to assist if available

Field Epi discussing data collection with local clinic staff (who have stopped reporting)

1. Ask what is going on, and discuss what additional support would be helpful
2. Explain the significance of the outbreak in terms of how it is affecting their local area (local stats so far), and how important their data is in contributing to the bigger picture of solving the outbreak.
3. Develop a feedback loop so they can see how their data is contributing to the big picture (ie brief 1 page epi report disseminated among health care clinics)

Method: Arrange a field visit to discuss in person. Be aware of cultural faux pas!

Handover to the next Field Epi

1. Contact details of MoH, WASH, etc people you were dealing with
2. Explain what stage the work is at
3. Hard and soft copies of all documents

Method: meet in person, connect over email prior if possible, leave soft/hardcopy backups if you can.

Annex 6D: Evaluation of MAE Teaching Session

Question	Response options	%
1. Please rate how you found the format of the session:	Not of use	0%
	Minimal use	4%
	Neutral	4%
	Useful	44%
	Highly useful	48%
2. Please rate how you found the presenter's style	Not of use	0%
	Minimal use	0%
	Neutral	7%
	Useful	45%
	Highly useful	48%
3. Please rate how you found the session content	Not of use	0%
	Minimal use	4%
	Neutral	7%
	Useful	52%
	Highly useful	37%